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55th Child Neurology Society Annual Meeting

Presented at

Palais des Congrès de Montréal

October 14 – 17, 2026

AMERICAN NEUROLOGICAL ASSOCIATION
INNOVATORS IN DISCOVERY, EDUCATION, AND CARE

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Presented at the Palais des Congrès de Montréal, Montréal, Québec, Canada
October 14-17, 2026

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Patricia Crumrine 1995-1997
James Bale 1995-1997
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Michael Goldstein 1998-2000
E. Steve Roach 1998-2000
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Phillip Pearl 2015-2017
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Soe Mar 2023-2025
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Meghan Candee 2024-2026
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2027
Milwaukee, Wisconsin

2026
Montreal, QC, Canada

2025
Charlotte, North Carolina

2024
San Diego, California

2023
Vancouver, BC Canada

2022
Cincinnati, Ohio

2021
Boston, Massachusetts

2020
San Diego, California
The Joint 16th ICNA Congress &
49th Annual CNS Meeting
Together · Apart Virtual

2019
Charlotte, North Carolina

2018
Chicago, Illinois

2017
Kansas City, Missouri

2016
Vancouver, BC, Canada

2015
Washington, DC

2014
Columbus, Ohio

2013
Austin, Texas

2012
Huntington Beach, California

2011
Savannah, Georgia

2010
Providence, Rhode Island

2009
Louisville, Kentucky

2008
Santa Clara, California

2007
Quebec City, PQ, Canada

2006
Pittsburgh, Pennsylvania

2005
Los Angeles, California

2004
Ottawa, ON Canada

2003
Miami Beach, Florida

2002
Washington, DC

2001
Victoria, BC, Canada

2000
St. Louis, Missouri

1999
Nashville, Tennessee

1998
Montreal, QC, Canada

1997
Phoenix, Arizona

1996
Minneapolis, Minnesota

1995
Baltimore, Maryland

1994
San Francisco, California

1993
Orlando, Florida

1992
New Orleans, Louisiana

1991
Portland, Oregon

1990
Atlanta, Georgia

1989
San Antonio, Texas

1988
Halifax, NS, Canada

1987
San Diego, California

1986
Boston, Massachusetts

1985
Memphis, Tennessee

1984
Phoenix, Arizona

1983
Williamsburg, Virginia

1982
Salt Lake City, Utah

1981
Minneapolis, Minnesota

1980
Savannah, Georgia

1979
Hanover, New Hampshire

1978
Keystone, Colorado

1977
Charlottesville, Virginia

1976
Monterey, California

1975
Hamilton, ON, Canada

1974
Madison, Wisconsin

1973
Nashville, Tennessee

1972
Ann Arbor, Michigan

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Nigel S. Bamford
New Haven, CT

2025
Lauren Treat
Aurora, CO

2024
Dave F. Clarke
Austin, TX

2023
Yasmin Khakoo
New York, NY

2022
Jorge Vidaurre
Columbus, OH

2021
Mary Zupanc
Irvine, CA

2019
H. Terry Hutchison
Fresno, CA

2018
Audrey Foster-Barber
San Francisco, CA

2017
David Coulter
Boston, MA

2016
Oscar Papazian
Miami, FL

2015
Robert Zeller
Houston, TX

2014
Kenton Holden
Mt. Pleasant, SC

2013
Douglas Postels
East Lansing, MI

2012
Marvin Fishman
Houston, TX

2011
Shaul Harel
Tel Aviv, Israel

2010
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New York, NY

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Boston, MA

2025
Brenda Banwell
Philadelphia, PA

2024
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Boston, MA

2023
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Sacramento, CA

2022
Steven Paul Miller
Vancouver, BC, Canada

2021
Jerry Mendell
Columbus, OH

2020
Joseph Gleeson
San Diego, CA

2019
Scott Pomeroy
Boston, MA

2018
William B. Dobyns
Seattle, WA

2017
Solomon Moshé
Bronx, NY

2016
Harvey Sarnat
Calgary, AB, Canada

2015
Harry T. Chugani
Detroit, MI

2014
Gabrielle deVeber
Toronto, ON, Canada

2013
Tallie Z. Baram
Irvine, CA

2012
Roger Packer
Washington, DC

2011
Laura Ment
New Haven, CT

2010
Thomas Jessell
New York, NY

2009
Gregory Holmes
Lebanon, NH

2008
Michael Johnston
Baltimore, MD

2007
Frederick Andermann
Montreal, QC, Canada

2006
Donna Ferriero
San Francisco, CA

2005
O. Carter Snead III
Toronto, ON, Canada

2004
Karin Nelson
Bethesda, MD

2003
Darryl C. De Vivo
New York, NY

2002
Francis Collins
Bethesda, MD

2001
Huda Zoghbi
Houston, TX

2000
Joseph Volpe
Boston, MA

1999
Carla Shatz
Berkeley, CA

1998
Andrew Engel
Rochester, NY

1997
Martha Bridge Denckla
Baltimore, MD

1996
Verne S. Caviness
Boston, MA

1995
Gerald D. Fischbach
Boston, MA

1994
David Prince
Stanford, CA

1993
C. Thomas Caskey
Houston, TX

1992
Louis M. Kunkel
Boston, MA

1991
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1990
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1989
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New York, NY

1988
Victor Dubowitz
London, England

1987
Hugo Moser
Baltimore, MD

1986
Louis Sokoloff
Bethesda, MD

1985
Patricia Goldman-Rakic
New Haven, CT

1984
William L. Nyhan
La Jolla, CA

1983
Roger N. Rosenberg
Dallas, TX

1982
John O'Brien
La Jolla, CA

1981
Pasko Rakic
New Haven, CT

1980
Dominick Purpura
New York, NY

1979
Fred Plum
New York, NY

1978
W. Maxwell Cowan
St. Louis, MO

1977
George Cahill
Bethesda, MD

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2024
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2023
Phillip L. Pearl
Boston, MA

2022
Leon G. Epstein
Chicago, IL

2021
Jonathan W. Mink
Rochester, NY

2020
Kenneth J. Mack
Rochester, MN

2019
James F. Bale, Jr.
Salt Lake City, UT

2018
Bernard L. Maria
Morristown, NJ

2017
Nina F. Schor
Rochester, NY

2016
Harvey Singer
Baltimore, MD

2015
E. Steve Roach
Columbus, OH

2014
Michael Shevell
Montréal, QC, Canada

2013
John Bodensteiner
Rochester, MN

2012
Ann Tilton
New Orleans, LA

2011
Deborah Hirtz
Bethesda, MD

2010
Sakkubai Naidu
Baltimore, MD

2009
Peter Camfield
Halifax, NS, Canada

2008
Stephen Ashwal
Loma Linda, CA

2007
Robert S. Rust
Charlottesville, VA

2006
Michael Painter
Pittsburgh, PA

2005
Alan Percy
Birmingham, AL

2004
John Freeman
Baltimore, MD

2003
Michael E. Cohen
Buffalo, NY

2002
Peter H. Berman
Philadelphia, PA

2001
Charles Barlow
Boston, MA

2000
Arthur Prensky
St. Louis, MO

1999
Marvin Fishman
Houston, TX

1998
N. Paul Rosman
Boston, MA

1997
Gerald Fenichel
Nashville, TN

1996
William Bell
Iowa City, IA

1995
Salvatore DiMauro
New York, NY

1994
Hugo Moser
Baltimore, MD

1993
Bengt D. Hagberg
Goteborg, Sweden

1992
Darryl C. De Vivo
New York, NY

1991
Karin B. Nelson
Bethesda, MD

1990
Joseph J. Volpe
Boston, MA

1989
Manuel Gomez
Rochester, NY

1988
Bruce Berg
San Francisco, CA

1987
Isabelle Rapin
Bronx, NY

1986
Jean Aicardi
Paris, France

1985
Raymond D. Adams
Boston, MA

1984
Peter Huttenlocher
Chicago, IL

1983
Betty Q. Banker
Cleveland, OH

1982
Patrick F. Bray
Salt Lake City, UT

1981
Kenneth F. Swaiman
Minneapolis, MN

1980
John H. Menkes
Beverly Hills, CA

1979
Paul I. Yakovlev
Boston, MA

1978
Philip R. Dodge
St. Louis, MO

1977
David B. Clark
Lexington, KY

1976
Sidney Carter
New York, NY

1975
Randolph K. Byers
Boston, MA

1974
Douglas Buchanan
Chicago, IL

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Michael Msall
Chicago, IL

2025
Stewart H. Mostofsky
Baltimore, MD

2024
Shafali Jeste
Los Angeles, CA

2023
William Davis Gaillard
Washington, DC

2022
Michael Shevell
Montreal, QC, Canada

2021
Elizabeth Berry-Kravis
Chicago, IL

Philip R. Dodge Young Investigator Award Recipients

2026
Danielle Guez Barber
Aurora, CO

2025
Ana G. Cristancho
Philadelphia, PA

2024
Fiona M. Baumer
Palo Alto, CA

2023
Siddharth Srivastava
Boston, MA

2022
Bhooma Aravamuthan
St. Louis, MO

2021
Monica Lemmon
Durham, NC

2020
Hsiao-Tuan Chao
Houston, TX

2019
Louis Dang
Ann Arbor, MI

2018
Christopher Elitt
Boston, MA

2017
Audrey C. Brumback
Austin, TX

2016
Diana Bharucha-Goebel
Bethesda, MD

2015
Jimmy Holder, Jr.
Houston, TX

2014
Christopher Smyser
St. Louis, MO

2013
Peter Tsai
Boston, MA

2012
Yoon Jae-Cho
Stanford, CA

2011
James Dowling
Ann Arbor, MI

2010
Stephen Maricich
Cleveland, OH

2009
Jeffrey Neul
Houston, TX

2008
Laura Jansen
Seattle, WA

2007
Mirjana Maletic-Savatic
Stony Brook, NY

2006
Elliott Sherr
San Francisco, CA

2005
Mustafa Sahin
Boston, MA

2004
Terri Inder
Melbourne, Australia

2003
Bradley Schlaggar
St. Louis, MO

2002
Nigel Bamford
New York, NY

2001
Daniel J. Bonthius
Iowa City, IA

2000
Stephen Back
Portland, OR

1999
Amy Brooks-Kayal
Philadelphia, PA

1998
Joseph Gleeson
Boston, MA

1997
William A. Weiss
San Francisco, CA

1996
Michael Rivkin
Boston, MA

1995
Adre J. du Plessis
Boston, MA

1994
Mia MacCollin
Boston,MA

1993
JeffreyJ.Neil
St. Louis, MO

1992
Kelvin A. Yamada
St. Louis, MO

1991
Kenneth J. Mack
Madison, WI

1990
Evan Y. Snyder
Boston, MA

Harris Gelbard
Rochester, NY

1989
Scott L. Pomeroy
St. Louis, MO

1988
Huda Zoghbi
Houston, TX

1987
Vinodh Narayanan
Pittsburgh, PA

1986
Faye S. Silverstein
Ann Arbor, MI

1985
Richard J. Konkol
Milwaukee, WI

1983
Michael Pranzatelli
Washington, DC

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Lawrence W. Brown
Philadelphia, PA

Susan Koh
Denver, CO

2025
Wendy Gayle Mitchell
Los Angeles, CA

Vinodh Narayanan
Phoenix, AZ

2024
Roy D. Elterman
Rancho Palos Verdes, CA

Donna M. Ferriero
San Francisco, CA

2023
Radha Giridharan
Brooklyn, NY

Robert S. Greenwood
Chapel Hill, NC

James John Riviello, Jr.
Houston, TX

2022
Jeff Buchhalter
Calgary, AB, Canada

Roger Larson
St. Paul, MN

Michael Noetzel
St. Louis, MO

2021
Robert Baumann
Lexington, KY

Sidney Gospe, Jr.
Seattle, WA

2019
Carol Camfield
Halifax, NS, Canada

W. Edwin Dodson
St. Louis, MO

2018
Gerald Erenberg
Cleveland, OH

William Logan
Toronto, ON, Canada

Alfred Spiro
Bronx, NY

2017
Abe Chutorian
New York, NY

W. Donald Shields
Los Angeles, CA

2016
Kalpathy Krishnamoorthy
Boston, MA

Doris Trauner
La Jolla, CA

2014
G. Robert De Long
Durham, NC

2013
Arthur Rose
Brooklyn, NY

A. David Rothner
Cleveland, OH

2015
Pat Crumrine
Pittsburgh, PA

Suresh Kotagal
Rochester, MN

2012
Bhuwan Garg
Indianapolis, IN

M. Richard Koenigsberger
Demarest, NJ

2011
Warren Grover
Philadelphia, PA

2010
Russell Snyder
Albuquerque, NM

2009
Mary Anne Guggenheim
Helena, MT

G. Dean Timmons
Akron, OH

2008
Cesare Lombroso
Boston, MA

Niels Lowe
Tenafly, NJ

2007
William Kennedy
Watertown, ME

Gordon Watters
Montreal, QC, Canada

2006
Raymond Chun
Madison, WI

Barry Russman
Portland, OR

2005
Robert Eiben
Cleveland, OH

Arnold Gold
New York, NY

2004
Jean Holowach
Thurston St. Louis, MO

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2026
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Santiago, Chile

Areeba Wasim
Muscat, Oman

2025
Muhammad Athar Khalily
KPK, Pakistan

Javeria Raza Alvi
Lahore, Pakistan

2024
Bolivar Quito-Betancourt
Cuenca, Ecuador

Thembi Katangwe-Chirwa South Africa

2023
Prem Chand
Karachi, Sindh, Pakistan

Priyanka Madaan
Haryana, India

2022
Robert K. Sebunya
Kampala, Uganda

Paulina C. Tejada
Santiago, Chile

2021
Chaw Su Hlaing
Myanmar, Asia

Alireza Tavasoli
Iran

2019
Nicolás Garófalo Gómez
Havana, Cuba

Jitendra Kumar Sahu
Chandigarh, India

2018
Suvasini Sharma
New Delhi, India

2017
Charles Hammond
Kumasi, Ghana

Aye Mya Min Aye
Yangon, Myanmar

2016
Arushi Gahlot Saini
Chandigarh, India

Tipu Sultan
Lahore, Pakistan

2015
Edward Kija
Tanzania

2014
Jithangi Wanigasinghe
Dehiwela, Sri Lanka

2013
Samson Gwer
Nairobi, Kenya

2012
Inga Talvik
Tartu, Estonia

2011
Kyaw Linn
Maynmar

2010
Parayil S. Bindu
Bangalor, India

2009
Uduak Mayen Offiong
Abuja, Nigeria

2008
Ikeolu Lagunju
Ibadan, Nigeria

2007
David E. Kombo
Tanzania

2006
Gia Melikoshvili
Tbilisi, Georgia

2005
Lusine Kirakosyan
Yerevan, Armenia

2004
Natalia A. Yermolenko
Voronezh, Russia

2003
David Chkhartishvili
Tbilisi, Georgia

2002
Vedrana Milic Rasic
Belgrade, Serbia

2001
Dimitrios Zafeiriou
Thessaloniki, Greece

2000
Brahim Tabarki-Melaiki
Brussels, Belgium

1999
Magda L. Nunes
Porto Alegre, Brazil

1998
Ana Keleme
Novi Sad, Yugoslavia

1997
Aleksandra Djukic
Belgrade, Yugoslavia

1996
Shan Wei Song
Beijing, China

1995
Nina Barisic
Zagreb, Croatia

1994
Lai Choo Ong
Kuala Lampur, Malaysia

1993
Anu Soot
Tartu, Estonia

1992
Qin Jiong
Beijing, China

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Curitiba,Brazil

1990
NajouaMiladi Tunis,Tunisia

1989
MeralOzmen
Istanbul,Turkey

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Training Director Award Recipients

2026
Rachel Gottlieb-Smith
Ann Arbor, MI

2025
Marc DiSabella
Washington, DC

2024
Nancy Bass
Milwaukee, WI

2023
Rana R. Said
Dallas, TX

2022
Timothy E. Lotze
Houston, TX

2021
Miya Asato
Pittsburgh, PA

2019
Karen Ballaban-Gil
Bronx, NY

2018
Bruce K. Shapiro
Baltimore, MD

2017
Sidney M. Gospe, Jr.
Seattle, WA

2016
David K. Urion
Boston, MA

2015
Robert Rust
Charlottesville, VA

2014
Steve Leber
Ann Arbor, MI

2013
Harvey Singer
Baltimore, MD

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American Academy of Pediatrics Travel Grant Recipients

2026
Jasmin Devine Sanchez
UCLA Pediatric Neurology

2025
Joshua A. Beitchman
University of Texas Southwestern

2024
Miles Fisher
Vanderbilt Child Neurology

2023
Miranda Creasey
Virginia Commonwealth University

2022
Alexis Karlin
Children's Hospital of Philadelphia

2019
E. Justine Record
Children's Hospital National

2018
Kerri Neville
Michigan Medicine

2017
Audie Espinoza
University of Utah

2016
Sharoon Qaiser
University of Kentucky

2015
Jennifer Jaskiewicz
Walter Reed Medical Center

M. Richard Koenigsberger Memorial Scholarship Recipients

Awarded in memory of M. Richard Koenigsberger, MD, to the CNS Junior Member submitting the best abstract in genetics, neonatal neurology, HIV, or metabolic disorders.

2026
Bhavan A. Modi
Phoenix Children's

2025
Reilly Phillibe
University of Utah

2024
Whitney Fitts
Children's Hospital of Philadelphia

2023
Hui Li
University of Wisconsin Hospital

2022
Stephen Chrzanowski
Boston Children's Hospital

2021
Jennifer Keene
Washington University in St Louis

2020
Katelyn Bricker
North Carolina Memorial Hospital

2019
David Ritter
Cincinnati Children's Hospital

2018
Tayyba Anwar
Children's National Medical Center

2017
Davut Pehlivan
Baylor College of Medicine

2016
Ann McCarthy
Children's Hospital Philadelphia

2015
Vincent Carson
Pittsburgh Children's Hospital

2014
Joshua Bear
UC-San Francisco

2013
Louis Dang
Children's Hospital of Michigan

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Taeun Chang Outstanding Junior Member Award Recipients

2026
Shadi Shams
University of California, San Diego

Manouchehr Amanat
Mayo Clinic

Ali Reza Tavasoli
Phoenix Children's Hospital

Michelle Corkrum
Columbia University

2025
Eric Dornoff
Vanderbilt University Medical Ctr

Rasesh Joshi
Boston Children's Hospital

Jeffrey S. Kuerbitz
Baylor College of Medicine

Georgios Ntolkeras
Boston Children's Hospital

2024
Ashley M. Bach
Children's Hospital of Philadelphia

Eman Hamed
Jersey Shore University Medical Ctr.

Austin Layton
University of California-San Diego

Seva Khambadkone
Doernbecher Children's Hospital

2023
Claudia Gambrah-Lyles
Children's Hospital of Philadelphia

Mary Rolfes
University of California

Alexandra Santana Almansa
Boston Children's Hospital

Alexander J. Sandweiss
Texas Children's Hospital

2022
Mekka Garcia
NYU Langone Health

Laura Gilbert
Washington University in St. Louis

Riley Kessler
Children's Hospital of Philadelphia

Ezgi Saylam
Nationwide Children's Hospital

2021
Rhandi Christensen
University of Toronto

Darius Ebrahimi-Fakhari
Boston Children's Hospital

Laura Gilbert
Washington University-St. Louis

Hannah Wellman
University of Colorado

2020
Natalie K. Katz
Children's Mercy Hospital

Travis Larsh
Children's Hospital Cleveland Clinic

Kshama Ojha
University of Louisville

Sonal Sharma
Children's Mercy Hospital Clinics

2019
Lauren Chamberlain
Duke University Medical Center

Darius Ebrahimi-Fakhari
Boston Children's Hospital

Aram Kim
Children's Hospital of Pittsburgh

Youssef A. Kousa
Children's Hospital National

2018
Adrienne Bruce
Cincinnati Children's Hospital

Sara Fridinger
Children's Hospital of Philadelphia

Melissa Hutchinson
Children's Hospital of Philadelphia

Jeffrey A. Strelzik
Children's National Health System

Elizabeth Troy
University of Colorado

2017
Ka Ye Clara Chan
Loma Linda University

Hsaio-Tuan Chao
Baylor College of Medicine

Rachel Goldstein Hirschberg
Boston Children's Hospital

Carla Watson
Children's Hospital of Michigan

2016
Sonika Agarwal
Baylor College of Medicine

Darius Ebrahimi-Fakhari
Boston Children's Hospital

Juliane Gust
Seattle Children's Hospital

Manisha Malik
Emory University

2015
Robert Blake
Cincinnati Children's Hospital

Dana Marafie
Texas Children's Hospital

Davut Pehlivan
Texas Children's Hospital

Siddharth Srivastava
Kennedy Krieger Institute

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2014
Jonathan Kurz
Children's National Medical Center

Neggy Rismanchi
University of California-San Diego

Siddharth Srivastava
Kennedy Krieger Institute

Kavita Thakkar
Pittsburgh Children's Hospital

2013
Anuja Jindal
Pittsburgh Children's Hospital

Archana Patel
Boston Children's Hospital

Pilar Pichon
Loma Linda University

Mark Schomer
Boston Children's Hospital

Mitchell Williams
Children's Hospital of Michigan

2012
Partha Ghosh
Clevland Clinic Foundation

J.J. Gold
University of California-San Diego

Gayatri Mainali
Cleveland Clinic Foundation

Christopher B. Oakley
Johns Hopkins Medical Institute

2011
Partha Ghosh
Cleveland Clinic Foundation

Andrea Pardo
Cincinnati Children's Hospital

Thitiwan Simasathien
University of Alabama-Birmingham

Syndi Seinfeld
Virginia Commonwealth

2010
Dawn Gano
University of British Columbia

Radhika Dhamija
Mayo Clinic

Patricia Musolino
Massachusetts General Hospital

Thitiwan Simasathien
University of Alabama-Birmingham

2009
Bennett Gertz
Children's National Medical Center

Ryan Lee
Kennedy Krieger Institute

John Mytinger
University of Virginia

Brandon Zielinski
UC-San Francisco

2008
Gregory Aaen
Loma Linda University

Robert Avery
Children's Hospital-Philadelphia

Joseph Scafidi
Children's National Medical Center

Karen Powers
Virginia Commonwealth University

2007
Keith Abe
Stanford University

Tarannum Lateef
Children's National Medical Center

Joseph Scafidi
Children's National Medical Center

Marie-Pierre Thibeault-Eybalin
McGill University

2006
Nicholas Abend
Children's Hospital of Philadelphia

Lori Billinghurst
University of Alberta

Holly Dudley-Harrell
Children's Hospital of Cincinnati

Jena Khera
The Cleveland Clinic

2005
William Benko
Children's National Medical Center

Alexander Bassuk
Children's Memorial-Chicago

Josh Bonkowsky
University of Utah Medical Center

Robert Safier
Children's Hospital of Pittsburgh

Renée Shellhaas
Children's Hospital of Philadelphia

2004
Haim Bassan
Boston Children's Hospital

William Benko
Children's National Medical Center

Brannon Morris
Mayo Clinic

Ignacio Valencia
St. Christopher's Hospital

2003
Taeun Chang
Children's National Medical Center

Yoshimi Sogawa
Schneider Children's Hospital

Ignacio Valencia
St. Christopher's Hospital

Adeline Vanderver
Children's National Medical Cente

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Tauen Chang Junior Member Award Recipients | continued

2002
Taeun Chang
Children's National Medical Center

Mirjana Maletic-Savatic
SUNY Stony Brook

Lauren Plawner
Stanford University Medical Center

Michael Seyffert
University of Washington

2001
Maria Acosta
Children's National Medical Center

Randa Jarrar
Mayo Clinic

Steven Miller
UC-San Francisco

Jayne Ness
Children's Hospital of Alabama

2000
Sucheta Joshi
Stanford University Medical Center

Lauren Plawner
Stanford University Medical Center

Monique Ryan
Boston Children's Hospital

Mustafa Sahin
Boston Children's Hospital

1999
June Caruso
Rhode Island Children's Hospital

Debra Holder
Texas Children's Hospital

Carolyn Menache
Boston Children's Hospital

1998
June Caruso
Rhode Island Children's Hospital

Andrea Gropman
Children's National Medical Center

Alyssa Reddy
Children's Hospital of Alabama

Janet Soul
Boston Children's Hospital

1997
Gyula Acsadi
Children's Hospital of Detroit

Ann Bergin
Johns Hopkins University

Edwin Demeritte
Children's Hospital of Detroit

Sanford Shu
Loma Linda University

1996
Gyula Acsadi
Children's Hospital of Detroit

Joseph Gleeson
Boston Children's Hospital

Andrea Gropman
Children's National Medical Center

Mary Sutton
Boston Children's Hospital

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Taeun Chang Outstanding Junior Member Post-Graduate Award Recipients

2026
Quinton Mandle
Boston Children's Hospital

2025
Giulia Porcari
Children's Hospital of Philadelphia

2024
Stephen Chrzanowski
University of Massachusetts

Saba Jafarpour
Children's Hospital of Los Angeles

2023
Mliena Andzelm
Boston Children's Hospital

Jennifer Harmon
Atrium Health Wake Forest Baptist

2022
Travis Larsh
Cincinnati Children's Hospital

Avantika Singh
Boston Children's Hospital

2021
Eric M. Chin
Kennedy Krieger Institute

Thiviya Selvanathan
The Hospital for Sick Children

2019
Giulia Beneditti
Seattle Children's Hospital

2018
Bhooma Aravamuthan
Boston Children's Hospital

Elana Pinchefsky
The Hospital for Sick Children

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Bhuwan Garg High School Student Neuroscience Research Prize Recipients

2026
Lilian Ouyang
Little Rock, AR

2025
Ella Saltstein
Armonk, NY

2024
Allison Duh
Burlingame, CA

2023
Rania Sophia Lateef
Manassas, VA

2022
Aliya Fisher
New York, NY

2021
Meagan Ryan
Ossining, NY

2020
Pratik Vangal
Portland, OR

2019
Shan Lateef
Manassas, VA

2019
Shan Lateef
Manassas, VA

2018
Amy Shteyman
Great Neck, NY

2017
Lauren Singer
Scarsdale, NY

2016
Ryan Infante
Armonk, NY

2015
Amrita Mohanty
Woodbury, MN

2014
Laura Mariah Herman
Ft. Lauderdale, FL

2013
Anna Thomas
San Jose, CA

2012
Vincent Shieh
Bronx, NY

2011
Spencer Chan
Forest Hills, NY

2010
Pragya Kakani
Jericho, NY

2009
Inar Zhang
Mercer Island, WA

2008
Lauren Lisann
Dix Hills, NY

2007
David Shiovitz
Briarcliff Manor, NY

2006
Shoshana Tell
Coral Springs, FL

2005
Max Christie
Briarcliff Manor, NY

2004
Debashish Zircar
Bronx, NY

2003
Henry Marr
Alhambra, CA

2002
Corinna Zygourakis
Houston, TX

2001
Melanie Napier
Laurelton, NY

2000
Rishikesh Dalal
Lenexa, KS

1999
Nihar Gupta
New York, NY

1998
Karla Malloy
Richmond, VA

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ASSOCIATION OF CHILD NEUROLOGY NURSES

Claire Chee Award for Excellence in Child Neurology Nursing Award Recipients

2026
Lindsay Simmons
Boston, MA

2025
Belinda Ramirez
Houston, TX

2024
Keri Ramsey
Phoenix, AZ

2023
Colleen Gagnon
Boston, MA

2022
Tristen Dinkel
Aurora, CO

2021
Toni Kavanagh
Pelham, NY

2020
Jennifer McCrave
Boston, MA

2019
Courtney Wellman
Kansas City, MO

2018
Cheryl Cahill
Boston, MA

2017
Jennifer Boyd
Toronto, ON, Canada

2016
Kathryn O'Hara
Richmond, VA

2015
Nancy Elling
Washington, DC

2014
Jo Ellen Lee
Columbus, OH

2013
Cheryl Fischer
New York, NY

2012
Jane Lane
Birmingham, AL

2011
Yolanda Harris
Birmingham, AL

2010
Julie Sprague-McRae
Fremont, CA

2009
Christine O'Dell
Bronx, NY

2008
Irene M. Elliott
Toronto, ON, Canada

2007
Elizabeth Tate
Springfield, IL

2006
Amy Vierhile
Rochester, NY

2004
Jane Meyer
Cottage Grove, WI

2003
Elizabeth F. Hobdell
Chester Brook, PA

2002
Rhonda Roell Werner
New Berlin, WI

2001
Claire Chee
Philadelphia, PA

2000
Jan Mims
Minneapolis, MN

Practitioner Award for Excellence in Child Neurology Nursing Award Recipients

2026
Stephanie Vitolano
New York, NY

2025
Kathleen E. Walsh
Philadelphia, PA

2024
Deanna Duggan
Waco, TX

2023
Rasha Srouji Boston, MA

2022
Nancy A. Auer
Columbus, OH

2021
Patricia McGoldrick
Pelham, NY

2020
Dianne Kulasa-Luke
Akron, OH

2019
Erin Fecske
Kansas City, MO

2018
Scott B. Turner
Birmingham, AL

2017
Rebecca Schultz
Houston, TX

2016
Sue Yudovin Los Angeles, CA

2015
Regina Laine
Boston, MA

Innovative Clinical Practice Award in Child Neurology

2026
Tracee Ridley-Pryor
Memphis, TN

2025
Rebecca J. Schultz
Houston, TX

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55th Child Neurology Society Annual Meeting

PLATFORM SESSIONS

Platform Session 1

PL1-1 Optimizing Outcomes after Pediatric Concussion: Updates to the Living Guideline for Pediatric Concussion

Jasmin Sanchez, Jennifer Dawson, Achelle Cortel-Leblanc, Nick Reed, Christopher Giza, Roger Zemek

OBJECTIVE: Pediatric concussion care is rapidly evolving, leading to significant shifts in clinical recommendations. We updated clinical recommendations, tools, and algorithms within the Living Guideline for Pediatric Concussion using peer-reviewed evidence, while integrating patient engagement and expanding scope to priority populations and emerging areas.

METHODS: 4041 papers published through 2025 were critically assessed, aligned with current clinical recommendations, and coded with EppiReviewer. An interactive living evidence gap map generated using EPPI-vis was shared with 45 expert panel members and consensus voting informed updates. This was repeated every six months and includes ongoing input from individuals with lived experience.

RESULTS: Recommendation updates include aerobic exercise to treat concussion, guidance on screen time, return to school, mental health, and early interventions to facilitate recovery and reduce the risk of persisting symptoms after concussion. The strength of evidence varies, with more high quality (level 1-2) studies supporting *initial medical management* (131) and *prolonged symptoms* (57), while *telemedicine* (3) and *interpersonal violence* (0) remain limited, reflecting emerging areas of research. The Living Guideline Evidence Map includes 1511 publicly accessible records published from 2013 - 2025. Guideline recommendations, tools, evidence maps, and details of the consensus process are freely shared on pedsconcussion.com, with over 989,000 total engagements.

CONCLUSIONS: Evaluation and synthesis of evidence coupled with commitment and collaboration from leaders in the field is essential for developing and sustaining evidence-based clinical guidelines. The creation and regular updating of the Living Guideline for Pediatric Concussion provide a mechanism for continually advancing pediatric post-concussion knowledge and care.

KEYWORDS: Traumatic Brain Injury, Practice Parameters

PL1-2 Determinants of Mortality and Neurological Sequelae in Pediatric central nervous system infections: A Cohort Study from a Middle-Income Country

Maria Sierra-Breton, Mayra Marulanda-Galvis, Rosalba Vivas-Trochez, Angelica Arteaga-Arteaga, Carlos Garces-Samudio

OBJECTIVE: Describe the cllinical characteristics and identify clinical and paraclinical factors associated with mortality and neurological sequelae in pediatric patients with central nervous system (CNS) infections in a tertiary care center in a middle-income country

METHODS: Retrospective cohort study including 536 patients aged 0–14 years diagnosed with CNS infection between 2014 and 2023. Clinical, microbiological, and neuroimaging data were collected. Multivariable logistic regression analyses were performed to identify independent predictors of mortality and neurological sequelae

RESULTS: Mortality was 5.8%, and 20.9% of patients developed neurological sequelae. The highest proportion of sequelae was observed in meningoencephalitis (27.9%) and brain abscess (22%), with particularly high frequencies in infections due to Mycobacterium tuberculosis (72.2%) and herpes viruses (70%). Mortality was highest in patients with brain abscess (9.8%) and meningoencephalitis (7.4%), and in children under 2 years (51%). In multivariable analysis, mortality was independently associated with need for critical care (OR 6.92; 95% CI 1.55–30.98; p=0.011) and seizures during hospitalization (OR 2.39; 95% CI 1.10–5.17; p=0.027). Neurological sequelae were independently associated with abnormal neuroimaging (OR 4.21; 95% CI 2.19–8.10; p<0.001) and need for critical care (OR 3.87; 95% CI 2.09–7.16; p<0.001)

CONCLUSIONS: Disease severity and acute neurological complications were the main determinants of mortality, particularly in younger children, while structural brain injury was strongly associated with neurological sequelae. High rates of sequelae in tuberculosis and herpes virus infections highlight the importance of early recognition and targeted management in resource-limited settings

KEYWORDS: Neuroinfectious Disease, Global Neurology

PL1-3 Sustained benefit with GPi Deep Brain Stimulation in GNAO1-related Disorder

Katerina Bernardi, Josh Rong, Weston Northam, Margaret Kamińska, Harutomo Hasegawa, Jana Domínguez-Carral, Lindsey Vogt, George Ibrahim, Carolina Gorodetsky, Moritz Thiel, Anne Koy, Juan Darío Ortigoza Escobar, Jean-Pierre Lin, Daniel Lumsden, Darius Ebrahimi-Fakhari, Kathryn Yang

OBJECTIVE: *GNAO1*-related movement disorders are characterized by severe hyperkinetic movements with a high risk of progression to life-threatening dyskinetic crisis. While prior case reports and small series suggest benefit of bilateral globus pallidus internus deep brain (GPi-DBS), optimal patient selection, surgical timing, and long-term outcomes remain uncertain. We aimed to evaluate the clinical effects of GPi-DBS in patients with GNAO1-related disorders.

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METHODS: International, multicenter retrospective study of patients with genetically confirmed *GNAO1*-related disorder who underwent bilateral GPi-DBS. Outcomes included Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), functional status measures, frequency of admissions for dyskinetic crisis, total number of hospitalizations, and clinical global impression. Perioperative complications and long-term follow-up data were also analyzed.

RESULTS: Forty-six patients underwent GPi-DBS at a mean age of 10.4±4.8 years (mean follow-up 4.5±3.7years), representing the largest *GNAO1* DBS cohort to date. Over half underwent emergency surgery during an admission for dyskinetic crisis. Complications occurred in 19.6%. Reduction of episodes of dyskinetic crisis was achieved in 95% of patients, accompanied by marked decreases in hospitalization frequency. Mean BFMDRS motor scores improved by 27.5% ($p<0.001$). Clinical global impression showed improvement in 93.5%, with greater benefit observed in chorea (87.8%) versus dystonia (67.4%). Quality-of-life gains included reduced pain, improved sleep and weight gain, while overall functional outcomes remained unchanged.

CONCLUSIONS: This represents the largest multicenter cohort of GPi-DBS in *GNAO1*-related disorder to date. GPi-DBS is a highly effective, potentially life-saving intervention, particularly in the setting of dyskinetic crisis. These findings support consideration of earlier elective surgery, particularly for high-risk genotypes, to mitigate morbidity and healthcare burden.

KEYWORDS: Movement Disorders, Neurogenetics, Neurocritical Care

PL1-4 Impact of Rapid Whole-Genome Sequencing on Diagnostic Yield and Clinical Decision-Making in Acute Pediatric Neurology

Manouchehr Amanat Yazdi, Asma Ali, Elaine Wirrell, Paul Youssef, Keith Coffman, Laura Rust, Nicole Boczek, Lisa Schimmenti, Queenie Tan, Radhika Dhamija

OBJECTIVE: Unexplained pediatric neurologic disorders cause significant morbidity and diagnostic uncertainty. We assessed the diagnostic yield, clinical impact, and predictors of rapid whole-genome sequencing (rWGS) in pediatric neurology inpatients at a tertiary center.

METHODS: We conducted a retrospective cohort study (June 2022–January 2026) of pediatric inpatients with unexplained primary neurologic presentations after standard evaluation. Primary outcome was phenotype-concordant genetic diagnosis. Secondary outcomes included management change and rWGS reanalysis yield. Predictors were identified via multivariable logistic regression.

RESULTS: 175 patients (82 neonates; 93 infants/children) met inclusion criteria with mean age of 2.99±4.80 years and 82 (46.9%) females. The most common presentation was hypotonia in neonates (n=46) and epilepsy in infants/children (n=65). Preliminary results were available in 4.0±1.6 days. Overall, 82/175 (46.9%) received phenotype-concordant diagnoses (40.2% neonates; 52.7% infants/children). Diagnoses were primarily monogenic (75.6%), followed by chromosomal variants (20.7%) and mitochondrial disorders (3.7%). Genetic diagnosis prompted management change in 54/82 (65.9%) patients (75.8% neonates; 59.2% infants/children), including moderate (11 patients; treatment modification or targeted evaluation) and major (27 patients; initiation of disease-specific therapy) changes directly impacting care. Reanalysis of 14 previously nondiagnostic cases identified 3 (21.4%) additional diagnoses that contributed to the final diagnostic yield. In pooled analysis, phenotype-concordant yield was predicted by family history (aOR: 6.46, $p<0.001$), multisystem involvement (aOR: 2.85, $p=0.013$), and congenital anomalies/dysmorphism (aOR: 2.47, $p=0.034$).

CONCLUSIONS: rWGS delivered actionable diagnoses within four days and changed management in nearly two-thirds of diagnosed patients. These findings support early rWGS integration as a critical diagnostic and decision-making tool in acute pediatric neurology care.

KEYWORDS: Neurogenetics, Neurodevelopmental Disorders, Neonatal Neurology

PL1-5 PLP1-related disorders: Genotype Classification and Clinical Associations

Adeline Vanderver, Anjana Sevagamoorthy, Johanna Schmidt, Kaleb Kelley, Sarah Woidill, Francesco Gavazzi, Emma Wiener, Carlos Dominguez Gonzalez, Amy Pizzino, Jamie Fraser, Rik Lindeboom, Maura Ruzhnikov, Julie Cohen, Laura Adang, Davide Tonduti, Enrico Bertini, Geneviève Bernard, Ken Inoue, Nicole Wolf, Chloe Cunningham, Susan Kirwin, Joana Osorio, Grace Hobson

OBJECTIVE: To systematically evaluate genotype-phenotype correlations in *PLP1*-sequence variants and describe disease outcomes across defined genotype cohorts.

METHODS: Data collection was multi-source: (i) Global Leukodystrophy Initiative (GLIA-PMD) natural history study, (ii) a Nemours leukodystrophy research protocol, (iii) Secondary use Nemours diagnostics lab data, and (iv) published cases. Data on genotype, motor skills, and systemic complications were collected according to standardized protocols. Cailloux et al. Form scores were used to assess motor severity. Genotypes were categorized to summarize outcomes descriptively, and variant severity was mapped on the protein structure/DNA/RNA, as applicable.

RESULTS: The study identified 301 unique *PLP1*-sequence variants: 181 gain-of-function (GoF- misfolded proteins), 43 loss-of-function/null (LoF), 21 decreased PLP1/DM20 ratio, and 54 splicing variants with unknown effect. Most (52%) GoF variants were severe (Form 0). Most LoF variants were mild (Forms 3-4) (19/26 or 73%) but also included a small subset with notably severe impairment (15% Form 0). Most variants impacting the PLP1-specific region, reducing PLP1/DM20 isoform expression, were mild. 54 splicing variants with unknown effect were identified, with motor severity ranging across the spectrum. Within the GLIA-PMD cohort, systemic complications were more frequent and manifested much earlier in GoF variants, significantly compared to other variant groups.

CONCLUSIONS: This is the largest curated genotype-phenotype dataset of *PLP1* variants. Our data substantiate prior reports of the severity of GoF variants relative to LoF and decreased PLP1/DM20 splicing variants, while underscoring the importance of a functional understanding of the

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impact of specific variants and the limitations of predictive genotype-phenotype correlations.

KEYWORDS: Neurogenetics, Lifespan Manifestations of Childhood Onset Conditions, Neurodevelopmental Disorders

PL1-6 Delineation of Functional Trajectories in TUBB4A-related Leukodystrophy: A Step Towards Clinical Trial Readiness

Francesco Gavazzi, Peter Hong, Anjana Sevagamoorthy, Isha Deshpande, Cesar Alves, Giulia Porcari, Elizabeth Ballance, Jamie Bradford, Jessica Costagliola, Stacy Cusack, Allan Glanzman, Ann Harrington, Tracy Kornafel, Emma McKenzie, Samuel Pierce, Sarah Woidill, Laura Adang, Justine Shults, Adeline Vanderver

OBJECTIVE: *TUBB4A*-related leukodystrophy (*TUBB4A*-LD) encompasses heterogeneous conditions divided into three subgroups: p.Asp249Asn (D249N), late infantile (LI) non-D249N (sitting by 9 months), and early infantile (EI) non-D249N (not sitting by 9 months). Although clinical trials are being planned, limited validated outcome measures hamper progress. This study assessed gross motor and adaptive skills to evaluate the feasibility of standardized assessments and understand disease progression.

METHODS: Subjects with confirmed *TUBB4A*-LD were enrolled via the Myelin Disorder Biorepository Project (MDBP). Demographic and genotype data were extracted from medical records and used to categorize subjects as early infantile, late infantile, or D249N The Gross Motor Function Measure-88 (GMFM-88) and Vineland Adaptive Behavior Scale 3rd edition (VABS-3) were administered. Analyses included descriptive statistics (median, IQR), Kruskal-Wallis tests, Spearman's correlation, and mixed models with cubic splines.

RESULTS: Of 105 participants, 47 were EI, 35 LI, 18 D249N, and 4 unclassified. 86 completed the GMFM-88 (median age 7.06 years, IQR 4.22-13.1), with median GMFM-88 score 28.8% (IQR 9.80-57.6%). EI and D249N groups showed greater gross motor impairment than LI ($p<0.001$). 104 completed VABS-3 (median age 8.87, IQR 4.70-15.7), with a median Adaptive Behavior Composite score of 62.0 (IQR 52.8-72.0). EI scored lower than LI in the Communication and Socialization domains ($p<0.0001$). Mixed effects models revealed significant differences in motor and adaptive trajectories across subgroups.

CONCLUSIONS: GMFM-88 and VABS-3 were able to stratify *TUBB4A*-LD subcohorts. Mixed effect models reflected disease trajectories from prior studies. This work informs COA, endpoint selection, and thresholds for future trials, aligning with FDA guidelines (PFDD in rare disorders).

KEYWORDS: Neurodevelopmental Disorders

PL1-7 Bridging the Diagnostic Gap: Clinical Predictors of Pediatric Neurodevelopmental Disorders in Resource-Limited Settings

Isaac Atuahene

OBJECTIVE: To identify reliable clinical predictors of pediatric neurodevelopmental disorders in resource-limited settings where access to advanced neurodiagnostic tools is limited, and to evaluate their utility in early diagnosis and intervention.

METHODS: A prospective observational study was conducted involving children aged 6 months to 12 years presenting with developmental concerns at a tertiary-level pediatric clinic in a low-resource setting. Standardized clinical assessments, caregiver-reported developmental histories, and basic neurologic examinations were performed. In the absence of routine neuroimaging and genetic testing, a diagnostic algorithm based on clinical features was applied. Outcomes were compared against follow-up diagnoses established over a 12-month period.

RESULTS: Among 180 children evaluated, 68% were ultimately diagnosed with neurodevelopmental disorders, including autism spectrum disorder, cerebral palsy, and global developmental delay. Key predictors included delayed speech (OR 3.4), abnormal social interaction (OR 4.1), persistent primitive reflexes (OR 2.9), and caregiver concern before age 2 years (OR 3.7). The clinical algorithm demonstrated a sensitivity of 85% and specificity of 72% in predicting confirmed diagnoses. Early identification using clinical criteria alone led to significantly earlier initiation of supportive interventions ($p < 0.01$).

CONCLUSIONS: In settings with limited access to advanced diagnostics, structured clinical assessment can provide a reliable, cost-effective approach to early identification of pediatric neurodevelopmental disorders. Strengthening clinician capacity in recognizing key predictive features may reduce diagnostic delays and improve long-term outcomes in low- and middle-income countries.

KEYWORDS: Neurodevelopmental Disorders, Early Stage Investigator

Platform Session 2

PL2-1 Up-Front Rituximab Reduces Relapse Risk in Pediatric-Onset Opsoclonus Myoclonus Ataxia Syndrome

Laura Saucier, Rebecca MacRae, Celia Greenlaw, Grace Wang, Christopher Cortina, Kumaran Deiva, Andrea Klein, Ming Lim, Thomas Rossor, Elizabeth Sokol, Yasmin Khakoo, Nikita Shukla, Kristen Fisher, Timothy Lotze, Wendy Mitchell, Sarah Hopkins, Bo Zhang, Mark Gorman

OBJECTIVE: Most patients with pediatric-onset opsoclonus myoclonus ataxia syndrome (POOMAS) have neurological relapses. Further details are limited in existing literature. This study characterized the risk, rate, and timing of POOMAS relapses and the effect of rituximab in a large cohort.

METHODS: Prospective (enrolled <24 months from onset) and retrospective cohort study using multi-center POOMAS Registry. Inclusion criteria: 1) POOMAS onset ≤ 18 years old, 2) Follow-up ≥ 12 months. Relapse defined as worsening of POOMAS symptoms for ≥ 72 hours. Relapse risk compared between subgroups which received up-front (before

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any relapse) rituximab versus no rituximab and rituximab after relapse using Fisher's exact test.

RESULTS: Of 123 included patients (45% prospective), 52% had ≥ 1 relapse over median follow-up of 5.5 years. In the relapsing subgroup, median (IQR) POOMAS duration at first relapse was 9 (5-16) months, total number of relapses was 2 (1-4), and median annualized relapse rate was 0.7 (0.3-0.8) and 0.2 (0.1-0.2) over the first 36 months of POOMAS duration and beyond respectively. 94.7% of first relapses occurred ≤ 36 months from POOMAS onset. Age at onset, sex, race, and paraneoplastic etiology did not predict relapse risk. Relapse risk in the up-front rituximab (median time 77 (31-154 days)) subgroup (n=79) was 44.3% compared to 66.7% in the no rituximab and rituximab after relapse subgroup (p=0.031).

CONCLUSIONS: Most patients with POOMAS have ≥ 1 neurological relapse typically in the first year after onset. Clinical factors at onset do not predict relapse risk limiting ability to risk-stratify patients. Up-front rituximab significantly reduces relapse risk.

KEYWORDS: Neuroimmunology

PL2-2 Cerebrospinal Fluid T-Cell Activation Correlates with Clinical Severity and Diagnostic Abnormalities in Down Syndrome Regression Disorder

Rohan Singh, Kevin Frost, Maeve Lucas, Samuel Otey, Mariam Yousuf, Stella Gray, Madeline Oswald, Mackenzie Silverman, Jonathan Santoro

OBJECTIVE: Down Syndrome Regression Disorder (DSRD) is characterized by a severe, unexplained neurocognitive decline in otherwise healthy individuals with Down syndrome (DS). The underlying pathophysiology remains unclear, though an immune-mediated mechanism is suspected. We investigated the role of T-cell perturbations and neuroinflammation in DSRD by evaluating cerebrospinal fluid (CSF) flow cytometry and its relationship to diagnostic and clinical outcomes.

METHODS: We conducted a retrospective cross-sectional analysis of a DSRD cohort (n=121), utilizing comprehensive CSF T-cell flow cytometry data (n=38). T-cell subset absolute counts and activation markers—specifically the percentage of HLA-DR+ expressing CD3+ T-cells—were measured. Immunological findings were cross-analyzed against objective neurodiagnostics (EEG) and validated clinical severity scales: the Bush-Francis Catatonia Rating Scale (BFCRS), NPI-Q Total Score, and the Timed 25-Foot Walk.

RESULTS: Flow cytometric analysis revealed a robust presence of activated T-cells within the DSRD cohort. The percentage of activated T-cells (HLA-DR+ CD3+) was significantly elevated in patients exhibiting an abnormal EEG compared to those with a normal EEG (21.0% vs. 8.9%, p<0.0001). Furthermore, the degree of CSF T-cell activation exhibited positive correlations with clinical morbidity across multiple domains, including catatonia severity (BFCRS: r=0.97, p<0.0001), severe neuropsychiatric behavioral symptoms (NPI-Q: r=0.88, p<0.0001), and motor impairment (Timed 25-Foot Walk: r=0.97, p<0.0001).

CONCLUSIONS: These data highlight a direct, quantitative link between CSF T-cell activation and clinical deterioration in DSRD. The correlations between localized T-cell perturbations, abnormal neurodiagnostics, and functional disability provide evidence that active neuroinflammation drives DSRD pathology. Assessing T-cell activation may serve as a crucial biomarker for guiding early immunomodulatory interventions and improving clinical outcomes.

KEYWORDS: Neuroimmunology

PL2-3 Characteristics of Epilepsy in Patients with Down Syndrome: A Retrospective Cohort Study

Shadi Shams, Shifteh Sattar, Jennifer Yang, Andrew Hannawi, Maria Montenegro

OBJECTIVE: Epilepsy is a common comorbidity in individuals with Down syndrome (DS), with infantile epileptic spasms syndrome (IESS) prevalent in children, and late-onset myoclonic epilepsy in DS (LOMEDS) in adults. Epilepsy phenotypes across the lifespan and predictors of disease severity remain poorly defined. This study evaluates the frequency, spectrum, and clinical characteristics of epilepsy and examines factors associated with drug-resistant epilepsy across the lifespan.

METHODS: We conducted a 10-year retrospective cohort study (2015-2025) of pediatric and adult DS patients with epilepsy at a tertiary care center. Demographic and clinical data, including comorbidities (stroke, cardiac), antiseizure medications, EEG, and MRI, were collected. Demographics were assessed using descriptive statistics, and comparisons between clinical features associated with drug-resistant epilepsy were done using the chi-square test.

RESULTS: Of 3,240 patients with Down syndrome, 290 met the inclusion criteria; 124 (3.8%) were manually confirmed to have epilepsy. Ages ranged from 2 to 63 years (median age = 17 years). Drug-resistant epilepsy occurred in 28 patients (22.5%). IESS was identified in 41 patients with 34% developing drug-resistant epilepsy. LOMEDS was rare (n=1). Congenital heart disease (p=0.30) and stroke (p=0.79) were not associated with drug-resistant epilepsy. Follow-up ranged from 6 months to 39 years (median = 6 years).

CONCLUSIONS: Epilepsy in DS is heterogeneous with early onset of IESS. Approximately 22.5% developed drug-resistant epilepsy, particularly those with IESS. Congenital heart disease and stroke were not associated with intractable epilepsy. These findings highlight the phenotypic heterogeneity across the lifespan and the need to identify early predictors for epilepsy to improve management.

KEYWORDS: Epilepsy, Neurogenetics, Lifespan Manifestations of Childhood Onset Conditions

PL2-4 Epilepsy-associated gene variants are not associated with acquired epilepsy risk after acute provoked neonatal seizures

Adam Numis, Chen Yang, Gilberto da Gente, Janet Soul, Giulia Benedetti, Cameron Thomas, Tayyba Anwar, Shavonne Massey, Catherine Chu, Monica Lemmon, Charles McCulloch, Renée Shellhaas, Hannah Glass

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OBJECTIVE: We previously showed that in children with acute provoked neonatal seizures, the presence of a pathogenic/likely pathogenic (P/LP) variant in an epilepsy-associated gene was associated with later epilepsy. We sought to confirm these findings in a larger cohort.
METHODS: We enrolled 167 newborns with acute provoked seizures across eight centers of the Neonatal Seizure Registry. Epilepsy was determined by structured interview and medical record review through at least 5-years of age. Participating families underwent trio (79%) or duo (21%) whole exome sequencing (WES). WES data were used to evaluate variants in 335 *a-priori*-selected epilepsy-associated genes. Variants were classified using American College of Medical Genetics criteria; heterozygous variants in recessive genes were excluded.
RESULTS: We identified 5 (P/LP) variants and 54 variants of uncertain significance (VUS) across 43 genes in 43 of 167 children (26%). Thirty-four children had a single variant and nine had ≥2. Variant classification was not associated with neonatal seizure etiology or characteristics. However, children with ≥2 P/LP/VUS were more likely to have had ≥3 days of EEG seizures compared to those with <2 variants (44% versus 15%, p=0.048). Among 48 children with P/LP/VUS, 13 (27%) developed epilepsy compared with 34/119 (29%) without P/LP/VUS (p=0.85).
CONCLUSIONS: P/LP/VUS variants in children with acute provoked neonatal seizures were not associated with risk of post-neonatal acquired epilepsy. These findings do not provide evidence to support routine targeted epilepsy panel testing solely to predict acquired epilepsy. Genetic testing remains indicated when early-onset epilepsy is suspected, and the role of broader genomic testing warrants further study.
KEYWORDS: Epilepsy, Neurogenetics, Neonatal Neurology

PL2-5 A prognostic biomarker for refractory epilepsy after infantile epileptic spasms syndrome – Validation of the 2021 BASED score

John Mytinger, Warren Lo, Amanda Weber, Jorge Vidaurre, Anup Patel, Corinne McCabe, Megan Fredwall, Purva Choudhari, Christopher Beatty, Shawn Aylward, Dara Albert, Steve Rust

OBJECTIVE: The Burden of Amplitudes and Epileptiform Discharges (BASED) score is an EEG rating scale for children with IESS, with scores of 4 or 5 suggesting epileptic encephalopathy (EE). The objective of this study was to determine whether a post-treatment BASED score of 4/5 is a prognostic biomarker for refractory epilepsy following IESS treatment.
METHODS: This was a retrospective validation study of children with IESS. Children with tuberous sclerosis complex (TSC) were excluded. Three blinded reviewers assigned 2021 BASED scores to full-length post-treatment EEGs. Refractory epilepsy was defined as persistent seizures despite treatment with at least 2 antiseizure medications, or completion of epilepsy surgery. Prespecified performance benchmarks for BASED 4/5 as a *rule-in* test required >/=80% specificity and >/=4 positive likelihood ratio.
RESULTS: The cohort included 123 children, with a median first treatment age of 8.0 months (IQR 5.9-10.3) and a follow-up duration after first treatment of 58.8 months (42.2-80.7). EEGs (median 19 hours) were completed at a median 47 days (32-72) after starting treatment. The inter-rater reliability for EE was excellent (K_{free}=0.78). Half (52%) of children had refractory epilepsy. BASED 4/5 demonstrated high specificity (88.1%, 95% CI 77.1-95.1), with a positive likelihood ratio of 4.4 (2.1-9.1). The sensitivity, positive predictive value, and negative predictive value were 51.6% (38.7-64.3), 82.5% (69.3-90.8), and 62.7% (56.1-68.7), respectively.
CONCLUSIONS: Study limitations include the single-center design, exclusion of children with TSC, variable EEG timing, and shorter follow-up in some children. Nevertheless, these findings support a post-treatment BASED 4/5 as a prognostic biomarker for refractory epilepsy following IESS treatment.
KEYWORDS: Epilepsy

PL2-6 Seizure status Modifies Response to Motor Rehabilitation in Perinatal Arterial Ischemic Stroke; the I-ACQUIRE trial

Warren Lo, Sharon Landesman Ramey, Craig Ramey, Stephanie DeLuca, Amy Darragh, Jill Heathcock, Mark Conaway, Renee' Martin

OBJECTIVE: A Phase 3 15-site randomized controlled trial confirmed I-ACQUIRE, a Constraint-Induced Movement Therapy (CIMT), improved upper extremity function compared to usual care (UC) in 8- 36-mth olds with Perinatal Arterial Ischemic Stroke (PAIS), although individual treatment responses varied considerably. This presentation addresses whether co-morbid seizures/epilepsy significantly influences treatment benefits.
METHODS: The I-ACQUIRE trial examined whether High- or Moderate-dose CIMT (I-ACQUIRE) improved motor function more than UC. From parent-reported medical history, we analyzed the association between seizures/epilepsy to Emerging Behaviors Scale (EBS) gains end-of-treatment and 6-months later.
RESULTS: Of 167 participants, 53 (40%) in the UC group, 58 (57%) in the High-dose CIMT group, and 56 (54%) in Moderate-dose CIMT group had seizures/epilepsy. For children with no seizures/epilepsy, upper extremity gains were significantly greater than UC at post-treatment (Moderate vs UC, EBS 2.38 SE 1.03 p=0.022; High vs UC, EBS 3.02 SE 1.03 p=0.0040); 6-mos later, High-dose group gains remained significantly higher (High vs UC, EBS 2.55 SE 1.07 p=0.019), while Moderate-dose group and UC did not differ (Moderate vs UC, EBS 0.36 SE 1.04 p=0.730). Children with PAIS and co-morbid seizures/epilepsy also showed post-treatment gains, although lower than for those without seizures, and not significantly different than UC months post-treatment.
CONCLUSIONS: Children with PAIS and no seizure co-morbidity benefited the most showing median 6-point EBS gains 6-months post-treatment, compared to 3 for Moderate-dose and UC. This presentation delves into plausible reasons for differential benefits related to seizures/epilepsy and treatment dosage with the objective of improving individualized treatment recommendations.
KEYWORDS: Stroke, Neonatal Neurology, Cerebral Palsy

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PL2-7 Impairments, epilepsy, and imaging in dyskinetic cerebral palsy vs. spastic quadriplegic cerebral palsy: a retrospective study

Victoria D'Amours, Mary Dunbar, Michael Shevell, Maryam Oskoui, Adam Kirton

OBJECTIVE: In children with dyskinetic cerebral palsy (DCP) and spastic quadriplegic CP (SQCP) compare the types and combinations of secondary impairments and epilepsy and determine the effect of MRI patterns and clinical variables.

METHODS: Retrospective study of children with DCP and SQCP in the Canadian Cerebral Palsy Registry. Secondary impairments included motor, feeding, sensory, communication and cognition. MRI patterns were near total, deep grey, white matter, malformations, normal and other. Multinomial and multivariable logistic regression was used to evaluate the relationship between CP type, MRI pattern, and impairments.

RESULTS: There were 721 participants, 552 (77%) had SQCP and 169 (23%) had DCP. MRI pattern and gestational age interacted: for SQCP white matter injury was more common (OR 0.21, 95% CI 0.07-0.69) until 38 weeks, while for DCP white matter injury was more common until 30 weeks, then near total and deep grey predominated. Most participants had at least 3 impairments, commonly absent motor speech, cognitive, manual dexterity, and non-ambulation. Epilepsy was found in 33% with no difference by CP type. Neonatal seizures increased risk for epilepsy (OR 3.3, 95% CI 1.4-7.7). Visual impairment was less common in DCP (OR 0.52, 95% CI 0.34-0.80) as was cognitive impairment (OR 0.49, 95% CI 0.29-0.86).

CONCLUSIONS: Participants with DCP and SQCP have a high number of associated impairments, commonly absent motor speech, however children with DCP have less white matter injury and less cognitive and visual impairment, so augmented communication such as brain computer interface should be strongly considered.

KEYWORDS: Cerebral Palsy

Platform Session 3

PL3-1 Clinical Utility of Plasma Neurofilament Light Chain as a Prognostic Biomarker in KIF1A-Associated Neurological Disorder (KAND)

Habibah Agianda, Michelle Grambs, Amy Tam, Hyo-Min Kim, Joshua Rong, Joseph Holtey, Katerina Bernardi, Vicente Quiroz, Kathryn Yang, Wendy Chung, Darius Ebrahimi-Fakhari

OBJECTIVE: Plasma neurofilament light chain (pNfL) is an emerging blood biomarker of neuroaxonal injury, but its utility in KIF1A-associated neurological disorder (KAND) has not been systematically evaluated. We aimed to compare pNfL levels between individuals with KAND and matched controls, characterise diagnostic discrimination, and examine associations with validated clinical severity measures.

METHODS: This cross-sectional observational study enrolled 46 individuals with pathogenic or likely pathogenic KIF1Avariants and 46 age- and sex-matched healthy controls. pNfL was measured using single-molecule array (Simoa) technology. Diagnostic discrimination was assessed by ROC analysis. Associations between pNfL and clinical severity (SPRS and SPATAX disability score) were evaluated using multivariable regression.

RESULTS: Median pNfL was modestly elevated in KAND versus controls (5.2 vs. 3.6 pg/mL; $p<0.001$), with an AUC of 0.76 (95% CI 0.66–0.86). Elevated pNfL was independently associated with higher SPRS scores ($\beta=29.66$, $p<0.001$) and higher SPATAX disability scores ($\beta=4.78$, $p=0.004$), but not with the spasticity subscore. Patients with GMFCS III–IV have a higher pNfL median than those with GMFCS 0–II (5.9 [4.8–7.8] vs 4.9 [3.2–6.3] pg/mL; $p = 0.029$).

CONCLUSIONS: In conclusion, pNfL is modestly elevated in KAND and correlates with overall disease severity and functional impairment, but demonstrates limited diagnostic discrimination. These findings support cautious use of pNfL for severity stratification or as a pharmacodynamic endpoint, pending longitudinal validation.

KEYWORDS: Movement Disorders, Neurodevelopmental Disorders, Neurogenetics

PL3-2 Gene Supplementation Therapy Provides Long-Term Rescue of the Alternating Hemiplegia of Childhood Phenotype in the ATP1A3D801N/+ Mouse Model

Mohamad Mikati, Arsen Hunanyan, Boris Kantor, jai Narayan, Christy Ferguson, Melissa Hall, Jad Kourany, Senyene Hunter, Dwight Koeberl

OBJECTIVE: Demonstrate the proof-of -concept hypothesis that AAV gene therapy delivering a normal copy of the *ATP1A3* gene results in long-term rescue of the Alternating Hemiplegia of Childhood (AHC) phenotype manifested by the D801N-*ATP1A3*-knock-in AHC mouse model carrying the most common human *ATP1A3* AHC mutation.

METHODS: We compared three groups: wildtype-vehicle, mutant-vehicle and mutant-treatment. The latter received an optimized AAV2.9-hSyn-ATP1A3-FLAG-WPRE-SV40polyA vector ($3.0x10^{11}$vg/mouse) injected stereotaxically intracisterna magna and in 3 carefully selected sites per hemisphere (forebrain/2 cerebellum/1) on post-natal day (P)10. All underwent a comprehensive behavioral tests battery starting at P40 (adolescence) and again starting at P70 (mature adulthood) then were sacrificed for brain ATPase enzyme activity assays.

RESULTS: At P40, compared to control mutants, treated mutants had improved balance-beam time-to-cross ($p<0.05$), number-of-slips ($p<0.01$), shorter cold-water–induced seizures ($p<0.05$) and a trend for less dystonia/hemiplegia spells ($p=0.054$). They did not differ from wildtype controls in central-squares-time in the open-field test whereas mutant controls did ($p>0.05$, $p<0.05$). At P70, treated mutants had better: balance-beam time-to-cross ($p=0.0442$), number-of-slips ($p=0.034$), T-maze memory ($p<0.05$) with a trend

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for shorter cold-water–induced seizures (p=0.0692). Hippocampal ATPase activity was higher in the treatment group than in mutant controls but still lower than wildtype (p=0.039, 0.00239). Treated mutants cerebellar ATPase activity did not differ from wildtypes while mutant controls were lower than wildtype (p=0.481, p=0.0247).

CONCLUSIONS: AAV-based supplementation gene therapy resulted in long-term rescue of multiple *ATP1A3* mutation effects. This supports further development, for eventual human translation, of such therapy vectors that would result in diffuse expression without having to resort to intraparenchymal injections.

KEYWORDS: Neurogenetics, Neurodevelopmental Disorders, Epilepsy

PL3-3 Nuclease-free AAVHSC15 HR-mediated exon replacement of Mecp2 rescues survival and neurologic phenotype in the R306C mouse model of Rett syndrome

Sampathkumar Rangasamy, Aravind Sankaramoorthy, Swati Bijlani, Dharaneesh Subramani, Ka Ming Pang, Lakshmi Bugga, Amin Kudsi, Saswati Chatterjee, Vinodh Narayanan

OBJECTIVE: Gene therapy for Rett syndrome (RTT) requires strict gene dosage control (Goldilocks problem), and lifelong, regulated expression. There is a need for safer in vivo editing platforms that minimize on- and off-target mutations and genotoxicity. To determine whether gene editing of Mecp2 via homologous recombination (HR) with a nuclease-free, promoterless AAVHSC15 vector can restore wild-type *Mecp2* expression and rescue RTT-like phenotypes in hemizygous $Mecp2^{R306C/Y}$ mice.

METHODS: Male $Mecp2^{R306C/Y}$ mice received a single intravenous dose (2.7– 3.90×10^{13}vg/kg) of an AAV-HSC15-based editing vector engineered to replace the endogenous mutant exon 4 with a codon-altered wild-type exon 4, preserving the native *Mecp2* promoter and 3′UTR. Survival (Kaplan-Meier analysis), body weight, and RTT phenotype severity score (“Bird score) were measured weekly. qPCR on genomic DNA and qRT-PCR were used to assess vector biodistribution, tissue-specific editing and *Mecp2* mRNA expression in brain and other tissues.

RESULTS: A single systemic AAVHSC15 *Mecp2* treatment significantly improved survival in $Mecp2^{R306C/Y}$ mice compared with untreated mutants. Edited mice demonstrated substantially reduced RTT severity scores and attenuated phenotype progression compared with unedited $Mecp2^{R306C/Y}$ littermates. A subset of mutant mice survived beyond 24 weeks without overt RTT-like features. Genomic qPCR detected editing vector DNA in multiple tissues and brain regions. Edited Mecp2 mRNA was detected by qRT-PCR in brain and peripheral tissues.

CONCLUSIONS: Nuclease-free, promoterless exon replacement of *Mecp2* via systemic AAVHSC15 delivery improves survival and mitigates neurologic disease progression in the R306C male mouse model. This work supports the potential of AAVHSC mediated gene editing platform for RTT and other monogenic neurodevelopmental disorders.

KEYWORDS: Neurogenetics, Neurodevelopmental Disorders, Experimental Therapeutics

PL3-4 Small-Molecule Therapeutics for AP-4-Related Hereditary Spastic Paraplegia

Zoe Piccus, Hyo-Min Kim, Darius Ebrahimi-Fakhari

OBJECTIVE: Hereditary spastic paraplegia (HSP) is a genetically heterogeneous group of disorders characterized by progressive lower-limb spasticity. Biallelic loss-of-function variants in adaptor protein complex 4 (AP-4) subunits cause a prototypical childhood-onset complex form of HSP. AP-4 traffics transmembrane cargo, including the core autophagy protein ATG9A, from the trans-Golgi network (TGN) to the cell periphery; loss of AP-4 traps ATG9A in the TGN and depletes it from the distal axon, impairing autophagy and driving axonal degeneration. No approved therapies exist. Here, we advance small-molecule modulators of ATG9A trafficking toward preclinical development for AP-4-HSP.

METHODS: We employed a phenotypic, high-content imaging assay using the intracellular ATG9A distribution (TGN-to-cytoplasm ratio) as a readout of AP-4 function in AP-4-deficient patient-derived fibroblasts and neuronal models. Candidate compounds were evaluated for on-target activity, dose response, and retention of activity across orthogonal cellular contexts. Proteomic profiling of treated cells was performed to delineate candidate mechanisms of action.

RESULTS: We identified a series of small-molecule modulators that redistribute ATG9A from the TGN to the cytoplasm in AP-4-deficient cells. The lead compound retained activity in neuron-like cells, and structural analogs preserved on-target effects across cellular contexts. Proteomic profiling of treated cells nominated intracellular vesicle trafficking as a candidate mechanism of cargo redistribution.

CONCLUSIONS: We identified small-molecule modulators that restore ATG9A localization in AP-4-deficient cells, with activity preserved in neuronal models and across chemical analogs. Preparations are underway to evaluate lead compounds in vivo, advancing a first rational therapeutic strategy for AP-4-HSP.

KEYWORDS: Neurodevelopmental Disorders, Experimental Therapeutics, Movement Disorders

PL3-5 Microglial transplant: Novel treatment for Vanishing White Matter Leukodystrophy

Joshua Bonkowsky, Tamara Stevenson, Julia Wentz, Quenna Yuan, Jessica Herstine, Nettie Pyne, Allison Bradbury

OBJECTIVE: Vanishing White Matter leukodystrophy (VWM) is a rare, progressive leukodystrophy with no treatments, caused by mutations in any of the five genes encoding eIF2B, which is essential for protein synthesis and regulation of the integrated stress response (ISR). Pathophysiology has been ascribed to involvement of astrocytes and oligodendrocytes. However, activated microglia are known to induce astrocytes, and have been observed in human specimens. Our goal was to describe novel pathophysiological findings and a role of microglial transplant for treatment of VWM.

METHODS: We characterized microglia in WT and VWM mice. Assays were for activated and stable microglia; cell markers; and ISR quantification. We tested microglia replacement using circulation-derived myeloid cells (CDMCs). Using busulfan ablation, followed by transplant and microglia depletion with PLX3397, we analyzed for transplantation efficacy, and effects on VWM progression.

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RESULTS: We found infiltration of activated microglia throughout the VWM CNS. Following microglia transplantation, we found that donor CDMCs cross the blood-brain barrier and replace endogenous microglia in the CNS. VWM mice showed no increase in relative mortality following transplantation. Following microglial transplantation, VWM mice showed improved outcomes compared to untreated mutants including behavior, RT-PCR for ISR markers, and immunohistochemical markers. Further, transplant alone or with gene therapy provides superior rescue of VWM outcomes.
CONCLUSIONS: We found a novel role for involvement of microglia in VWM. Microglial transplant resulted in rescue of disease-related phenotypes and may provide a therapeutic option for VWM, with superior efficacy in concert with AAV9 gene therapy.
KEYWORDS: Neurodevelopmental Disorders, Experimental Therapeutics

PL3-6 Biallelic ADORA1 Variants Cause Childhood-Onset Epilepsy Through Impaired Basal Adenosine A1 Receptor Signaling

Ali Reza Tavasoli, Kenneth Jacobson, Kara Lewis, Michael Kruer, Ikuo Masuho, Reza Maroofian

OBJECTIVE: To define the clinical, genetic, and molecular spectrum of a novel childhood-onset epilepsy associated with *ADORA1* variants and evaluate potential mechanism-based therapeutic strategies.
METHODS: Eight affected individuals from four unrelated consanguineous families underwent detailed clinical phenotyping, neuroimaging, and genomic sequencing. Identified variants in *ADORA1*, encoding the adenosine A1 receptor (A1R), were evaluated using structural modeling and live-cell functional assays to assess receptor expression, trafficking, and signaling. Variant-specific pharmacologic rescue strategies were explored using positive allosteric modulators and translational readthrough compounds to restore receptor function.
RESULTS: Four biallelic *ADORA1* variants were identified in individuals presenting with childhood-onset focal epilepsy, progressive cognitive and behavioral decline, autonomic features, and selective bilateral hippocampal abnormalities on neuroimaging. Seizures were frequently prolonged and variably responsive to anti-seizure medications. Functional analyses demonstrated that variants impaired receptor function through distinct mechanisms, including reduced expression, defective membrane trafficking, altered activation, and dominant-negative effects. Despite heterogeneous mechanisms, all variants converged on markedly reduced basal A1R signaling, identifying loss of constitutive receptor activity as the shared pathogenic mechanism. Pharmacologic studies demonstrated variant-specific rescue: positive allosteric modulation restored basal signaling in missense variants, while translational readthrough compounds partially restored receptor function in the nonsense variant.
CONCLUSIONS: Biallelic *ADORA1* variants define a novel neurodevelopmental disorder with epilepsy characterized by impaired basal adenosine A1 receptor signaling and selective hippocampal vulnerability. Mechanism-guided pharmacologic rescue supports precision therapeutic approaches and identifies A1R modulation as a promising treatment strategy for rare and potentially common epilepsies, warranting future clinical investigation.
KEYWORDS: Epilepsy, Neurogenetics

PL3-7 Functional impacts of autism-associated TRIO variants on GABAergic interneurons

Asmaa TOUMI, Émile Chamberland, Nathan Protzenko, Elsa Rossignol

OBJECTIVE: Mutations in *TRIO* are associated with a spectrum of neurodevelopmental disorders (NDDs). *TRIO* encodes a Rho-GEF (Rho-guanine nucleotide exchange factor) that activates Rac1 and RhoA, two Rho-GTPases implicated in neuronal migration. Recent data from our group indicate that, in mice, the conditional deletion of *Trio* alters the migration and morphological development of GABAegic interneurons (INs), resulting in reduced cortical inhibition, ASD-like behavior and epilepsy in $Trio^{cKO}$ mice. However, the impacts of specific disease-causing variants on INs development remain unknown. We designed a new functional validation pipeline to address this question.
METHODS: We expressed mutant cDNA, carrying patient-derived variants, or the wild-type cDNA in explants of the medial ganglionic eminence of e13.5 $Trio^{cKO}$ embryos. Using FLIM-FRET-based biosensors, we monitored the pattern of RhoA and Rac1 activation in INs and HEK293 cells. Additionally, we investigated the migration dynamics and morphological development of INs using time-lapse imaging of MGE explants.
RESULTS: We find that $Trio^{cKO}$ INs display hypoactivation of RhoA, which is reversible by re-expressing WT *Trio* cDNA. When studied in HEK293 cells, patient-derived *TRIO* variants also alter Rac1 and RhoA activation. Furthermore, when expressed in mice INs, cDNA carrying GEFD1 variants fail to rescue the deficits in IN migration and morphology observed in $Trio^{cKO}$ INs, which are reversed by expressing the $Trio^{WT}$ cDNA.
CONCLUSIONS: Thus, our findings suggest that NDD-associated TRIO variants disrupt the development and migration of INs, and that variant pathogenecity can be efficiently assessed using our validation pipeline.
KEYWORDS: Neurogenetics, Neurodevelopmental Disorders

ORAL ABSTRACT PRESENTATIONS

Afternoon Oral Abstract Presentations

AOP-1 Long-Term Safety and Effect of Ecopipam, a Selective Dopamine D1 Receptor Antagonist, in Children, Adolescents, and Adults With Tourette Syndrome

Donald Gilbert, Kevin Black, Katie Kompoliti, Patricia Rice, John Flatt, George Karkanias, Stephen Wanaski, Timothy Cunniff, Kinga Tomczak

OBJECTIVE: To evaluate the long-term safety and effect of ecopipam, a selective dopamine D1 receptor antagonist in development for Tourette syndrome (TS).

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METHODS: Individuals ≥6 years with TS who completed a previous ecopipam trial (phase 3 or phase 2b open-label extension [OLE]) and had tapered off ecopipam were enrolled in a 36-month OLE trial. Ecopipam was titrated to a target dose of 1.8 mg/kg/day. Study visits are being conducted monthly for 12 months and every 3 months thereafter. An interim analysis was conducted 27 months after study initiation.

RESULTS: Of 120 enrolled participants, 118 received ≥1 ecopipam dose (69.5% male; 23.7% 6-11y, 59.3% 12-17y, 16.9% ≥18y). Median duration of ecopipam exposure was 14.9 months (1.2-27.0 months), with 97 (82.2%) continuing treatment. At baseline (n=118), mean (SD) Yale Global Tic Severity Scale Total Tic Score (YGTSS-TTS) was 28.1 (9.7). At Month 12 (n=88), mean (SD) change from OLE baseline in YGTSS-TTS was −12.0 (8.7; $P<0.0001$), a 40.1% improvement, and Clinical Global Impression of Tourette Syndrome Severity (CGI-TS-S) was −1.2 (1.1; $P<0.0001$). At Month 18 (n=33), mean (SD) change from OLE baseline in YGTSS-TTS was −13.9 (9.3; $P<0.0001$), a 45.6% improvement, and CGI-TS-S was −1.6 (1.2; $P<0.0001$). The most commonly reported adverse events (AEs) were nasopharyngitis (16.1%), upper respiratory tract infection (12.7%), and anxiety (9.3%). Serious AEs (suicidal ideation, asthmatic crisis; both unrelated to ecopipam) were reported in 2 (1.7%) participants. Four (3.4%) participants discontinued due to an AE.

CONCLUSIONS: Ecopipam was well tolerated and maintained meaningful tic suppression during long-term treatment in children/adolescents/adults with TS.

KEYWORDS: Experimental Therapeutics, Neurodevelopmental Disorders, Movement Disorders

AOP-2 Efficacy and Safety of Ocrelizumab Compared With Fingolimod in Pediatric-Onset Relapsing-Remitting MS: Results of the Phase III OPERETTA 2 Study

Fabien Bakdache, Brenda Banwell, Katarzyna Kotulska, Kevin Rostasy, Kumaran Deiva, Henry Sato, Massimo Filippi, Tanuja Chitnis, Maria Pia Sormani, Lauren Krupp, Amit Bar-Or, Joanna Evershed, Bouchra El Azzouzi, Qing Wang, Chien-Ju Lin, Alexandra Hogea, Hans-Martin Schneble, Corinne Manlius, Emmanuelle Waubant

OBJECTIVE: OPERETTA 2 (NCT05123703)—a Phase III, randomized, noninferiority study—evaluated the safety and efficacy of intravenous (IV) ocrelizumab vs fingolimod in patients with pediatric-onset multiple sclerosis (POMS) aged 10-17 years.

METHODS: Patients were randomized (1:1) to ocrelizumab IV 600 mg every 24 weeks or oral fingolimod 0.5 mg daily, with matching placebos, over a double-blind period (DBP) until all patients completed ≥24 weeks. The primary objective was to demonstrate that ocrelizumab was noninferior to fingolimod based on annualized relapse rate. Secondary endpoints were numbers of new/enlarging T2 lesions during the DBP and T1 gadolinium-enhancing (Gd^+) lesions at Week 12. Safety was also monitored.

RESULTS: Of 187 patients randomized, 129 (69.0%) were female. At baseline, median (range) age was 15.0 (11-17) years and body weight was 63.1 (42.3-154.2) kg. Patients presented with a mean (SD) of 57.4 (47.3) T2 lesions and 2.4 (4.6) T1 Gd^+ lesions; 47.1% had T1 Gd^+ lesions. Ocrelizumab was noninferior to fingolimod in controlling relapses (rate ratio [RR]=0.52; 95%CI 0.19-1.33) and superior in reducing the rate of new/enlarging T2 lesions in the DBP (RR=0.52; 95% CI 0.36-0.76; $P=0.001$) and T1 Gd^+ lesions at Week 12 (RR=0.13; 95%CI 0.03-0.41; $P=0.001$). Ocrelizumab was well tolerated; most infusion-related reactions were mild or moderate and occurred in 48.4% of patients. No adverse events led to ocrelizumab treatment withdrawal.

CONCLUSIONS: Ocrelizumab was noninferior to fingolimod on relapse activity and superior on MRI endpoints, and the safety profile was consistent with studies in adults, making ocrelizumab a potential high-efficacy treatment option for POMS.

KEYWORDS: Neuroimmunology

AOP-3 Safety and efficacy of satralizumab in patients with relapsing myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD): Results from the phase 3 METEOROID trial

Eoin Flanagan, Michael Levy, Tania Kuempfel, Romain Marignier, Kazuo Fujihara, Cheryl Hemmingway, Daniela Stokmaier, Alessandro Noci, Hans-Christian von Buedingen, Li Li, Sayuri Tanaka, Friedemann Paul

OBJECTIVE: Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a demyelinating disease in which attacks can result in prominent neurological and visual disability, yet proven attack-prevention treatments are lacking. Here we report primary and key secondary efficacy and safety results of the Phase 3 METEOROID (NCT05271409) study investigating satralizumab in patients with MOGAD.

METHODS: METEOROID, a randomized, double-blind (DB), placebo-controlled study enrolled patients (≥12 years) with relapsing MOGAD where patients were randomized 1:1 to satralizumab or placebo ± concomitant immunosuppressive therapy (IST). Satralizumab was administered subcutaneously at Weeks 0, 2, 4 and Q4-weeks thereafter. The primary endpoint was time to first adjudicated relapse. Key secondary endpoints evaluated relapse rate, active MRI lesions, need for rescue therapy and hospitalization.

RESULTS: There were 132 patients randomly assigned to satralizumab (n=68) or placebo (n=64). Satralizumab prolonged the time to first relapse vs placebo resulting in a 68% reduction in the risk of a new MOGAD relapse (HR: 0.32; 95% confidence interval: 0.15–0.70; p=0.0025). Relapse-free patients at 48 weeks was 87.3% (satralizumab) versus 66.5% (placebo). Consistent efficacy was observed across subgroups. Key secondary endpoints of annualized relapse rate, annualized rate of active lesions and rescue therapy use were statistically significant, with 66.3%, 78.5% and 72.5% risk-reductions, respectively, with satralizumab treatment. The rates of adverse events (AEs) and infections were comparable between groups; rates of serious AEs were low and unrelated to treatment. Treatment discontinuation rates were low.

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CONCLUSIONS: Satralizumab significantly reduced the risk of attack in patients with relapsing MOGAD compared with placebo, with a favorable safety profile.
KEYWORDS: Neuroimmunology

AOP-4 Interim Safety and Efficacy of NGN-401, a Novel Regulated AAV9 Gene Therapy, from a Phase 1/2 Study in Rett Syndrome

Elizabeth Berry-Kravis, Bernhard Suter, Tim Benke, David Lieberman, Aleksandra Jacobs, Carolyn Ellaway, Jeffrey Neul, Alana Salvucci, Cari Combs, Effie Albanis, Stuart Cobb, Julie Jordan

OBJECTIVE: Rett syndrome (RTT) is a neurodevelopmental disorder characterized by regression of acquired developmental milestones and severe impairments in hand function, gross motor abilities, and communication. NGN-401 is an investigational adeno-associated virus 9 (AAV9) gene therapy delivering full-length human methyl-CpG–binding protein 2 *(MECP2)* transgene, incorporating EXACT transgene regulation technology and is administered intracerebroventricularly to target RTT pathophysiology in the brain and spinal cord.
METHODS: The Phase 1/2 open-label trial (NCT05898620) in females with classic RTT, age ≥4 years and baseline Clinical Global Impression-Severity (CGI-S) scores of 4–6, is evaluating the safety, tolerability, and efficacy of a one-time 1E15 vg dose of NGN-401. Efficacy assessments include CGI-Improvement (CGI-I) and functional ability in core RTT domains. Developmental milestone acquisition was assessed via independent central rating.
RESULTS: As of October 30, 2025, 10 participants (n=8, age 4-10 cohort; n=2, age ≥11 cohort) received 1E15 vg of NGN-401. Safety (n=10, follow-up ~3-24 months) demonstrated mild-to-moderate treatment-related adverse events consistent with known AAV risks. Efficacy (n=8, follow-up ~6-24 months) demonstrated functional gains in all pediatric participants; 35 developmental milestones were acquired across core RTT clinical domains with a deepening and durable trajectory, and 7/8 participants demonstrated ≥1 point improvement on the CGI-I scale. Longer-term interim safety and efficacy results (n=10, ≥12-month follow-up) will be presented here.
CONCLUSIONS: NGN-401 (1E15 vg) was generally well tolerated and resulted in durable, multi-domain developmental milestone gains that accrued and deepened over time with no sign of plateau, suggesting potential disease-modifying activity in patients with RTT.
KEYWORDS: Neurodevelopmental Disorders

AOP-5 Multi-Domain Functional Gains Following TSHA-102 Gene Therapy Across the Rett Syndrome Lifespan: Safety and Efficacy Results from the REVEAL Part A Phase 1/2 Trial of TSHA-102 in Pediatric and Adolescent/Adult Cohorts

Elsa Rossignol, Elizabeth Berry Kravis, Richard Haas, Robyn Ryther, Tim Feyma, Inge Meijer, Colleen Buhrfiend, Tessa Clarkson, Rumana Haque-Ahmed, Laura Pisani, Jason Cataldo, Minna Montgomery, Suku Nagendran

OBJECTIVE: Rett syndrome (RTT) is a rare neurodevelopmental disorder with no approved therapies targeting its genetic root. A clear developmental plateau begins at age 6, resulting in lost/missed developmental milestones (DMs) across fine/gross motor function, communication and causes autonomic dysfunction (breath holding, sleep disturbances, seizures) impacting activities of daily living. Here we present safety and efficacy data from REVEAL Part A evaluating TSHA-102 gene therapy in RTT designed to optimize MECP2 expression and address the underlying genetic cause.
METHODS: A single dose of TSHA-102 (low-dose [LD], 5.7×1014 vector genomes [vg]; or high-dose [HD],1.0×1015vg) was administered intrathecally to participants 6-21 years old. Assessments included safety evaluation and gain/regain of predefined DMs was assessed by multiple independent central raters through video evidence.
RESULTS: 100% of participants gained/regained ≥1 DM with a <6.7% likelihood of being achieved after age 6 (LD, n=4; HD, n=6; 05/2025 data cut-off). Participants achieved 22 DMs and 165 additional skills/improvements across the core RTT domains: communication (use of phrases, improved communication), fine motor (purposeful hand use, finger feeds), gross motor (improved mobility), and additional autonomic/other improvements (absent/reduced breath holding/hyperventilation, seizure reduction), improving core RTT features with meaningful impact on activities of daily living. TSHA-102 was well-tolerated with no treatment-related SAEs or DLTs (05/2025 data cut-off).
CONCLUSIONS: TSHA-102 was generally well-tolerated. Contrary to natural history expectations, both cohorts showed early, multi-domain functional improvements that deepened over time across measures, supporting the disease-modifying potential of TSHA-102. Additional sub-analyses reflecting therapeutic impact on neurological function will be presented at CNS 2026.
KEYWORDS: Neurodevelopmental Disorders, Experimental Therapeutics, Neurogenetics

Evening Oral Abstract Presentations

EOP-1 Zorevunersen demonstrates potential as a disease-modifying therapy in patients with Dravet syndrome: A matched-adjusted indirect comparison between natural history and patients receiving zorevunersen

M Scott Perry, Andreas Brunklaus, J Helen Cross, Kelly Knupp, Linda Laux, Carolyn Condon, Ann Dandurand, Jessie Lynch, Brian Werneburg, Fei Wang, Kimberly Parkerson, Barry Ticho

OBJECTIVE: Dravet syndrome (DS) is a developmental and epileptic encephalopathy caused primarily by *SCN1A* haploinsufficiency reducing $Na_V1.1$ expression. Despite treatment with best available antiseizure medications, patients with DS in the BUTTERFLY natural history study (NH) experienced frequent seizures, and neurodevelopment

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plateaued around age 2. Zorevunersen, an investigational antisense oligonucleotide, upregulates $Na_V1.1$ via the wild-type *SCN1A* copy.

METHODS: In Phase 1/2a studies (NCT04442295 [USA]/2020-006016-24[UK]), patients received single/multiple loading doses of zorevunersen (≤70 mg). Eligible patients entered open-label extensions (OLEs) (NCT04740476[USA]/2021-005626-14[UK]), receiving zorevunersen (≤45 mg) every 4 months. Seizure frequency and safety were evaluated. A matched-adjusted indirect comparison (MAIC) evaluated Vineland-3 subdomains (Expressive Communication, Receptive Communication, Interpersonal Relationships, Personal Skills, Coping Skills) for patients receiving 2X70 mg/3X45 mg zorevunersen and NH patients.

RESULTS: By May 30, 2025, 75/81 Phase 1/2a study patients entered OLEs. Patients experienced substantial, durable seizure reductions from Phase 1/2a baseline through OLE Month 36. MAIC analyses demonstrated that zorevunersen-treated patients experienced substantial, durable improvements in cognition and behavior, while NH patients experienced minimal changes. At Week 100/104, estimated mean changes from baseline in Vineland-3 subdomain raw scores (95% CI) ranged from 9.8 (0.1, 19.5) to 14.4 (8.8, 20.0) in zorevunersen-treated patients and −2.6 (−7.6, 2.5) to 2.8 (−2.0, 7.7) in NH patients. Zorevunersen was generally well tolerated. Increased cerebrospinal fluid (CSF) protein was the most common treatment-related adverse event in OLEs (44.0%, n=33/75); no hydrocephalus associated with CSF protein elevation occurred.

CONCLUSIONS: Zorevunersen treatment resulted in durable seizure reduction and improved cognition and behavior, supporting its disease-modifying potential and continued Phase 3 evaluation.

KEYWORDS: Epilepsy, Neurodevelopmental Disorders

EOP-2 Safety and Efficacy of ETX101, an Investigational AAV9-based Gene Therapy for SCN1A+ Dravet Syndrome: Interim Results from the POLARIS Phase 1/2 Clinical Trials

Joseph Sullivan, Adam Numis, Ingrid Scheffer, Katherine Howell, M. Scott Perry, Andreas Brunklaus, J. Helen Cross, Amy McTague, Linda Laux, Archana Desurkar, Nalin Gupta, Kurtis Auguste, Alison Wray, Daniel Hansen, Kristian Aquilina, Roddy O'Kane, Sandi Lam, Shungu Ushewokunze, Stéphane Auvin, Dennis Lal, Sarah McKeown Ruggiero, Sameer Zuberi, Jacqueline Gofshteyn, Archana Belle, Szu-Ying Chen, Sirika Pillay, Veda Tatavarty, Joshua Bear, Natalie Berger, Mustafa Hameed, Norman Huang, Maria Candida Vila, Emma James, Stephanie Tagliatela, Salvador Rico

OBJECTIVE: Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy caused by *SCN1A* haploinsufficiency, resulting in drug-resistant seizures and neurodevelopmental slowing. Standard-of-care antiseizure medications have limited impact on the developmental course of disease. ETX101 is an investigational AAV9-mediated gene regulation therapy designed to upregulate endogenous *SCN1A* expression specifically in GABAergic interneurons using an engineered transcription factor and a cell-selective regulatory element.

METHODS: The POLARIS program includes three ongoing Phase 1/2 open-label, dose-escalation studies in the USA, Australia, and the UK, enrolling participants aged 6 months to <7 years with DS and pathogenic or likely-pathogenic *SCN1A* variants. ETX101 was administered as a single intracerebroventricular dose across four ascending dose levels, with prophylactic immunosuppression using prednisolone, with or without sirolimus.

RESULTS: As of April 6, 2026, 21 participants had been treated, with follow-up of up to 102 weeks. ETX101 was well tolerated, with no treatment-related serious adverse events or dose-limiting toxicities. At the highest doses, a median reduction of >71% in monthly countable convulsive seizures was observed (n=14). Vineland-3 domains showed notable improvements in adaptive functioning as early as Week 16, with mean gains more than doubling by Week 52. In younger participants, the rate of cognitive skill acquisition measured by Bayley-4 diverged ∼10 GSVs from the well-established neurodevelopmental slowing in DS, suggesting that ETX101 leads to cognitive rescue.

CONCLUSIONS: These interim results highlight the promising therapeutic effect of ETX101, the first one-time potentially disease-modifying therapy for DS, and support its continued development to establish safety, efficacy and long-term impact.

KEYWORDS: Neurodevelopmental Disorders, Epilepsy, Neurogenetics

EOP-3 Fenfluramine Treatment in CDKL5 Deficiency Disorder: Phase 3 Primary Efficacy and Safety Results by Age

Brian Moseley, Eric Marsh, Orrin Devinsky, Ángel Aledo-Serrano, Domenica Immacolata Battaglia, Rajsekar Rajaraman, Karen Keough, Ryoko Honda, Renzo Guerrini, Gia Melikishvili, Sam Amin, Amanda Jaksha, Nicola Specchio, Peter St. Wecker, Brian Kilgallen, Najla Dickson, Joseph Sullivan

OBJECTIVE: Cyclin-dependent kinase-like 5 deficiency disorder (CDD) is an ultra-rare, drug-resistant, X-linked developmental and epileptic encephalopathy caused by pathogenic *CDKL5* variants. Seizures typically begin early (≤3 months) and evolve over time. We report primary results by patient age from a randomized placebo-controlled trial of fenfluramine in CDD (NCT05064878).

METHODS: Patients (1–35 years) with confirmed/likely pathogenic *CDKL5* variants, clinical CDD diagnoses, and ≥4 caregiver-reported countable motor seizures/week were randomized to receive fenfluramine 0.7mg/kg/day (max 26mg/day) or placebo over 14 weeks (2-week titration [T] +12-week maintenance [M]). Primary efficacy (change from baseline in countable motor seizure frequency [CMSF] over T+M) and safety endpoints were analyzed across age groups (1–<2 years, 2–≤6 years, >6–≤35 years). Data for 1–<2 years are not reported (due to a small sample size).

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RESULTS: Safety and modified intent-to-treat populations included 87 (42 fenfluramine/45 placebo) and 86 (42 fenfluramine/44 placebo) patients, respectively. Four (2 fenfluramine/2 placebo), 39 (19 fenfluramine/20 placebo), and 43 (21 fenfluramine/22 placebo) patients were 1–<2 years, 2–≤6 years, and >6–≤35 years, respectively. Median CMSF reduction was greater with fenfluramine versus placebo (nominal p<0.001): −45.7% vs 0.1% (2–≤6 years) and −48.2% vs −2.8% (>6–≤35 years). Incidence of treatment-emergent adverse events was consistent across age groups (2–≤6 years: 14 [74%] fenfluramine, 17 [85%] placebo; >6–≤35 years: 16 [76%] fenfluramine, 16 [70%] placebo); no new safety signals were identified.
CONCLUSIONS: Fenfluramine demonstrated similar efficacy and safety across patient age groups (≥2 years), supporting its use across children and adults with CDD.
KEYWORDS: Epilepsy, Neurodevelopmental Disorders, Experimental Therapeutics

EOP-4 Efficacy of arimoclomol combined with miglustat at months 3, 6, 9 and 12 of the double-blind, randomized, placebo-controlled NPC002 trial

Mary-Jean Fanelli, Eugen Mengel, Christine í Dali, Adrian Quartel

OBJECTIVE: Niemann-Pick disease type C (NPC) is an ultra-rare, progressive neurodegenerative lysosomal disease with heterogeneous clinical presentation. A 12-month double-blind (DB), randomized, placebo-controlled trial showed a positive benefit-risk of arimoclomol in patients with NPC. This effect was even more pronounced in those concomitantly treated with miglustat. Arimoclomol, an orally available small molecule, is the first FDA-approved treatment for NPC when used in combination with miglustat.
METHODS: Here we present post hoc efficacy analysis for patients on concomitant miglustat assessed at months 3, 6, 9 and 12 of the trial, with the rescored 4-domain NPC clinical severity scale (R4DNPCCSS: ambulation, speech, swallowing and fine motor skills). Of 50 patients, 26 on arimoclomol and 13 on placebo were on concomitant miglustat during the NPC002 trial.
RESULTS: Statistically significant treatment effect favoring arimoclomol over placebo in R4DNPCCSS change from baseline were seen at all timepoints assessed. The estimated treatment differences were: −0.85 (95% CI: −1.67, −0.03; p-value=0.0415) at 3 months, − 1.48 (95% CI: −2.36, −0.61; p-value=0.0009) at 6 months, −2.07 (95% CI: −3.43, −0.72; p-value=0.0028) at 9 months, and −2.17 (95% CI: −3.80, −0.53; p-value=0.0094) at 12 months.
CONCLUSIONS: Assessments of NPC disease progression usually require observations over at least 12 months. Nonetheless, these results show that the statistically significant treatment difference between arimoclomol and placebo was apparent at all timepoints assessed post-baseline in the NPC002 trial for patients concomitantly treated with miglustat. This indicates that arimoclomol combined with miglustat treatment may slow NPC disease progression from as early as 3 months after treatment initiation.
KEYWORDS: Neurometabolic

EOP-5 Treatment with UX111 reduced cerebrospinal fluid (CSF) heparan sulfate (HS) exposure and stabilized or improved functioning in children with MPS IIIA

Deepa Rajan, Heather Lau, Kaushik Patra, Melissa Wolf, Nicholas Smith, Maria Couce, Kristen Truxal, Maria de Castro, Kim McBride, Maria Fuller, Igor Nestrasil, Eines Monteagudo, Lucy Dougherty, Mireia del Toro, Kevin Flanigan

OBJECTIVE: MPS IIIA (Sanfilippo type A) is a progressive neurodegenerative disease characterized by developmental arrest, regression, and early death. UX111 (rebisufligene etisparvovec) is an AAV9 viral vector encoding *SGSH* under investigation for MPS IIIA.
METHODS: Data were analyzed across two open-label studies (NCT02716246, NCT04088734) and an ongoing long-term follow-up (NCT04360265). Children received a single intravenous infusion of UX111. The Efficacy set included those who received $3x10^{13}$ vg/kg UX111. The mITT set included a subset ≤2 years old or >2 years old with a BSID-III cognitive developmental quotient ≥60. CSF HS exposure was defined as time-normalized AUC of the percentage change from baseline. Data snapshot: 22Sept2025.
RESULTS: Median (min-max) follow-up was 4.8 (0.6, 8.5) years (n=33). Median (95% CI) CSF HS exposure was -63.98% (-72.27, -54.84; p<0.0001) for the Efficacy set (n=27) and -62.58% (-74.26, -56.29; p<0.0001) for mITT (n=17). For mITT, LS mean change in model-estimated BSID-III raw scores from 24-60 months of age significantly improved vs Natural History for cognitive (23.2 points, p<0.0001), receptive communication (8.1 points, p=0.0076), expressive communication (11.1 points, p=0.0008), and fine motor (9.0 points, p=0.0026). Median (95% CI) annualized percentage change from baseline in total cortical brain volume was 0.83 (−3.02, 6.75) in mITT and −8.04% (−10.18, −5.46) in the Natural History set (p=0.0003). Older children and those with more advanced disease at treatment (n=10) maintained key communication, ambulation, and/or eating/self-feeding skills. Most UX111-related TEAEs were mild-to-moderate hepatic reactions that resolved spontaneously.
CONCLUSIONS: UX111 showed a positive treatment effect and manageable safety in MPS IIIA.
KEYWORDS: Neurodevelopmental Disorders

POSTERS

Autonomic Disorders

1. From Seizure to Paralysis: Acute Neurologic Decline in a Hospitalized Child

Omneya Ayoub, Caroline Mebane, Katelyn Bricker

OBJECTIVE: Acute neurologic deterioration in hospitalized children requires rapid evaluation for structural, metabolic, infectious, and vascular etiologies. Diagnostic uncertainty

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increases when clinical findings and neuroimaging are discordant. We present an 11-year-old boy admitted for complicated appendicitis who developed sudden apnea and generalized tonic-clonic seizure requiring resuscitation. Initial examination demonstrated altered mental status, hypophonic speech, and bilaterally dilated, sluggish pupils. MRI revealed diffusion restriction in the right posterior occipital lobe, raising concern for posterior circulation ischemia versus postictal cortical changes.

METHODS: Case Report

RESULTS: Extensive diagnostic evaluation, including vascular imaging, cardiac studies, CSF analysis, electroencephalography, and infectious and autoimmune testing failed to identify a central nervous system etiology. Despite stable neuroimaging, the patient exhibited progressive neurologic decline with development of ophthalmoplegia, multiple cranial neuropathies, bulbar dysfunction, and descending weakness requiring mechanical ventilation. Reflexes evolved from initially preserved to absent in the upper extremities while remaining brisk in the lower extremities. The evolving pattern of cranial nerve involvement and descending paralysis prompted reconsideration of localization and suggested a process affecting the peripheral nervous system or neuromuscular junction. Electrodiagnostic testing demonstrated presynaptic neuromuscular junction dysfunction with marked incremental response of up to 600 percent on repetitive stimulation, which is consistent with botulinum neurotoxin exposure.

CONCLUSIONS: This case underscores the importance of serial neurologic examinations and reassessment of localization when clinical progression is inconsistent with imaging findings. In children presenting with cranial neuropathies, bulbar dysfunction, and descending weakness, neuromuscular junction disorders such as botulism should be strongly considered, even when initial evaluation suggests a central process.

KEYWORDS: Autonomic Disorders, Neuromuscular, Neuroinfectious Disease

2. Neurodevelopmental Contributions to Pediatric Dysautonomia: Autism Associated Phenotypes in a Multidisciplinary POTS Clinic

Meeryo Choe, Alice Hoftman, Madison Harris

OBJECTIVE: Autistic youth appear overrepresented in clinical dysautonomia populations, but mechanisms and care implications are unclear. The objective of this study was to characterize autism spectrum disorder (ASD) within a large pediatric dysautonomia cohort, and to examine how these features relate to clinical presentation and healthcare utilization. We additionally sought to examine how these features intersected with sex and gender identity.

METHODS: We conducted a retrospective review of 515 patients evaluated in an academic-based Pediatric POTS Clinic from 2018–2025. Inclusion criteria were referral for dysautonomia evaluation. Variables included demographics, time to clinic, dysautonomia subtype, other comorbidities, and referrals to occupational therapy and dietician. Statistical analyses included chi-square and Fisher exact tests.

RESULTS: Autism was present in 19.4% (n=100), higher than general-population estimates. The cohort was 76.1 female, 13.4% male, 10.5% gender-diverse. Autism prevalence differed by gender identity: 44.4% among gender-diverse youth versus 16.5% among cisgender (OR 4.0, $p < 0.0001$). Autistic patients demonstrated significantly elevated rates of hypermobility/EDS and other rheumatologic conditions ($\chi^2=14.31$, $p=0.026$). Psychiatric comorbidities were common, including anxiety (45.2%) and depression (31.8%). Dysautonomia subtype did not differ meaningfully by neurodevelopmental status. Time to clinic averaged 30 months, suggesting delays in recognition of dysautonomia symptoms. Referral patterns were similar across groups, though gender-diverse youth trended toward higher dietician utilization.

CONCLUSIONS: Autism is markedly overrepresented in pediatric dysautonomia and is associated with multisystem comorbidity. Gender-identity patterns provide additional context for understanding neurodevelopmental risk and medical needs. Early screening, inclusive documentation, and multidisciplinary pathways are essential for autistic and gender-diverse youth with dysautonomia.

KEYWORDS: Autonomic Disorders, Neurodevelopmental Disorders

3. Diagnostic Criteria of Postural Tachycardia During Active Standing Test in Adolescents

Imad Jarjour, Sukru Aras, Laila Jarjour

OBJECTIVE: To establish heart rate increments (DHR) criteria for diagnosing postural tachycardia syndrome (POTS) in adolescents using active standing test (AST).

METHODS: 15 normal controls ages 13-19 (15.1 ± 2.1) years underwent AST with recording of HR and blood pressure (BP) after 5-minutes supine, and at 3, 5,7, and 10 minutes of standing. Postural DHR was assessed during AST in controls and compared with 32 patients ages 13-17 (15.5 ± 1.2) years who were diagnosed with POTS using head-up tilt (HUT) criteria and underwent both HUT and a 10-minutes AST at their initial evaluation for POTS. Receiver Operating Characteristics (ROC) was performed to determine ideal cutoff values for DHR that identify postural tachycardia.

RESULTS: The Area Under the ROC Curve (AUC) for DHR was 0.810 (P <0.001; 95% CI 0.667,0.954). The optimal DHR cutoff value to diagnose POTS using AST is at least 28 beats per minute (bpm), with a sensitivity of 84.4% and specificity of 73.3% (OR=14.85; 95% CI 3.35,65.89; P<0.001), with a positive likelihood ratio of 3.16 and a positive predictive value of 87.1%. DHR during AST was significantly higher in patients with POTS versus controls (mean $\pm$ SD, 35.4 ± 11.2 vs 23.1 ± 10.8, bpm, respectively, with 95% CI -19.3, -5.4, P<0.001).

CONCLUSIONS: DHR cutoff of 28 bpm during AST can identify postural tachycardia in 84.4% of adolescents with POTS. While AST is less sensitive than HUT in identifying tilt-based POTS, its wide availability makes it a valuable screening test in the clinical setting of adolescents with chronic orthostatic intolerance.

KEYWORDS: Autonomic Disorders, Practice Parameters, Neuromuscular

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4. Standardized Diagnosis and Management of Paroxysmal Sympathetic Hyperactivity

Laura Perez-Arnold, Afaf Ahmed, Maria Galardi, Taylor Hanson, Natasha Mehta, Alyssa Smith, Janette Coble

OBJECTIVE: Paroxysmal Sympathetic Hyperactivity (PSH) is an under-recognized condition. In 2023, a pediatric clinical practice guideline was proposed (Carozza et al. 2023). Our institution undertook a quality improvement (QI) project to educate neurology residents on how to apply these guidelines in clinical practice aiming to improve recognition of PSH in high-risk patients, to increase use of appropriate diagnostic coding, and to standardize management using targeted therapies.

METHODS: Intervention included resident education about PSH and the 2023 guideline via lectures and physical materials. Records were reviewed for patients aged 12 months - 18 years at risk for PSH, including those with traumatic brain injury (TBI), meningitis, or encephalitis. Patients with prior history of TBI, dystonia, or hypertension were excluded. Patient data were reviewed 6 months prior to and post intervention to determine whether the appropriate diagnosis code for PSH (ICD10 G90.8) was used. Use of medications recommended by the PSH guideline was also reviewed.

RESULTS: 83 patients at risk for PSH were identified in the 6 months prior to intervention with only 1 having the ICD10 G90.8 (1%) and 67 in the 6 months thereafter with only 4 having the ICD10 G90.8 (6%). Of these 5 patients, 4 were diagnosed with acute TBI and 1 with NMDA encephalitis. Utilization of all medications recommended in the PSH guideline (baclofen, clonidine, diazepam, gabapentin, propranolol) increased except for propranolol.

CONCLUSIONS: This QI initiative improved recognition of PSH and promoted standardized language and management through resident education and the use of structured tools.

KEYWORDS: Autonomic Disorders, Traumatic Brain Injury, Education

Behavioral Neurology

5. Affirmative Experiences and Resilience in Tourette Syndrome: A Qualitative Study of Key Stakeholders

Jaclyn Martindale, Leah Chapman, Kandice Reilly, Melina Malli, John Salsman, Christine Conelea, Eric Storch, Joyce Yi-Frazier, Stephanie Daniel

OBJECTIVE: Tourette syndrome (TS) is associated with significant psychosocial challenges, yet limited attention has been given to experiences that affirm individuals and support adaptation. This study explored how individuals with TS and those in their lives describe affirmative experiences, how they conceptualize resilience, and how they perceive these experiences have influenced cognitive, emotional, and behavioral adaptation over time.

METHODS: Using a phenomenological qualitative design, we conducted 35 in-depth, semi-structured interviews with youth and adults with TS, caregivers and partners, clinicians, and community advocates. Interviews explored lived experiences with TS, including resilience, support, and adaptation. Transcripts were analyzed using reflexive thematic analysis.

RESULTS: Participants described affirmative experiences as moments, relationships, or environments characterized by understanding, validation, and acceptance in the context of TS. Affirmation most often occurred within supportive relationships, peer and community connection, and affirming healthcare or educational environments. Participants had diverse and evolving definitions of resilience, commonly emphasizing perseverance and adaptability. Affirmative experiences were perceived to shape self-beliefs, including self-acceptance and confidence, and to influence behaviors such as coping strategies, disclosure decisions, advocacy, and participation in valued activities. Narratives highlighted heterogeneity and complexity, including ambivalence toward framing adversity itself as inherently growth-producing.

CONCLUSIONS: Individuals with TS and those in their lives described affirming experiences as closely intertwined with how they adapt and engage in daily life. These findings suggest that resilience in TS appears to be shaped by contextual and relational factors and suggest opportunities for patient-centered care and supportive interventions that intentionally foster affirming environments alongside symptom-focused treatment.

KEYWORDS: Behavioral Neurology, Movement Disorders

6. Safety and Cognitive Outcomes of Methylphenidate in Pediatric Epilepsy: A Systematic Review and Meta-Analysis

Shaun Nevil, Anton Charles, Chaitra C.S

OBJECTIVE: To assess the effects of methylphenidate on seizure control, adverse events, and cognitive performance in pediatric epilepsy through a systematic review and meta-analysis of randomized controlled trials.

METHODS: A systematic search of PubMed, Embase, Scopus, and Cochrane CENTRAL was conducted from all evidences available till date for RCTs assessing methylphenidate use in children (<18 years) with epilepsy. Two reviewers independently screened studies and extracted data. The primary outcome was seizure exacerbation. Secondary outcomes included attention and executive function scores. A random-effects meta-analysis was performed to estimate pooled risk ratios (RR) for seizure outcomes. Heterogeneity was assessed using the I^2 statistic.

RESULTS: Three RCTs comprising 186 participants met inclusion criteria. Methylphenidate was not associated with a significant increase in seizure risk compared to placebo or control (RR 1.08, 95% CI 0.72–1.62; $I^2 = 21\%$). Cognitive outcomes showed significant improvement in attention and executive function measures across trials, with moderate effect sizes. Adverse events were mild, most commonly decreased appetite and insomnia.

CONCLUSIONS: RCT evidence suggests that methylphenidate is safe and effective for cognitive enhancement in

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children with epilepsy, without significantly increasing seizure risk. However, limited sample size warrants larger trials to confirm long-term safety and efficacy.

KEYWORDS: Behavioral Neurology, Epilepsy, Experimental Therapeutics

7. Analyzing Child Neurologist's Diagnosis of Pediatric Vitamin C Deficiency in a Single Healthcare System: A Five-Year Retrospective Review

Marielena Villaran, Sheridan Langford, Chris Barton

OBJECTIVE: Vitamin C deficiency is increasingly recognized in children in developed healthcare settings, particularly among neurology patients with restrictive eating patterns and comorbid conditions. We sought to describe clinical characteristics of pediatric vitamin C deficiency across a single healthcare system identified by child neurologists and autism specialists over a 5-year period, including presenting symptoms, comorbidities, and setting of diagnosis.

METHODS: We performed a single-center retrospective chart review of children ages 0-18 years seen in a single pediatric healthcare system between June 30, 2020, and June 30, 2025, with a documented diagnosis of vitamin C deficiency (ICD-10 code E54). Cases were identified through Epic SlicerDicer and underwent manual chart review for confirmation. Demographic data, insurance status, comorbid conditions, diagnosing provider type, presenting symptoms, documented nutritional history, and vitamin C levels were extracted. IRB Exempt RO# 25-N0343 / IRB# 25.0825.

RESULTS: Epic query initially identified 114 children; after chart review, 101 confirmed cases were included. 26 were diagnosed by neurology or our autism clinic, managed by child neurology. Mean age at diagnosis was 8.8 years, with 85% male, and 50% public insurance vs private. 65% had autism or global delay, 42% had noted eating problems, and 23% with diagnosed ARFID or recognized eating disorder. 0 patients had bleeding gums, tooth loss, or hair loss, and only 1 patient had rash or bruising.

CONCLUSIONS: Pediatric vitamin C deficiency can be a common concern in child neurology and developmental patients and often do not present with typical symptoms. Low threshold for screening in this population is recommended.

KEYWORDS: Behavioral Neurology, Neurometabolic, Lifespan Manifestations of Childhood Onset Conditions

8. Electroencephalography features in ADHD to close the diagnostic gap: A systematic review

Gonca Bektas, Rasesh Joshi, Tobias Loddenkemper

OBJECTIVE: Attention-deficit hyperactivity disorder (ADHD) diagnosis relies on subjective clinical criteria. We systematically evaluate the diagnostic performance of electroencephalography (EEG) features for ADHD as a potential objective tool for ADHD diagnosis.

METHODS: We conducted a systematic review in accordance with PRISMA-DTA guidelines and registered the protocol in PROSPERO (CRD420251172000). PubMed, Embase, Web of Science, and PsycINFO were searched from January 1994 to November 2025. Eligible studies included patients diagnosed with ADHD based on the DSM-IV or DSM-5 criteria who had a resting-state EEG recording while off medication. We performed data extraction and risk-of-bias assessment using the QUADAS-2 tool.

RESULTS: Of 8,011 studies identified, 78 were included. Spectral power features were most frequently investigated (69%), followed by functional connectivity (27%), entropy-based measures (5%), microstates analysis (5%), and other non-linear/dynamical systems-based measures (5%). Classification analysis used classical statistical classifiers (15%), machine learning models (6%), and deep learning models (4%). Risk of bias was high or unclear across multiple domains in all studies, driven by the case–control design, lack of blinding, and incomplete reporting. Diagnostic accuracy ranged from 72.7% to 99.5%, with values exceeding 90% in studies that used convolutional neural networks. Reporting of performance metrics and validation strategies was inconsistent.

CONCLUSIONS: EEG features demonstrate variable diagnostic performance for ADHD. Although deep learning models show discriminative potential, the current literature provides insufficient evidence to support the use of any specific EEG feature in the diagnosis of ADHD.

KEYWORDS: Behavioral Neurology, Neurodevelopmental Disorders, Early Stage Investigator

9. Home-Administered Low-Level Laser Therapy for Pediatric Autism Spectrum Disorder: Design of A Randomized, Double-Blind, Placebo-Controlled Trial

Jahnavi Tatachar, Sarah Ward, Garrett Gianneschi

OBJECTIVE: To evaluate the efficacy of home-administered low-level laser therapy (LLLT) in reducing core symptoms of moderate to severe autism spectrum disorder (ASD) in children, building on prior evidence suggesting sustained neurobehavioral improvement following photobiomodulation.

METHODS: This study is a prospective, double-blind, randomized, placebo-controlled trial with crossover extension. Sixty-four children aged 5–16 years with DSM-5–confirmed ASD and baseline Childhood Autism Rating Scale-2 (CARS-2) scores of 30–45 will be enrolled and randomized 1:1 to active or sham device groups using concealed allocation. Caregivers will administer daily 5-minute treatments for 28 consecutive days, followed by a 4-week post-treatment observation period. The primary endpoint will be change in CARS-2 total score at 8 weeks post-baseline. Secondary outcomes will include Clinical Global Impressions–Improvement (CGI-I), Children's Sleep Habits Questionnaire (CSHQ), and caregiver satisfaction. A ≥4.5-point reduction in CARS-2 will define clinically meaningful response. Between-group differences in responder proportions will be analyzed using Fisher's exact test.

RESULTS: Enrollment is planned/ongoing, and primary outcome data is not yet available. We hypothesize that participants receiving active LLLT will be associated with a higher CARS2-ST responder rate, greater clinician-rated improvement, improved caregiver-reported sleep outcomes, adverse events and acceptable tolerability. Based on prior studies,

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these effects are expected to persist beyond the treatment period.

CONCLUSIONS: This trial is designed to evaluate a scalable, non-invasive, caregiver-administered noninvasive photobiomodulation intervention with hypothesized neuromodulatory effects. If effective, LLLT may represent a novel therapeutic modality with potential for durable clinical benefit in pediatric ASD.

KEYWORDS: Behavioral Neurology

10. Pediatric Acute-onset Neuropsychiatric Syndrome in Children With Autism Spectrum Disorder

Jenny Wilson, Brian Gomringer

OBJECTIVE: To evaluate how often children diagnosed with Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) at a single academic center carry a diagnosis of autism, compare symptom burden of PANS patients with and without autism spectrum disorder (ASD), and explore differences in treatment response between these groups.

METHODS: We conducted a retrospective review of patients ages 2–18 years diagnosed with PANS at Oregon Health & Science University pediatric neurology clinic between January 2015, and October 2025. A total of 60 patients were included in the study. Patients with alternative primary neurologic or psychiatric diagnoses explaining acute symptom onset were excluded. Independent variables were presence/absence of ASD. Dependent variables were number of symptoms, age of onset, time to diagnosis, and response to intravenous immunoglobulin (IVIG). Primary analyses were conducted using non-parametric testing with medians reported.

RESULTS: ASD was present in 26.7% of patients with PANS. Patients with ASD demonstrated a later median age of PANS symptom onset (10 vs 7 years, $p=0.013$) and greater symptom burden (3 vs 2, $p=0.005$) compared to those without ASD. Median time to diagnosis was longer in the ASD group (22.5 vs 12 months), though not statistically significant ($p=0.21$). Among patients receiving IVIG, ASD was associated with non-significantly higher likelihood of treatment response (OR 3.37, $p=0.11$).

CONCLUSIONS: In a review of PANS patients at a single institution, ASD was common and associated with later age of onset and greater number of symptoms. Physicians should consider PANS in children with autism and acute neuropsychiatric symptoms, as affected children may be severely impacted.

KEYWORDS: Behavioral Neurology, Neuroimmunology

11. Late Adolescent Regression in Autism Spectrum Disorder Following Bereavement: A Case Report

Shailja Sharma, Jasmin Kumar, Angela Herrera, Rooman Ahad, Steve Alcazar, Kavita Batra

OBJECTIVE: While regression in early childhood among individuals with Autism Spectrum Disorder (ASD) is well documented, similar decline in older adolescents is rarely reported. This case highlights a rare presentation of behavioral and functional regression in an older adolescent following a major life event.

METHODS: A single-patient case report was conducted following CARE guidelines. Evaluation included Magnetic Resonance Imaging (MRI), electroencephalography (EEG), and whole-exome sequencing. Medication management included mirtazapine and fluoxetine.

RESULTS: A 19-year-old female with a history of ASD, moderate intellectual disability, and adjustment disorder with mixed anxiety and depressive features, presented with severe loss of previously acquired skills following the death of her mother, her primary caregiver. Symptoms included social withdrawal, markedly reduced speech, refusal to bathe, reduced oral intake, marked disorganization, inappropriate affect, verbal aggression, and hallucinations. Neurological and genomic evaluations excluded structural or genetic causes. Despite pharmacological and psychological interventions, significant clinical improvement was not observed. The onset of symptoms closely following bereavement suggests a stress-related functional decline.

CONCLUSIONS: Regression in older adolescents with ASD following significant psychosocial stress is an underrecognized phenomenon that can mimic neurodegenerative decline, requiring targeted evaluation. Early identification of functional deterioration is essential to guide appropriate diagnostics and management. Increased awareness may facilitate timely, multidisciplinary care involving neurological, psychiatric and psychosocial modalities. Larger observational studies are needed to better characterize this presentation and clarify the association between major stressors and functional decline in adolescents with ASD.

KEYWORDS: Behavioral Neurology, Neurodevelopmental Disorders

12. Social Determinants and Psychiatric Hospitalization in Pediatric Autism

Shreya Tripathy

OBJECTIVE: To evaluate the association between social determinants of health (SDOH) and psychiatric hospitalization outcomes in pediatric patients with autism spectrum disorder (ASD).

METHODS: We analyzed pediatric hospitalizations with ASD using National Inpatient Sample (n=48,582). Psychiatric hospitalization was defined by a primary psychiatric diagnosis. Multivariable logistic regression assessed associations between SDOH surrogates and psychiatric hospitalization, adjusting for age, sex, illness severity, and clinical comorbidities. Secondary outcomes included suicidal ideation/self-harm, length of stay (LOS), and total hospital charges.

RESULTS: Compared to White patients, Black patients (OR 0.62, $p<0.001$) and Hispanic patients (OR 0.76, $p=0.014$) had lower odds of psychiatric admission. Large metropolitan areas demonstrated higher odds than non-urban settings (OR 1.31, $p<0.001$). Older age and clinical complexity were also associated with increased odds ($p<0.001$). Suicidal ideation/self-harm showed similar disparities, with lower odds of hospitalization among Black (OR 0.64, $p<0.001$)

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and Hispanic patients (OR 0.71, p=0.020) compared to White patients, and higher odds in the highest income quartile (OR 1.13, p=0.032) compared to the lowest quartile.
CONCLUSIONS: Socioeconomic and racial disparities in psychiatric hospitalization persist among pediatric ASD patients, independent of clinical severity. Lower rates of hospitalization in disadvantaged populations may reflect differences in access or recognition rather than true disease burden, underscoring the need for equitable mental health care and early intervention.
KEYWORDS: Behavioral Neurology, Diversity, Equity, Inclusion, Neurodevelopmental Disorders

13. The Genetic Landscape of Catatonia in Autism Spectrum Disorder and Other Neurodevelopmental Disorders

Shreya Tripathy, Ayush Tripathy

OBJECTIVE: Catatonia is reported in 4–17% of individuals with autism spectrum disorder (ASD) and at higher rates in neurodevelopmental disorders (NDDs); however, its molecular underpinnings remain poorly characterized. We evaluated current literature to define genetic architecture of catatonia in ASD and NDDs.
METHODS: We conducted a systematic literature review of studies reporting genetic analyses of catatonia in NDDs. Data were extracted on gene-level findings, chromosomal abnormalities, and associated clinical phenotypes.
RESULTS: Across 35 publications, catatonia in ASD/NDDs converged on three major classes of genetic alterations. First, monogenic synaptopathies—most prominently SHANK3 haploinsufficiency at 22q13.33 (Phelan–McDermid syndrome), in which catatonia is reported in up to 53% of affected individuals with a female predominance, and FMR1—implicate excitatory postsynaptic density scaffolding and glutamatergic signaling. Both 22q13 deletions and SHANK3 point mutations produce this phenotype, suggesting that SHANK3 haploinsufficiency alone is sufficient. Second, ion channelopathies define distinct catatonic subtypes: pathogenic variants in SCN2A and CACNA1A have been associated with ASD-related catatonia and may reflect divergent pathophysiologic mechanisms. Third, chromosomal disorders carry the highest catatonia burden, including Down syndrome (where catatonia is a core feature of Down syndrome regression disorder), 22q11.2 deletion syndrome, and Prader–Willi syndrome (15q11–q13), with evidence suggesting convergence on neuroimmune dysregulation. Notably, no genome-wide association studies or large-scale exome sequencing studies of NDD-associated catatonia have been reported; current evidence remains predominantly case-based.
CONCLUSIONS: Catatonia in ASD/NDDs is genetically heterogeneous but functionally convergent on synaptic imbalance, ion channel dysfunction, and neuroimmune pathways. Systematic genomic studies in well-characterized cohorts are needed to clarify pathogenic mechanisms and refine genotype–phenotype relationships.
KEYWORDS: Behavioral Neurology, Neurogenetics, Neurodevelopmental Disorders

Cerebral Palsy

14. The Effect of Maternal Diabetes, Obesity, and Preeclampsia on the Incidence of Cerebral Palsy (CP) in Offspring: Review of the Literature

Anshvir Bhangoo, Sophie Lou, Rozen Naama, Ram Mishaal

OBJECTIVE: This work aims to summarize the evidence found on the influence of maternal diabetes, obesity and preeclampsia on the incidence of Cerebral Palsy (CP) in offspring.
METHODS: A literature search was conducted using PubMed, Ovid Medline, and Ovid Embase, including primary research studies, systematic reviews, and meta-analyses. Articles examining maternal obesity, preeclampsia, or diabetes and their associations with CP were included. Two reviewers independently extracted and analyzed data.
RESULTS: Maternal obesity increased CP risk in a dose-dependent manner, with Class III obesity associated with 2.0-2.7 higher risk, mediated by systemic inflammation, placental dysfunction, fetal hypoxia, macrosomia, and labour complications. Preeclampsia did not independently increase risk for CP, but did indirectly increase CP risk by contributing to preterm birth. Maternal diabetes increased CP risk overall (HR 1.84, 95% CI 1.59-2.14), with type 1 diabetes specifically associated with a 2.1-fold increased risk via preeclampsia, preterm delivery and neonatal hypoglycemia. Evidence for gestational diabetes was mixed but recent large-scale epidemiological studies suggest it may independently increase neurodevelopmental risk, including CP. Type 2 diabetes mellitus (T2DM) remained under-studied despite its global prevalence.
CONCLUSIONS: Maternal obesity, preeclampsia, and diabetes increase CP risk in the offspring through both direct (placental and metabolic effects) and indirect (preterm birth and macrosomia) pathways. Early identification and management of maternal risk factors may reduce CP incidence and promote early diagnosis and intervention for children with CP. Future research should focus on mechanistic pathways, maternal T2DM as an independent risk factor, and potential implementation of standardized screening for infants with maternal risk factors.
KEYWORDS: Cerebral Palsy

15. Unexpected Scurvy Diagnosis in Child with Cerebral Palsy and G-tube Dependence

Sarah Fine, Casaundra Gutowski, Dayna Feller, Florence Sun, Eva Kurtz-Nelson, Matthew Miller

OBJECTIVE: While scurvy (vitamin C deficiency) has been regarded as a historical disease with rare occurrence in high income countries, recent studies suggest a resurgence in the United States. Numerous studies implicate marked selective oral intake as the causative factor, often in the setting of neurodevelopmental disorders. However, gastrostomy tube (G-tube) dependent pediatric patients who receive complete nutrition under the guidance of a registered dietician should be at minimal risk for vitamin deficiencies. As such, scurvy

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and other vitamin deficiencies may not be initially suspected when these patients present with complications.
METHODS: A 7-year-old female with cerebral palsy, VACTERL syndrome, and G-tube dependence on a home blended formula presented with persistent lower extremity pain over 2 months, with presumed diagnosis of viral related transient synovitis following 2 prior Emergency Department evaluations.
RESULTS: Hip and pelvis MRI showed diffuse metaphyseal marrow signal abnormality with distal femoral subperiosteal fluid collections. These findings prompted us to assess vitamin C level, which was undetectable. Supplemental enteral vitamin C resulted in full recovery.
CONCLUSIONS: This patient had been receiving a home blended diet guided by our medical nutrition team, which should have accounted for over 3 times the dietary vitamin C needs for a 7-year-old. Possible causes for the deficiency include vitamin C instability at certain stored temperatures or its more rapid breakdown through various preparation methods. This case highlights the importance of including scurvy in the differential diagnosis for patients with lower extremity pain and identifies a need for standardized screening of G-tube dependent patients receiving home blends.
KEYWORDS: Cerebral Palsy, Neurodevelopmental Disorders, Education

16. Novel presentation of a FOXP1-related disorder including craniosynostosis and cerebral palsy

Kelly Pring, Benjamin Ramsey, Elaine Conrad, Michelle Curtin, Neelam Makhijani

OBJECTIVE: FOXP1-related neurodevelopmental disorder is known to cause dysmorphic facial features, strabismus, ataxia, and global developmental delay. We share a novel presentation including craniosynostosis with autosomal dominant (AD), de novo heterozygous pathogenic variant in FOXP1 (c.1541 G>A (p.Arg514His)) discovered as part of a cerebral palsy (CP) workup.
METHODS: Chart and literature review were performed.
RESULTS: Patient was delivered via C-section for non-reassuring fetal heart tracing and found to have metopic ridge. Rapid microarray showed 12q21 deletion, unknown significance. Computed tomography showed findings of metopic craniosynostosis, treated with metopic suturectomy at age 2 months. He was noted to have fine motor delays by age 4 months and gross motor delays and strabismus by age 6 months. Pediatric Neurology consult occurred at 11 months old for abnormal movements, hypotonia, contractures, and delays. Presentation was consistent with clinical CP due to a low Hammersmith Infant Neurological Exam (HINE) score (56/78 at age 12 months). MRI brain showed no structural abnormality, gliosis, or leukomalacia, but was notable for ex-vacuo dilation of third and lateral ventricles. MRI spine showed incidental fatty filum terminale, otherwise normal. Exome sequencing was diagnostic in revealing AD, heterozygous pathogenic variant in FOXP1. FOXP1 phenotype was consistent with the patient's presentation of hypotonia, global developmental delay and strabismus, but craniosynostosis had not previously been described.
CONCLUSIONS: This report offers potential expansion of the phenotype of FOXP1-related neurodevelopmental disorder with craniosynostosis. This case also illustrates the utility of expanded genetic testing via exome sequencing in the workup of suspected CP.
KEYWORDS: Cerebral Palsy, Neurogenetics

17. Variations in Clinical Features of Cerebral Palsy in Rural vs. Urban Canada

Victoria D'Amours, Margaret Efraim, Nafisa Husein, Michael Shevell

OBJECTIVE: The literature suggests that variability in cerebral palsy phenotype (CP) in part stems from socioeconomic inequalities, notably in terms of access to care. However, the role of geographical location in national CP presentation has been relatively understudied. This study aims to describe and compare the clinical presentation, severity, and etiologic profile of children with CP born in rural versus urban regions of Canada.
METHODS: Data from 1,875 children with CP from the Canadian Cerebral Palsy Registry were analyzed based on residential address (postal code) at birth (rural vs. urban) assigned by Statistics Canada. Pearson Chi-Square analyses were conducted to examine differences in CP subtypes, prenatal risk factors, MRI lesions, symptom severity and associated comorbidities, and parental education levels.
RESULTS: Children living in rural settings showed more severe forms of CP with increased severity of gross motor impairment (GMFCS, $p<0.01$), and more frequent comorbidities, including cortical blindness, feeding tube dependence, and non-verbal communication impairment ($p<0.05$). No significant differences were found regarding prenatal risk factors or MRI findings. A higher proportion of parents in urban areas held degrees beyond high school ($p<0.01$).
CONCLUSIONS: Children with CP residing in rural areas present with more severe features in terms of gross motor impairments and associated comorbidities. Nonetheless, prenatal risk factors and etiology of CP did not differ between groups. Therefore, the phenotypic variability likely stems from social factors, reinforcing the importance of considering social determinants of health, including geography, in current practices and public health policy.
KEYWORDS: Cerebral Palsy

18. Prognostic Utility of Electroencephalography and General Movement Assessment for Cerebral Palsy in Neonates with Hypoxic-Ischemic Encephalopathy

Jody Tao, Allie Cui, Cristina Go, Ram Mishaal, Nandy Fajardo, Mor Cohen Eilig

OBJECTIVE: Early prediction of cerebral palsy (CP) in infants with hypoxic-ischemic encephalopathy (HIE) is critical for timely intervention; however, the role of neonatal electroencephalography (EEG) in predicting CP remains poorly defined. We aimed to characterize the prognostic utility of EEG for CP and its association with outcomes on motor assessments, including the General Movement Assessment

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(GMA) and Hammersmith Infant Neurological Examination (HINE).

METHODS: Chart review was conducted for 20 infants born ≥35 weeks' gestation between January 2022 and August 2024. All infants were diagnosed with HIE and assessed at the CP Diagnosis Clinic at BC Children's Hospital. Demographic data and EEG features were extracted. Logistic regression was used to examine associations between EEG findings and GMA/HINE/CP results.

RESULTS: Absent/abnormal GMA fidgety movements (OR=11.25,p=0.0345) and diffuse background suppression (OR=16,p=0.0296) were associated with increased odds of CP. Diffuse background suppression was linked to rhythmic sharp/spike activity (OR=9.33,p=0.0333) and excessive background discontinuity (OR=13.5,p=0.0352). In turn, excessive background discontinuity was associated with excessive positive (OR=33,p=0.008) and negative (OR=30,p=0.011) sharp waves. Infants with CP had HINE scores averaging 22 points lower than those without CP (p=0.0076). Increased HIE severity showed a trend toward more abnormal GMA findings but was not significantly associated with CP.

CONCLUSIONS: GMA and HINE remain robust tools for early identification of CP, whereas EEG alone may have limited predictive value for CP diagnosis. However, background EEG abnormalities are associated with other epileptiform features and may provide complementary information. HIE severity classification was not a reliable predictor of CP, supporting the need for multimodal assessment strategies.

KEYWORDS: Cerebral Palsy, Neonatal Neurology

19. Clinical Trial in Progress: Galassia, CP-201, a Phase 2, Randomized, Double-Blind, Vehicle-Controlled Study of Intranasal Cenegermin in Pediatric Spastic Cerebral Palsy

Domenico Romeo, Andrea Guzzetta, Jessica Galli, Antonio Trabacca, Susanna Staccioli, Luigi Piccinini, Silvia Faccioli, Elena Carraro, Elisa De Grandis, Antoine Lampron, Kristi Aleksi, Elizabeth Gavioli

OBJECTIVE: Cerebral palsy (CP) is the most common cause of motor disability in children, with spastic CP accounting for majority of cases and lifelong impairment. There are currently no disease-modifying therapies. Nerve growth factor (NGF) may support neuroprotection, neuroplasticity, and modulation of neuroinflammation in CP. Intranasal administration of cenegermin (recombinant human NGF) offers a non-invasive central nervous system delivery by targeting olfactory neurons and NGF-TrkA signaling. Previous clinical case reports in pediatric brain injuries describe neurodevelopmental functional improvements with favorable tolerability. This study will evaluate the safety and tolerability of intranasal cenegermin in children with spastic CP.

METHODS: This ongoing phase 2, randomized, double-blinded, vehicle-controlled, crossover study (EU-CTR 2025-522786-29-00) will evaluate intranasal cenegermin in approximately 60 children (2-6 years old) with spastic CP, GMFCS-E&R Levels I-V, and Modified Ashworth Scale ≥ 2. This is a 2-part study; participants will be randomized 1:1 to receive cenegermin or vehicle followed by crossover to the alternate treatment. Each part includes four 28-day treatment cycles followed by 36 weeks of follow-up, for an approximate duration of 52 weeks. The primary endpoint is the incidence of treatment-emergent adverse events through week 52. Secondary endpoints include safety, motor and neurodevelopment function, clinician- and caregiver-reported outcomes, pharmacokinetics, and immunogenicity through week 104.

RESULTS: The study is ongoing at 12 sites in Italy. The primary analysis is planned for week 52 with a final analysis at week 104.

CONCLUSIONS: This Phase 2 study will evaluate cenegermin in children with CP.

KEYWORDS: Cerebral Palsy

Diversity, Equity, Inclusion

20. Equity of Access to Whole Exome Sequencing in Pediatric Epilepsy Patients: A Mixed Methods Study

Alysha Lee, Shelin Adam, Cyrus Boelman, Michelle Demos

OBJECTIVE: Whole Exome Sequencing (WES) can provide a diagnosis in approximately 30% of patients, enabling targeted treatment and minimizing unnecessary investigations. Genetic epilepsies are thought to be equally distributed across the population; however, data is limited. Anecdotal observations at our center and others raise questions about whether diverse ethnic and socioeconomic backgrounds affect access to WES. This study aimed to determine whether there is equity of access to WES and to identify what factors affect access.

METHODS: An explanatory sequential mixed methods design was implemented at our children's hospital. Quantitative: retrospective chart review of 352 pediatric epilepsy patients who received WES in 2021-2023. Variables collected included ethnicity, language, and socioeconomic status (SES) from postal codes. Qualitative: semi-structured interviews with 9 rural families, utilizing reflexive thematic analysis to identify barriers and facilitators.

RESULTS: Compared with the BC population, our cohort had a greater proportion of patients with the highest SES (27% vs 20%), more English speakers (92% vs 79%), more Visible Minorities (43% vs 34%), and a similar rural distribution (15% vs 14%). Qualitative analysis from the interviews identified five themes: easy decision-making, factors affecting testing process, preference for tertiary hospitals, systemic rural challenges, and supports for challenges.

CONCLUSIONS: Findings suggest non-English speakers and those of lower SES may face barriers participating in WES. Factors that facilitate testing may include English speaking, comfort with the medical system, social supports, and rapport with doctors. Further study of families facing barriers may improve equitable uptake of genomic testing in neurology and across specialties.

KEYWORDS: Diversity, Equity, Inclusion, Epilepsy, Neurogenetics

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21. Assessing Neurology Clinicians' Comfort with Screening for Social Determinants of Health: A Focus on Energy Insecurity as an Equity Issue

Samuel Belfer, Rudmila Rashid, Sonika Agarwal

OBJECTIVE: Social determinants of health (SDOH) significantly influence clinical outcomes and health care utilization. Energy insecurity—defined as limited or unreliable access to essential utilities such as electricity, gas, and water—is an under-recognized SDOH that disproportionately affects medically complex and low-income populations. Patients with neurologic conditions may be uniquely vulnerable due to reliance on electricity-dependent medical equipment, medication refrigeration, and high care coordination needs. However, how neurology clinicians assess and address energy insecurity in clinical practice remains unclear. We evaluated clinician comfort, practices, and perceived barriers to SDOH screening, with a focus on energy insecurity.

METHODS: We conducted a prospective, descriptive survey study of 97 neurology clinicians at the Children's Hospital of Philadelphia. An anonymous REDCap-based survey assessed clinician-reported comfort with SDOH screening, current screening practices, perceived clinical relevance of energy insecurity, awareness of available resources, and barriers to implementation. Responses were summarized using descriptive statistics, with exploratory comparisons across clinician roles and practice settings.

RESULTS: Clinician comfort and screening practices for SDOH and energy insecurity varied substantially. Fewer than 50% of respondents were able to identify available protections against utility shutoffs or recognize commonly prescribed neurologic medications requiring refrigeration.

CONCLUSIONS: Energy insecurity is a modifiable health-related social need with direct relevance to neurologic care but remains infrequently assessed. Improved clinician awareness and integration of screening into routine care may represent actionable strategies to reduce disparities and improve outcomes in vulnerable neurologic populations.

KEYWORDS: Diversity, Equity, Inclusion, Education, Lifespan Manifestations of Childhood Onset Conditions

22. BrainIACS: A Community-Based Health Literacy Approach to Pediatric Epilepsy

Laxhmi Ramjit, Sravani Ravipati, Taylor Smith, Sarah Delima

OBJECTIVE: Caregivers of children with epilepsy face significant barriers to health literacy, including language access, cultural relevance, and limited community-based education. BrainIACS is a physician- and medical student-led initiative that developed original, simplified, and culturally adapted educational materials using evidence-based resources to bridge this gap. This study evaluates the clarity, accessibility, cultural appropriateness, and perceived usefulness of these multilingual materials delivered in community settings, with findings informing future programming.

METHODS: BrainIACS delivers language-concordant, culturally responsive epilepsy education to English-, Spanish-, and Haitian Creole-speaking caregivers in community settings. Multimodal strategies include low-text pictorial materials and QR-linked multilingual videos. Core content covers seizure recognition and first aid, anti-seizure medication use and side effects, and emergency care criteria. Education is delivered via plain language, interpreter integration, and interactive small-group learning. Sessions last 45-90 minutes and are offered periodically at community sites. Anonymous pre- and post-session surveys assess caregiver knowledge, confidence, and understanding of emergency care thresholds.

RESULTS: Fifteen caregivers attended the inaugural session; 3 completed matched pre- and post-session surveys. Preliminary data demonstrate improved knowledge and self-reported confidence in seizure response, medication use, and emergency care criteria. Additional sessions are ongoing with continued data collection.

CONCLUSIONS: This low-cost, scalable, and replicable intervention addresses pediatric epilepsy disparities by improving caregiver knowledge, removing language barriers, and ensuring cultural appropriateness- equipping families to manage seizures safely at home. Its innovative community-based model holds strong potential for broad dissemination, with meaningful impact on health literacy, caregiver-driven outcomes, and preventable emergency care utilization.

KEYWORDS: Diversity, Equity, Inclusion, Epilepsy, Early Stage Investigator

23. Impact of an Inclusive Public Transit Training Program on Self-Efficacy and Transit Use in Adolescents with Neurodevelopmental Disorders

Suhantee Sathananthan, Claire Croteau, Isabelle Gélinas, Diane Morin, Philippe. Archambault, Alexandra Tessier, Julie McIntyre, Mathilde LeBouedec

OBJECTIVE: To evaluate the effectiveness of an inclusive public transit training program for adolescents with neurodevelopmental disorders (NDD) by assessing changes in public transit use and self-efficacy.

METHODS: A longitudinal study was conducted with 65 adolescents with NDD (aged 12–18) participating in an inclusive mobility training program delivered in high schools in the Greater Montréal area, Canada. Self-efficacy and frequency of public transit use were measured at baseline (T0, pre-training), immediately post-training (T1), one month post-training (T2), and three-month follow-up (T3). Quantitative data were analyzed descriptively and longitudinally.

RESULTS: The proportion of adolescents not using public transit decreased from 52% at baseline (T0) to 13% at three-month follow-up (T3), while those using transit at least five times per week increased from 19% to 47%. Improvements were evident immediately post-training (T1) and sustained at one-month (T2) and three-month (T3) follow-ups. Self-efficacy improved, with the proportion reporting feeling completely capable of planning their trip independently increasing from 40% at baseline to 63% at three months.

CONCLUSIONS: Inclusive public transit training may substantially improve transit use and self-efficacy among adolescents with neurodevelopmental disorders. These findings highlight the potential of school-based interventions to support independent mobility and enhance community participation.

KEYWORDS: Diversity, Equity, Inclusion, Neurodevelopmental Disorders, Education

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24. Reducing Barriers to Participation in Pediatric Neurodevelopmental Research: Application of the Framework-Guided Recruitment Strategies

Emma Cardwell, Siri Dommata, Stephanie Peck, Senyene Hunter

OBJECTIVE: Social determinants of health (SDOH, e.g., rurality, socioeconomic status, language, race, ethnicity) influence health disparities in children with neurodevelopmental disorders. To reduce disparities and improve generalizability, studies are prioritizing inclusive enrollment. We applied new and existing recruitment strategies to address SDOH.

METHODS: Equity-informed recruitment strategies, adapted from traditional practices and guided by the NIMHD Research Framework, were implemented to address SDOH-related barriers. Patients with childhood-onset (≤18 years) neurodevelopmental disorders were enrolled in a prospective cross-sectional study to identify and phenotype genetic disorders. Participants were referred by neurologists and recruited in collaboration with the Malan Syndrome Foundation. To prioritize inclusion, referring providers were encouraged to identify barriers to participation. Demographic data was obtained from study participants or medical records.

RESULTS: Of the 243 enrolled, 144 (59%) were male; median age at enrollment was 9 years. 84% had at least one SDOH factor associated with health disparities. 12% preferred a language other than English: Spanish (8%), Arabic (1%), Telugu (1%), as well as Dari, Hindi, Russian, Hungarian, Italian, and French (0.5% each). Participants identified as White (61%), African American (20%), American Indian/Alaska Native (4%), Asian (3%), Other race (17%), and Hispanic/Latino (15%). 23% of U.S. participants resided in small towns/rural areas. International participants resided in Australia, New Zealand, Canada, England, and Scotland. Of the 195 with data provided, 53% were from tier 1 or 2 designated counties (i.e., economic distress), and 59% had public or no insurance.

CONCLUSIONS: Structured, equity-informed recruitment strategies addressing SDOH-related barriers can improve inclusivity in neurodevelopmental research.

KEYWORDS: Diversity, Equity, Inclusion, Neurodevelopmental Disorders, Neurogenetics

25. Racial, Ethnic, and Socioeconomic Disparities in ASD Diagnosis Among Children: A Systematic Review of the Diagnostic Care Pathway, 2000–2025

Nikhila Archakam, Akhila Archakam, Wesley Kim, Harshal Parmar, Iram Fatima, Rahul Mittal

OBJECTIVE: Black and Hispanic/Latino children experience persistent delays in autism spectrum disorder (ASD) diagnosis compared to non-Hispanic White peers. No systematic review has comprehensively examined this disparity across the full diagnostic care pathway since 2020.

METHODS: A systematic review was conducted in accordance with PRISMA guidelines across PubMed, Embase, Cochrane, and Web of Science (2000–April 2025). Of 730 identified records, 23 duplicates were removed and 707 screened, yielding 91 included studies. Study quality was assessed using RoB 2 for randomized controlled trials and ROBINS-I for observational studies, independently by two reviewers with consensus-based resolution of disagreements. Data were synthesized qualitatively given heterogeneity in outcome reporting. This review was not prospectively registered.

RESULTS: Among 91 included studies comprising cohort, cross-sectional, and surveillance designs, later ASD diagnosis among Black and Hispanic/Latino children was consistently reported compared to non-Hispanic White peers. Treatment delays approached 3 years, with Black children showing up to 2.5-fold lower likelihood of timely screening and referral. Low income, Medicaid enrollment, and limited English proficiency compounded racial disparities. These disparities followed a sequential diagnostic cascade, with progressive attrition occurring at screening, referral, and specialist evaluation stages, suggesting a cumulative rather than single-point model of diagnostic delay. Racial disparities persisted after accounting for socioeconomic status, implicating structural and clinical factors independent of income.

CONCLUSIONS: Single-stage interventions are unlikely to eliminate ASD diagnostic disparities. Findings highlight multilevel targets across clinical practice, insurance policy, and community outreach, suggesting culturally adapted screening tools and structured referral protocols at pediatric neurology intake as critical levers for equitable early intervention.

KEYWORDS: Diversity, Equity, Inclusion, Neurodevelopmental Disorders, Early Stage Investigator

26. Joseph H. French: The First Black Board-Certified Child Neurologist

Alison Christy, Gazala Hitawala

OBJECTIVE: To reflect on the legacy and advocacy work of Joseph H. French (1928-1999) and his wife, Marilyn Doss French (1929-1987), while highlighting diversity present in the early years of the Child Neurology Society.

METHODS: We reviewed the personal and family papers in the Joseph Henry French and Marilyn Doss French collection in the Chesney Archives at Johns Hopkins, as well as other historical records.

RESULTS: Isabelle Rapin's obituary of French published in Neurology notes that he was a founding member of the Child Neurology Society, where he also served as Councillor from 1977–1979. He was board-certified in Neurology in 1965, and with special qualifications in Child Neurology in 1969. He is one of the first Black neurologists to complete a neurology residency and - as the American Board of Psychiatry and Neurology created the qualifications for Child Neurology in 1968 - almost certainly the first Black board-certified pediatric neurologist. Beyond his work in neurology, French marched to Selma with Dr. Martin Luther King and actively worked for social justice and civil rights within his community. The activism of French and his wife is extensively documented in the collection held at Johns Hopkins.

CONCLUSIONS: French's life demonstrates how neurologists - even those from vulnerable populations - can combine activism, politics, and passionate community work with excellent patient care.

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KEYWORDS: Diversity, Equity, Inclusion, Ethics, Global Neurology

27. Center-Reported Barriers to Applied Behavior Analysis Access for Children with Autism Spectrum Disorder Across New Jersey: A Survey of Providers

Olivia Pavin, Samantha Maguire, Garrett Gianneschi

OBJECTIVE: Applied Behavior Analysis (ABA) is an evidence-based therapy commonly used to treat patients diagnosed with autism spectrum disorder (ASD). However, access can be limited. The objective of this study is to identify center-reported barriers to ABA treatment for ASD in NJ.

METHODS: We conducted a preliminary phone survey of 11 NJ ABA providers. AI-assist search strategy generated a preliminary statewide list of NJ ABA providers, followed by manual review for eligibility. The 21 open-ended survey questions included length/frequency of treatment, size of center, format of sessions, and barriers to initiation and access. Responses were summarized descriptively and data collection is ongoing.

RESULTS: Of the 11 centers contacted, providers from 6 centers completed our survey (54.5%). All 6 centers required a formal ASD diagnosis before initiating insurance-based ABA services. 3 of 6 centers accepted Medicaid/NJ Family Care Plans. 5 of 6 centers identified insurance coverage changes and loss of insurance as common reasons for early cessation of treatment. All centers provided services in English. 5 of 6 provided variable Spanish services. No centers reported Portuguese or Haitian Creole services. 1 of 6 centers provided virtual services primarily for parent training or when clinically appropriate. Additional reported barriers included scheduling, transportation and staffing limitations.

CONCLUSIONS: This preliminary center-reported survey identified significant barriers to treatment with ABA for ASD in New Jersey. Reported barriers include diagnostic prerequisites, insurance-related barriers, limited language services and lack of virtual services. These barriers can lead to disparities in healthcare equity in various patient populations and demographics.

KEYWORDS: Diversity, Equity, Inclusion, Ethics, Behavioral Neurology

Early Stage Investigator

28. BRIDGING GAPS IN CHILD NEUROLOGY: LESSONS FROM AFRICAN CLINICAL PRACTICE

Mabel Owusu Afriyie

OBJECTIVE: Child neurological disorders contribute significantly to morbidity and long-term disability in low- and middle-income countries. However, limited diagnostic resources, shortages of trained specialists, and delayed recognition of neurological symptoms continue to hinder effective care in many African settings. This study aims to examine key clinical challenges encountered in child neurology within African healthcare environments and to highlight practical lessons that can improve early identification, diagnosis, and management of pediatric neurological conditions.

METHODS: A qualitative observational approach was employed, drawing on clinical experiences and routine pediatric neurological assessments within resource-limited healthcare settings. Observations focused on common presentations of neurological conditions among children, patterns of delayed diagnosis, caregiver health-seeking behavior, and systemic barriers to care. Insights were compared with existing literature on pediatric neurology in developing countries to identify recurring clinical and structural gaps affecting early detection and treatment outcomes.

RESULTS: Findings indicate that many children present with neurological conditions such as epilepsy, developmental delay, cerebral palsy, and neurodevelopmental disorders at advanced stages due to delayed recognition and referral. Contributing factors include limited public awareness, cultural interpretations of neurological symptoms, scarcity of specialized diagnostic tools, and insufficient access to trained pediatric neurologists. Despite these challenges, community-based observation, strengthened clinical suspicion among frontline healthcare providers, and caregiver education significantly improved early identification and referral patterns in several observed cases.

CONCLUSIONS: Addressing gaps in child neurology across African healthcare systems requires strengthening frontline clinical training, promoting community awareness, and integrating neurological screening into routine pediatric care to improve early detection and long-term outcomes.

KEYWORDS: Early Stage Investigator, Behavioral Neurology, Education

29. NIH and NINDS: Funding Updates and Opportunities to Advance Neuroscience

Adam Hartman, Nicole Farhat, Rebecca Hommer, Alva Recinos, Kristina Hardy

OBJECTIVE: The US National Institute of Neurological Disorders and Stroke (NINDS) and National Institutes of Health (NIH) recently released new initiatives and data on their budgets and funding success rates for investigators at different career stages.

METHODS: Data were identified from NIH public-facing databases and NINDS Council presentations.

RESULTS: The extramural budget represents most NINDS expenditures; only a small amount supports the intramural program. The annual financial support requested for NINDS Parent R01s has increased by 36% in the last six years. Grant applications were discussed across NIH study sections (review) at similar rates from 2021-2025 for early stage (ESI), established, new non-ESI, and "at risk" investigators. Grant application success decreased for each of these investigator categories over the same period. However, success rates for ESI and established investigators were similar to each other. New initiatives at NIH include website modernization, central consolidation of grant application review, simplified review criteria, introduction of Highlighted Topics, simplification of Data Management and Sharing plans, discontinuation of requests for letters of intent and approval of >$500K

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applications prior to grant application submission, revision of the foreign subaward process, emphasis of scientific rigor, and increased use of human biology-based new approach methodologies (NAMs) to complement animal models.
CONCLUSIONS: NIH policies and processes continue to be updated. The information provided here should be of use to all NIH applicants and grantees, regardless of career stage.
KEYWORDS: Early Stage Investigator, Education

30. Novel Therapy for Alternating Hemiplegia of Childhood: Four Lead Deep Brain Stimulation

Mohamad Mikati, Ashley Lin, Gerald Grant, Steve Harward, Shruti Agashe, Joan Jasien, April Boggs

OBJECTIVE: Determine if Deep-Brain-Stimulation (DBS) ameliorates drug-resistant/disabling Alternating Hemiplegia of Childhood (AHC) paroxysmal dystonias, hemiplegias and epileptic seizures given that DBS has never been used in AHC and that DBS has failed in other *ATP1A3*-related-dystonias.
METHODS: Clinical and mutation criteria to confirm AHC diagnosis. Four-electrode-DBS insertion at these tip locations (mm) relative to anterior-posterior commissural (AC-PC) line: L/R=lateral from midline, A=anterior to mid-commissural point, S/I=superior or inferior to AC-PC plane: Left ANT–L 3.8, A 3.2, S 6.3; Right ANT-R 2.3, A 3.4, S 7.8; Left GPi–L 19.8, A 2.0, S 3.8; Right GPi–R 20.6, A 3.8, S 3.4. To optimize response, GPi electrodes were repositioned three months after initial insertions: Left GPi–L 19.6, A 1.8, I 2.5; Right GPi–R 19.5, A 2.0, I 3.5.
RESULTS: This girl with *ATP1A3*-D801N mutation had, since infancy, severe episodes of dystonias, hemiplegias, focal-impaired-awareness and generalized-tonic-clonic seizures (FCs, GTCs) all refractory to medications. At age 15-years when having (during 1-year baseline) 2-10 painful dystonias/day, >5 hemiplegias/day, 15 FCs/month and 5 GTCs/month she underwent four-electrode-DBS. Final settings: L-ANT: 1.5 mA, 90 μs, 60Hz; L-GPi: 2.0 mA, 50 μs, 139 Hz; R-ANT: 1.5 mA, 90 μs, 60Hz; R-GPi: 1.5 mA, 50 μs, 139 Hz, continuous stimulation. Spells steadily decreased between 0-6 months. During 6-12 months after initial insertion frequencies were: dystonias 0/day with rare ones during sporadic intercurrent infections, hemiplegias 0-1/day, FCs 12-16 /month, GTCs 0/month resulting in major improvement in quality-of-life.
CONCLUSIONS: The above supports considering/investigating DBS in refractory AHC-related paroxysmal dystonias/hemiplegias and seizures.
KEYWORDS: Early Stage Investigator, Movement Disorders, Epilepsy

31. International clinical guideline for diagnosis and management of Wolfram syndrome - a modified Delphi study.

Saumel Ahmadi, Josephine Elliott, Patrick Yu Wai Man, Sarah Gladstone, Stephanie Gebel, Tracy Lynch, Timothy Barrett, Fumihiko Urano

OBJECTIVE: Wolfram syndrome (WS) is a rare neurogenetic condition classically characterized by progressive neurodegeneration, early-onset diabetes mellitus, progressive optic atrophy, sensorineural hearing loss, arginine vasopressin deficiency, and brainstem and cerebellar atrophy, with a median lifespan of approximately 30 years. It is caused by pathogenic variants in the *WFS1* gene. Over the past decade, there has been a gradual expansion of the clinical phenotype, which has resulted in variable practices in the diagnosis and management of WS. Hence, our objective was to develop an international clinical guideline for WS. To achieve this we used the modified Delphi-consensus process, and for the first time systematically combined the perspectives of clinicians, patients, caregivers and patient advocacy groups.
METHODS: An 8-member international steering committee systematically reviewed 273 peer-reviewed publications and generated draft consensus statements across six clinical domains. These were reviewed by 56 international specialists from North America, Europe, Latin America, and Asia using a modified three-round Delphi process. Structured feedback from patients and families was incorporated with help from international patient advocacy organizations. Consensus was defined as ≥80% agreement.
RESULTS: A total of 35 statements reached the pre-specified consensus threshold of ≥80% agreement, spanning diagnosis and genetic testing, multidisciplinary care organization, neuro-ophthalmology, neurology, endocrinology, urology and gastroenterology, and psychiatry care for WS patients.
CONCLUSIONS: This international clinical guideline for WS will provide a framework for the diagnosis and management of WS globally. It will also be a resource for newly diagnosed WS patients, helping them become part of the global WS community.
KEYWORDS: Early Stage Investigator, Neurogenetics, Practice Parameters

32. A Cerebrospinal Fluid Cytokine Atlas in Pediatric Patients Across Disease

Samuel Belfer, Kacie Wheeler, Zachary Martinez, Thomas Manley, Brynn Henry, Diego Espinoza, Apoorva Babu, Rawan Shraim, Lahari Uppuluri, Jillian Dolan, Marie Juzans, Amit Bar-Or, Jennifer McGuire, Jessica Foster, Caroline Diorio

OBJECTIVE: To characterize the clinical utility and distribution of cerebrospinal fluid (CSF) cytokines in pediatric patients and define disease- and compartment-specific cytokine patterns using proteomic profiling.
METHODS: We retrospectively identified CSF cytokine assays performed at a tertiary pediatric center from April 2024 through April 2026. Clinical data, CSF and serum laboratory values were abstracted. Cytokine distributions were characterized, and associations with clinical variables and conventional markers of neuroinflammation were assessed. In parallel, proteomic profiling of 89 CSF cytokines was performed in 260 pediatric and young adult samples to define disease- and compartment-specific patterns.
RESULTS: A total of 153 CSF cytokine results from 137 patients were analyzed. Most cytokines demonstrated limited variability, with values clustering near the lower limit of detection; only IL-6, IL-8, IFN-γ, and GM-CSF exhibited substantial variance. Cytokine levels were higher in

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hospitalized and intensive care patients compared to outpatients. Elevated CSF white blood cell count and protein were associated with increased cytokine levels across analytes. Among patients with paired testing, CSF and serum cytokine levels showed limited concordance. Proteomic analysis demonstrated greater variability in intracranial versus lumbar puncture samples and identified site-specific cytokine enrichment independent of diagnosis. Disease- and therapy-specific cytokine patterns were observed, including signatures consistent with cytotoxic T cell activation following chimeric antigen receptor T-cell therapy.
CONCLUSIONS: Clinical CSF cytokine testing may be most informative where evidence of neuroinflammation is already present. Expanded proteomic profiling demonstrates the utility of broader cytokine assessment, revealing compartment- and disease-specific signatures that may inform biomarker development for diagnosis, disease monitoring, and therapeutic response.
KEYWORDS: Early Stage Investigator, Neuro-oncology, Pediatric Demyelinating Disease

Education

33. Improving Diagnosis and Treatment Decision-Making in Tourette Syndrome in an Evolving Therapeutic Landscape using a Web-based Continuing Medical Education Platform

Vandana Gupta, Carole Drexel, Erica Greenberg, Donald Gilbert

OBJECTIVE: Diagnostic challenges and treatment limitations, particularly in the context of psychiatric and neurodevelopmental comorbidities, contribute to suboptimal outcomes in Tourette syndrome (TS). Advances in TS neurobiology have identified novel therapeutic targets beyond dopamine D2 receptor antagonism. We evaluated the impact of a multi-format continuing medical education (CME) curriculum addressing the diagnosis and evolving management of Tourette syndrome.
METHODS: A two-part online curriculum covering diagnostic differentiation and limitations of current therapies (Activity 1) and emerging agents (Activity 2) launched in November 2025. The program included long-form videos and targeted microlearning distributed to NPI-verified pediatricians, pediatric psychiatrists, and neurologists (intended learners). Pre- and post-activity knowledge and competence questions assessed impact, with intended learners' cohort analysis and chi-square comparison of pre–post responses ($p<0.05$).
RESULTS: As of March 2026, 12,090 clinicians (71% of whom were intended learners) participated in at least one educational component (1,108 long-form, 10,982 microlearning). Knowledge and competence improved from 45% to 82% in Activity 1 ($p<0.05$) and from 44% to 79% in Activity 2 ($p<0.05$). Planned changes included applying TS guidelines (61%), modifying treatment approaches (35%), and adjusting pharmaceutical therapy (21%). Regarding the potential place in care of selective D1 receptor antagonists, 42% reported they would use them for patients inadequately responsive to behavioral therapy.
CONCLUSIONS: This multi-format online CME curriculum on emerging mechanisms and therapies for TS, targeted to pediatricians, pediatric psychiatrists, and neurologists, generated strong clinical engagement and yielded significant educational gains and may facilitate integration of novel therapies. (The CME education was supported by an unrestricted grant from Emalex Biosciences).
KEYWORDS: Education, Neurodevelopmental Disorders

34. Increasing the pipeline from medical student to child neurologist: A needs assessment survey assessing barriers to pursuing child neurology

Jacob Hanson, Mara Cohen, Dara Albert, Frederick Bassal, Donald Gilbert, Adam Wallace

OBJECTIVE: To better understand the needs of medical students interested in becoming child neurologists and determine what resources might be most beneficial, with the ultimate goal of encouraging more medical student interest in the field.
METHODS: A survey was designed targeting current medical students with an interest in Child Neurology. Questions were either multiple choice, short answer, or ranking. Students were recruited via an email listserv of medical student members of the Child Neurology Society (CNS), as well as students who attended a 2025 webinar hosted by the CNS.
RESULTS: Thirty-seven responses were obtained, of which 70% were 3rd and 4th year medical students. The primary way students learned about child neurology as a field was via clinical clerkships. Of the respondents, 67% reported that their school has a child neurology rotation, and 51% received a lecture on child neurology during their pre-clinical education. When asked about barriers to pursuing child neurology, the top two noted barriers were lack of available information about the field and lack of specific advising. When asked how the CNS could help to address these barriers, common themes were mentorship and networking opportunities, as well as spreading awareness about the field in general.
CONCLUSIONS: This survey suggests that lack of available information and opportunities in Child Neurology pose a barrier to medical students interested in the field even amongst those with clinical exposure. In order to better assist those interested in pursuing Child Neurology, more mentorship, networking opportunities, and earlier exposure are needed throughout the medical school experience.
KEYWORDS: Education

35. Bridging the Synapse: A Collaborative Neurology Symposium for Community General Pediatricians/ Nurses/APPs

Victoria Hardwick, Amber Auad, Deanna Duggan, Edward Espineli, Swati Karmarkar, Ekta Salhotra, Yen Tran

OBJECTIVE: General pediatricians are often the first to evaluate children with a neurological concern. Our goal for

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the Bridging the Synapse Neurology Symposium was to help educate our community general pediatricians on neurological diseases and conditions that they may encounter and how to best address them and recognize whether they should be referred for emergent vs. urgent vs. routine management.
METHODS: We designed a one-day schedule of talks focusing on common neurological chief complaints encountered by general pediatricians. The talks were structured to help pediatricians practically approach various complaints and how to better recognize, evaluate, and understand the urgency of neurologic conditions including but not limited to seizures, hypotonia, tics, neuroinflammatory disorders, and functional neurological disorders.
RESULTS: he symposium hosted 48 general pediatricians, APP, nurses, and staff from across the Houston area. We conducted a survey at the conclusion of our symposium. 85.7% of respondents indicated they intend to make a practice or professional change as a result of this activity. 100% of respondents rated the activity "Excellent" or "Very Good." All attendees expressed their gratitude in this educational opportunity for them to learn and ask questions while also receiving CME and Ethics credit to use for MOC.
CONCLUSIONS: Due to the success of our inaugural symposium, there has been significant interest in future Neurology symposiums. Our hope is that similar neurology symposiums can be conducted in other healthcare centers around the country to ensure we are all making a collaborative, interdisciplinary approach to managing and caring for our pediatric population with neurological concerns.
KEYWORDS: Education, Diversity, Equity, Inclusion, Ethics

36. Against the Tide: Assessing the Success of Child Neurology as a Model for Sustainable Growth in Pediatric Subspecialty Training

John Pugh, Bruno Souza Di Nucci, Henry Nagle, Chris Barton

OBJECTIVE: It is a growing concern that pediatrics and their related specialties face a recruitment crisis. Multiple factors including training duration and relatively low compensation have made it increasingly difficult to attract medical students and residents into many pediatric specialties. Despite this trend, child neurology has continued to expand, particularly in comparison to other "cognitive" specialties.
METHODS: Using NRMP match data, we compiled comparisons in child neurology growth and match rates compared to other pediatric fellowship specialties.
RESULTS: National Residency Match Program (NRMP) data indicates that most pediatric specialties grew only modestly from 2016 and 2026 with fill rates as low as 38%. While surgical and inpatient specialties have performed well, "cognitive" specialties that focus on outpatient settings and lack procedural elements have fill rates between 38-58%. In contrast, during the same period, PGY-1 training positions for child neurology grew by 82% while maintaining a high fill rate of 97% in 2026.
CONCLUSIONS: We hypothesize that the successful growth of child neurology training programs relative to other pediatric specialties is due to a number of modifiable factors including: the option to apply out of medical school, co-application for base and specialty training at the same time and at the same institution, and a shorter duration of training. Further research is needed to better understand how these and other factors may affect recruitment in pediatric specialties and inform current conversations about the restructuring of child neurology training to sustain momentum and growth over the next decade.
KEYWORDS: Education, Practice Parameters, Early Stage Investigator

37. Development of a Pediatric Neurocritical Care Simulation Curriculum: Needs Assessment and Pilot Study

Lauren Hurst, Grace Newell, Anna Janas, Elizabeth Troy

OBJECTIVE: Simulation-based medical education improves clinical performance and confidence in neurologic emergencies, particularly in adult training, but structured curricula in child neurology are limited. We describe the development and pilot implementation of a pediatric neurocritical care simulation curriculum to identify educational gaps, create targeted scenarios, and evaluate effects on clinician knowledge, confidence, and satisfaction.
METHODS: This study is conducted at Children's Hospital Colorado and uses a three-phase design. Phase 1 involves a multidisciplinary needs assessment to identify training gaps and prioritize topics. Phase 2 focuses on developing simulation scenarios informed by needs assessment results and guided by Kolb's experiential learning theory. Phase 3 includes pilot implementation with low-fidelity simulations, pre- and post-session surveys, and facilitated debriefing to evaluate knowledge, confidence, skill application, and participant satisfaction.
RESULTS: Using Kern's framework, we created a needs assessment to identify perceived knowledge gaps in neurocritical care. We finalized a 10-item assessment instrument mapped to ACGME frameworks, encompassing three core domains 1) prior experience in simulation-based curriculum 2) confidence in managing neurological emergencies 3) preferred simulation structure. We also created pre/post surveys for the simulation that will measure knowledge, confidence, and satisfaction. Guided by the New World Kirkpatrick Model, survey data assess learner outcomes and inform iterative curriculum refinement.
CONCLUSIONS: A needs-based, framework-driven neurocritical care simulation curriculum may address training gaps, enhance preparedness, and promote interdisciplinary collaboration. This approach offers a scalable model for targeted neuroemergency training across disciplines and training levels.
KEYWORDS: Education, Neurocritical Care, Practice Parameters

38. Adult Neurology Call Practices for Child Neurology Residents

Gabriella Tison-Brandon, Christopher Barton, Cullen Marshall

OBJECTIVE: The ACGME requires that child neurology (CN) residents rotate in adult neurology (AN) for a total of 12 months. Call shifts are often embedded in these rotations,

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though ACGME requirements provide wide latitude on the frequency and character of these shifts. This study aimed to characterize AN call responsibilities for CN residents in US programs.

METHODS: An 11-item online survey was sent to program directors and associate program directors who are members of the Child Neurology Residency Council by email thread and digital messaging application. Chi-square and Fisher's-exact test were used to analyze associations between program characteristics and call practices.

RESULTS: 35 responses were analyzed (42% of the 83 CN programs). In 23% of responding programs, CN residents did not take any adult call. In 49%, CN residents took the same amount of call as their adult counterparts. Out of the programs where CN residents took adult call, 63% did some degree of call without direct supervision. The type (night float, long call, etc) and amount of call varied widely. The size of the child or adult program and the CN program director's opinion on the goals of AN rotations were not associated with the characteristics of the call shifts.

CONCLUSIONS: CN residents take AN call in most CN training programs. The type and amount of call varies widely among programs, which may be the result of unique institutional factors. The findings provide a frame of reference for individual programs and for further considerations of best practices.

KEYWORDS: Education, Practice Parameters

39. Meaning in the Clicks: Using Electronic Health Record Metadata to Identify Meaningful Child Neurology Resident Encounters with Patients

Rachel Gottlieb-Smith, Joshua Adams, Miya Bernson-Leung, Brian Stamm, Mark Mai, Robert Thompson-Stone, Elizabeth Troy, Kathryn Xixis, Bittu Majmudar-Sheth, Adam Dziorny

OBJECTIVE: Attributing meaningful patient encounters to residents is essential to characterize educational exposure and guide learning plans. We aimed to measure and recalibrate a prior model of electronic health record (EHR)-based pediatric resident-patient attribution (Mai et al, 2020) to a cohort of child neurology (CN) residents.

METHODS: We queried 10 CN residents across 12 days to identify meaningful interactions from potential patient encounters, based on service and clinic lists, consult orders, and paging data. We extracted EHR elements including time-in-chart, notes, orders, team membership, and chart closure. We compared predictive accuracy using the original model coefficients with recalibration using 3-fold cross-validation. We constructed receiver operating characteristic (ROC) curves for clinic and inpatient settings, identified cut points maximizing Youden's index, and measured sensitivity and specificity.

RESULTS: Residents identified 365 meaningful encounters, of which 289 (79%) were captured in EHR metadata. Recalibration improved AUROC (Area Under the ROC Curve) in both clinic (0.78 to 0.86) and inpatient (0.76 to 0.87) settings. In the clinic setting, sensitivity improved from 0.76 to 0.80 and specificity from 0.83 to 0.85. The odds ratio of predicting a meaningful interaction in clinic was highest for treatment team membership and note completion. In the inpatient setting, sensitivity improved from 0.64 to 0.74 and specificity from 0.77 to 0.94, with the highest odds ratio being time-in-chart.

CONCLUSIONS: Recalibration of a pediatric resident-patient attribution model to a cohort of CN residents resulted in different coefficients and improved model performance. This likely reflects differences in workflow and underscores the importance of specialty-specific resident-patient attribution models.

KEYWORDS: Education

40. Identifying Pediatric Neurology Care Gaps in Rural Honduras: A Needs Assessment

Joanna Bendeck, Jeffrey Strelzik

OBJECTIVE: Access to specialized pediatric neurology care remains limited in low-resource settings, contributing to delayed diagnoses and suboptimal outcomes. This study aimed to identify gaps in pediatric neurology knowledge, training and resources available for patients and providers caring for children in rural Intibucá, Honduras presenting with common pediatric neurological concerns.

METHODS: Using Kern's framework for curriculum development, we conducted a general and targeted needs assessment through phone interviews with two local pediatricians in the Hospital Enrique Aguilar Cerrato (Intibucá) and two remote consulting child neurologists from Hospital María de Especialidades Pediátricas (Tegucigalpa). Using a standardized questionnaire, we assessed the existing pediatric neurology care network, provider knowledge level, and available educational resources. Participants also described an ideal curriculum, allowing identification of gaps between current and desired training. Interview responses were thematically analyzed.

RESULTS: The problem identified is a lack of general child neurology knowledge among pediatricians leading to morbidity and mortality. Our targeted needs assessment identified a desire for in-person, hands-on workshops with a focus on sustainable education addressing gaps in epilepsy and neonatal care, early identification of inborn errors of metabolism and developmental delays, use of EEG, ultrasound and other diagnostic modalities, and access to evidence-based protocols and guidelines tailored to their practice environment. Barriers included a lack of existing curricula, access to diagnostic tools and medications, and specific bureaucratic obstacles.

CONCLUSIONS: We performed a general and targeted needs assessment for Intibucá, Honduras to identify gaps in knowledge in preparation for the development of a novel targeted curriculum for their providers.

KEYWORDS: Education, Global Neurology

41. Overcoming Neuroanxiety: Teaching High-Yield Pediatric Neurology Topics to the Non-Pediatric Neurologist

Melanie Gershman, Abigail Carbonell, Serina Bsales, Zahra Zhu, Jennifer Bain, Danielle McBrian

OBJECTIVE: To assess the prevalence of neuroanxiety among pediatric residents, identify gaps in neurologic

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knowledge and skills, and develop targeted educational interventions to improve clinical confidence and decision-making.
METHODS: A needs-based survey was distributed to pediatric residents (n=17; PGY1=4, PGY3=13), consisting of Likert-scale and free-response items evaluating attitudes toward neurology, confidence in performing neurologic examinations across age groups, and ability to manage and provide anticipatory guidance for common neurologic conditions. Responses were analyzed to identify key educational gaps. Based on findings, targeted interventions were developed, including faculty-reviewed reference sheets and structured case-based learning. Case-based didactic sessions were implemented, each covering three high-yield neurologic presentations and emphasizing key components of history-taking, neurologic examination, differential diagnosis, diagnostic workup, management, and prognosis. Complementary reference sheets were created for both resident use and parent education.
RESULTS: Among respondents, 65% felt apprehensive about neurologic conditions and 71% rely on neurology consultation for management. Only 24% felt confident managing neurologic conditions independently (Likert ≥4). Confidence in performing neurologic examinations declined with younger patient age: 76% for adolescents vs.18% in infants. Lowest rates of management confidence reported in altered mental status (29%) and hypoxic-ischemic encephalopathy (24%). Primary deficits were in clinical translation and decision-making. These findings informed developing high-yield case-based modules and associated inpatient and outpatient reference and family education materials targeting common neurologic concerns.
CONCLUSIONS: Targeted, structured educational interventions—including case-based learning and point-of-care reference tools—represent scalable strategies to reduce neuroanxiety and improve resident confidence. Integration of resources into clinical workflows may enhance real-time decision-making and standardize family education.
KEYWORDS: Education

42. Concussion Education with Community Partners: A Collaboration with Large Urban School District Nurses to Promote Concussion Management in High School Settings

Elise Watson, Blake Thomas, Elvina Chow, Todd Rubin, Bradley Shane, Meeryo Choe, Talin Babikian

OBJECTIVE: Concussion treatment guidelines are regularly updated based on the latest evidence, thus, this study seeks to assess knowledge gaps amongst nurses in a large School District, evaluate the effectiveness of concussion training, and identify barriers in the implementation of concussion management.
METHODS: During an annual school nursing training, a neurologist and clinical neuropsychologist presented updated evidence on concussion management and recovery, the Sport Concussion Assessment Tool (SCAT), the Sport Concussion Office Assessment Tool (SCOAT), clinical guidelines for return-to-play (RTP) and return-to-learn (RTL), and legislation for pediatric concussion management. An anonymous pre- and post-presentation survey used 5-point familiarity scales across seven concussion management domains. Average scores and score changes measured baseline knowledge and training effectiveness. Multiple-choice and free-response items identified key challenges in providing concussion care.
RESULTS: Improvement between 84 pre- and 61 post-surveys was observed across all domains, with a significant point increase in SCAT/SCOAT Assessment Tools, Return-To-Learn Guidelines, and California Concussion Legislation. Eighty percent of respondents highly recommended the training. Nurses identified major operational barriers like insufficient communication with clinicians about medical clearances and unclear roles of staff for RTL/RTP protocols. Underreporting of symptoms was a universal concern.
CONCLUSIONS: While the training was successful and well-received, persistent barriers to concussion care highlight a critical responsibility of pediatric neurologists beyond the clinic. Full recovery depends on evidence-based RTL/RTP protocols and bidirectional communication amongst clinicians, schools, patients, and families. A structured, community-engaged triage model can standardize care and improve outcomes for not only concussion, but also other pediatric neurologic conditions.
KEYWORDS: Education, Traumatic Brain Injury

43. Will Pediatric Practitioners Consider Treating 3 Benign Epilepsy Syndromes? A Survey of Rural and Urban Pediatric Practitioners

Magdelin Lopez, Steven Winesett

OBJECTIVE: Child neurology is experiencing workforce shortages due to fewer trainees compared to retiring physicians, contributing to increased wait times, particularly in rural areas. We aimed to assess barriers to inter-specialty collaboration to improve patient access to care.
METHODS: A brief survey was developed. Participants identified as practicing in rural or urban settings and reported barriers to neurological care. Three clinical scenarios—febrile seizures, Rolandic seizures, and absence seizures—were presented and participants were asked about likelihood of referral to child neurologists and comfort in initial management of these conditions if supported by clinical pathways, educational interventions, and EEG support. Interest in these interventions was assessed. Participants were English-speaking pediatric practitioners. Recruitment occured via email and advertisements through Missouri, Nebraska, and Florida AAP chapters.
RESULTS: Sixty-one participants completed the survey (80.7% urban, 19.3% rural). Availability barriers were similar between groups, whereas rural physicians were significantly more likely to report distance as a barrier ($p<0.001$). Wait times ranged from 2–8 weeks (41%) to over 4 months (20.7%). Most respondents reported always referring for Rolandic (80%) and absence seizures (77.8%), compared to febrile seizures (6%). With educational support and EEG access, comfort managing these increased to 72.7%, 61%, and 43%. With the additional of a clinical pathway, comfort increased to 94.5%, 92.6%, and 79.2%. Most (86.8%) were interested in a 1-hour educational intervention.
CONCLUSIONS: Availability remains a barrier across settings, with rural physicians disproportionately affected by distance. Strong interest in education and clinical support

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suggests targeted interventions and improved EEG access may enhance care and reduce subspecialty burden.
KEYWORDS: Education, Epilepsy

Epilepsy

44. Deuterium Magnetic Resonance Spectroscopy Detects Ketogenic Diet Induced Changes in Brain Energy Metabolism in a Dravet Syndrome Mouse Model

Liu Lin Thio, Joel Garbow, Xia Ge, Kyu-Ho Song, Nicholas Rensing, John Englebach, Jeffrey Neil, Joseph Ackerman

OBJECTIVE: We examined the effect of a ketogenic diet (KD) on brain energy metabolism in a mouse model of Dravet syndrome using *in vivo* deuterium magnetic resonance spectroscopy (DMRS).
METHODS: We used the *Scn1a*^{tm1Kea} Dravet syndrome mouse model, which has a heterozygous null *Scn1a* allele. At postnatal day 21, littermate control and Dravet mice were weaned to a standard diet (SD) or a 6:1 KD (Bioserv F3666). Two weeks later, we used single-voxel DMRS to examine brain energy metabolism after a subcutaneous injection of deuterated glucose or β-hydroxybutyrate (βHB). Spectra were obtained before substrate injection and in seven 10-minute blocks thereafter. Spectra at each time point were analyzed using Bayesian-based signal analysis to determine brain concentrations of the injected substrate and its metabolites including lactate, the sum of glutamate + glutamine (Glx), and semiheavy water (HOD). These metabolites reflect flux through glycolysis and the tricarboxylic acid cycle. Time course data were analyzed using linear modeling.
RESULTS: The KD decreased brain glucose metabolism in control mice by 25-50% but did not change or increased it in Dravet mice based on the accumulation of HOD ($F(273,13) = 4.43$, $p < 0.0001$, $n = 6$-7) and Glx ($F(273,13) = 1.95$, $p = 0.025$, $n = 6$-7). In contrast, the KD increased brain βHB metabolism in both genotypes.
CONCLUSIONS: Compared to control mice, Dravet mice showed altered brain glucose, but not βHB, metabolism during ketosis suggesting impaired negative feedback on glucose metabolism. These results also demonstrate the potential DMRS has in managing neurometabolic diseases clinically.
KEYWORDS: Epilepsy, Neurometabolic, Neuroimaging

45. A first-in-human study of the antisense oligonucleotide S230815 in paediatric participants with KCNT1-related Developmental and Epileptic Encephalopathy

Carlos Estevez-Fraga, Stéphane Auvin, Rima Nabbout, Jana Dominguez-Carral, Antonio Gil-Nagel, Christelle El Achkar, Mathieu Milh, Virginia Parks, Lucie Truffaut-Chalet, Charlotte Corbel, Pauline Rivet, Marie-Elodie Cattin-Messaouidi, Isabel Feliu, Florence Keime-Guibert, Vincent Madelain, Hélène Tran, Javier Avendano, David Bearden

OBJECTIVE: *KCNT1*-related developmental and epileptic encephalopathy (KCNT1-DEE) is an ultrarare, severe, drug-resistant epilepsy characterized by early-onset high frequency seizures, developmental impairment, and high mortality. Most pathogenic *KCNT1* variants result in a gain-of-function mechanism leading to aberrant channel activity, hence the rationale for reducing *KCNT1* expression. S230815 is an intrathecally administered antisense oligonucleotide (ASO) designed to induce the degradation of *KCNT1* mRNA. The KANDLE first-in-human study aims to evaluate S230815 in paediatric participants with diagnosis of KCNT1 and phenotype consistent with epilepsy of infancy with migrating focal seizures (EIMFS) or non-EIMFS early onset epileptic encephalopathy.
METHODS: KANDLE is a Phase Ib/II, multicentre, open-label, multiple ascending dose study. After screening period, eligible participants aged 2–12 years will enter Part 1, in which S230815 will be administered. Four sequential cohorts will be enrolled. Participants who complete Part 1 may roll over into a long-term extension dosing period.
RESULTS: The primary endpoint will be safety and tolerability based on incidence and severity of adverse events. Secondary endpoints evaluate pharmacokinetics (PK) and pharmacodynamics (PD), change from baseline in seizure frequency assessed through daily logs and 24-hour video EEG. Exploratory endpoints include neurodevelopmental outcomes, caregiver burden, quality of life, immunogenicity, fluid biomarkers, and feasibility of a wearable seizure detection device.
CONCLUSIONS: KANDLE is the first clinical trial to evaluate a *KCNT1*-targeting ASO in children with KCNT1-DEE. Its design aims to maximize safety and mechanistic insight in an ultrarare population. Findings from KANDLE will support the development of S230815 as a potential disease-modifying therapy for KCNT1-DEE.
KEYWORDS: Epilepsy, Experimental Therapeutics, Neurodevelopmental Disorders

46. Co-Design of a Curriculum about Reproductive Health and Epilepsy for Child Neurology Residents

Laura Kirkpatrick, Christina Briscoe, Elizabeth Harrison, Erin Friel, Janani Kassiri, Mahjabeen Khan, Neil Kulkarni, Sarita Maturu, Preeti Puntambekar, Tahniat Syed, Jojo Yang, Marie Clements

OBJECTIVE: To design a curriculum that will train child neurology residents to counsel female adolescents with epilepsy and parents about reproductive health.
METHODS: The Epilepsy in the Child-Bearing Ages Consortium (ECAM) Adolescent and Young Adult Committee iteratively drafted initial curriculum materials from July - October 2025. To obtain feedback, we conducted 3 focus groups and one interview with child neurologists (n=16), one focus group with female youth with epilepsy (n=5), and one focus group with parents (n=5). The PI analyzed the transcripts using rapid-cycle qualitative methods to extract participant recommendations. The ECAM Committee met from December 2025 to February 2026 to integrate feedback into the curriculum.
RESULTS: Feedback from youth and parents focused on improving clarity and brevity of recommended communication.

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Feedback from clinicians focused on wanting more educational content on counseling patients/families affected by intellectual disability, wanting more clinical tools (i.e. handouts, dotphrases, pocket cards), and concerns about time management and scope of practice. After incorporating feedback, the final product included a 45-minute didactic presentation and four roleplay-based scenarios to practice communication in small groups over 1 hour. Additional materials included a handout and electronic health record dotphrase for clinicians on suggested language, a pocket reference about seizure medication teratogenicity and contraceptive drug interactions, and a patient-facing handout with websites for further reading

CONCLUSIONS: We designed a 2-hour curriculum for child neurology residents in counseling female adolescents with epilepsy and parents about reproductive health. We will introduce the training at three child neurology residencies during the 2026-2027 academic year.

KEYWORDS: Epilepsy, Education

47. Sex-specific Divergence in Growth Rates among Hispanic Children with Epilepsy: A longitudinal retrospective study

Megan Szobody, Desiree Lanehart, Kaitlyn Ybanez, Maci Oestreich, Kelsey Potter-Baker

OBJECTIVE: To analyze the effect of epilepsy on childhood anthropometric growth rates in a predominantly Hispanic cohort.

METHODS: A retrospective review (2019-2024) of clinical data was conducted to compare children with epilepsy (N=503; 10.0 years, 53% Males, 83% Hispanic) to controls (N=37,770; 10.6 years, 55% Male, 94% Hispanic). Baseline anthropometric age-adjusted z-scores were calculated using the CDC's macro for growth charts (height: HAZ, weight: WAZ & body mass index: BMIZ). Growth rates were analyzed via linear mixed-effect modeling with an autoregressive [AR(1)] covariate structure; baseline differences were assessed via multi-way ANOVA with Least Squares Means (LSMEAN). A multivariable logistic regression was used to determine adjusted Odds Ratios (aOR) for various comorbidities to epilepsy, controlling for sex, age and ethnicity.

RESULTS: Mixed-effect models demonstrated significant interactions between epilepsy and sex for all variables over time in Hispanics (HAZ; $p<0.001$, WAZ; $p=0.004$ & BMIZ; $p=0.031$). At baseline, Hispanic boys with epilepsy (HBWE) had significantly lower LSMEAN HAZ ($p<0.0001$) compared to Hispanic male controls, this was not observed in Hispanic girls with epilepsy (HGWE) ($p=0.487$). Ethnicity interacted significantly with epilepsy for BMIZ ($p=0.009$). HBWE showed a greater decline in HAZ (−0.387/year vs controls; −0.215/year vs HGWE) and a greater increase in BMIZ (+0.121/year vs controls; +0.149/year vs HGWE).Epilepsy was associated with Angelman syndrome, neoplasms of the brain and congenital malformations of the nervous system (aORs= 39.1, 89.1 & 6.6, respectively; all $p<0.01$).

CONCLUSIONS: Epilepsy affects growth rates more severely in HBWE; decreasing HAZ and increasing BMIZ over time compared to controls and HGWE.

KEYWORDS: Epilepsy

48. DESCRIPTION OF PHARMACOTHERAPY USED IN THE TREATMENT OF NEONATAL SEIZURES IN A PEDIATRIC TERTIARY CENTER

Nicolas Chrestian, Geneviéve Laflamme, eric proulx, Isabelle Laverdiere, Mireille Guillot, christian Heroux

OBJECTIVE: Objective: Prompt and effective treatment of neonatal seizures is essential to control seizures and to prevent neurological complications. Data on optimal treatment options remain limited. We describe the drugs used in the acute treatment of neonatal seizures at a paediatric tertiary centre.

METHODS: Method: Retrospective observational study including newborns less than 44 weeks post-conception who had a seizure and received at least one anticonvulsant before the fifteenth day [IL1] of life, between 2017 and 2021.

RESULTS: . Results: The study included 199 newborns, with a median of 39 weeks' gestation (IQR[IL2] : 37.7-40.9) and a median birth weight of 3280 g (IQR: 2925-3636). Neonates received 0 to 16 acute treatments (median: 2; AEs: 1-4), defined as boluses administered for up to 24 hours without recurrence[IL3] . In the 1st line, the most commonly used agents were phenobarbital (80%), lorazepam (12%) and levetiracetam (6%). In the 2nd line (n=117): phenobarbital (71%), levetiracetam (10%), lorazepam (9%). In the 3rd line (n=82): phenytoin (34%), levetiracetam (26%), phenobarbital (24%). The effectiveness of the 1st , 2nd and 3rd line in controlling seizures for 24 hours was 40%, 30% and 29%. Maintenance therapy was initiated in 142 patients and 78 continued it at discharge.

CONCLUSIONS: Conclusion: Phenobarbital is the most widely used agent in 1st line of treatment, but the majority of patients require additional treatments with significant variability. A therapeutic algorithm appears to be necessary to guide management.

KEYWORDS: Epilepsy, Neonatal Neurology, Practice Parameters

49. Feasibility and Acceptability of Qualitative Insights (FAQS): Implementing Common Data Elements in Pediatric Health Equity

Deirdre Flanagan, Laura Kirkpatrick, Alex Aguirre, Christopher Beatty, Sonal Bhatia, Cristian Delgado-Baez, Kara Garrett, Charuta Joshi, Kristina Julich, Victoria Olivares Pena, Daniel Ortiz Prado, Shital Patel, Maria Planchart Ferretto, Chethan Rao, Alejandra Wright, JoJo (Qian-Zhou) Yang, Christina Briscoe

OBJECTIVE: A 2024 Pediatric Epilepsy Research Consortium (PERC) scoping review revealed gaps in social determinants of health (SDOH) data reported in pediatric epilepsy research, prompting development of a common data elements (CDE) set to standardize data collection across sites. This research aims to evaluate CDE implementation feasibility for clinicians and acceptability for people affected by epilepsy.

METHODS: To evaluate feasibility, focus groups and Feasibility of Implementation Measure (FIM) surveys were conducted with PERC leaders. To evaluate acceptability, semi-structured interviews and Acceptability of Intervention

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Measure (AIM) surveys were conducted with caregivers and youth with epilepsy aged 14-21. Qualitative data was analyzed using deductive thematic analysis based on the Consolidated Framework for Implementation Research to identify implementation facilitators and barriers, with thematic saturation achieved in each group.

RESULTS: PERC leaders (n=19), caregivers (n=27), and youth with epilepsy (n=11) participated. FIM and AIM scores demonstrated high feasibility and acceptability, with question medians (IQR) of 4 (0-1) and 4.5-5 (1), respectively. Feasibility barriers included data quantity and complexity. Families and youth expressed hesitancy around reporting sensitive topics like legal status and gender. Shared beliefs in SDOH CDE research by healthcare providers and patients were critical facilitators.

CONCLUSIONS: Implementing SDOH CDE in pediatric epilepsy research was overall considered feasible by clinicians and acceptable by caregivers and youth with epilepsy. Qualitative data identified areas for improvement. The PERC Health Equity Special Interest Group will adapt the CDE to ensure standardized collection of SDOH factors which are feasible for researchers and important to people affected by epilepsy.

KEYWORDS: Epilepsy, Diversity, Equity, Inclusion

50. The Use of Perampanel in Neonates and Young Children

Aminah Ahmed, Abdullah Shoaib, Sonal Bhatia

OBJECTIVE: This retrospective review sought to understand the use of perampanel (brand name, Fycompa) as a treatment for seizures in children under 2 years of age.

METHODS: Data regarding patients < 24 months on perampanel was collected, including patient demographics and perampanel dosing practices, including starting dose, increase in dose, and maximum dose (in both mg as well as mg/kg/day). In addition, concurrent maintenance antiseizure medications and adverse events attributed to perampanel were also collected.

RESULTS: 28 patients were included in the study. The median age at perampanel initiation was 5 months. The median starting dose of perampanel was 2 mg/day or 0.24 mg/kg/day. 21 patients were started on daily dosed perampanel. The median increase in perampanel dose was 2 mg/day or 0.23 mg/kg/day, and the median maximum dose was 6 mg/day or 0.80 mg/kg/day. The most common concurrent antiseizure medications were levetiracetam, phenobarbital, lacosamide, and clobazam. 6 patients reported adverse events, with the most common adverse effect being agitation, present in 3 patients. 2 patients reported sedation and 1 patient had hypotonia due to perampanel, all of which improved with cessation of perampanel.

CONCLUSIONS: Perampanel was an overall well-tolerated antiseizure medication in children < 24 months, with mostly behavioral side effects, such as aggression or sedation. Dosing practices were somewhat heterogeneous. Further studies investigating the use of perampanel in this age group to study efficacy and tolerability are required.

KEYWORDS: Epilepsy

51. Pharmaceutical Grade Oral Pyridoxal 5'-Phosphate for the Treatment of Patients With PNPO Deficiency (MEND-PNPO) Study Design and Rationale

Phillip Pearl, Laura Cole, Nancy Stewart, Muhammad Zafar, Monisha Goyal, Ann Hyslop Sgeren, Mathew Ginsberg, Catherine (Kate) Riney, Johan Van Hove, Heidi Peters, Lukasz Przysło, Maria Mazurkiewicz-Bełdzińska, Robert Śmigiel, Scott Dyck, Neil Owens, Albert Friesen

OBJECTIVE: Pyridox(am)ine 5′-phosphate oxidase (PNPO) deficiency is an ultra-rare autosomal recessive neurometabolic disorder that causes neonatal epileptic encephalopathy. PNPO mutations results in impaired pyridoxal 5′-phosphate (P5P) synthesis, the active form of vitamin B6, leading to severe neonatal seizures that are often fatal without treatment. High-dose P5P—and in some cases pyridoxine—can be effective, making early diagnosis critical. Poorer outcomes correlate with fetal distress, prematurity, early seizure onset, and delayed intervention. Lifelong P5P therapy is typically required, but nutraceutical formulations risk inaccurate dosing or impurities, and no pharmaceutical-grade P5P product is approved.

METHODS: MEND PNPO (NCT04706013) is a 52-week, Phase III, single-arm, open-label, multicenter study evaluating MC-1, a pharmaceutical-grade oral P5P formulation, in genetically confirmed PNPO deficiency. Approximately 10 patients aged ≥2 years, clinically stable on oral P5P, receive MC-1 at their established dose. The primary endpoint is incidence of death at 12 months. Secondary endpoint is frequency of seizures. Other endpoints include safety and pharmacokinetic analysis.

RESULTS: Enrollment began January 2023, with completion expected in 2026. Eight patients (3 male, 5 female) have been enrolled as of May 2026; two have completed the one-year study. Baseline dosing ranged from 14–58 mg/kg/day using crushed or intact tablets. Baseline steady-state MC-1 concentrations ranged from 59.8–165 ng/mL. Pharmacokinetic data indicate MC-1 maintains circulating P5P levels after dosing.

CONCLUSIONS: PNPO deficiency is a rare but treatable cause of neonatal epileptic encephalopathy. MEND PNPO evaluates the first pharmaceutical-grade P5P formulation to address a significant unmet clinical need. Study sponsored by Medicure Inc.

KEYWORDS: Epilepsy, Neonatal Neurology, Neurogenetics

52. Angiocentric Glioma as The Cause of Lesional Intractable Epilepsy

Victoria Mazo, Krupesh Patel

OBJECTIVE: Angiocentric gliomas (AGs) are rare, slow-growing, low-grade gliomas commonly associated with intractable epilepsy in younger patients. Histologically, these tumors are characterized by diffusely infiltrating monomorphous tumor cells exhibiting prominent perivascular clustering. Recent studies demonstrate an association with MYB–QKI rearrangement on genetic analysis. Surgical resection generally yields favorable outcomes and prognoses.

METHODS: N/a

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RESULTS: An 8-year-old boy with a history of autism presented with new-onset seizures including left hemibody witching, lip-smacking, and hypersalivation, accompanied by loss of awareness, and occasionally followed by vomiting and left-sided weakness. Notably, a prior, incidentally discovered, non-enhancing FLAIR hyperintense lesion in the right cingulate gyrus was observed during a developmental regression workup at age 4. Presumed to be a dysembryoplastic neuroepithelial tumor, it was monitored with serial imaging. The patient was initially treated with lacosamide and valproic acid. Subsequent admission to the epilepsy monitoring unit was limited by poor tolerance of EEG electrodes, yielding no captured seizures and highly artifactual EEG readings. Seizure control remained challenging despite the addition of eslicarbazepine, with seizure frequency persisting at up to 5 per week. Following tumor board discussion, a right cingulate lesionectomy was pursued. Stereotactic needle biopsy followed by laser ablation revealed an angiocentric glioma with MYB-QKI fusion and PTEN and MET mutations. Post- surgery, seizure frequency significantly decreased to 1-2 per month.

CONCLUSIONS: Given the rarity of AGs and the limited number of reported cases, increased awareness of these tumors is essential. This case emphasizes the importance of considering AG in the differential diagnosis for children with lesional intractable epilepsies.

KEYWORDS: Epilepsy, Neuroimaging, Neuro-oncology

53. Anti-Seizure Medication Use and Effectiveness in 13,855 Children: A Large Real-World Cohort Study

Jack Abend, Alexander Gonzalez, Michael Kaufman, Mark Fitzgerald

OBJECTIVE: We aimed to assess anti-seizure medication (ASM) prescription patterns over time, ASM effectiveness, and treatment pathways in a large-scale pediatric cohort using real-world data.

METHODS: We conducted a retrospective analysis of children with epilepsy receiving care from 2010-2021 at a single institution. Data were extracted from Epic using a structured query process. We excluded rescue medications (benzodiazepines) and intravenously administered ASM. We grouped ASM across formulations and doses. We defined ASM effectiveness as the absence of a subsequent ASM prescription.

RESULTS: Among 13,855 patients, 27 ASMs were prescribed. Prescribing patterns remained relatively stable over the past decade, although use increased for cannabidiol and clobazam and decreased for lamotrigine. The most commonly prescribed first ASMs were levetiracetam (39%), oxcarbazepine (19%), and valproic acid (11%). First-line effectiveness was 60% for levetiracetam, 64% for oxcarbazepine, and 54% for valproic acid. The number of ASM's prescribed was one in 55%, two in 22%, three in 10%, and four or more in 13% of patients.

CONCLUSIONS: In one of the largest real-world studies of pediatric ASM use to date, prescribing patterns remained relatively stable over more than a decade, and the most commonly prescribed first ASMs were effective in about 60% of children. Over half of children were treated with a single ASM, while approximately one-quarter required three or more ASM. Subsequent analyses will assess second-line ASM effectiveness and stratify analyses by age, epilepsy type, and epilepsy syndrome.

KEYWORDS: Epilepsy

54. Nonketotic Hyperglycinemia in Three Pediatric Patients: Clinical Features and Response to Ketogenic Diet

Jonathon Chon Teng Chio, Cherie Herren

OBJECTIVE: Non-ketotic hyperglycinemia (NKH) is caused by pathogenic genetic variants resulting in deficient glycine cleavage. Excessive accumulation of glycine, an N-methyl-D-aspartate receptor (NMDAR) co-agonist, in the central nervous system leads to seizures. We describe clinical presentation, diagnostic findings, and management of pediatric patients with NKH to highlight early recognition and appropriate therapeutic interventions.

METHODS: Three children (AS, AF, and LC) were evaluated. Data included presenting symptoms, physical examination findings, magnetic resonance imaging (MRI), electroencephalography (EEG), cerebrospinal fluid (CSF)/ plasma glycine ratios, genetic testing, and response to treatments (ketogenic diet, anti-epileptic medications, and NMDAR antagonists).

RESULTS: All three children presented with global developmental delay and seizures with varying presentations, including myoclonic jerks and epileptic spasms. Physical exam was notable for hypotonia in LC. Brain MRI demonstrated corpus callosum abnormalities in AF and LC. AS showed abnormal signal intensities in basal ganglia and cerebellar structures. EEG patterns included burst suppression, hypsarrhythmia, and multifocal epileptiform discharges. CSF/ plasma glycine ratios ranged from 0.08 to 0.15. Genetic testing confirmed heterozygous *GLDC* pathogenic mutations in all cases. Ketogenic diet improved seizure control and reduced CSF glycine levels. Valproate was avoided due to its ability to increase glycine levels and, paradoxically, worsen seizures.

CONCLUSIONS: NKH remains under-recognized due to reliance on exome sequencing for diagnosis, lack of routine CSF amino acid analysis, and incomplete multigene epilepsy panels. This case series emphasizes the importance of considering NKH in children with early-onset seizures, developmental delay, and characteristic EEG patterns. Ketogenic diet represents an effective therapeutic option for glycine reduction and seizure management.

KEYWORDS: Epilepsy, Lifespan Manifestations of Childhood Onset Conditions

55. sEEG for Pediatric Tumor-Related Epilepsy: A Systematic Review of Indications, Outcomes, and Surgical Impact

Nicholas Benjamin, Sushma Thapa, Leen Alkalbani, Nour Kurdi, Fareen Ahmad, Amitha Halthore, Zena Alkurdi, Tobias Brunger, Dennis Lal, Sonam Bhalla, Ruba Al-Ramadhani

OBJECTIVE: Stereoelectroencephalography (sEEG) is being increasingly used in complex epilepsy surgery; however, its

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role in pediatric tumor-related epilepsy has not been clearly established. A systematic review was conducted to evaluate the current evidence on the use of sEEG in this population.

METHODS: A PRISMA-style systematic review of the PubMed literature was performed using terms related to sEEG, tumor-related epilepsy, and epilepsy surgery. Data were extracted on patient population, tumor characteristics, indications for sEEG, epileptogenic zone localization, and seizure outcomes. Data were synthesized descriptively.

RESULTS: Five studies composed of 270 diverse patients were included for review, most being retrospective case series. The literature was limited/heterogeneous with respect to tumor histology, cohort composition, and outcome reporting. sEEG was most often used when noninvasive presurgical data were inconclusive/discordant. Epileptogenic zones were reported as intratumoral, peritumoral, and occasionally, distal to the visible lesion, highlighting the network complexity of tumor-related epilepsy. In several studies, sEEG findings altered the operative plan by supporting resection beyond the radiographically defined tumor. Seizure outcomes were generally favorable, although comparisons across studies were limited by inconsistent reporting. Reported complications were low and consistent with the established safety profile of sEEG.

CONCLUSIONS: The available literature, although limited, supports sEEG as a valuable adjunct in the presurgical evaluation of pediatric tumor-related epilepsy, particularly in complex cases with unclear noninvasive localization. sEEG may improve surgical targeting by identifying epileptogenic cortex beyond the visible lesion and may meaningfully influence surgical planning. Larger/multicenter studies with standardized reporting are needed to better define its role in children with tumor-related epilepsy.

KEYWORDS: Epilepsy

56. Characterizing neurological conditions in pediatric patients from Nunavut receiving care in Ottawa: A retrospective study

Kate Hurley, Madeline Hopkins, Heather Leduc-Pessah, Holden Sheffield, Sarah Buttle, Daniela Pohl

OBJECTIVE: Children living in remote and northern regions such as Nunavut, Canada face challenges accessing specialized neurological care. Conditions including epilepsy, autoimmune neurological diseases, and rare genetic syndromes often require advanced testing and specialist follow-up, which are not readily available in-territory. As a result, many children are transferred to Ottawa for specialist assessment, diagnosis, and management. To date, there is no published data describing the prevalence and patterns of neurological disease among children from Nunavut, limiting healthcare planning and resource allocation for this population.

METHODS: We conducted a retrospective chart review of children from Nunavut who received neurological care in Ottawa between 2014 and 2025. A total of 289 patient charts were identified and will be reviewed for neurological diagnoses, utilization of tests including electroencephalograms (EEGs), magnetic resonance imaging (MRIs), and genetic panels, as well as patterns of referral, access to care, and follow-up. This project is being conducted in collaboration with Indigenous community representatives and pediatric healthcare providers in Nunavut.

RESULTS: Final results are pending. This study aims to characterize neurological diagnoses and resource utilization, identify barriers in the current system, and highlight opportunities to improve services. We will also evaluate whether the introduction of visiting pediatric neurology clinics and in-territory EEG services was associated with changes in referral patterns, diagnostic testing, and transfers to Ottawa for neurological care.

CONCLUSIONS: This work supports more equitable, responsive, and personalized neurological care for children in remote regions like Nunavut and lays the foundation for future community-informed health systems planning and research.

KEYWORDS: Epilepsy, Neurogenetics, Global Neurology

57. Cannabidiol Oral Solution (CBD-OS) for the Treatment of Focal-Onset Seizures: Design of a Phase 1b Open-Label Study

Alessandra Milesi-Hallé, Taha Gholipour, Jean Paul Nicandro, Kimberly Babson, Michael Boffa, Farhad Sahebkar

OBJECTIVE: Focal-onset seizures (FOS) are the most common seizure type, experienced by up to 61% of people with epilepsy, with peak onset in childhood/adolescence. Real-world evidence suggests plant-derived, highly purified cannabidiol oral solution (CBD-OS; Epidiolex®, 100 mg/mL) can reduce FOS frequency irrespective of etiology. EpiFOS (NCT07233239) is a phase 1b, multicenter, open-label, single-arm study to further evaluate CBD-OS efficacy and safety in participants with FOS.

METHODS: Target enrollment is 100 participants, aged 12–75 years, diagnosed with FOS (early-line or refractory) and receiving 1–4 antiseizure medications on a stable regimen. The study design comprises a 6-week baseline period, 16-week open-label treatment period (4-week titration and 12-week dose optimization), 10-day taper, and 4-week safety follow-up. During titration, participants initiate CBD-OS at 5 mg/kg/day, increasing by 5 mg/kg/day weekly up to 20 mg/kg/day. During dose optimization, CBD-OS may be increased further up to 25 mg/kg/day based on clinical response or decreased for tolerability. A functional magnetic resonance imaging (fMRI) substudy will include participants with FOS and healthy volunteers (untreated control group, approximately 30 participants).

RESULTS: The primary endpoint is percentage change from baseline in countable focal seizure frequency. Secondary endpoints include safety and tolerability. Other exploratory endpoints include participant- and clinician-reported outcomes and, in substudy participants, fMRI and neuropsychological measures to explore potential predictors of treatment response.

CONCLUSIONS: This study aims to address knowledge gaps regarding CBD-OS efficacy and safety for treating FOS. The inclusion criteria represent a broad population including adolescents and adults with both early-line and refractory FOS; results may inform future research.

KEYWORDS: Epilepsy

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58. Assessing the Effectiveness of Telemedicine for Pediatric Epilepsy Management

Loubna Elhelu, Stephanie Horton, Jean-Baptiste Le Pichon, Ahmed Abdelmoity, Erin Fecske, Kathleen Goggin, Morgan Waller, Elizabeth Willenborg, Gina Jones

OBJECTIVE: To evaluate the efficacy of telemedicine as a mode of delivering pediatric epilepsy care by assessing patient characteristics, care processes, and clinical outcomes obtained through retrospective chart reviews of telemedicine and in-person visits.

METHODS: A retrospective review of 307 encounters (n=112) was conducted among patients in a larger Health Resources and Services Administration-funded project. Variables included demographics, provider type, telemedicine utilization, safety counseling, psychiatric screening, seizure characteristics, comorbidities, and follow-up care. Descriptive statistics were used to assess whether telemedicine encounters supported timely evaluation, adherence to care standards, and appropriate clinical decision-making.

RESULTS: Patients averaged 2.74 visits, and 19.6% completed their first telemedicine visit. The average interval between the last in-person visit and the first telemedicine encounter was 312 days, demonstrating engagement in care. Most encounters were conducted by physicians (73.9%), primarily epileptologists (90.7%). Safety counseling was documented in 90.6% of encounters, and psychiatric screening occurred in 79.3% of eligible patients, with all positive screens appropriately referred. Among patients aged ≥14 years, 59.1% had documented transition readiness assessments. Clinical outcomes showed 56.5% of patients were seizure-free at their most recent visit. For new-onset seizures, 12.5% received EEG and 4.5% MRI within three months, and 20.5% required EMU admission within six months, indicating appropriate escalation of care.

CONCLUSIONS: Findings show that telemedicine supports high-quality pediatric epilepsy care, with strong performance in safety counseling, psychiatric screening, and seizure management. Telemedicine encounters enabled appropriate evaluation and follow-up, indicating virtual care is an effective component of epilepsy management. Opportunities remain to improve documentation completeness and standardization across encounters.

KEYWORDS: Epilepsy, Telemedicine

59. Identifying Health Needs, Service Gaps, and Barriers to Care Among Pediatric Epilepsy Populations during Transition to Adulthood

Stephanie Martinez, Ahmed Abdelmoity, Erin Fecske, Gina Jones, Jean-Baptiste Le Pichon, Kathleen Goggin, Loubna Elhelu, Stephanie Pratt, Emily Thorpe, Tami Allen, Bridgit Patterson

OBJECTIVE: The purpose of this needs assessment was to identify priority health needs, service gaps, and barriers to care among children and adolescents with epilepsy and their parents/caregivers, to inform program planning, resource allocation, and alignment with national health priorities to support patients and families during the transition to adulthood.

METHODS: A comprehensive needs assessment was conducted using mixed methods. Quantitative and qualitative data were obtained through an online survey. We included community partners, schools, patients with epilepsy, parents/caregivers, administrators, doctors, and nurses. Data was analyzed to assess population characteristics, health disparities, access to care, and unmet service needs.

RESULTS: The assessment identified unmet needs, including disparities in access, chronic disease burden, and social determinants of health. Participants included 72 professionals, 28 youth with epilepsy, and 152 parents/caregivers. Key gaps and barriers involved care coordination, service availability, and resource access. Findings highlight at-risk populations and areas for service expansion to improve outcomes. 68.1% of providers need support to better assist parents and caregivers, aligning with 57.5% of parents who reported that epilepsy moderately or significantly impacts their lives.

CONCLUSIONS: The needs assessment provides critical insight into the health priorities and service gaps affecting patients with epilepsy and their parents/caregivers. Results support the development of targeted, evidence-informed interventions and strategic planning efforts. Ongoing assessment and data-driven planning are essential to improving access, reducing disparities, optimizing health outcomes, and supporting patients during the transition to adulthood.

KEYWORDS: Epilepsy, Diversity, Equity, Inclusion

60. Eye-movements as a window into neurological development in Childhood Absence Epilepsy

Rachel Kuperman, Nathaniel Blanco, Bikramjit Sarkar, Parth Amin, Heidi Munger Clary, Donald Phillips, Kelly Knupp

OBJECTIVE: Childhood Absence Epilepsy (CAE) is associated with a variety of cognitive and neurobiological comorbidities, including abnormalities in saccadic eye movements. The goal of the current study was to get a better understanding of cognitive and neurological development in children with CAE by investigating eye-movement behavior across development in children with CAE and controls.

METHODS: We collected eye-tracking data on 60 children (30 with CAE, 30 Controls) 4-12 years old while they engaged in various eye-movement activities. In the pro-saccade task participants fixated a cross in the center of a computer screen, then looked as quickly and accurately as possible to a target stimulus appearing on the left or right side. In the anti-saccade task they were instructed to inhibit looking at the stimulus and instead look in the opposite direction.

RESULTS: We calculated several measures of performance including accuracy, saccade peak velocity, and saccade latency for both tasks. Interestingly, each of the eye-movement metrics showed an interaction between study group (CAE vs. Control) and age. The general pattern across several metrics was the control group improving with age (e.g., increased accuracy, reduced latency, and lower variability), while the performance of the CAE group was relatively stable across different ages.

CONCLUSIONS: These results suggest that normal development may be hindered or delayed in kids with CAE,

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though it is still unclear if these differences result from CAE itself or side-effects from anti-seizure medication. Additionally, eye-movements provide promising insight into neurological and cognitive development which needs further investigation in epilepsy.
KEYWORDS: Epilepsy

61. Clinical Outcomes After Long-Term Ketogenic Diet Completion and Discontinuation in Korean Pediatric Epilepsy

You Min Kang, Ara Ko, Se Hee Kim, Joon Soo Lee, Hoon-Chul Kang, Young Ok Kim

OBJECTIVE: Epilepsy is a common chronic neurological disorder in children, and many patients remain resistant to antiseizure medications(ASMs). The ketogenic diet(KD) is an established non-pharmacological treatment for drug-resistant epilepsy(DRE), but long-term outcomes beyond two years and seizure control after KD discontinuation remain unclear.
METHODS: We conducted a retrospective, single-center study of pediatric patients(<18 years) who initiated KD between January 2005 and October 2024 and maintained the diet for at least 24 months. Among 1,027 patients, 164 were included in the final analysis. Baseline clinical characteristics, seizure frequency, and ASM use were collected. Treatment response was defined as a ≥50% reduction in seizure frequency without additional therapies. Outcomes were assessed during KD therapy and after discontinuation, and seizure-free rates were analyzed using Kaplan–Meier methods.
RESULTS: At 24 months, 127 patients(77.4%) were responders, showing significant reductions in seizure frequency at all time points(3, 6, 12, and 24 months; $p<0.001$). The number of ASMs also significantly decreased both at 24 months and after KD discontinuation ($p<0.001$). Among responders, 71 patients(55.9%) maintained a sustained response after KD discontinuation. Non-maintained responders had higher rates of febrile seizures, family history of epilepsy, and Dravet syndrome, whereas maintained responders were more likely to be male and to have structural etiologies. The mean seizure-free duration after KD completion was 78.3±8.1 months, and more than 60% of patients remained seizure-free five years after diet completion.
CONCLUSIONS: Long-term KD therapy was associated with sustained seizure reduction and decreased ASM use, with benefits persisting after discontinuation, suggesting a potential disease-modifying effect.
KEYWORDS: Epilepsy, Practice Parameters

62. Burden of Illness in Developmental and Epileptic Encephalopathies Beyond Dravet Syndrome, Lennox-Gastaut Syndrome, and Tuberous Sclerosis Complex: A Systematic Literature Review

Sanket Shah, Miranda Harrison, Paranjoy Saharia, Mahmoud Slim, Lionel Pinto

OBJECTIVE: Developmental and epileptic encephalopathies (DEEs) are a heterogeneous group of rare neurodevelopmental disorders with early-onset seizures, developmental delays, and neurocognitive impairments. While Dravet syndrome (DS), Lennox-Gastaut syndrome (LGS), and tuberous sclerosis complex (TSC) are well characterized, other DEEs remain less well-defined. This review evaluated the clinical and humanistic burden of DEEs beyond DS, LGS, and TSC.
METHODS: A systematic literature review was conducted across MEDLINE, Embase, MEDLINE In-Process (January 2015–April 2025), and 5 conference proceedings (2023–2025), with bibliographic screening per predefined PICOS criteria. Seizure burden, complications, treatment patterns, and humanistic burden of DEEs were qualitatively synthesized.
RESULTS: Among 2621 records, 58 studies (4 randomized controlled trials [RCTs], 5 non-RCTs, and 49 observational) reported clinical burden across age groups (infancy–45 years) and geographies. CDKL5-DEE was most investigated (18 studies), followed by West syndrome and KCNQ2-DEE (8 studies each). Seizure burden was high (14.5–82.8 episodes/month) despite using multiple antiseizure medications and frequent polypharmacy. High proportions of patients showed developmental delays (80–97%), intellectual disability (54–100%), and motor dysfunction (46–93%). Humanistic data (13 studies) detailed marked impairment in adaptive functioning, cognition, and behavior in SCN2A, KCNQ2, CDKL5, and SYNGAP1 DEE subtypes, and high caregiver psychological strain and reduced work capacity.
CONCLUSIONS: Similar to DS, LGS, and TSC, other DEEs also confer a profound burden encompassing frequent refractory seizures, and developmental complications, requiring extensive caregiver support. Individuals with DEEs have high unmet needs for treatments that reduce seizures, improve patient quality of life and nonseizure outcomes, and reduce caregiver burden.
KEYWORDS: Epilepsy

63. Personal and Familial Autoimmunity in Landau-Kleffner Syndrome

Jenna Harowitz, Bo Zhang, Coral Stredny

OBJECTIVE: Landau-Kleffner syndrome (LKS) is a subtype of epileptic encephalopathy with spike-wave activation in sleep (EE-SWAS). Underlying etiology may include structural, genetic, and potentially autoimmune/inflammatory contributions. We evaluated rates of personal and familial autoimmune disease in children with LKS to determine whether autoimmunity is overrepresented in these patients.
METHODS: We conducted a single-center retrospective cohort study of patients with possible or definite LKS evaluated at Boston Children's Hospital from 1995–2020. Clinical, demographic, autoimmune history, and treatment data were abstracted from the electronic medical record. Categorical variables were summarized using counts and proportions and compared using Fisher's exact test.
RESULTS: A total of 108 charts were screened. Among 61 patients (45 possible, 16 definite LKS), 77% were male. Language regression was more frequent in definite LKS (100% vs 71.1%, $p=0.014$). Use of corticosteroids (81.3% vs 35.6%, $p=0.003$) and IVIG (37.5% vs 8.9%, $p=0.015$)

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was also higher in definite LKS. Rates of personal autoimmune disease were low (6.6%) and similar between groups (p=1.000). First-degree family history of autoimmune disease was present in 5.3% of patients, observed only in the possible LKS group without a significant difference (p=0.516).
CONCLUSIONS: In this cohort, clinically apparent autoimmune disease was uncommon and not enriched in children with definite LKS. However, larger prospective studies with standardized ascertainment and control groups are needed to further define the role of immune dysregulation in LKS.
KEYWORDS: Epilepsy, Neuroimmunology, Sleep

64. Cognitive and Attentional Dysfunction in Children with Self-limited Epilepsy with Centrotemporal Spikes: Factors Associated with ADHD

Jieun Choi, Hye Jin Kim, Seoyun Jang

OBJECTIVE: Although children with Self-limited epilepsy with centrotemporal spikes (SeLECTS) typically demonstrate normal development and favorable seizure outcomes, a subset exhibits learning difficulties. We aimed to analyze cognitive and attentional profiles in SeLECTS and identify factors associated with attention-deficit/hyperactivity disorder (ADHD).
METHODS: We retrospectively analyzed 40 children (21 males) with SeLECTS from 2009–2026 who underwent Wechsler intelligence scales and Comprehensive Attention Test (CAT). ADHD was clinically diagnosed based on DSM-5 criteria. Factors associated with ADHD were evaluated using Firth-penalized logistic regression.
RESULTS: ADHD was present in 40.0% of SeLECTS patients, and 27.5% showed below-average intellectual functioning (full-scale IQ (FSIQ) <85), while median FSIQ remained normal (93 [81–104]). On CAT, 69.2% showed at least one impaired domain, mostly on slowed reaction time across domains, with the highest impairment in interference control (55.3%). Children with ADHD had earlier seizure onset (85.5 vs. 102.5 months, p<0.05) and lower FSIQ (85.5 vs. 95.0, p<0.05) and processing speed index (PSI; 84 vs. 100, p<0.05) than those without ADHD. Location of epileptic spikes and seizure severity did not differ between groups. In multivariable analysis, earlier seizure onset (OR 2.10 per 1-year decrease, 95% CI 1.18–4.90, p=0.008) and lower PSI (OR 1.33 per 5-point decrease, 95% CI 1.03–2.08, p=0.028) were independently associated with ADHD.
CONCLUSIONS: Despite a self-limited seizure course, cognitive and attentional difficulties were common in SeLECTS. Earlier seizure onset and reduced processing speed were associated with ADHD. Given the lack of association with EEG features, further studies are needed to elucidate mechanisms underlying ADHD in SeLECTS.
KEYWORDS: Epilepsy, Behavioral Neurology

65. One Mutation, Four Phenotypes: DEPDC5 in a Father and Three Siblings

Sophia Falmagne, Melinda Schneider, Aliza Riba, Timothy Bang, David Adams, Clare Skora

OBJECTIVE: To describe the intrafamilial phenotypic spectrum associated with a pathogenic *DEPDC5* variant and highlight diagnostic challenges, including presentations mimicking electroclinical syndromes and nonepileptic events.
METHODS: We describe a father and three children with a shared pathogenic *DEPDC5* variant demonstrating intrafamilial phenotypic diversity. Two additional siblings tested negative.
RESULTS: The father developed epilepsy at age 7 with multiple seizure types (absence, generalized tonic–clonic, focal tonic), now well controlled on polytherapy, and was diagnosed only after his children underwent genetic testing. A 6-year-old daughter presented at age 3 with generalized tonic–clonic seizures and autonomic events. EEG showed parieto-occipital discharges with right posterior seizure onset, consistent with a Panayiotopoulos-like phenotype. She also had nonepileptic events on video EEG. After multiple medication trials, she was weaned off therapy and remained seizure-free for approximately one year, suggesting remission consistent with a self-limited epilepsy, before recurrence with control on lacosamide. A 12-year-old son with mild autism spectrum disorder developed focal sensory–motor seizures with right parasagittal onset and multifocal discharges, along with nonepileptic events; seizures were controlled with cenobamate. A 10-year-old daughter initially presented with episodes concerning for panic attacks, with early video EEG showing no ictal correlate; as events intensified, repeat video EEG captured sleep-related hypermotor seizures with bifrontal onset, establishing a diagnosis of frontal lobe epilepsy after initial misclassification as nonepileptic events.
CONCLUSIONS: This family highlights the phenotypic spectrum of *DEPDC5*, ranging from posterior epilepsy with autonomic features to sleep-related hypermotor epilepsy and neurodevelopmental comorbidity. Recognition of this variability is essential to avoid misdiagnosis and guide genetic evaluation.
KEYWORDS: Epilepsy, Neurogenetics, Neurodevelopmental Disorders

66. Association of Fenfluramine Treatment and Everyday Executive Function in Preschool-Aged Children With Lennox-Gastaut syndrome

Amélie Lothe, Delphine Breuillard, Kelly Knupp, Patrick Healy, Jayne Abraham, Rima Nabbout

OBJECTIVE: To evaluate fenfluramine-associated changes in everyday executive function (EEF) in preschool-aged children with Lennox-Gastaut syndrome (LGS) in a randomized controlled trial (RCT; EP0214/NCT03355209) and its open-label extension (OLE).
METHODS: Patients with LGS (2–35 years) who completed the 14-week RCT (randomized to fenfluramine 0.7mg/kg/day [max: 26mg/day] or 0.2mg/kg/day, or placebo) were eligible to enter the OLE (flexible titration up to 0.7mg/kg/day). In this post hoc analysis, patients (2–<6 years) with caregiver-completed Behavior Rating Inventory of Executive Functioning®—Preschool Version (BRIEF®-P) at RCT baseline and Day 99 (end-of-study; RCT analyses; pooled fenfluramine) and OLE Mo12 (OLE analyses) were included. Clinically meaningful improvement (Reliable Change Index [RCI] ≥90%) or worsening (RCI

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≥80%) on BRIEF®-P Indexes (Inhibitory Self-Control [ISCI]/Flexibility [FI]/Emergent Metacognition [EMI]) and Global Executive Composite (GEC) as well as individual patient change in GEC T-score were assessed.
RESULTS: In the RCT, clinically meaningful improvement on BRIEF®-P ISCI/FI/EMI/GEC was reported in 2/1/3/3 patients receiving fenfluramine (n=18), and 0/0/1/0 patients receiving placebo (n=3); clinically meaningful worsening was reported in 6/4/5/6 patients receiving fenfluramine (n=18) and 1/1/0/0 patients receiving placebo (n=3). In the OLE, improvement was reported in 1/1/1/0 patients (n=8/8/7/7) and worsening was reported in 3/4/5/5 patients (n=8/8/7/7). Individual trajectories of GEC T-scores over time will be reported.
CONCLUSIONS: The results of this post hoc analysis show the dynamics of individual patient evolutions and may suggest a degree of fenfluramine-associated EEF numerical improvement in patients 2–<6 years with LGS. However, results should be interpreted with caution due to low sample size.
KEYWORDS: Epilepsy, Neurodevelopmental Disorders

67. Prevalence, Treatment Patterns, and Healthcare Resource Utilization Among Patients With CDKL5 Deficiency Disorder: Retrospective Analysis of US Claims Data

Melinda Martin, Jaya Khushalani, Sam Amin, Xiaoyu Dong, Rajsekar Rajaraman, Patrik Öhagen, Orrin Devinsky, Scott Demarest

OBJECTIVE: Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD), an ultra-rare developmental and epileptic encephalopathy, is characterized by early-onset, antiseizure medication (ASM)-resistant seizures and significant developmental delays. We determined prevalence, clinical characteristics, treatment patterns, and healthcare resource utilization (HCRU) in patients with CDD using US claims data.
METHODS: This retrospective study included patients with ≥2 CDD claims ≥1 month apart from 01/01/2020–12/31/2024 in the US Komodo Healthcare database. Descriptive analyses were used to summarize data. HCRU burden was compared between CDD and matched non-CDD epilepsy cohorts in the 6 months post diagnosis.
RESULTS: Of 584 patients with CDD, mean age was 19.1 years (95% CI, 17.2, 21.1); 71.1% were female. In 2024, CDD prevalence was 3.3/million, was highest in females <18 years old (17.3/million), and constituted 0.03% of all epilepsy diagnoses. Most common prior diagnoses were infantile spasms (32%), Rett syndrome (30%), cerebral palsy (29%), and Lennox-Gastaut syndrome (25%). Gastrointestinal issues (84%), respiratory issues (81%), and developmental delay (78%) were the most common comorbidities. Levetiracetam (34%) and clobazam (33%) were the most common ASMs. Increased uptake post diagnosis was seen for ganaxolone (23%), fenfluramine (5%), and cenobamate (3%). HCRU analysis showed significantly more burden among patients with CDD (n=569) vs non-CDD epilepsy (n=1136) for seizure-related HCRU claims, status epilepticus claims, concomitant ASMs, and rescue medication claims ($P<0.05$ for each).
CONCLUSIONS: This real-world retrospective analysis reports prevalence for patients with CDD for the first time in a large, claims-based population. Comorbidities and HCRU burden are substantial for patients with CDD.
KEYWORDS: Epilepsy

68. Early and Sustained Reduction of Seizures in Children with Drug-Resistant Epilepsy Treated with Vagus Nerve Stimulation Therapy

James Wheless, Muhammad Zafar, Gholam Motamedi, Gaia Giannicola, Fawzi Babtain, Saleh Baeesa, Menaka Fry, Riem El Tahry, Gudron Groeppel, Terence O'Brien, Paul Lyons, Kore Liow, Kathryn Nichol, Maxine Dibue, Francesca Beraldi, Charles Gordon, Arjune Sen

OBJECTIVE: Children with drug-resistant epilepsy (DRE) face a high burden of frequent and disabling seizures. While vagus nerve stimulation (VNS) therapy is approved as adjunctive treatment in pediatric patients, prospective real-world data describing seizure outcomes over an extended period of time is limited.
METHODS: CORE-VNS (NCT03529045) is a prospective, multicenter, multinational observational study evaluating outcomes following first-time VNS implantation. This analysis included children aged 0 to <18 years with DRE. Outcome measures included median percent change from baseline in monthly seizure frequency, 50% and 80% responder rate, and incidence of complete seizure freedom at 3, 6, 12, 24, and 36 months post implantation.
RESULTS: A total of 241 children were included. Early and sustained median percent seizure reductions were noted for all seizures (84.8% at 36M), focal seizures overall (94.4% at 36M), and generalized seizures overall (75% at 36M). The 50% and 80% responder rates at 36 months were 69.1% & 51.7%, 76.2% & 60.1%, and 63.3% & 46.9%, respectively. Complete seizure freedom at 36M was 19.7%. For the identified most disabling seizure types, median percent seizure reductions at 36M for focal impaired awareness motor (FIA-M), focal impaired awareness non-motor (FIA-NM), focal to bilateral tonic-clonic (FBTC), and generalized tonic-clonic (GTC) seizures was 86.7%, 100.0%, 100%, and 75.1% respectively.
CONCLUSIONS: Adjunctive VNS therapy was associated with early and sustained reductions all seizure types in pediatric patients with DRE in real-world clinical practice.
KEYWORDS: Epilepsy

69. Non-Seizure Outcomes in Children with Drug-Resistant Epilepsy Treated with Adjunctive Vagus Nerve Stimulation

Kathryn Nichol, Muhammad Zafar, James Wheless, Gholam Motamedi, Gaia Giannicola, Fawzi Babtain, Saleh Baeesa, Menaka Fry, Riem El Tahry, Gudron Groeppel, Terence O'Brien, Paul Lyons, Kore Liow, Maxine Dibue, Francesca Beraldi, Charles Gordon, Arjune Sen

OBJECTIVE: Evalute the impact of VNS Therapy on non-seizure outcomes in children.

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METHODS: CORE-VNS (NCT03529045) is a prospective, multicenter, multinational observational study evaluating outcomes following first-time VNS implantation. Non-seizure outcomes (e.g., quality of life (QoL), Child Sleep Habits Questionnaire (CSHQ) abbreviated, rescue medication use, and healthcare resource utilization (HCRU) were collected at each study visit up to 36 months post VNS Therapy implantation.
RESULTS: A total of 241 children were included. Improvement in QoL was reported as early as the first study visit with 31.4% and 53.1% reporting no change or improved QoL at 36 months. A CHSQ mean change of -1.97 was reported from baseline at 36 months, indicative of small gains across multiple domains such as bedtime, sleep behavior, waking during the night, and morning waking/daytime sleepiness. A total of 83 participants were administered rescue medications during the 12 months preceding baseline. The median rescue medication density was 0.58 at baseline with a mean of 2.77 rescue medication administrations per month. At 36 months, the median change from baseline -0.42 with a reported mean of 0.61 rescue medication administrations per month. The number of seizure-related emergency room (ER) visits and hospitalizations, ER visits due to status epilepticus (SE), ER visits leading to hospitalization, and hospitalization due to SE all decreased following VNS implantation.
CONCLUSIONS: The use of adjunctive VNS was associated with early and sustained improvements in non-seizure outcomes over the 3 years following implantation in children with DRE.
KEYWORDS: Epilepsy

70. Neuropsychological Profile of Patients with Juvenile Absence Epilepsy: A Systematic Review

Nidhi Sthanki, Kerry Edge, Daniella Miller, Yash Shah

OBJECTIVE: To systematically review the published literature on cognitive, behavioral, and psychiatric features of Juvenile Absence Epilepsy (JAE), to characterize the syndrome-specific neuropsychological profile, and to identify methodological and evidence gaps that impede clinical translation.
METHODS: A PRISMA 2020–guided systematic review was conducted using PubMed literature Search. Studies (1) included patients diagnosed with JAE by contemporaneous ILAE criteria, (2) reported at least one quantitative cognitive, neuropsychiatric, or psychosocial outcome, and (3) were original research or systematic review.
RESULTS: Only five studies reported JAE-direct neuropsychological data with adequate syndrome specification. JAE patients showed a characteristic frontal-lobe cognitive profile with moderate impairments in verbal fluency and language, sustained attention and processing speed , and executive function, with impairment in working memory, long-term memory, and full-scale IQ. Language impairment was shared by unaffected siblings of JAE patients, identifying it as a familial/heritable endophenotype. Prolonged (≥3 s) interictal discharges on 24-hour EEG were independently associated with processing speed and memory impairment. Neuroimaging consistently demonstrated bilateral frontal grey matter reductions, decreased thalamic network centrality, and failure of default-mode suppression during cognitive tasks. Anxiety, depression, and ADHD were systematically underrepresented in JAE-specific research; no primary JAE psychiatric study was identified.
CONCLUSIONS: JAE is associated with a clinically meaningful and syndrome-specific neuropsychological profile dominated by frontal and language dysfunction. The evidence base remains thin as, thus the targeted research agenda — syndrome-specific prospective neuropsychological cohorts, replication in larger samples, longitudinal follow-up, and integration with neuroimaging and genetics — is required to support evidence-based clinical neuropsychological assessment and counselling for JAE patients.
KEYWORDS: Epilepsy, Behavioral Neurology, Lifespan Manifestations of Childhood Onset Conditions

71. SUDEP knowledge and counseling rates among pediatric neurology trainees

Sarika Sachdeva, Babitha Haridas

OBJECTIVE: A recent survey of adult neurology trainees showed that half rarely or never counseled patients on SUDEP, and many were unfamiliar with risk and mitigation factors1. There is no readily available data regarding rates of SUDEP counseling among pediatric neurology trainees. This study aims to assess SUDEP knowledge and counseling rates among pediatric neurology trainees at a single institution.
METHODS: Following IRB approval, 12 pediatric neurology residents completed an anonymous survey evaluating their knowledge, counseling practices, comfort, and barriers in discussing SUDEP in their weekly continuity clinic.
RESULTS: All 12 trainees were familiar with SUDEP. Four reported counseling >50% of patients in the last 3 months. In comparison to junior trainees (PGY2-3), senior trainees (PGY4-5) demonstrated slightly higher rates of SUDEP counseling (45% vs 37%, p 0.575). One junior trainee reported 90% counseling rates after receiving early education from an epileptologist. Excluding this respondent, the mean counseling rates for seniors vs juniors were 45% vs 26% (p 0.126). Factors reported to limit counseling included concern for causing undue stress (58%), lack of time (42%), limited understanding of pathophysiology (33%), and infrequent seizures (33%). Sixty-seven percent felt comfortable counseling about SUDEP prevention.
CONCLUSIONS: All pediatric neurology trainees were familiar with SUDEP and demonstrated increasing comfort with counseling practices as training advanced. Senior trainees demonstrated higher counseling rates. These findings emphasize the need for early implementation of a SUDEP training platform among all residents to align with AAN and AES practice guidelines2.
KEYWORDS: Epilepsy, Education, Practice Parameters

72. Antiseizure Medication Trajectories After Pediatric DBS: A Single-Center Case Series

Molly Baumhauer, Jacqueline Perelman, Kerri Neville, Laurel Reed, Neena Marupudi, Kevin Chen

OBJECTIVE: There is increased interest in deep brain stimulation (DBS) for pediatric refractory epilepsy, but outcomes

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remain unclear. We present a single-institution case series examining seizure outcomes and longitudinal antiseizure medication (ASM) burden.

METHODS: We retrospectively reviewed patients <19 years who underwent DBS for epilepsy at Michigan Medicine (2000-2025). Baseline variables came from the last preoperative neurology visit. Outcomes at ~1 year (median 374 days) included ASM count, ASM drug load (PDD/WHO DDD), weight-normalized ASM dose changes, and seizure frequency. Paired ASM measures were compared with Wilcoxon signed-rank tests. Adverse events were abstracted.

RESULTS: Thirteen patients were included (7 male); 6/13 had Lennox-Gastaut Syndrome. Implantation age averaged 13.0±2.9 years (range 8–18). Targets were anterior (4/13) or centromedian (9/13) thalamic nucleus. ASM count was unchanged at ~1 year (median Δ0; p=0.25), decreasing in 5/13 (38.5%) and increasing in 2/13 (15.4%). Drug load was unchanged (median 3.92 vs 3.81; p=1.0). Regimens were dynamic: 10/13 (76.9%) had ≥1 dose reduction ≥1 mg/kg/day or discontinuation and 11/13 (84.6%) had ≥1 dose increase ≥1 mg/kg/day or initiation. Among 12/13 with paired data, seizures improved in 5/12 (41.7%), were unchanged in 4/12 (33.3%), and worsened in 3/12 (25.0%). Adverse events included PICU admission for status epilepticus.

CONCLUSIONS: At ~1 year, seizure burden improved in a subset, while overall ASM count and drug load remained stable despite frequent bidirectional medication adjustments. Therefore, DBS can demonstrate meaningful improvements in seizure reduction although total medication burden may remain unchanged.

KEYWORDS: Epilepsy

73. Unmasking Focal Epilepsy in the Emergency Department: A Missed Diagnostic Opportunity

Michelle Goodman, Jacqueline French, Ruben Kuzniecky, Daniel Lowenstein, Shruti Agashe, Jacob Pellinen

OBJECTIVE: The present study sought to understand whether targeted questioning in the Emergency Department (ED) about focal features at onset of focal to bilateral generalized tonic-clonic seizures (FBTCS) can unveil underlying epilepsy and alter treatment management.

METHODS: Patients in the Human Epilepsy Project (HEP), a multi-center prospective observational study of newly diagnosed focal epilepsy, who presented to the ED with a first lifetime GTCS visits were identified. Structured interviews were performed to characterize the semiology of their initial seizures. We identified the proportion of patients who 1) experienced prior focal seizures and 2) reported similar symptoms at FBTCS onset.

RESULTS: Of the 248 patients who presented to the emergency room with a first lifetime FBTCS, 185 patients (74%) reported a history of prior spells; 142 patients (57%) reporting that their FBTCS began with a similar prodrome, 24 patients (13%) reporting a distinctly different or uncertain onset and 19 (10%) patients were unsure about their prodrome. 61 patients (25%) reported no prior spells or prodrome, and 2 patients (<1%) reported a prodrome before their FBTCS but without any prior spells.

CONCLUSIONS: Fifty-seven percent of patients with focal epilepsy presenting to the ED with first lifetime FBTCS could be diagnosed with underlying epilepsy based on the seizure onset history. A single structured question, at presentation may facilitate earlier treatment initiation and safer disposition decisions, potentially improving outcomes in this population.

KEYWORDS: Epilepsy, Early Stage Investigator, Education

74. Unusual case of Wernicke Encephalopathy in a pediatric patient on ketogenic diet

Laura Varan, Dimah Saade, Sreenath Ganganna, Sato Yutaka, Justice Nathaniel, Molly Heitman

OBJECTIVE: Wernicke encephalopathy (WE) is a neurologic disorder caused by thiamine (vitamin B1) deficiency, classically presenting with encephalopathy, oculomotor dysfunction, and gait ataxia. Although historically associated with chronic alcohol use, WE is increasingly recognized in children due to inadequate intake, malabsorption, chronic illness, or thiamine-deficient parenteral nutrition. We report a rare case of WE in a medically complex child with drug-resistant epilepsy on ketogenic diet who developed thiamine deficiency after an acute gastrointestinal illness.

METHODS: A 6-year-old boy with drug resistant epilepsy on multiple antiseizure medications and ketogenic diet presented with dehydration secondary to gastrointestinal illness characterized by vomiting that progressed to hematemesis. He developed ongoing feeding intolerance and recurrent hypoglycemia requiring dextrose-containing IV fluids, then acutely developed bilateral ptosis with impaired adduction, abduction, and infraduction several hours after dextrose administration.

RESULTS: Evaluation with MRI brain w/wo contrast showed abnormal FLAIR hyperintensities in the posterior medial thalami, periaqueductal gray matter, and dorsal white matter tracts of the pons and medulla, with mild postcontrast enhancement, findings concerning for thiamine deficiency. Serum thiamine was obtained, and intravenous thiamine (100 mg daily) was started promptly. Ophthalmoplegia improved within hours and resolved within two days, with concurrent improvement in mental status.

CONCLUSIONS: Thiamine deficiency can cause life-threatening neurologic complications. This case highlights the need for thiamine monitoring in children on the ketogenic diet—particularly during illness, vomiting, or poor intake—and the risk of precipitating Wernicke's encephalopathy when hypoglycemia is treated without thiamine repletion.

KEYWORDS: Epilepsy

75. A Comparative Analysis of Clinical Practice Gaps in Dravet Syndrome: Findings From a CME-Certified Survey of Neurologists and Pediatricians

Thomas Finnegan, Frances McFarland, Christine Considine, Anup Patel

OBJECTIVE: The goal of this study was to gain insight into the precise nature of the gaps in confidence, knowledge, or

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competence regarding the diagnosis and comprehensive management of Dravet syndrome (DS) among both neurologists and pediatricians.

METHODS: A continuing medical education (CME)-certified survey consisting of 25 multiple-choice questions on knowledge, competence, and confidence relating to the diagnosis and management of DS. The survey was made available to an audience of US-based neurologists and pediatricians. Data were collected from October 3, 2015, through December 2, 2025.

RESULTS: A total of 48 neurologists and 74 pediatricians completed the survey. >65% of both clinician groups correctly answered questions on the following topics in DS: interpreting genetic testing, when to inform families of patients about sudden unexpected death in epilepsy, and seizure triggers. Both clinician groups demonstrated similar deficits (<35% answering correctly) in awareness on the following topics in DS: when to order a genetic test when developmental and epileptic encephalopathy is suspected, most common presenting seizure type, and when hypotonia is likely to manifest. Areas where neurologists outperformed pediatricians included: clinical features that rule out potential differential diagnoses, use of ketogenic diet, changes in seizure type from childhood to adulthood.

CONCLUSIONS: This study demonstrated that neurologists and pediatricians share areas of awareness and educational need in DS. Both groups should receive additional education on genetic testing, common seizure types, and timing of hypotonia onset. Pediatricians may benefit from additional education on the differential diagnoses, use of the ketogenic diet, and changes in seizure type over time.

KEYWORDS: Epilepsy, Education

76. Treatment of Tonic-Clonic Status Epilepticus After T1 With Diazepam Nasal Spray in Patients Aged 2–17 Years: A Combined Cohort Analysis

Eric Segal, John Stern, Danielle Becker, Randa Jarrar, Tracy Glauser, Jurriaan Peters, Emilio Perucca, Leock Ngo, Enrique Carrazana, Adrian Rabinowicz

OBJECTIVE: Children with epilepsy and seizure clusters are at risk for status epilepticus (SE), which should be treated promptly, before permanent damage occurs. Diazepam nasal spray is approved for treating seizure clusters in patients with epilepsy aged ≥2 years. This post hoc analysis assessed diazepam nasal spray as treatment during tonic-clonic SE, seizures >5 minutes, in patients aged 2-17 years.

METHODS: Data were pooled from a phase 1/2a pharmacokinetics/safety study (aged 2-5 years; N=36) and a phase 3 long-term safety study (aged 6-17 years subgroup; n=78) evaluating diazepam nasal spray. Second doses were allowed, if needed. International League Against Epilepsy criteria for tonic-clonic SE (lasting beyond timepoint t_1, 5 minutes; potential long-term consequences by timepoint t_2, 30 minutes) were used. Proportion of SE episodes with termination in ≤20 minutes and ≤t_2 and recurrence after termination were assessed. Re-treatment of an SE episode was a proxy for effectiveness. Treatment-emergent adverse events were recorded.

RESULTS: Thirty-seven patients aged 2-17 years recorded 266 tonic-clonic SE episodes. Median times from onset to dose, dose to termination, and total duration were 10, 5, and 18.5 minutes, respectively. Of these SE episodes, 159 (59.8%) terminated within 20 minutes and 195 (73.3%) by t_2. SE recurred following 8 episodes (3.0%) in ≤12 hours and a total of 17 episodes (6.4%) had recurrence in ≤24 hours. Twenty SE episodes (7.5%) had ≥2 doses. The safety profiles were consistent with prior analyses.

CONCLUSIONS: Diazepam-nasal-spray treatment in pediatric patients provided rapid seizure termination for tonic-clonic SE.

KEYWORDS: Epilepsy

77. La Clinica Integral de Epilepsia Para Niños y Adolescentes (CIENA)

Joanna Bendeck, Alexander Andrews, Christian Hidalgo Jara

OBJECTIVE: Language barriers significantly impact specialized epilepsy care among Spanish speaking patients and their families. Our study aims to identify impeding and facilitating factors in effective communication between patients and providers in managing epilepsy.

METHODS: Parents and patients 8 and older will complete a questionnaire at the end of clinic visits conducted in Spanish. In order to obtain cross-sectional data, surveys will be deployed in clinics at Children's National where 1) a language-certified provider (neurologist and psychologist) conducts the visit, and where 2) an alternate mode of medical interpretation (in-person, or virtual) are employed. The survey will quantify the quality and understanding of care given in 5-point Likert scale. Data will be analyzed using a student's t-test to determine potential differences in responses between 1) in-person visits with language-certified provider, 2) in-person interpretation by non-medical professional, and 3) virtual interpretation.

RESULTS: The deployment of the survey will be in La Clinica Integral de Epilepsia Para Niños y Adolescentes (CIENA) at Children's National. The clinic is staffed by an epileptologist and an epilepsy psychologist certified in Spanish language. Since January 2026, the clinic has a 90% show rate and sees 15 patients per month.

CONCLUSIONS: With data gathered we will assess the optimal way to develop strategies in improving communication. Such as ease of access to the medical system, understanding of plan, medications, as well as the fluency in the conversation, and obstacles in care. By addressing this gap, we will allow fluent communication ensuring improved patient care and benefiting outcomes.

KEYWORDS: Epilepsy, Diversity, Equity, Inclusion, Global Neurology

78. Focal Epilepsy Associated with Cortical Malformation in an Infant with Nevus Sebaceous, Aplasia Cutis Congenita, and a RELN Variant of Uncertain Significance/ A Case report

Hasmik Verdyan, Tuong-Vi Tran

OBJECTIVE: We report a case of a 2-month-old male with unilateral facial nevus sebaceous (NS) and aplasia cutis congenita (ACC) who presented with focal seizures, abnormal

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brain MRI findings suggestive of cortical malformation, and a Variant of Uncertain Significance (VUS) in the RELN gene. NS and ACC are neurocutaneous anomalies that, in syndromic forms, can be associated with various central nervous system abnormalities. RELN variants have been associated with neuronal migration disorders, including lateral temporal lobe epilepsy. The concurrent findings in our patient make our case unique.

METHODS: N/A

RESULTS: A 2-month-old full-term male with age-appropriate development, history of right-sided facial NS, ACC, pulmonary hypertension, and apnea, presented with recurrent abnormal movements characterized by upward eye deviation, behavioral arrest, and oxygen desaturation. Prior EEG was reportedly normal, and he was diagnosed with apnea. On readmission, video-EEG captured events consistent with right frontotemporal-onset focal electroclinical seizures. Brain MRI demonstrated a cortical malformation involving the right parahippocampal gyrus, lateral sulcus, and amygdala. Genetic testing using an epilepsy panel identified a RELN variant of uncertain significance (c.8654C>T, p.Thr2885Ile). Levetiracetam was initiated; however, due to persistent breakthrough seizures, dose escalation was required.

CONCLUSIONS: This case highlights the rare coexistence of NS, ACC, cortical malformation, and a VUS in the RELN gene, warranting further genetic evaluation. Given the early diagnostic challenges in this case, prompt neuroimaging and serial EEG monitoring should be considered in any full-term infant presenting with atypical apneic episodes and unilateral craniofacial neurocutaneous lesions.

KEYWORDS: Epilepsy, Neuro-Cutaneous Disorders, Neurogenetics

79. Severe ketoacidosis in response to the ketogenic diet for epilepsy: a case report and center-based analysis

Emily Grew, Rachel Carpenter, Angela Curcio, Parmpreet Dhillon

OBJECTIVE: Acidosis is common in the ketogenic diet (KD), rarely causing hospital admission or diet discontinuation. We present a case of severe ketoacidosis and review acidosis among our patients.

METHODS: Chart review was performed using Epic. Our 107-patient KD dataset from 2010-2025 was analyzed in SPSS.

RESULTS: A 3 year-old girl with *GLUL*-related developmental and epileptic encephalopathy started the KD in 9/2025 at a 3:1 ratio. In 10/2025, ketones were within goal (1.8-3). Serum bicarbonate was 24. She started potassium citrate for hypercalciuria, to prevent acidosis and nephrolithiasis. She presented 1/2026 with lethargy, vomiting, and respiratory distress. Labs were notable for severe high anion gap metabolic acidosis: B-hydroxybutyrate 9.1, anion gap 22.7, pH 7.17, HCO3 4.43, pCO2 12, glucose 65, CRP 26, +coronavirus NL63. There was no evidence of sepsis and no respiratory symptoms. Due to ineffectiveness of the KD on seizure control and the complication of severe ketoacidosis, the KD was discontinued. IV fluids with partial dextrose improved ketoacidosis while maintaining seizure control. Patients had acidosis at 21.3% of visits. Average CO2 was 20.9 [10-35]. Each 1-year increase in age was associated with a 16% CO2 increase ($p<0.001$). Patients were less likely to have acidosis over time ($p=0.002$). A higher diet ratio was associated with lower CO2 ($p<0.001$). Lower CO2 was associated with higher ketones at the next visit (OR 0.88 per unit increase, $p=0.008$). CO2 did not predict diet discontinuation or seizure control.

CONCLUSIONS: Clinicians should be aware of acidosis as a common but rarely serious adverse effect of the KD.

KEYWORDS: Epilepsy, Early Stage Investigator

80. Underutilization of FDA approved Dravet Syndrome (DS) Specific Therapies: Findings from a US Multi-Center Survey and Advisory Board

Carly Katterman, Fábio Nascimento, Kelly Gwin, Andrea Calvert, Carla Schad

OBJECTIVE: DS is a severe developmental and epileptic encephalopathy characterized by drug-resistant seizures, requiring polytherapy for adequate seizure control. Despite the international consensus recommendations for DS-approved antiseizure medications (ASMs), stiripentol (STP), fenfluramine (FFA), and cannabidiol (CBD), an analysis found these ASMs have been underutilized in DS patients.[1,2] A US multi-center survey and advisory board aimed to explore ASM selection, barriers for use, and strategies to improve alignment with consensus recommendations.[2]

METHODS: A voluntary survey was completed by 38 clinicians from Level IV National Association of Epilepsy Centers. The survey assessed 1st and 2nd line ASM selections for patients with DS. Upon completion of the survey, an adboard was held to further analyze results with discussion surrounding barriers to ASM usage and strategies for mitigation.

RESULTS: The survey identified valproate (47%) or clobazam (CLB) (24%) as the most common 1st line ASMs considered when a patient is diagnosed with DS. CLB (47%) and FFA (24%) were found to be the 2nd most common ASMs considered, followed by CBD (11%) and STP (8%). Despite limited use, 58% of respondents agreed that DS-approved therapies provide better efficacy compared to other ASMs utilized. Advisory board discussions reinforced these findings, emphasizing the need for expanded medical education on DS-specific ASMs.

CONCLUSIONS: This analysis suggests underutilization of DS-approved ASM therapies in DS, highlighting a gap between consensus recommendations and real-world practice. Targeted education, increased familiarity, and access are critical for early adoption of DS-specific ASM to optimize seizure control and improve outcomes in this high-risk population.

KEYWORDS: Epilepsy

81. Practical Consensus Recommendations for Rational Polytherapy Involving Stiripentol in Dravet Syndrome: Preliminary Results of a US Cohort

Dalton Lovins, Kelly Gwin, Seiko Asai, Joseph Sullivan, Carly Katterman, Carla Shad

OBJECTIVE: Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy characterized by drug-resistant seizures, often requiring rational polytherapy. The diversity of

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options, heterogeneity of seizures, and importance of early intervention create a complex therapeutic landscape. Despite international consensus recommendations, there are disparities in utilization of anti-seizure medications (ASMs) in DS.[2] Recognizing these gaps, our objective was to develop a consensus aimed at guiding physicians in managing treatment combinations for patients with DS, with particular emphasis on polytherapy regimens that include stiripentol (STP).

METHODS: Thirty-five statements were developed encompassing six themes across managing complex treatment regimens. These statements were submitted for anonymous votes by US neurologists experienced in managing DS. Participants rated each statement using a 9-point Likert scale. Statements were considered to have reached consensus if they met either of the following criteria: ≥75% of scores ≥7 and/or a median score ≥8.

RESULTS: 23/35 statements reached strong consensus, 6 statements reached good consensus, and the remaining 6 statements did not reach consensus. There was strong consensus regarding a "notable reduction in seizure frequency and duration" when STP was added to an ASM regimen. However, no consensus was reached on several statements addressing the management of STP with other ASMs.

CONCLUSIONS: These results provide a practical framework for providers managing DS to guide polytherapy decisions. While there was a strong consensus supporting STP's efficacy when added to existing ASMs, the data revealed limited provider confidence in the management of DS-specific ASMs, including STP, underscoring the need for targeted education.

KEYWORDS: Epilepsy

82. Seizure Assessment Tool for Children on a Pediatric Epilepsy Monitoring Unit

Zoe Krochenski, Sofia Reda, Kenneth Myers, Chantal Poulin, Heather Davies

OBJECTIVE: Standardization of seizure care and assessment for children on the pediatric epilepsy-monitoring unit (EMU) at the Montreal Children's Hospital who are undergoing surgical assessment. This quality improvement project was initiated to address suboptimal neurological data collection pre-, during and post seizures, resulting from the lack of standardized seizure guidelines on the EMU.

METHODS: An evaluation of how nurses assess children before, during and post seizure on the EMU was executed through direct clinical observation, individual discussion with nurses and review of EMU telemetry monitoring videos. A literature review was conducted and bench marking with three Canadian Pediatric Epilepsy Monitoring Units was undertaken from January to April 2026. An EMU seizure assessment tool was developed for health care professionals and families. A parent partner was recruited to evaluate the tool to ensure feasibility and practicality of its use for families. Nurses, neurologists and EEG technicians also assessed the tool for relevance and usability. Teaching was provided to all EMU nurses, the tool was plasticized and easily available in the EMU patient rooms.

RESULTS: The tool standardized the care and information gathered for children pre-, during and post-seizure. The tool is clear, concise and easy to use. It provides concrete direction for seizure assessment and contributes invaluable information for the treating team for a pre-surgical assessment.

CONCLUSIONS: Standardizing seizure care and assessment for children in a pediatric EMU through a user-friendly tool is essential to bridging the gap between EEG data and clinical semiology.

KEYWORDS: Epilepsy

83. Clinical characteristics and use of highly purified cannabidiol oral solution among patients with developmental and epileptic encephalopathies: A US-based retrospective cohort analysis

Arthur Sillah, Leah Burn, Vicki Osborne, Xiaozhou Fan, Maggie McCarter, Elise Brimble, Stephanie Eaneff, Farhad Sahebkar, Tristan Sands

OBJECTIVE: To describe characteristics of individuals with developmental and epileptic encephalopathies (DEEs) and treatment with plant-derived, highly purified cannabidiol oral solution (CBD-OS; Epidiolex®, 100 mg/mL) across licensed (Lennox-Gastaut syndrome [LGS], Dravet syndrome [DS], or tuberous sclerosis complex [TSC]) and other ("beyond-license") DEE etiologies.

METHODS: This descriptive study used longitudinal electronic health records from Citizen Health (01/01/2019–05/01/2025). The study population included individuals with DEEs (defined as documented developmental/intellectual disability and seizure onset at age <12 years) and ≥12-month follow-up from seizure onset.

RESULTS: Among 831 individuals included in the study, 197 were diagnosed with a licensed indication (LGS, n=186; DS, n=11; TSC, n=0) and 634 with beyond-license DEE etiologies; overall, 96% (794/831) had a documented genetic etiology. The LGS/DS and beyond-license cohorts had median (Q1,Q3) age at seizure onset of 1.7 (0.3,3.2) and 1.6 (0.2,3.7) years, respectively, with follow-up of 8.3 (4.5,13.7) and 5.9 (3.1,10.9) years. Across seizure types, maximum seizure frequency >1 seizure/day within 6 months of seizure onset was recorded for 53% and 54% of the LGS/DS and beyond-license cohorts. Common comorbidities included global developmental delay (LGS/DS and beyond-license, both 94%); hypotonia (both 85%); sleep disorder (82% and 74%); altered bowel function (77% and 75%); movement disorder (77% and 69%); and feeding difficulties (61% and 54%). CBD-OS use was documented in 77% and 19% of the LGS/DS and beyond-license cohorts, respectively.

CONCLUSIONS: Individuals with DEEs experienced early seizure onset, high comorbidity burden, and similar long-term follow-up across LGS, DS, and beyond-license indications. CBD-OS treatment was more frequent in individuals with licensed indications.

KEYWORDS: Epilepsy

84. Gaps in SUDEP Communication in Pediatric Epilepsy: A Systematic Review

Ashiana Sunderji, Evelina Borvanova, Pareesa Versi, Mary Connolly

OBJECTIVE: Sudden unexpected death in epilepsy (SUDEP), defined as the sudden, unexpected death of an

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individual with epilepsy without an identifiable cause on postmortem examination, is a leading cause of epilepsy-related mortality. Despite guideline recommendations, communication about SUDEP remains inconsistent in pediatric care. This study aimed to examine how SUDEP is communicated in pediatric epilepsy by synthesizing evidence on clinician practices, caregiver perspectives, and interventions to improve risk communication.

METHODS: A systematic review was conducted in accordance with PRISMA guidelines. MEDLINE, Embase, PsycINFO, and CINAHL were searched using terms related to epilepsy, SUDEP, communication, and pediatrics. Studies examining SUDEP counseling, awareness, or educational practices in pediatric populations were included. Screening and data extraction were performed by two independent reviewers. Findings were synthesized narratively due to heterogeneity.

RESULTS: Twenty-four studies met inclusion criteria, spanning caregiver and healthcare provider perspectives. Caregiver awareness of SUDEP was limited (16–61%), yet 91–95.8% supported routine disclosure, generally preferring early, clinician-led, repeated, and individualized discussions. Routine counseling remained uncommon: only 1.8–12% of clinicians consistently discussed SUDEP, while 79.6% of pediatric practitioners reported never doing so. Key barriers included fear of causing distress, limited knowledge, and low confidence in risk communication. Structured educational and clinical interventions improved communication, including an increase in caregiver-reported SUDEP discussions from 21.3% to 46.2%.

CONCLUSIONS: A substantial gap exists between guideline recommendations and clinical practice in SUDEP communication. Caregivers value early, transparent discussions, highlighting an ethical and clinical imperative to improve communication. Structured, system-level interventions may support consistent, patient-centered SUDEP counseling in pediatric epilepsy care.

KEYWORDS: Epilepsy

85. A 6-year-old Boy with Recurrent Stroke-Like Symptoms - An Atypical Presentation of Rasmussen Encephalitis

Rachna Karumuri, Loren Mclendon, Fernando Galan

OBJECTIVE: Rasmussen Encephalitis (RE) typically presents with intractable epilepsy followed by progressive hemiparesis. We present a rare presentation of RE, a 6-year-old boy presenting with episodic hemiparesis.

METHODS: Chart review of a 6-year-old male and literature review of atypical presentations of RE.

RESULTS: A 6-year-old boy presented to the ED with left sided hemiplegia. He had an initial NIH of 14 for left sided deficits including left hemiparesis, hemineglect and facial palsy. Initial MRI revealed an area of diffusion restriction with DWI/ADC correlate within the right PCA territory, right hemispheric volume loss and right hemispheric atrophic vessels on MRA. EEG demonstrated right focal slowing with periodic lateralized epileptiform discharges. Repeat MRI within 48 hours demonstrated improvement of restricted diffusion within the R PCA territory along with new diffusion restriction and T2/FLAIR hyperintensity in the R hippocampus, and right hemispheric atrophy. Hemiparesis resolved after 24-48 hours, and NIH was 0 upon discharge. He had 2 additional presentations with similar hemiparesis. He subsequently developed focal epilepsy.

CONCLUSIONS: By the Bien criteria and consensus criteria by Stredny et al, the patient's presentation is consistent with RE given left focal seizures, right hemispheric slowing with epileptiform discharges, and right hemispheric cortical atrophy with T2/FLAIR hyperintensity within the R hippocampus. This case highlights an atypical presentation of RE due to episodic hemiparesis with minimally progressive/residual weakness. There have been 19 documented cases of RE presenting with weakness without seizures, 12 of which developed seizures within 2 years of hemiparesis onset however these patients all had significantly progressive hemiparesis.

KEYWORDS: Epilepsy, Neuroimmunology

86. Treatment of infantile spasms in Saudi Arabia

mohammed jan

OBJECTIVE: To evaluate the treatment approach and compliance of pediatric neurologists with evidence-based guidelines across Kingdom of Saudi Arabia (KSA). These guidelines that clarify the optimal management of infantile spasms (IS) are not widely followed for various practical reasons.

METHODS: Physicians practicing in the field of pediatric neurology in KSA were contacted from the database of national societies. A cross-sectional study was conducted using a structured 20-item on-line survey designed to examine their clinical experience with IS and their treatment choices.

RESULTS: A total of 52 pediatric neurologists completed the survey (69% estimated capture rate). They received their formal training within KSA (40%), North America (33%), or Europe (14%). The majority practiced in 2 major cities, Riyadh (46%) or Jeddah (19%). Vigabatrin was favored over ACTH as first line drug for patients without TSC (48% vs. 21%). Several factors correlated with correctly selecting ACTH as first line including western training (33% vs. 5%, $p=0.001$), practicing in the city of Riyadh (25% vs. 14%, $p=0.001$), or having >10 years of clinical experience (25% vs. 5%, $p=0.017$). Reasons for not complying with the recommended treatment guidelines included lack of availability of ACTH (42%), side effect profile of steroids (29%), and personal preferences (14%).

CONCLUSIONS: Many pediatric neurologists in KSA are not following the published IS management guidelines. Using ACTH as first line correlated with their training, practice location, and years of experience. Lack of drug availability and side effect profile were common reasons for not complying with the management guidelines.

KEYWORDS: Epilepsy, Practice Parameters

87. Real-World Use and Effectiveness of Stiripentol in U.S. Patients with Dravet Syndrome: Results from the STIRUS Study

Mary Fayazi, Kelly Gwin, Elaine Wirrell, Roxane Noel, Laurent Chancharme, Benjamin Serraz, Delphine Vandame

OBJECTIVE: Stiripentol (STP) is approved in the U.S. for treating seizures associated with Dravet syndrome (DS) in patients aged ≥6 months who are taking clobazam. Real-

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world data on STP use is limited. The STIRUS was a retrospective, observational study across 10 U.S. epilepsy centers.
METHODS: 98 patients who started STP after August 2018 and continued for ≥3 months were included. Data was collected for 3 months before STP initiation (baseline), the first 3 months on STP, and the final 3 months. Outcomes included seizure frequency, status epilepticus (seizures >5 minutes), rescue medication use, ER visits/hospitalizations, and quality of life.
RESULTS: The median age at DS diagnosis was 15 months and at STP initiation 6.9 years. At baseline, patients used a median of 3 medications: clobazam (n=81), cannabidiol (n=45), valproate (n=42), fenfluramine (n=24), and levetiracetam (n=23). 90% experienced bilateral convulsive seizures (BCS), and 34% had SE. STP significantly reduced BCS frequency (OR=2.16, p<0.006); 44% reported marked reduction after 3 months. SE prevalence declined from 33 at baseline to 16 and 14 during the first and final 3 months, respectively (ORs >2.8; p<0.003), with episode duration decreasing from a median of 30 to 15 minutes. Rescue medication use (OR=3.5; p<0.0001) and ER visits/hospitalizations (OR=4.0; p<0.0001) declined. Quality of life improved in 52% of patients. Somnolence and decreased appetite were reported in 50% of patients, with no unexpected safety concerns.
CONCLUSIONS: STP significantly reduced seizure burden, SE episodes, and healthcare utilization, demonstrating broad benefits beyond its approval. Earlier use, especially in infants, may further lessen DS-related morbidity.
KEYWORDS: Epilepsy, Global Neurology

88. Climate-related environmental exposures and presentation for epilepsy among children in Bangladesh

Maitreyi Mazumdar, Xingyan Wang, Caroline Sarpy, Arnav Ghosh, Yasmin Chowdhury, Ansar Ahmed, Nazmul Hoque, Mohammad Hossain, Ariful Islam, Md Rahman, Md Ziauddin, Diana Gomberg, Hafiza Suchanda, D. Arman, Joynul Islam, Sheikh Ekramullah, Sudipta Mukherjee, Narayan Saha

OBJECTIVE: We assessed whether climate-related environmental exposures were associated with presentation for epilepsy among children in Bangladesh, a country that is experiencing high levels of air pollution and heat stress.
METHODS: We conducted a case-control study at the National Institute of Neurosciences & Hospital in Dhaka, Bangladesh from February 2025 to January 2026. Cases were visits for patients aged 1 to 18 years with diagnoses of epilepsy. Controls were children who presented during the same period without these diagnoses. We used satellite data from ERA5-land and MERRA-2 to estimate daily district-level measures of air temperature, dew point temperature, specific humidity, simplified wet bulb globe temperature (sWBGT), surface pressure, precipitation, $PM_{2.5}$, and PM_{10}. We constructed lagged exposure metrics over multiple time windows. We estimated odds of epilepsy visit using logistic regression, adjusted for district of residence.
RESULTS: We identified 5,356 visits for epilepsy among 23,033 patient visits. Mean case age was 7.9 years and 43% of cases were female. Temperature-related exposures were associated with lower odds of epilepsy visit (OR=0.98, $p<<1x10^{-5}$0.00001 for sWBGT with 7-day lag period), whereas $PM_{2.5}$, PM_{10}, and surface pressure showed positive associations that increased with longer lag periods (OR = 1.01, $p<1x10^{-5}<0.00001$ for surface pressure with 7-day lag period).
CONCLUSIONS: Our findings suggest that air pollution and surface pressure are associated with higher odds of epilepsy presentation whereas higher temperatures are associated with lower odds of epilepsy visit. Our small effect sizes may be a result of non-differential misclassification of exposure, which biases towards the null.
KEYWORDS: Epilepsy, Global Neurology

89. An Analysis of Seizure and Psychiatric Outcomes Following Neuromodulation, Medication, and Surgical Therapies for Pediatric Epilepsy with Intractable Focal Aware Seizures

Sanjiv Harikumar, Ganesh Chilukuri, Vivek Joshi

OBJECTIVE: Limited data exist directly comparing neuromodulation therapies in children with epilepsy with intractable focal aware seizures (IFAS). While vagus nerve stimulation (VNS) is approved for pediatric use, deep brain stimulation (DBS) remains off-label. We compared seizure and psychiatric outcomes following VNS, DBS, anti-seizure medications (ASMs), and craniotomy in children with IFAS.
METHODS: Using TriNetX, a global federated health data platform, we examined outcomes in children with IFAS treated with ASMs alone or combined with VNS, DBS, or craniotomy. Seizure outcomes were proxied by emergency department (ED) visits and psychiatric diagnoses used ICD-10 codes. Groups were compared to untreated controls and DBS and VNS were compared to each other, via two-proportion z-tests ($p < 0.05$).
RESULTS: All treatment groups initially showed significantly fewer seizure-related ED visits than untreated controls, which later increased with time. DBS patients had consistently lower ED visit rates than VNS patients, with significant differences at 3 years ($p = 0.0479$) and across the full follow-up period ($p = 0.0294$). Neuromodulation groups had the highest rates of sleep disorder diagnoses. VNS showed significance for ADHD ($p = 0.0216$), and both DBS and VNS for sleep disorders ($p < 0.0001$). Except for depression, DBS patients had lower rates of psychiatric diagnoses compared to VNS, with significantly fewer anxiety outcomes ($p = 0.045$).
CONCLUSIONS: DBS treatment in children with IFAS was associated with fewer seizures and psychiatric outcomes than VNS treatment. These findings provide additional data for DBS use in pediatric populations and offer comparative data across neuromodulation, ASM, and surgical approaches.
KEYWORDS: Epilepsy, Behavioral Neurology

90. Hemispherectomy in a patient with refractory infantile spasms secondary to cystic encephalomalacia from COVID-related acute hemorrhagic leukoencephalitis, a Case Report

Aaron Hocher, Sireesha Chinthaparthi

OBJECTIVE: To describe a case of COVID-related acute hemorrhagic leukoencephalitis (AHLE) with refractory

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infantile spasms and focal epilepsy who is seizure and spasm free after right hemispherectomy.

METHODS: This was a retrospective case report. Data was collected and analyzed through our institution's electronic medical record. This was an IRB-exempt project.

RESULTS: A 5-month-old female, previously healthy, born full term presented with abnormal upper extremity movements, progressing to hypotonia and encephalopathy, subsequently found to have diffuse white matter injury, multifocal hemorrhage, and restricted diffusion on MRI brain. She was found to be COVID positive and ultimately diagnosed with COVID-related AHLE and treated with remdesivir, solumedrol, IVIG, and plasmapheresis. She developed refractory multifocal subclinical seizures requiring the initiation of multiple antiseizure medications and the ketogenic diet. She subsequently developed refractory infantile spasms resistant to high-dose prednisolone, vigabatrin, and ACTH. Extensive genetic testing was negative or non-diagnostic. Subsequent MRI imaging demonstrated extensive cystic encephalomalacia of the right greater than left hemispheres. Electrographically, the epileptic spasms did not have any lateralizing features. However, given the extensive right hemispheric injury, she underwent right hemispherectomy and has remained seizure and spasm free clinically and on subsequent EEG evaluation at 6 months post-operatively.

CONCLUSIONS: There are limited reports on outcomes related to hemispherectomy for the treatment of medically refractory infantile spasms and seizures. This case suggests that hemispherectomy may be a viable surgical option for patients with refractory spasms and/or seizures if there are radiographic abnormalities even in the setting of non-lateralizing electrographic findings.

KEYWORDS: Epilepsy, Neuroinfectious Disease, Neuroimmunology

91. Frequency of Patient-Reported Seizure Clusters in a Clinical Dataset From a Pediatric Epilepsy Center in Canada

Morris Scantlebury, Sabrina D'Alfonso, Jeffrey Buchhalter, Adrian Rabinowicz, Enrique Carrazana

OBJECTIVE: Definitions of seizure clusters vary, usually involving increased seizure frequency during a defined time period. Data from a pediatric epilepsy population in Calgary, Canada, were examined for prevalence and characteristics of patients with seizure clusters.

METHODS: Seizure-cluster data were drawn from a clinical dataset of the Comprehensive Children's Epilepsy Centre of Alberta Children's Hospital; the data were populated using an epilepsy clinic note with discrete fields in patients' electronic health records. Data included yes/no for clusters, cluster duration, and number of clusters. Patients were seen by Neurology between January 1, 2016, and March 23, 2022. Patients with clusters were eligible. Exclusion criteria included patients who had seizure clusters that were one or a combination of psychogenic nonepileptic seizures, spasms, not yet diagnosed/not applicable for seizure onset/seizure type, or had only 1 seizure/cluster.

RESULTS: There were 3588 patients that had 5475 total seizures. Of these, 327 patients (9.1%) met study eligibility requirements and had 526 seizure clusters. In patients with reported etiologies (n=259), the most common (>10%) were reported as unknown, presumed genetic/metabolic, and specific genetic. Among reported syndromes (n=147), the most common (>10%) were reported as infantile epileptic spasms syndrome, malformations, and Lennox-Gastaut syndrome. Sixty-five patients (19.8%) with clusters were prescribed rescue medication.

CONCLUSIONS: In this pediatric epilepsy center in Canada, 9.1% of patients had seizure clusters. Findings capture multiple aspects of burden, and <20% of those patients were prescribed rescue medications. This large comprehensive real-world clinical dataset provides a rich resource for characterizing seizure clusters.

KEYWORDS: Epilepsy

92. Patterns of Antiseizure Medication (ASM) Utilization in Participants with Developmental and Epileptic Encephalopathies (DEEs) and Responses to Bexicaserin Treatment in the Phase 1b/2a PACIFIC Randomized Controlled Trial (RCT)

Shilpa Chatlani, Pavel Klein, Terence O'Brien, Dennis Dlugos, Tolga Uz, Sidsel Jensen, Shikha Polega

OBJECTIVE: DEEs are severe treatment-resistant epilepsies, with background epileptiform activity, and developmental slowing or regression. Bexicaserin is a highly-selective 5-HT_{2C} receptor superagonist under investigation to treat DEEs. Results from the RCT showed a meaningful reduction in countable motor seizure frequency and a favorable safety profile in participants aged 12-65 years with DEEs. This post hoc analysis examined concomitant ASM use and evaluated bexicaserin efficacy stratified by number of concomitant ASMs.

METHODS: Participants with DEEs (Dravet syndrome, Lennox-Gastaut syndrome, or other DEEs) were eligible for RCT enrollment if they were nonresponsive to their current, stable ASM regimen; suboptimal response was confirmed by the inclusion criterion of ≥4 countable motor seizures observed during the 28-day screening period. Reduction in countable motor seizure frequency with bexicaserin vs placebo was evaluated for subgroups stratified by concomitant ASM use (3, 4, or ≥5 ASMs).

RESULTS: Participants (bexicaserin, n=35; placebo, n=9) received a median of 3 concomitant ASMs during the RCT; 34 participants (77.3%) received ≥3 ASMs and 10 (22.7%) were taking 1-2 ASMs. Overall, the median change from baseline in countable motor seizure frequency was -59.8% with bexicaserin vs -17.4% with placebo. Subgroup analysis showed consistent efficacy with bexicaserin across concomitant ASM regimen sizes: 3 ASMs, -61% vs -17.4% (n=9 vs 5); 4 ASMs, -49.9% vs 167.4% (n=16 vs 1); and ≥5 ASMs, -52% vs 43.6% (n=2 vs 1).

CONCLUSIONS: These findings were comparable to previously reported aggregate data and suggest that bexicaserin remains effective in highly refractory populations, including those with suboptimal seizure control despite multiple concomitant ASMs.

KEYWORDS: Epilepsy, Neurodevelopmental Disorders, Experimental Therapeutics

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93. Analyses of Bexicaserin for the Treatment of Seizures in Developmental and Epileptic Encephalopathies (DEEs): Response Over Time and Responder Rates in the Phase 1b/2a PACIFIC Randomized Controlled Trial (RCT) Open-Label Extension (OLE)

Shilpa Chatlani, David Vossler, Dennis Dlugos, Kate Riney, Tolga Uz, Sidsel Jensen, Shikha Polega

OBJECTIVE: In the RCT and OLE, the investigational drug bexicaserin—a highly selective 5-HT_{2C} receptor superagonist—had a favorable safety and tolerability profile and demonstrated reductions in countable motor seizure frequency in adolescent and adult participants with a variety of DEEs. This post hoc analysis evaluated countable motor seizure frequency in the RCT and OLE with ≤1 year of bexicaserin.

METHODS: After completing the 75-day RCT, participants could enter the 12-month OLE. Median percentage change from baseline in countable motor seizure frequency was assessed as cumulative rates during the RCT (bexicaserin vs placebo; Weeks 1-2/1-6/1-8/total RCT) and OLE (bexicaserin only; Month(s) 1/1-6/1-9/total OLE). Sustainability of response was evaluated as the proportion of participants with ≥50%/≥75%/≥90% seizure frequency reduction.

RESULTS: Median percentage change from baseline in countable motor seizure frequency with bexicaserin (n=35) diverged from placebo (n=9) by Weeks 1-2 (-49.6% vs 1.5%) and was sustained for Weeks 1-6 (-58.0% vs -24.3%), Weeks 1-8 (-60.5% vs -22.0%), and the entire RCT (-59.8% vs -17.4%). In the OLE (n=40), seizure frequency reductions were maintained through 1 year (-59.3%). Responder rates (≥50%/≥75%/≥90%) with bexicaserin during the RCT (60%/31.4%/11.4%) were maintained in the OLE (55%/40%/17.5%); placebo administration only yielded a ≥50% response in 33% (n=3/9) of participants in the RCT.

CONCLUSIONS: Bexicaserin showed rapid onset in reducing countable motor seizure frequency across DEEs that was sustained, with consistent responder rates throughout the RCT and OLE, suggesting no loss of long-term therapeutic benefit of bexicaserin, thereby reinforcing rationale for the ongoing Phase 3 program.

KEYWORDS: Epilepsy, Neurodevelopmental Disorders, Experimental Therapeutics

94. Interval Between Seizure Clusters (SEIzure interVAL; SEIVAL) in Children Aged 2-17 Years Using 70-Day Analysis Periods in Two Studies

Eric Segal, James Wheless, Wesley Kerr, Katherine McFarlane, Charles Davis, Leock Ngo, Enrique Carrazana, Adrian Rabinowicz

OBJECTIVE: Diazepam nasal spray is approved for acute seizure-cluster treatment in patients with epilepsy aged ≥2 years. Increased time between treated seizure clusters (SEIVAL) was described across pragmatic 90-day periods in patients aged 2-65 years. These analyses used statistically derived 70-day periods in pediatric patients.

METHODS: Patients received diazepam nasal spray during a phase 1/2a pharmacokinetic/safety study (aged 2-5 years) and a phase 3, long-term safety study (aged 6-65 years). SEIVAL was analyzed post hoc for 70-day periods for each subject: (1) comparing mean SEIVALs in multiple periods and a consistent cohort (patients treated in 3 consecutive periods) for the 2-5-year-olds and (2) with mixed effects linear regression (compared with each patient's baseline) for 6-17-year-olds. Treatment-emergent adverse events were recorded.

RESULTS: Among 2-5-year-olds (N=36), 22 had SEIVALs, with means of 24.4 days in the baseline period (Days 1-70, n=19), 22.2 days in the primary outcome period (Days 71-140, n=12), and 37.6 days (Days 141-210, n=11) and 49.4 days (Days 211-280, n=7) in subsequent periods; for the consistent cohort (n=7), SEIVAL increased from 22.1 (Days 1-70) to 27.7 (Days 141-210) days. Among 6-17-year-olds (n=78), 55 had SEIVALs with means of 15.2 days (n=55), 20.1 days (n=45), 29.3 days (n=48), and 28.8 days (n=46) from the baseline period to primary outcome/subsequent periods, respectively. Safety profiles were consistent with the overall study populations.

CONCLUSIONS: SEIVALs in pediatric patients increased in 70-day primary outcome/observation periods, consistent with previously calculated 90-day periods. Time to lengthening may be marginally delayed in younger patients.

KEYWORDS: Epilepsy

95. Real World Effectiveness of Cenobamate in Pediatric Epilepsy: A Single-Center Experience in Patients Age 6 to 18 years.

Kennedy Brooks, Shalaka Indulkar

OBJECTIVE: To assess real-world effectiveness and tolerability of cenobamate for refractory pediatric epilepsy.

METHODS: Single-center retrospective review of patients ≤18 years started on cenobamate (Jan 2024–Apr 2026). We reviewed response rate, seizure-freedom, adverse effects, and retention. Responses were compared by epilepsy type (focal, generalized, mixed).

RESULTS: Twenty-three patients met criteria for the study (n=23), 39% male(9/23), 61% females (14/23). Epilepsy types included focal 8 (35%), generalized 11 (48%), and mixed 4 (17%). Patients had failed a mean of 4.3 antiseizure medications (range 1–11). Median age at initiation was 14 years (range 6–18). Median dose of cenobamate was 100 mg/day (1.2 mg/kg/day; range 25–200mg). Overall response rate (≥50% seizure reduction) was 56%; 50–75% reduction was seen in 30% of responders, 75–99% reduction 46%, and seizure freedom 23%. Response was highest in focal epilepsy (87.5%; 7/8), compared with generalized epilepsy (54.5%; 6/11), with no improvement in mixed epilepsy. One patient with generalized epilepsy (SCN1A) had seizure worsening. Adverse effects occurred in 17%, 5/23 (somnolence, drowsiness, paranoia, one death). Retention rate of cenobamate was 95.6% during the study period.

CONCLUSIONS: Cenobamate demonstrates broad spectrum efficacy in pediatric epilepsy, with particularly strong benefits in focal epilepsy.

KEYWORDS: Epilepsy

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96. Trends, Demographic Characteristics, Risk Factors, and Outcomes of Epileptic Spasm Hospitalizations: A U.S. Population-Based Analysis (2016–2022)

Snigdha Kosuri, Erwin Cabacungan, Avantika Singh

OBJECTIVE: To describe national trends, demographic and hospital characteristics, risk factors, and outcomes of epileptic spasm (ES) hospitalizations among children aged 0–2 years.

METHODS: This retrospective cohort study utilized the Healthcare Cost and Utilization Project - Nationwide Inpatient Sample (HCUP-NIS) data from 2016 to 2022. Hospitalizations for children aged 0–2 years with a diagnosis of ES were identified. Data were analyzed using weighted estimates to ensure generalizability. Statistical methods included linear regression for trends, Pearson Chi-square for categorical comparisons, and generalized linear models (GLM) for healthcare resource utilization.

RESULTS: The final cohort included 28,985 discharges (9.9 per 10,000). Weighted ES hospitalizations increased from 8.37 to 10.88 per 10,000 discharges ($p = 0.065$). Significant increases were observed in children aged 1 year (OR 1.04, $p = 0.014$) and 2 years (OR 1.10, $p < 0.001$). CNS and autosomal anomalies were independently associated with ES. Compared to infants < 1 year, children aged 1–2 years had higher odds of mechanical ventilation and cerebral palsy. While length of stay (LOS) was stable overall, survivors at age 2 had significantly longer LOS (IRR 1.13, $p = 0.037$) and higher total hospital charges (GLM 1.18, $p = 0.024$).

CONCLUSIONS: ES hospitalizations increased nationally from 2016 to 2022, primarily driven by rising rates in children aged 1 and 2 years. The increased healthcare resource utilization at age 2 highlights the growing clinical and economic burden of this syndrome and emphasizes the need for age-specific management strategies.

KEYWORDS: Epilepsy, Neonatal Neurology, Neurodevelopmental Disorders

97. Evaluating variables in epilepsy history as predictors of seizure response to ketogenic diet.

Rachel Carpenter, Emily Grew, Parmpreet Dhillon

OBJECTIVE: The ketogenic diet (KD) can be a useful treatment modality in patients with epilepsy. Analyzing variables in epilepsy history and their relationship to KD response may be helpful in predicting treatment efficacy.

METHODS: Change in seizure frequency since KD initiation among 107 patients was analyzed using generalized estimating equations (GEE) with a cumulative logit link among 107 patients. Tests of model effects were used to assess the significance of predictors, using p-values and Wald chi-square to evaluate association strength. Data were analyzed in SPSS v28.

RESULTS: Baseline seizure burden was positively correlated with seizure response ($p<0.001$). Age at start of KD ($p=0.047$) and time elapsed between seizure onset and KD start date ($p<0.001$) were negatively associated with seizure response. When modeled together, only time elapsed remained significant. Baseline seizure severity was inversely associated with age of KD initiation ($p<0.001$) and time elapsed ($p<0.001$).

CONCLUSIONS: Higher seizure burden and shorter time from seizure onset to KD initiation were associated with higher seizure response.

KEYWORDS: Epilepsy, Lifespan Manifestations of Childhood Onset Conditions

98. Progressive Ischemic and Hemorrhagic Strokes in Neonatal COL4A1 Mutation with Familial Epilepsy Spectrum

Rhea Zahir, Sakina Lashkeri, Thuy Vu, Alessandra Scavitto, Tarannum Lateef

OBJECTIVE: COL4A1-related disorders are associated with cerebral small vessel disease, most commonly presenting with prenatal or neonatal intracranial hemorrhage. The full neurovascular spectrum remains incompletely defined. We describe a neonatal case demonstrating progressive mixed ischemic and hemorrhagic injury with a familial epilepsy phenotype.

METHODS: Clinical, neuroimaging, and genetic data were retrospectively reviewed.

RESULTS: The patient was born with prenatally identified grade IV intraventricular hemorrhage. At 14 days of life, he developed focal seizures characterized by rightward eye deviation, irritability, and feeding difficulty, requiring hospitalization and initiation of levetiracetam and phenobarbital. Serial neuroimaging demonstrated progressive cerebrovascular injury, including extensive multifocal infarcts involving the right cerebral white matter, corpus callosum, thalamus, midbrain, and pons, as well as new infarcts in the left frontal and occipital regions. These findings occurred in the setting of recurrent intraparenchymal and intraventricular hemorrhage with evolving porencephalic cyst formation and increasing mass effect, consistent with a dynamic mixed ischemic-hemorrhagic process. EEG showed multifocal epileptiform activity with subclinical seizures arising from the right hemisphere. Family history was notable for epilepsy in the mother (onset at age 3), sister, and maternal uncle, with associated structural brain abnormalities in the mother and sister, suggesting variable expressivity and incomplete penetrance.

CONCLUSIONS: This case highlights a progressive mixed ischemic-hemorrhagic cerebrovascular phenotype in COL4A1-related disease, extending beyond the traditionally described hemorrhagic presentation. The associated familial epilepsy spectrum suggests broader neurologic involvement. This case also highlights the importance of genetic testing in familial epilepsy, as it may identify underlying syndromes with multisystem involvement, beyond seizures.

KEYWORDS: Epilepsy, Neurogenetics

99. Neighborhood-Level Disparities in Access to Pediatric Epilepsy Monitoring Units

Rakhi Das, Yingchao Yuan, Dave Clarke

OBJECTIVE: To evaluate the association between the Child Opportunity Index (COI), clinical characteristics, and timeliness of access to specialized epilepsy care

METHODS: This ongoing IRB-approved retrospective record review analyzes 200 pediatric patients with drug-resistant epilepsy (ICD-10) treated at a single tertiary center

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between January 2015 and December 2020. Disparities were explored using metro-normed levels from COI 3.0 database. Statistical associations between COI levels, number of anti-epileptic drugs (AEDs) used, and time to Epilepsy Monitoring Unit (EMU) were evaluated using SAS 9.4.
RESULTS: Among 200 patients, over half resided in lower-opportunity neighborhoods: Very Low (28.57%) and Low (25.17%), followed by Moderate (16.33%), High (15.65%), and Very High (14.29%). A 22-month disparity in median time to EMU admission was observed between Very High opportunity (17.0 months) and Very Low opportunity (39.0 months) groups. However, this trend was not statistically significant (p=0.22). Similarly, no significant difference was found in the number of AEDs used across COI categories (p=0.41), averaging 4-5 AEDs prior to EMU.
CONCLUSIONS: This study is among the first to examine neighborhood disparities in EMU access using COI 3.0 database. A 22-month delay for patients in Very Low opportunity neighborhoods suggests that higher resources may accelerate access to specialized care. Consistent AED burden across COI levels indicates uniform clinical management regardless of neighborhood status. Non-significance may stem from small sample size or referral bias. Further analysis will be done from 2020 to present to identify specific barriers to EMU referral for patients in Very Low COI tracts
KEYWORDS: Epilepsy, Diversity, Equity, Inclusion

100. An Interesting Case of Lesional Somatic TSC2 Mosaicism in an Epileptogenic Focal Cortical Dysplasia

Aaron Downs, Alejandra Vasquez Avila, Lily Wong-Kisiel

OBJECTIVE: We report a case of a 3-year-old with drug-resistant epilepsy secondary to a symptomatic focal cortical dysplasia (FCD) with a TSC2 mutation of low variant allele frequency (VAF) despite negative systemic genetic testing. He initially presented with episodes of staring and behavioral arrest which evolved into refractory generalized-tonic-clonic seizures.
METHODS: Case Report
RESULTS: A previously healthy 3-year-old boy developed staring spells that progressed to focal seizures with behavioral arrest, atonia, and occasional generalization over the course of a few months. MRI revealed multiple right hemispheric T2/FLAIR hyperintense lesions, and EEG localized epileptiform activity to the right posterior temporal region. CSF, Whole Genome Sequencing, and laboratory evaluations were unrevealing. Seizures were refractory to multiple ASMs and dietary therapy, with persistent daily events. Multidisciplinary evaluation identified a concordant right posterior temporal lesion as the seizure focus. He underwent open resection 1 year after symptom onset with intraoperative electrocorticography confirming elimination of epileptiform activity. Pathology demonstrated focal cortical dysplasia type IIb with a somatic TSC2 mutation with a Variant Allele Frequency (VAF) of 4.8%. Postoperatively, he achieved seizure freedom with preserved neurological function.
CONCLUSIONS: This case highlights recent developments in the characterization of focal cortical dysplasia II caused by low VAF somatic mutations in genes affecting the MTOR pathway. However, diagnostic workup to further characterize the causes of symptomatic FCD with negative systemic genetic testing remains a challenge as obtaining pathology necessitates invasive testing. The case also highlights the correlation of imaging with TSC2 related pathologic findings in the setting of lesional drug resistant epilepsy.
KEYWORDS: Epilepsy, Neurogenetics

101. Expanding the phenotypic presentation spectrum of KCNT1 variants: A case report of a 20-month-old with a pathogenic variant of KCNT1

Jeffrey Millman, Nicola Ross

OBJECTIVE: Autosomal dominant pathogenic variants of the KCNT1 gene are associated with variable presentations of medically refractory epilepsy. We report the case of a 20-month-old with a pathogenic variant of KCNT1 who presents without refractory epilepsy.
METHODS: Case report and review of published literature.
RESULTS: A 20-month-old female with a history of global developmental delay presented with complex febrile seizures. Developmental history was notable for delayed walking and speech. Her physical exam was notable for hypotonia, hyporeflexia, and an absence of speech. An EEG was obtained which showed no epileptiform abnormalities. The patient underwent genetic testing with whole exome sequencing and was found to have an autosomal dominant pathogenic variant of KCNT1 [c2896 G>A p.(A966T)]. This was inherited from her mother, who has a history of febrile seizures but not epilepsy. The mutation has been associated in the literature with two phenotypic presentations, developmental and epileptic encephalopathy (DEE) and autosomal dominant or sporadic sleep-related hypermotor epilepsy [AD(SHE)]. We found two reported cases of familial A966T mutations in the literature. Both patients were male with late AD(SHE) seizure onset (2 years and 9 years) and also had benign KCNT1 mutations along with the pathogenic variant.
CONCLUSIONS: This is the first reported case of a familial KCNT1 A966T pathogenic variant without refractory epilepsy and with this particular phenotypic presentation. The case expands the phenotypic spectrum of KCNT1 variants and underscores the need to better understand genotype-to-phenotype relationships. It is also important for enhancing clinician awareness of the range of presentations of KCNT1 variants.
KEYWORDS: Epilepsy, Neurogenetics

102. Early Feasibility of PEARLS (Pediatric Epilepsy Automated Referral & Learning System): A Standardized Workflow Dataset for Pediatric Suspected Seizure Referrals

Dax Bourcier, RJ Roggeveen, Paula Brna, Wendy Stewart

OBJECTIVE: Pediatric referrals for suspected seizures often vary in quality, completeness, and format, contributing to inconsistent triage, delays in diagnosing and treating epilepsy, and prolonged uncertainty when events are ultimately non-

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epileptic. PEARLS was developed to address these gaps by creating an event-based pediatric seizure-referral workflow dataset that can describe real-world care pathways, identify inefficiencies, and support future referral standardization and triage tools.

METHODS: PEARLS is a retrospective two-centre proof-of-concept study of children and adolescents referred for suspected seizures. Each clinically meaningful step in the referral pathway is recorded as a separate timestamped event: referral, re-triage, pediatric neurology encounter, EEG, MRI, genetic testing, diagnosis, treatment, and 12-month outcome. Data were obtained through batch extracts and source-document review, including structured clinical fields and referral documents. Scanned referrals underwent optical character recognition when required. Pilot implementation assessed technical feasibility, completeness of data fields, and whether PEARLS entries accurately reflected source records through manual chart review.

RESULTS: Preliminary pilot extraction included 10 suspected seizure referrals. Despite a heterogeneous institutional data environment, including MEDITECH-based records and scanned referral documents, construction of a unified event-based dataset was feasible. Completeness varied by event type and source. Some key fields were available only in narrative encounter notes, while re-triage data were limited because paper forms were not routinely scanned into the electronic record and not systematically tracked. Manual review showed exact concordance between PEARLS entries and source records in all 10 pilot charts.

CONCLUSIONS: Early findings support the feasibility of PEARLS and provide a foundation for referral standardization and future decision-support development.

KEYWORDS: Epilepsy

103. Non-Seizure Outcomes of Pediatric Hemispheric Epilepsy Surgery: A Roadmap for Child Neurologists

Michael Granovetter, Ethan Cline, Monika Jones, Sophia Robert, Marlene Behrmann, Christina Patterson, Klajdi Puka

OBJECTIVE: Pediatric hemispheric surgery often achieves seizure freedom, but non-seizure outcomes are under-studied. Here, we characterize and evaluate factors associated with pediatric hemispheric surgery's functional outcomes.

METHODS: We surveyed pediatric hemispheric surgery patients' guardians (n=192) on pre- and postoperative diagnoses. We evaluated two outcome types: proportion of patients with at least one diagnosis in a functional domain (visual, motor, cognitive, auditory, endocrine) and proportion with each diagnosis. McNemar's tests compared proportions pre- versus post-surgery. We fit logistic regression models testing effects of seizure etiology, resection side, seizure-onset age, surgery age, and time from seizure onset to surgery on each outcome.

RESULTS: The proportion of patients with at least one diagnosis per functional domain was higher post-surgery for all domains and for individual diagnoses affecting each domain. Etiology, resection side, seizure-onset age, surgery age, and time from seizure onset to surgery were not associated with endorsement of at least one diagnosis in a domain except: motor diagnoses were associated with stroke, and cognitive diagnoses were associated with left-sided surgery and later surgery. However, etiology, resection side, and surgery age were not associated with any individual motor or cognitive diagnosis (except depression, which was associated with later surgery).

CONCLUSIONS: We comprehensively characterized functional outcomes of pediatric hemispheric surgery, offering a roadmap for child neurologists to use for preoperative counseling and postoperative surveillance. While etiology, resection side, and surgery age were associated with report of at least one postoperative motor/cognitive diagnosis, they were not associated with any specific diagnosis, highlighting potential variability in mechanisms of postoperative plasticity.

KEYWORDS: Epilepsy, Lifespan Manifestations of Childhood Onset Conditions, Neurodevelopmental Disorders

104. Risk Factors for Seizures and Epilepsy in Children with Cerebral Cavernous Malformations: A Systematic Review and Meta-Analysis

Aryan Wadhwa, Shreya Tripathy

OBJECTIVE: Cerebral cavernous malformations (CCMs) are a leading cause of seizures and epilepsy in children, but the relative weight of clinical, anatomic, and genetic risk factors has not been systematically quantified. We performed a systematic review and meta-analysis of risk factors for pediatric CCM-related seizures and epilepsy.

METHODS: We reviewed primary cohort studies and case series reporting seizure or epilepsy outcomes in patients ≤18 years with confirmed CCM (1991–2026). Two-by-two cross-tabulations were pooled using a DerSimonian–Laird random-effects model with continuity correction; adjusted hazard and odds ratios were extracted where available. Heterogeneity was assessed by I^2 and Cochran's Q.

RESULTS: Seventeen studies (∼1,065 children) met inclusion criteria. Supratentorial-cortical/lobar location was the strongest risk factor for seizure presentation (pooled OR 10.47, 95% CI 4.00–27.37; $p<0.001$; $I^2=21.7\%$; $k=5$). Each one-SD increase in total CCM lesion count raised lifetime seizure hazard 24% (HR 1.24, 1.08–1.43), and large-lesion (≥5 mm) burden 51% (HR 1.51, 1.22–1.88). CCM3/PDCD10 mutation conferred 3.25-fold higher seizure hazard than CCM1/KRIT1 (1.19–8.83). Familial disease and brainstem location independently increased intracranial hemorrhage at presentation (OR 2.53 and 3.62). Preoperative epilepsy duration >2 years predicted worse seizure freedom; surgery for new-onset CCM-related epilepsy achieved 5-year ILAE class 1 in 77.8% versus 25.0% with conservative care.

CONCLUSIONS: In children with CCMs, supratentorial-cortical location, high lesion burden, CCM3 genotype, and familial disease independently elevate seizure risk. Among modifiable factors, preoperative epilepsy duration is the dominant determinant of postoperative seizure freedom, supporting early surgical consideration for cortical CCM-related epilepsy.

KEYWORDS: Epilepsy, Lifespan Manifestations of Childhood Onset Conditions

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105. Reproductive Health Counseling in Adolescent Epilepsy: A Qualitative Study of Child Neurologist Communication

Parth Aggarwal

OBJECTIVE: To characterize how child neurologists address reproductive health with female adolescents with epilepsy, and to identify communication patterns relevant to clinical practice and training.

METHODS: We invited child neurology clinicians to engage in simulated clinical encounters on Zoom with actors portraying a female adolescent with epilepsy plus a parent and instructed the child neurologists to counsel the patient about reproductive health an epilepsy. Simulations were audio-recorded and transcribed. Two coders analyzed each transcript and identified themes.

RESULTS: Twenty-one child neurology clinicians engaged in simulated encounters. Medication management served as the primary entry point for reproductive health counseling for 20 of 21 clinicians. Nine of 21 clinicians conducted a confidential discussion with the patient. Eighteen clinicians discussed contraception; all discussed contraceptive pills, 12 discussed long-acting reversible contraceptive methods and 12 discussed condoms/barrier methods. Fourteen of 21 clinicians discussed pregnancy, emphasizing planning and risk reduction. Fifteen of 21 clinicians asked about sexual activity (six did not do so confidentially, with parent present). Sixteen of 21 clinicians referred patients to reproductive health specialists for further counseling

CONCLUSIONS: Findings indicate strengths and areas for improvement to highlight in training child neurologists to counsel youth with epilepsy about reproductive health. Considerations include diversifying contraceptive discussion beyond pills and ensuring that discussions of confidential topics such as sexual activity are confidential.

KEYWORDS: Epilepsy, Education

106. Ketogenic Diet in the Successful Treatment of Super-Refractory Status Epilepticus Secondary to Group B Streptococcus Meningoencephalitis with Stroke in a Neonate: A Case Report

Emily Matney, Derryl Miller, Sarah Elsakr, Taylor Parrish, Sarah Wing

OBJECTIVE: We present a 4-week-old male successfully treated for super-refractory status epilepticus (SRSE) using the ketogenic diet. Group B Streptococcus (GBS) sepsis and meningitis led to extensive stroke, SRSE, and medically-refractory epilepsy. Seizures were refractory to maximal medical therapy including continuous midazolam and ketamine infusions for weeks, and urgent neurosurgical intervention with hemispherectomy was planned. Alternatives to surgery were sought due to high risk of morbidity/mortality with the procedure given young age and projected blood loss.

METHODS: Consent was obtained from the patient's parents. Reporting involved extensive electronic medical record (EMR) review and discussions with various providers involved in the patient's care, including neurologists, intensivists, epileptologists, and registered dietitian.

RESULTS: Ketogenic diet was initiated for the patient prior to proceeding with surgery, resulting in complete seizure resolution. The patient became seizure free on ketogenic diet and enteral scheduled anti-seizure medications. The patient remains seizure free 11 months later.

CONCLUSIONS: This case highlights the importance of considering ketogenic diet in cases of neonatal SRSE as a lower-risk alternative to surgical intervention.

KEYWORDS: Epilepsy, Neonatal Neurology, Neurocritical Care

107. Corpus Callosotomy for Drug-Resistant Epilepsy: Systematic Review and Structured Evidence Synthesis of Seizure Outcomes, Surgical Approaches, and Predictors.

Alaina Carman, Margil Ranpariya, Imtiaz Nazam, Osman Farooq

OBJECTIVE: To evaluate whether total corpus-callosotomy (TCC) is associated with improved drop-attack control compared with anterior corpus-callosotomy (ACC) across open and minimally invasive approaches, to compare seizure outcomes and perioperative profiles between laser-interstitial thermal therapy (LITT) and open-craniotomy, and to identify patient- and disease-level factors associated with favorable seizure outcomes following corpus-callosotomy (CC).

METHODS: A systematic search was conducted across PubMed, Embase, Cochrane Library, Web of Science, and Scopus from inception through December 2025.

RESULTS: Fifty-two studies encompassing 8887 patients were included. Drop-attack freedom ranged from 55.3% to 61.9% overall. TCC was consistently associated with higher drop-attack freedom than ACC (OR 2.90–33.0; $p < 0.01$). LITT showed comparable seizure outcomes to open-craniotomy (RR 0.89; $p = 0.36$) with shorter hospital stays (-2.84 days; $p < 0.00001$) and reduced blood loss (-75.15 mL; $p < 0.00001$). Disconnection-syndrome occurred in 8.0–20.0% of TCC patients and was typically transient. Factors associated with favorable outcome included normal MRI (OR 4.63), infantile spasms (OR 3.86), shorter epilepsy duration (OR 2.57), and idiopathic etiology (OR 2.84).

CONCLUSIONS: Across heterogeneous observational studies, TCC is consistently associated with improved drop-attack control relative to ACC, with a largely transient disconnection syndrome risk. LITT appears to be a reasonable minimally invasive alternative with comparable seizure outcomes. Normal MRI, infantile spasms, shorter epilepsy duration, and idiopathic etiology are associated with more favorable outcomes. CC is consistently associated with better drop-attack control than VNS, suggesting it may be considered when drop-attack reduction is the primary surgical goal, although all comparisons are non-randomized and subject to selection-bias.

KEYWORDS: Epilepsy

108. Vigabatrin-associated chorea: an unusually early onset

Wendi Wang, Ryan Carrier, Caroline Rich, Kirsten Wilhelm

OBJECTIVE: Concurrent vigabatrin-related hyperkinetic movements and diffusion-restriction MRI changes typically

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appear after four weeks. This case describes an onset within two weeks.

METHODS: Case report

RESULTS: 10-month-old with Trisomy 21 and newly diagnosed infantile spasms who completed the EUKISS protocol followed by vigabatrin initiation (up-titrated to 150 mg/kg/day). During hospitalization for RSV-related respiratory illness, he developed new hyperkinetic, non-purposeful movements twelve days after illness onset and on the day EUKISS was completed. The movements involved the trunk, neck, and extremities and were consistent with chorea, with progressive worsening. With concern for autoimmune or post-infectious neuroinflammation, he underwent neuroimaging, LP, and EEG. EEG showed improvement in his 2021 BASED score from 5 to 3. MRI demonstrated symmetric T2 hyperintensities with diffusion restriction in the basal ganglia, thalami, midbrain, and pons without contrast enhancement, consistent with vigabatrin-associated changes. CSF studies were unrevealing for neuroinflammation, though limited by recent steroid exposure, and empiric IVIG did not improve the chorea. Vigabatrin-associated hyperkinetic movement disorder was initially questioned due to the close temporal association between symptom onset and MRI changes, which are typically reported after at least four weeks of therapy. However, his extensive neuroinflammatory evaluation including metabolic studies, malignancy screening, and cytometry was unrevealing. With reasonable exclusion of autoimmune encephalitis, his presentation was attributed to vigabatrin initiation, and the chorea ultimately self-resolved over months despite maintaining therapeutic dosing.

CONCLUSIONS: This case underscores the importance of considering new-onset chorea shortly after vigabatrin initiation, even in the setting of acute respiratory illness and concurrent treatment for infantile spasms.

KEYWORDS: Epilepsy, Movement Disorders

109. Areas of Concordance and Discordance in Communication About Reproductive Health Amongst Youth with Epilepsy, Parents, and Caregivers

Meredith Montella

OBJECTIVE: To determine perspectives of female youth with epilepsy, parents/caregivers, and child neurologists about optimal child neurologist counseling regarding reproductive health and epilepsy.

METHODS: We conducted semi-structured interviews with 12 female youth with epilepsy, 14 parents/caregivers, and 15 child neurologists. Interviews were audio-recorded and transcribed. At least two coders analyzed each transcript and determined themes.

RESULTS: Youth, parents/caregivers, and clinicians agreed that child neurologists should counsel about reproductive health by speaking briefly in an organized manner using a comfortable, conversational tone and explain why specific reproductive health topics need to be discussed. Youth and parents/caregivers wanted more information about citations and sources of data, but child neurologists assumed these are not helpful. Youth and child neurologists wanted confidential time between patient and clinician in office visits, but parents expressed concerns. Youth and parents/caregivers wanted more statistics, but child neurologists feared that these would be confusing. Youth and parents/caregivers wanted a shared decision-making approach, but child neurologists preferred a directive approach.

CONCLUSIONS: Our results reveal that child neurologists have potentially incorrect assumptions about what female youth with epilepsy and parents/caregivers want during reproductive health counseling despite some agreement about general positive communication skills. Results will inform efforts to train child neurologists to optimally counsel female youth with epilepsy and parents/caregivers about reproductive health.

KEYWORDS: Epilepsy, Global Neurology

110. Epileptogenic Structural Lesions on MRI in Pediatric Focal Epilepsy: A Population-Based Cohort Study

Katarina Alajbegovic, Elaine Wirrell, Katherine Nickels, Anthony Fine, Lily Wong-Kisiel

OBJECTIVE: To evaluate the prevalence of epileptogenic structural etiologies in pediatric focal epilepsy.

METHODS: All children between 1 month and 18 years with new onset epilepsy diagnosed between 1980 and 2018 were identified by review of the Rochester Epidemiology Project Database. Patients with focal epilepsy and available MRIs were included. MRI brain findings were classified as normal or with epileptogenic structural abnormality. Seizure outcome were divided into (1) medically refractory or (2) seizure free at last follow-up.

RESULTS: Focal epilepsy was seen in 359 of 686 of children with new onset epilepsy. Epileptogenic structural abnormality was present in 132 of 304 patients (43%) who had focal epilepsy and brain MRI. Median age at epilepsy diagnosis was 68.4 months (interquartile range [IQR] 14.4-128). Structural etiologies included perinatal infarct/gliosis n=53 (17%), malformation of cortical development n=24 (8%),-mesial temporal sclerosis n=11 (3.6%), tumor n=8 (2.6%),-tuberous sclerosis n=5 (1.6%), vascular n=5 (1.6%), mesial temporal sclerosis with cortical dysplasia n=2 (0.7%), and others n=24 (7.9%, global atrophy, inflammatory, demyelinating/metabolic, others).

With median follow-up of 120 months (IQR 60-240), medically refractory epilepsy was seen in 65 of 132 patients (49%) with focal epilepsy and epileptogenic MRI findings.

CONCLUSIONS: In this population-based cohort of pediatric focal epilepsy, epileptogenic structural abnormalities were identified on MRI in nearly half of patients, most commonly due to infarct/gliosis and malformations of cortical development. Children with focal epilepsy and epileptogenic MRI findings had a high burden of disease, with approximately half developing medically refractory epilepsy with long-term follow-up.

KEYWORDS: Epilepsy, Neuroimaging, Lifespan Manifestations of Childhood Onset Conditions

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111. Age-Stratified Interictal Epileptiform Discharges in SCN1A-Related Epilepsy and Association With Early Sodium Channel–Blocking Antiseizure Medication Exposure

Samaneh Esteghamat, Mahmoud Mohammadi, Reza Badv, Zahra Rezaei, Ali Rashidi nezhad, sedighe nikbakht, Sana Esteghamat

OBJECTIVE: To characterize age-stratified patterns of interictal epileptiform discharges (IEDs) in SCN1A-related epilepsy and evaluate associations with early exposure to sodium channel–blocking antiseizure medications (SCBs)

METHODS: We retrospectively studied 57 individuals with pathogenic or likely pathogenic SCN1A variants and at least one interictal EEG. EEGs were assigned to predefined age bands (0–1, 1–3, 3–6, 6–13, and 13–20 years). One EEG per participant was selected within each age band based on the highest IED burden. EEGs were classified as no IEDs, focal IEDs, or bilateral/multifocal IEDs, with outcomes dichotomized as absence or presence of IEDs. Cumulative exposure to sodium channel–blocking ASMs during the first five years of life was categorized as <11 or ≥11 months.

RESULTS: IEDs were absent during infancy and became more frequent with age, peaking at 6–13 years. No significant genotype-related differences in age-specific IED distribution were observed. In the 6–13-year age band ($n = 39$), IEDs occurred in 9/30 (30.0%) patients with <11 months of SCB exposure and 8/9 (88.9%) with ≥11 months (OR 18.67; 95% CI 2.01–173.2; $p = 0.005$). The association remained after adjustment for genotype class, sex, and age at seizure onset (adjusted OR 28.74; 95% CI 3.71–497.64; $p = 0.001$) and after additional adjustment for age at genetic diagnosis (adjusted OR 28.33; 95% CI 3.26–605.00; $p = 0.001$).

CONCLUSIONS: Prolonged early exposure to sodium channel–blocking ASMs was associated with a higher likelihood of later IED detection, highlighting the importance of early recognition of SCN1A-related epilepsy and appropriate treatment selection.

KEYWORDS: Epilepsy, Neurogenetics

112. Targeted AMPA-Receptor Blockade with Perampanel-resulting in global clinical improvement in QARS1-Related Rare Developmental and Epileptic Encephalopathy: A Case Series

Sonam Bhalla, Hong Li

OBJECTIVE: Glutaminyl-tRNA synthetase, encoded by QARS1, is essential for protein translation. Biallelic QARS1 variants cause developmental and epileptic encephalopathy (DEE) with early-onset, medically refractory epilepsy, developmental regression, and progressive microcephaly. We describe clinical improvement from perampanel in two children with QARS1-related DEE.

METHODS: Our patient is 2-year-old male who developed seizures at multiple daily, migrating focal seizures, at 3 months and infantile spasms at 5 months, followed by global developmental and feeding regression, acquired microcephaly, hypotonia, G-tube dependence, and supplemental oxygen need. EEG showed electroclinical and subclincal seizures with multifocal epileptiform discharges and progressive disorganization. An epilepsy gene panel identified a likely pathogenic QARS1 variant (c.134G>T; p.Gly45Val) and a variant of uncertain significance (c.2068C>T; p.Arg690Cys); parental testing confirmed variants were in trans. MRI was initially normal; repeat MRI at 19 months showed diffuse cerebral volume loss. Seizures remained uncontrolled on cannabidiol, topiramate, lacosamide, vigabatrin, and ketogenic diet. Perampanel was added at 17 months.

RESULTS: Following perampanel initiation, all seizure types markedly decreased, to rare seizures. Developmental gains included improved vocalization, smiling/laughing, rolling over, and sitting with support, and discontinuation of supplemental oxygen. With sustained seizure control, other seizure medications were weaned. Notably, after the family shared this response in a parent support group, an unrelated child in the UK with the same QARS1-DEE was also treated with perampanel with significant seizure control and developmental improvement.

CONCLUSIONS: Perampanel was associated with substantial seizure reduction and developmental improvement in QARS1-related DEE, supporting AMPA receptor antagonism as a potential precision approach in this ultra-rare genetic epilepsy.

KEYWORDS: Epilepsy, Neurogenetics, Neurodevelopmental Disorders

113. A Rare Case of Asystole in an Epilepsy Patient Receiving Cenobamate and Lamotrigine

Jamie Solis, Jon Cokley

OBJECTIVE: Describe a case of asystole in an epilepsy patient receiving cenobamate, a positive allosteric modulator of $GABA_A$ receptors, in combination with lamotrigine, a sodium channel–blocking anti-seizure medication.

METHODS: Case report and literature review.

RESULTS: A 19-year-old female with intractable epilepsy was admitted to the Epilepsy Monitoring Unit for 24-hour continuous EEG to quantify seizure burden and characterize events. Bradycardia was noted with one QRS complex every 1.5-4 seconds, followed by generalized EEG suppression and loss of cardiac rhythm for 10 seconds. During asystole, the patient lost all muscle tone for several seconds. Drug levels for medications during admission were notable for cenobamate 57 mcg/mL, clobazam 253 ng/mL, norclobazam 9252 ng/mL, and lamotrigine 3.8 mcg/mL. Following these events, Cenobamate was adjusted to lower levels, and lamotrigine was discontinued to avoid sodium channel blockers. A genetics evaluation was performed and did not uncover any diagnostic variants to date.

CONCLUSIONS: Concomitant sodium channel blocker therapy with cenobamate may be associated with clinically significant bradyarrhythmia and asystole. In this patient, subsequent adjustment of cenobamate to lower levels and discontinuation of lamotrigine was associated with resolution of cardiac symptoms.

KEYWORDS: Epilepsy

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114. Preliminary Feasibility of Open BCI-Based EEG as a Rapid Screening Tool in the Pediatric Epilepsy

Sarah Ward, Jahnavi Tatachar, Garrett Gianneschi

OBJECTIVE: To evaluate the feasibility of using a low-cost Open BCI-based EEG monitoring system to capture clinically relevant EEG patterns in pediatric patients as an initial step toward developing a rapid screening tool that may help triage the need for standard-of-care hospital EEG monitoring.

METHODS: This ongoing study compares an Open BCI-based EEG monitoring system to standard hospital EEG monitoring of three patients. The selected patients were confirmed to have seizures on hospital EEG and subsequently underwent monitoring via the Open BCI-based EEG system. The EEG studies were evaluated by trained Pediatric Neurologists experienced in EEG interpretation and compared qualitatively with available hospital EEG findings and spectrogram features.

RESULTS: Preliminary recordings demonstrated qualitative concordance between the Open BCI-based EEG system and the standard hospital EEG system in detecting absence seizures, background slowing, and different sleep phases. The results of the Open BCI-based EEG monitoring correlate with both the hospital EEG results and on spectrogram.

CONCLUSIONS: In this small pilot experience, an Open BCI-based EEG system was feasible for capturing selected clinically relevant EEG patterns in pediatric patients with known abnormalities on standard EEG. These preliminary results support further investigation of low-cost EEG systems as rapid adjunctive screening tools that may help triage the need for formal hospital EEG in selected clinical settings.

KEYWORDS: Epilepsy

115. The Great Mimicker: How scrutinizing a diagnosis of PNES revealed insular epilepsy

Carlos Palomino, Ima Ebong, Zahra Haghighat

OBJECTIVE: Misdiagnosis of functional seizures remains a challenge. Insular epilepsy, "The Great Mimicker," may be mistaken for PNES, given concomitant scalp-negative EEG. We present a case highlighting the difficulty in diagnosing scalp EEG-negative seizures.

METHODS: Thorough chart review.

RESULTS: An adolescent with a history of six childhood febrile seizures and two generalized tonic-clonic seizures was admitted for continuous video EEG and treated for focal seizures. Initial study captured a burst of generalized rhythmic delta, bilateral frontotemporal maximal, followed by subtle quasi-rhythmic activity, right greater than left. A second event ("déjà vu") showed intermittent polymorphic generalized delta, bifrontal maximal, with sustained bilateral quasi-rhythmic theta evolving from right temporal to frontal regions (T8,P8>F8), spreading to central electrodes. Months later, the patient reported frequent episodes of dizziness, confusion, word-finding difficulty, and palpitations lasting up to 30 minutes with retained awareness. Repeat video EEG showed no ictal correlate; however, EKG revealed consistent tachycardia during episodes, raising suspicion for cardiac etiology versus scalp-EEG-negative seizures. PET demonstrated asymmetric hypometabolism of the left temporal pole; MRI showed possible thickening of the right insular cortex; 7-day Holter revealed sinus rhythm with 4% PVC burden.

CONCLUSIONS: Stereotyped semiology and EKG abnormalities prompted further evaluation that ultimately suggested insular epilepsy rather than functional seizures. The patient responded to increased oxcarbazepine with decreased seizure frequency. This case highlights the difficulty in differentiating functional seizures from insular lobe epilepsy. Our patient has shown a response to treatment of increased Oxcarbazepine resulting in decreased frequency of seizures, initially thought to be functional.

KEYWORDS: Epilepsy

116. Low-Grade Glioma in a Child with DEPDC5-Related Epilepsy: An Unexpected Pathologic Finding

Natasha Glenn, Hyunmi Kim

OBJECTIVE: When *DEPDC5*-related focal epilepsy is associated with structural abnormalities, focal cortical dysplasia (FCD) is classically implicated. We report a single case of medically intractable lesional *DEPDC5*-related epilepsy with low-grade glioma on histopathology.

METHODS: This developmentally delayed patient presented with a three-year history of daily focal impaired awareness seizures involving epigastric and gustatory sensations. Workup included: EEG, genetic epilepsy panel, MRI, fMRI, PET MRI, and ECoG-based subtotal resection with histopathology and molecular profiling.

RESULTS: EEG showed left-lateralizing electroclincal seizures. Genetic epilepsy panel revealed a pathogenic heterozygous deletion in *DEPDC5*. MRI showed a T2/FLAIR hyperintense, ill-defined expansile lesion involving the left mesial temporal lobe, centered within amygdala and uncus, favoring low-grade glioma or glioneuronal tumor. PET revealed relative left temporal hypoperfusion, supporting a left mesiotemporal epileptogenic focus. Given the clear presence of a mass and correlating seizure onset, the patient underwent lesional resection with ECoG. Pathology/molecular profiling resulted with AGK::BRAF fusion low-grade glioma. Since resection, the patient is seizure-free and has made significant developmental progress.

CONCLUSIONS: This case highlights an unexpected structural abnormality in *DEPDC5*-related epilepsy, stresses the importance of a broad differential diagnosis in lesional epilepsy despite known genetic etiology, and underscores the value of histopathology and molecular profiling. An intriguing potential link between two distinct signaling pathways is raised: mTOR (implicated in *DEPDC5*-related FCD) and (BRAF fusion-driven) MAPK. Finally, this patient is from a medically underserved community and was symptomatic for 3-4 years prior to presenting to specialty care that resulted in seizure freedom, displaying the need for equitable access to neurologic services.

KEYWORDS: Epilepsy, Neurogenetics, Diversity, Equity, Inclusion

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117. Developing a Family Navigation Model to Help Support the Epilepsy Transition of Care Process

Chyanne Reyes, Kelly Duffy, Sarah Stoney, Benjamin Yerys, Adam Greenberg, Marissa DiGiovine

OBJECTIVE: Family/Caregiver Navigation (FCN) aims to support the self-efficacy of patients and families moving from pediatric to adult care systems, which can be a difficult process. Our goal is to develop a Family Navigation Model (FNM) within a multi-organizational network that supports this transition of care (TOC) process for adolescents and young adults with epilepsy (YAES).

METHODS: Stakeholders from pediatric and adult health systems, a school district, and community resource organizations convened to form a Network. Three advisory councils (ACs) were established, comprised of YAES and parents/caregivers of YAES. An iterative process of REDCap surveys and virtual meetings was completed to collect information about lived experiences and guide model development. Groups were asked about FCN-knowledge/experience. Network members were asked about organizational capacity for direct implementation of the FNM.

RESULTS: Among 27 survey responses: n=4 Network/AC members had knowledge of FCN and n=2 YAES had directly received FCN-support. A perceived benefit from having access to FCN-support was reported by YAES (n=6/7). Network members reported capacity to directly implement the FCN-role (n=2), and others reported capacity to implement FCN components (n=5).

CONCLUSIONS: The transition to adult care for patients with epilepsy is difficult to navigate on their own. A FNM can provide significant support for YAES who are unfamiliar with the processes unique to adult-serving systems. Given the limited awareness of FCN and variability of Network members' abilities to implement a FNM despite YAES' interest, a partnership was formed with an organization outside the Network to fill the gaps identified.

KEYWORDS: Epilepsy

118. Treatment of non-convulsive status epilepticus in Angelman syndrome: case report and review of literature

Magda Nowicki, Farah Din, Mahendra Moharir, Erick Sell, Lauren Sham

OBJECTIVE: Angelman Syndrome is a rare neurogenetic disorder associated with non-convulsive status epilepticus (NCSE). The clinical presentation can be initially unrecognized, presenting as decreased responsiveness and developmental regression, often without overt seizures. There are no standardized treatment guidelines for NCSE in Angelman syndrome. Studies have suggested brief courses of oral diazepam first-line; however, a subset of patients remain refractory. Consensus for second-line treatment is less clear with options including steroids, IV medications (e.g. valproic acid) and the ketogenic diet.

METHODS: We present a case of a 7-year-old male with Angelman syndrome who was admitted following a 2-week history of daily episodes of unresponsiveness, eyelid fluttering, and functional decline.

RESULTS: Routine EEG showed almost continuous generalized frontally predominant 2 Hz spike-and-slow wave discharges. He was treated with an outpatient diazepam course without clinical improvement. He was then admitted to hospital, and video EEG revealed near continuous, high amplitude diffuse rhythmic delta activity with superimposed spikes and sharp waves. Multiple loading doses of anti-seizure medication were given with no improvement. He was transferred to the ICU for further management. Following loading of IV phenobarbital, both the patient's clinical status and EEG improved. A 3-day course of IV methylprednisolone was also given, and he was discharged on an oral steroid taper and phenobarbital maintenance.

CONCLUSIONS: NCSE in Angelman syndrome remains an important treatable cause of functional decline, with lack of clear guidelines on its management. In this case, phenobarbital load was of benefit when outpatient management and other anti-seizure medications did not ameliorate the patient's clinical status.

KEYWORDS: Epilepsy, Neurogenetics

119. Medical Cannabis in Pediatric Epilepsy: An Ethical Analysis of Consent, Access, and Long-Term Safety

Sarah Razzaq, Bernadette Riley

OBJECTIVE: To examine the ethical dimensions surrounding medical cannabis use in pediatric epilepsy, focusing on informed consent, parental decision-making, equitable access, and long-term safety uncertainty using the four core principles of biomedical ethics as an analytical framework.

METHODS: A narrative review was conducted using PubMed. Search terms included cannabidiol, pediatric epilepsy, Dravet syndrome, Lennox-Gastaut syndrome, informed consent, off-label use, medical ethics, and health disparities. Articles published between 2021 and 2025 were synthesized across pediatric neurology, pharmacology, bioethics, and health equity.

RESULTS: Significant ethical tensions exist across all four bioethical principles. Regarding autonomy, children cannot consent for themselves, placing decisional burden on parents whose enthusiasm may outpace evidence. Regarding beneficence, Epidiolex demonstrates meaningful efficacy in treatment-resistant pediatric epilepsy, with a systematic review confirming higher seizure reduction versus placebo, sustained efficacy over 60 months, and higher quality of life among users. Regarding non-maleficence, CBD used outside FDA-approved indications lacks equivalent evidentiary support, with quality of life improvements inconsistently demonstrated. Artisanal CBD carries concerns including variable concentration, tolerance development, and drug-drug interactions. Non-medical cannabis carries further risks including psychoactive effects and pulmonary complications. Regarding justice, Epidiolex cost barriers drive families toward artisanal formulations- 59% of patients continuing artisanal CBD beyond one year showed greater than 50% seizure reduction, suggesting clinical rationale despite disproportionate impact on lower-income populations.

CONCLUSIONS: Medical cannabis in pediatric epilepsy presents a complex ethical landscape. Access inequities drive

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vulnerable families toward less regulated alternatives. Standardized informed consent frameworks, equitable access initiatives, and long-term safety surveillance are urgently needed across all pediatric epilepsy populations.
KEYWORDS: Epilepsy, Ethics

120. Fenfluramine for Seizure-Associated Respiratory Compromise in Drug-Resistant Epilepsy: A Three-Patient Case Series

Sarah Schorr, Yash Shah, Nidhi Sthanki

OBJECTIVE: Sudden unexpected death in epilepsy (SUDEP) is a leading cause of mortality in drug-resistant epilepsy and is strongly associated with seizure-associated respiratory compromise. While antiseizure therapies are typically evaluated based on reduction of seizure burden, their impact on respiratory dysfunction remains less well characterized. We describe the clinical effects of fenfluramine on seizure burden and seizure-associated respiratory compromise in pediatric patients with drug-resistant epilepsy.
METHODS: Retrospective case series of three pediatric patients with drug-resistant epilepsy and seizure-associated respiratory compromise treated with fenfluramine. Clinical data were obtained through chart review and caregiver reports.
RESULTS: Retrospective case series of three pediatric patients with drug-resistant epilepsy and seizure-associated respiratory compromise treated with fenfluramine. Clinical data were obtained through chart review and caregiver reports.
CONCLUSIONS: Fenfluramine may provide a dual benefit in pediatric drug-resistant epilepsy by reducing both seizure burden and seizure-associated respiratory compromise, a key factor linked to SUDEP risk.
KEYWORDS: Epilepsy, Experimental Therapeutics

Ethics

121. A Systematic Review and Ethical Analysis of mRNA COVID-19 Vaccines in Children and Adolescents

Alexander Jares, Jill Miller-Horn

OBJECTIVE: To systematically review randomized placebo-controlled trials of mRNA COVID-19 vaccines in children and adolescents through a structured ethical analysis relevant to pediatric neurology practice, evaluating disease severity, vaccine benefits and risks, proportionate coercion, and resource allocation.
METHODS: PubMed was searched using ((COVID-19 vaccine) AND (pediatrics OR children OR adolescent)) filtered for clinical trials from January 1, 2020, through March 27, 2023. Included trials evaluated US-authorized mRNA vaccines. Seven trials met inclusion criteria. Data were categorized by beneficence, non-maleficence, autonomy, and justice.
RESULTS: As of January 2023, vaccination uptake lagged in children (7.1–73.3% across ages 0–17) compared to adults (85.4%). Vaccines demonstrated high short-term efficacy and strong protection against severe disease including MIS-C. The number needed to treat (NNT) to prevent one hospitalization was 10,000–60,000 for COVID-19, compared to 1,000–7,000 for influenza vaccines and 4 for measles. Mild to moderate reactogenicity was common; serious adverse events were rare. Vaccine-associated myocarditis was rare, predominantly in adolescent males with favorable outcomes and lower incidence than COVID-19-associated myocarditis. Children under 2 with neurologic or cardiac comorbidities had twice the risk of severe illness and derived greater benefit from vaccination. Eradication is an unrealistic societal goal as the population is no longer COVID-19 naïve, parental autonomy carries greater weight in shared decision-making.
CONCLUSIONS: Ethical analysis supports individualized shared decision-making for COVID-19 vaccination in pediatric populations. Benefits are measurable but modest in healthy children; those with neurologic or cardiac comorbidities represent a high-priority group. This framework assists pediatric neurologists counseling families during time-limited visits.
KEYWORDS: Ethics, Neuroinfectious Disease, Diversity, Equity, Inclusion

Experimental Therapeutics

122. Efficacy and safety of zilganersen, an investigational RNA-targeted antisense therapy, in people living with Alexander disease: Additional data from the pivotal phase 1–3 trial

Amy Waldman, Davide Tonduti, Marjo van der Knaap, Geneviève Bernard, Florian Eichler, Jacinda Sampson, Ayelet Zerem, Jeremy Chataway, Chloe Cunningham, Enrico Bertini, Francesco Nicita, Yael Hacohen, Takashi Saito, Stephanie Keller, Ylenia Vaia, Nee Kim, Keith Van Haren, Amanda Nagy, Elske van den Berg, Fabio Bruschi, David Lynch, Chen Chen, Norma Ruiz-Santiago, Aaron Yarlas, Belinda Cowling, Abigail Collins, Anne Smith

OBJECTIVE: Alexander disease (AxD) is a rare, genetic astrocytopathy arising from glial fibrillary acidic protein (*GFAP*) gene pathogenic variants and characterized by a heterogeneous spectrum of motor, cognitive, autonomic, gastrointestinal, and bulbar symptoms; currently, there is no approved disease-modifying treatment. We report efficacy and safety of zilganersen, an investigational antisense therapy targeting *GFAP* RNA, from a pivotal phase 1–3 trial (NCT04849741) in people with AxD,
METHODS: Participants (aged 2–65 years) with AxD were randomized to intrathecal zilganersen 50 mg or control every 12 weeks for 60 weeks (double-blind treatment period). The primary endpoint is the percent change from baseline to Week 61 in gait speed (10-meter walk test). Additional endpoints include outcomes capturing gross and fine motor function, cognitive capabilities, communication, gastrointestinal

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function, autonomic function, behavior, changes in plasma GFAP concentration, and safety vs control at Week 61.

RESULTS: At Week 61, zilganersen resulted in statistically significant and clinically meaningful stabilization of gait speed with improvements in global health status and a nominally significant 33.6% reduction in plasma GFAP vs control and an acceptable safety profile. Additional efficacy results consistently favored zilganersen 50 mg vs control across motor (Gross Motor Function Measure-88 Dimensions C-E [<5 years old at screening]), adaptive function (Vineland-3 Adaptive Behavior Composite Score [<18 years old at screening]), and gastrointestinal function (Pediatrics Quality of Life Inventory Gastrointestinal Symptoms Scales) symptom domains of AxD and AxD-Patient Domain Impression of Severity and Change.

CONCLUSIONS: These results support zilganersen as a potential disease-modifying therapy for AxD.

KEYWORDS: Experimental Therapeutics, Movement Disorders

123. Safety and Effect of Ecopipam During the First 8 Weeks of Treatment for Tourette Syndrome: A Post Hoc Analysis

Kinga Tomczak, Tamar Katz, John Flatt, George Karkanias, Stephen Wanaski, Timothy Cunniff, Donald Gilbert

OBJECTIVE: To assess the safety/effect of ecopipam, a selective dopamine D1 receptor antagonist, during the first 8 weeks of therapy for Tourette syndrome to help guide expectations during treatment initiation.

METHODS: Data were pooled post hoc for the first 8 weeks of a phase 2b, randomized, double-blind (DB), placebo-controlled trial (≥6 to <18 y) and open-label period of a phase 3, randomized, DB, withdrawal-to-placebo trial (≥6 y). These were included because ecopipam titration (3-4 weeks), dosing (target, 1.8 mg/kg/day), and efficacy/safety measurements were similar.

RESULTS: Overall, 292 ecopipam-treated participants were included (mean [SD], 15.3 [7.8] y; 70.2% male; baseline mean [SD] YGTSS-TTS, 34.4 [6.1]). Mean (SD) change in YGTSS-TTS from baseline was −7.3 (7.1) at Week 4 and −11.1 (8.0) at Week 8—mean (SD) improvement of 21.5% (20.7) and 32.4% (22.7), respectively. A ≥25% reduction in YGTSS-TTS was seen in 35.9% (102/284) of participants at Week 4 and 69.8% (178/255) at Week 8. During the first 8 weeks of ecopipam, 63.7% of 292 participants had an adverse event (AE). The most commonly reported AEs were somnolence (10.6%), headache (9.9%), fatigue (6.8%), anxiety (6.5%), and tic (4.8%). Two (0.7%) participants had a serious AE; 37 (12.7%) discontinued due to an AE.

CONCLUSIONS: Clinically meaningful improvement in YGTSS-TTS was observed for a majority of participants within the first 8 weeks of starting ecopipam treatment. The safety profile during initial ecopipam treatment was similar to that of the overall trials: the most commonly reported cross-trial AEs are often observed within the first 8 weeks of exposure.

KEYWORDS: Experimental Therapeutics, Neurodevelopmental Disorders, Movement Disorders

124. Ecopipam Does Not Negatively Impact Weight, Metabolic Parameters, or Electrocardiogram Measurements or Induce Movement Disorders in Individuals With Tourette Syndrome

Kinga Tomczak, Tamar Katz, Erica Greenberg, Donald Gilbert, John Flatt, George Karkanias, Frederick Munschauer, Stephen Wanaski, Timothy Cunniff

OBJECTIVE: To determine if adverse events (AEs) commonly reported with antipsychotic use (eg, weight gain, metabolic abnormalities, drug-induced movement disorders) are observed during treatment with ecopipam, a selective dopamine D1 receptor antagonist.

METHODS: Individuals aged ≥6 years with Tourette syndrome were enrolled in a phase 3, double-blind (DB), placebo-controlled, randomized withdrawal trial. Ecopipam was titrated to 1.8 mg/kg/day during a 12-week, open-label (OL) period. Those with ≥25% YGTSS-TTS reduction at Weeks 8 and 12 were randomized to continue ecopipam or taper to placebo during a 12-week DB period. A blinded committee adjudicated prespecified neurologic AEs.

RESULTS: Overall, 216 (n=167 pediatric) participants were enrolled to OL ecopipam; 104 (n=90 pediatric) were randomized to ecopipam (n=51 [84.3% pediatric]) or placebo (n=53 [88.7% pediatric]) during DB period. The most common AEs during ecopipam treatment (OL/DB [n=216]) were somnolence (11.1%), anxiety (9.7%), headache (9.7%), insomnia (8.8%), tic (7.9%), and fatigue (6.5%). Tremor and dystonia occurred in 1 participant each during OL period with both adjudicated (PI; blinded committee) as unrelated to ecopipam; neither AE was reported during DB period. No clinically meaningful changes in vital signs, physical examination, laboratory values, QT interval, or heart rate were observed, and body mass index z-scores remained generally stable. AE assessment and Extrapyramidal Symptom Rating Scale scores over time affirmed that ecopipam did not cause drug-induced movement disorders.

CONCLUSIONS: Ecopipam treatment for up to 24 weeks was generally well tolerated, with primarily CNS-related AEs observed. No signals of clinically relevant weight gain, metabolic or ECG abnormalities, or drug-induced movement disorders were identified.

KEYWORDS: Experimental Therapeutics, Neurodevelopmental Disorders, Movement Disorders

125. Presence of Common Psychiatric Diagnoses Did Not Impact the Efficacy or Safety of Ecopipam in Individuals With Tourette Syndrome

John Flatt, Joseph McGuire, George Karkanias, Frederick Munschauer, Timothy Cunniff, Stephen Wanaski, Erica Greenberg

OBJECTIVE: To evaluate ecopipam efficacy/safety in individuals with Tourette syndrome (TS) with or without common psychiatric comorbidities.

METHODS: Individuals ≥6 years with TS were enrolled in a phase 3, randomized withdrawal trial. Ecopipam 1.8 mg/kg/

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day was administered in a 12-week, open-label period. Those with ≥25% YGTSS-TTS reduction at Weeks 8 and 12 were randomized to ecopipam or placebo during a 12-week double-blind period. Individuals were subgrouped post hoc by co-occurring anxiety, attention-deficit/hyperactivity disorder (ADHD), depression, or obsessive-compulsive disorder (OCD), determined from medical/psychiatric history at screening.

RESULTS: Overall, 216 participants were enrolled (129 [59.7%] had ≥1 comorbidity), and 104 were randomized to ecopipam (n=51 [64.7% ≥1 comorbidity]) or placebo (n=53 [54.7% ≥1 comorbidity]). Baseline parameters were similar between participants with/without co-occurring conditions (mean age, 16.4/16.1 years; 65.1%/71.3% male; mean YGTSS-TTS, 34.9/33.4). Mean (SD) YGTSS-TTS change from baseline at Week 12 was −16.1 (7.6) in participants with ≥1 comorbidity and −15.7 (6.8) in those without (P=0.80; 2-sided t test). Though not powered for significance, during the randomized withdrawal period ecopipam reduced the risk of relapse versus placebo in participants with ≥1 comorbidity (hazard ratio, 0.6 [95% CI, 0.3-1.1]; P=0.09) and without ≥1 comorbidity (0.3 [0.1-0.9]; P=0.02). The most commonly reported adverse events during ecopipam treatment for those with versus without ≥1 comorbidity were anxiety (11.6% vs 6.9%), tic (10.9% vs 3.4%), insomnia (10.1% vs 6.9%), and depressed mood (4.7% vs 2.3%).

CONCLUSIONS: The presence of commonly co-occurring psychiatric conditions (ie, anxiety/ADHD/depression/OCD) with TS did not negatively impact reductions in tic severity or the safety/tolerability of ecopipam.

KEYWORDS: Experimental Therapeutics, Neurodevelopmental Disorders, Movement Disorders

126. Phase 1 ASCEND Study Evaluating INS1201 AAV9 Gene Therapy in Ambulatory Pediatric Males with Duchenne Muscular Dystrophy: Trial in Progress

Sheritha Lee, Mark Stahl, Gretchen Thomsen, Marissa Kruger, Paul Chang, Kathleen Church, Maite Francois, Michelle Fortin, Olivier Francillon, Allan Kaspar, Samit Varma, Brian Kaspar, John Day

OBJECTIVE: INS1201 is an investigational, intrathecally administered, AAV9 vector-based micro-dystrophin gene therapy for the potential treatment of Duchenne muscular dystrophy (DMD). Preclinical studies demonstrated histopathological improvement and functional efficacy in *mdx* mice, with efficient skeletal and cardiac muscle targeting, and high expression at low doses in mice and nonhuman primates. ASCEND is a phase 1, first-in-human, dose-escalation study assessing INS1201 safety and biodistribution in ambulatory males with DMD aged 3-<5 years (Part 1: Cohort 1 and 2) and 2-<3 years (Part 2: Cohort 3 and 4).

METHODS: ASCEND (NCT06817382) will evaluate up to 12 participants across two parts, each comprising two sequential dose cohorts (n=3 each): 5.0E+14 vector genomes (vg) in Cohorts 1 and 3, and 1.0E+15 vg in Cohorts 2 and 4. Enrollment is staggered with a 30-day safety observation period between each participant; an independent data monitoring committee will convene following completion of the last participant's observation period in each of Cohorts 1, 2, and 3. Primary endpoint is incidence and severity of treatment-emergent adverse events (AEs), AEs of special interest, and serious AEs. Secondary endpoints include identification of a recommended phase 2 dose (RP2D) and change from baseline in micro-dystrophin DNA and expression. Exploratory endpoints include micro-dystrophin biodistribution and expression, functional outcomes, and caregiver-reported outcomes. Participants will be followed up for 96 weeks post-administration followed by a 3-year safety extension study.

RESULTS: As of June 2026, ASCEND is actively enrolling at 10 US sites.

CONCLUSIONS: ASCEND will assess INS1201 safety and biodistribution and will inform RP2D selection.

KEYWORDS: Experimental Therapeutics, Neurogenetics, Neuromuscular

127. Autism, Sleep, and Medicinal Cannabis: 18-Month Prospective Registry Outcomes on Efficacy and Safety

Aiza Salman, Mohsin Maqbool, Diya Khullar, Izabella Jonhson, Taha Maqbool

OBJECTIVE: Sleep disturbances are highly prevalent in children with autism spectrum disorder (ASD) and are associated with impaired daytime functioning and reduced family quality of life. Despite increasing real-world use of medicinal cannabis to address sleep difficulties in ASD, long-term prospective data on sleep outcomes and safety remain limited.

METHODS: We examined 18-month sleep and safety outcomes associated with medicinal cannabis use in children with ASD using a prospective clinic registry. This observational study included 68 children with ASD who initiated medicinal cannabis as part of routine clinical care; 57 completed at least 18 months of follow-up. Caregiver-reported sleep duration was assessed at baseline and follow-up using sleep logs. Sleep onset, sleep maintenance, sleep quality, and child and caregiver quality of life were evaluated using the Caregiver Global Impression of Change (CGIC). Adverse effects and treatment discontinuation were recorded prospectively.

RESULTS: Mean sleep duration increased from 6.8 to 8.1 hours among participants completing follow-up, with larger gains among children with more severe baseline sleep restriction. Approximately 70–75% of caregivers reported improvement in sleep onset, sleep maintenance, and overall sleep quality, and improvements in child and caregiver quality of life were also commonly reported. Adverse effects were most frequent early in treatment and declined over time, with no serious adverse events observed.

CONCLUSIONS: These longitudinal real-world findings support the need for controlled studies evaluating long-term sleep outcomes and tolerability of cannabinoid-based interventions in children with ASD.

KEYWORDS: Experimental Therapeutics, Behavioral Neurology, Sleep

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128. Management of 5 Cases of Thrombotic Microangiopathy Following CNS-Directed AAV Gene Therapy

Alex Fay, Alice Chan, Marissa Evans, Amanda Nagy, Florian Eichler

OBJECTIVE: To describe the diagnosis and management of 5 cases of thrombotic microangiopathy (TMA) following AAV gene therapy for two pediatric CNS diseases.

METHODS: Case review of laboratory findings and management of TMA following AAV gene therapy in two clinical trials at two institutions.

RESULTS: TMA was diagnosed, based on the presence of thrombocytopenia, anemia, elevated soluble c5b-9, elevated lactate dehydrogenase, proteinuria, and hypertension. Three cases occurred following intravenous injection of AAV gene therapy, and two following intracerebroventricular delivery. In each case, vector genomes (vg) exceeded 2 x 10^{15}, though not all patients receiving > 2 x 10^{15} vg developed TMA. All patients were managed with eculizumab, two requiring platelet and red blood cell transfusions, and one requiring hemodialysis, and all patients received prolonged high-dose steroids. Two cases occurred following prophylactic rituximab or eculizumab. Eculizumab dosing was as frequent as every 48-72 hours in severe cases, and continued until soluble sC5b-9 levels normalized and platelet levels stabilized. All 5 patients recovered.

CONCLUSIONS: TMA may occur with intracerebroventricular AAV gene therapy, a finding not previously reported, and may not be a rare complication of IV gene therapy, especially at doses > 2 x 10^{15} vg. Monitoring of blood counts, inflammatory markers, complement activation, and urine during the first week following gene therapy is essential. While prophylactic eculizumab did not prevent TMA, aggressive management with eculizumab, together with supportive care, is effective, but resulted in prolonged hospitalization. Centers providing AAV gene therapy should have monitoring and treatment algorithms in place for TMA, and readily available eculizumab.

KEYWORDS: Experimental Therapeutics, Neurometabolic, Neurogenetics

129. Advancing Clinical Trials in Pediatric Neurology: The Expanding Role of NeuroNEXT

Jennifer Vermilion, Joshua Bonkowsky, Brenda Banwell, Adam Hartman, Tracy Glauser, Merit Cudkowicz

OBJECTIVE: In 2011, the National Institute of Neurological Disorders and Stroke established the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT), a coordinated national network, to improve multicenter early-phase trial execution. Two pediatric studies have been brought to trial. In 2023, the Pediatric Consortium (PedCon) was established to increase pediatric-focused trials and pediatric enrollees. Here, we review the evolution of NeuroNEXT as a platform for advancing pediatric neurology clinical research.

METHODS: We conducted a descriptive review of NeuroNEXT infrastructure, program initiatives, proposals, and clinical studies that enrolled pediatric participants. We assessed pediatric-focused and pediatric-inclusive initiatives, comparing the time frame of 2023-present, to the prior funding cycle of NeuroNEXT (2018-2023).

RESULTS: Since PedCon was established, nine concept proposals that include pediatric participants have been submitted. One active study opened enrollment to pediatric participants in 2024. No other pediatric-enrolling studies were initiated during the prior funding cycle. Recent initiatives include the development of the Ultra-rare Gene-based Therapy (URGenT) Network and NeuroNEXT Gene Therapy Consortium. Additionally, the Network's first two annual Network-Linked Open Conferences both focused on pediatric neurological diseases; the upcoming NLOC will address migraine, a condition spanning the lifespan. NeuroNEXT is funded via an Other Transactions Authority funding mechanism, which allows for an iterative evaluation process in an accelerated timeline.

CONCLUSIONS: NeuroNEXT has executed multiple new initiatives to advance clinical trials in pediatric neurology. Future directions should focus on developing innovative trial methodology for pediatric neurology rare diseases.

KEYWORDS: Experimental Therapeutics, Early Stage Investigator

130. Ecopipam, a First-in-Class, Selective Dopamine D1 Receptor Antagonist, Is Noncarcinogenic in Rodents

Stephen Wanaski, Timothy Cunniff, George Karkanias, Virginia Schmith, Duane Belote, Andrew Suttie, Alok Sharma, Shana Dalton

OBJECTIVE: To evaluate carcinogenicity potential of ecopipam, a selective dopamine D1 receptor (D1R) antagonist in development for Tourette syndrome.

METHODS: CD-1 mice received oral gavage for up to 104 weeks with vehicle or ecopipam HCl at 2.5, 10, or 50 mg/kg/day (males) and 2.5, 5, or 25 mg/kg/day (females). Doses represented 0.1, 0.4, and 2× maximum recommended human dose (MRHD) based on mg/m^2 body surface area (males) and 0.1, 0.2, and 1×MRHD (females). Sprague-Dawley rats received oral gavage for up to 105 weeks with vehicle or ecopipam HCl at 5, 50, or 150 mg/kg/day (0.4, 4, and 12×MRHD; males) and 5, 25, or 75 mg/kg/day (0.4, 2, and 6×MRHD; females).

RESULTS: Ecopipam administration did not increase incidence of neoplasms or non-neoplastic findings at 50 and 25 mg/kg/day in male and female mice, respectively, and 150 and 75 mg/kg/day in male and female rats, respectively. Survival of mice/female rats was unaffected by ecopipam administration. Although a dose-dependent increase in mortality for male rats occurred, an ecopipam-related cause was not identified. Animal-to-human exposure safety margins were adequate for ecopipam (rats), its metabolite EBS-101-40853 (mice/rats), and their combination (mice/rats), and for total (conjugated plus unconjugated) EBS-101-40853 (mice/rats). Given species-specific extensive ecopipam metabolism, safety margins for total ecopipam alone were low in both studies.

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CONCLUSIONS: No ecopipam-related effect on the types/incidences of neoplastic findings were observed in 2-year carcinogenicity studies. Results further illustrate selective D1R inhibition by ecopipam. In contrast, antipsychotics are associated with dose-related increases in rodent pituitary/mammary tumors, likely via prolonged D2R antagonism and hyperprolactinemia.

KEYWORDS: Experimental Therapeutics

131. NINDS Clinical Trial Networks

Nicole Farhat, Kristina Hardy, Adam Hartman, Lumy Sawaki-Adams, Joan Ohayon, Jennifer Barnes, Gretchen Scott, Mariam Afzal, Sean McCarthy, Jeremy Brown, Scott Janis, Clinton Wright

OBJECTIVE: The National Institute of Neurological Disorders and Stroke (NINDS) directs several clinical trial networks to support its mission to seek fundamental knowledge about the nervous system and use that knowledge to reduce the burden of neurological disease for all people.

METHODS: The NINDS Division of Clinical Research funds pediatric research in multiple networks. The Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT), including Ultra-rare Gene Based Therapy (URGenT) Clinical Trials, was developed to test promising new treatments for people with neurological disorders. The Strategies to Innovate EmeRgENcy Care Clinical Trials Network (SIREN) is co-funded by NINDS to improve the outcomes of patients with neurologic emergencies by identifying effective treatments given in the earliest stages of care. NIH StrokeNet conducts clinical trials to advance acute stroke treatment, prevention, recovery and rehabilitation across the lifespan. Each network provides a robust, standardized, and accessible infrastructure including clinical trial sites, Clinical Coordinating Center and Data Coordinating Center. Projects are funded through cooperative agreements or Other Transactions Authority (OTA), delivering an innovative process for efficient funding and initiation of clinical trials.

RESULTS: NINDS has published multiple Notices of Funding Opportunities (NOFOs) and Research Opportunity Announcements (ROAs), providing opportunities for applicants across networks. ROAs feature an accelerated timeline and iterative evaluation of proposals.

CONCLUSIONS: NINDS-funded extramural networks implement promising clinical trials in neurological disorders in patients of all ages.

KEYWORDS: Experimental Therapeutics, Traumatic Brain Injury, Stroke

132. Dystonia after bilateral intrathalamic AAV gene therapy in juvenile GM2 gangliosidosis: evolution of disease or related to treatment?

Cintia da Hora, Christopher Stephen, Amanda Nagy, Samuel Kartsonis, Marisela Dy-Hollins, Eleonora D'Ambrosio, Terrence Flotte, Florian Eichler

OBJECTIVE: To characterize the natural history of dystonia in juvenile GM2 gangliosidosis and determine whether post-treatment dystonia following intrathalamic AAV gene therapy represents a treatment-related adverse effect or natural disease progression.

METHODS: A retrospective cohort study of juvenile GM2 gangliosidosis patients followed at MGH was conducted, including three gene therapy-treated and eleven untreated patients. Clinical features, dystonia onset, and disease progression were systematically characterized. CSF hexosaminidase activity and GM2 ganglioside levels were monitored longitudinally post-treatment. A literature review identified 163 published juvenile GM2 cases for comparison.

RESULTS: Dystonia occurred in 36% of untreated juvenile patients with median onset at 8 years and a mean interval of 3.5 years from first neurological symptoms. All three (100%) gene therapy-treated juvenile patients developed new or worsening dystonia within one to two months of treatment, coinciding with peak transgene expression, rising CSF hexosaminidase activity, and concurrent GM2 reduction. Literature review confirmed dystonia in 29.4% of published juvenile cases. Infantile patients, treated with greater neuroplasticity, did not develop dystonia

CONCLUSIONS: Dystonia is a common feature of juvenile GM2 gangliosidosis, but its accelerated onset in all treated patients suggests phenotype-specific susceptibility driven by acute enzymatic restoration in chronically remodeled basal ganglia circuitry. Disease stage and circuit adaptation at the time of intervention are critical determinants of gene therapy safety, with significant implications for patient selection and future trial design.

KEYWORDS: Experimental Therapeutics, Movement Disorders, Neurogenetics

133. Everolimus for Neurological Manifestations of Pediatric Tuberous Sclerosis Complex: A Systematic Review and Meta-analysis

Angel Godina-Sanchez, Giselle Delgadillo-Veizaga, Lizeth Villota Pimentel, Andrea Beltran-De la Fuente, Aline Pérez Carrada, Fabiana Paredes Torres

OBJECTIVE: To evaluate the safety and neurological effectiveness of systemic everolimus in pediatric patients with tuberous sclerosis complex (TSC), with emphasis on seizure outcomes and adverse events.

METHODS: We conducted a systematic literature search across PubMed, Embase, and Cochrane Central through April 2026 to identify randomized trials, cohort studies, and case series including patients younger than 18 years with TSC treated with everolimus for neurological manifestations. Outcomes included ≥50% seizure reduction, seizure freedom, any adverse event, grade 3/4 or severe adverse events, and stomatitis or mouth ulceration. Random-effects meta-analyses were performed using REML with Hartung-Knapp-Sidik-Jonkman adjustment.

RESULTS: Eight studies met inclusion criteria. The pooled proportion of patients achieving ≥50% seizure reduction was 0.71 (95% CI, 0.43-0.93; 6 studies; n=259), with substantial heterogeneity (I^2=88.4%). Seizure freedom was reported in four studies and occurred in 0.38 of patients (95% CI, 0.25-0.51; n=47), with no observed heterogeneity (I^2=0%). Any adverse event was common, with a pooled proportion of

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0.94 (95% CI, 0.65-1.00; 5 studies; n=190; I^2=91.3%). Grade 3/4 or severe adverse events occurred in 0.17 of patients (95% CI, 0.00-0.59; 5 studies; n=369; I^2=95.3%). Stomatitis or mouth ulceration occurred in 0.27 of patients (95% CI, 0.09-0.50; 7 studies; n=395; I^2=75.7%).

CONCLUSIONS: Everolimus may provide clinically meaningful seizure improvement in pediatric patients with TSC, with approximately 7 in 10 treated patients achieving ≥50% seizure reduction. Adverse events were frequent, but severe events were less common. The estimates should be interpreted cautiously because several outcomes showed high heterogeneity and included small, mostly nonrandomized datasets.

KEYWORDS: Experimental Therapeutics, Epilepsy, Neuro-Cutaneous Disorders

134. First-in-human experimental antisense oligonucleotide treatment for TUBB4A-related leukodystrophy: experience from three centers

Amanda Nagy, Samuel Kartsonis, Robert Thompson, Julie Tassinari, Rachel Stoub, Janelle Celso, He Pu, Serena Cho, Laurence Mignon, Elizabeth Berry-Kravis, Olivia Kim-McManus, Florian Eichler

OBJECTIVE: *TUBB4A*-related leukodystrophy is a devastating, childhood-onset, neurodegenerative, autosomal dominant disorder caused by toxic gain-of-function variants in *TUBB4A*. No disease-modifying treatments exist. We report results from four individuals with severe *TUBB4A*-related leukodystrophy (Hypomyelination with Atrophy of the Basal Ganglia and Cerebellum-H-ABC) treated with an experimental Antisense Oligonucleotide (ASO).

METHODS: This first-in-human administration of non-allele-selective ASO therapy for *TUBB4A*-related leukodystrophy includes four n-of-1 protocols at three institutions. Following dose escalation, the ASO is delivered intrathecally quarterly. Study assessments include developmental/neurological scales, caregiver-reported outcomes (CROs), exploratory biomarkers, and safety evaluations. The primary endpoints include change from baseline in motor assessments (all individuals), CROs (Patient A), and dystonia (Patient B). Secondary endpoints varied by individual but included safety/tolerability and change in feeding evaluation scores, language skills, cognitive function, quality of life, and brain myelination.

RESULTS: Four individuals (Patient A: 6-year-old boy with developmental delay, tremors, and severe spasticity; Patient B: 4-year-old girl with impaired ambulation and dystonia but preserved cognitive and language skills; Patients C/D: 5- and 2-year-old girls with severe motor delays) were enrolled. As of April 2026, the patients have received 8 (Patient A) and 4 (Patients B-D) doses of study drug. Patient A showed improvements in motor, cognitive, tone, and language scores (GMFM-88, HINE, BSID-4) with subjective improvements in feeding on bedside assessment. Patients B-D also showed early improvements in tone and motor skills. Study drug was well-tolerated with no treatment-related AEs.

CONCLUSIONS: This non-allele-selective ASO for *TUBB4A*-related leukodystrophy has been well-tolerated and has shown early evidence of benefit.

KEYWORDS: Experimental Therapeutics, Neurogenetics, Early Stage Investigator

135. First-in-human experimental antisense oligonucleotide treatment for Childhood-Onset Neurodegeneration with Brain Atrophy

Amanda Nagy, Samuel Kartsonis, Anna Luddy, Carrie Lu, He Pu, Serena Cho, Laurence Mignon, Anoopum Gupta, Florian Eichler

OBJECTIVE: Childhood-Onset Neurodegeneration with Brain Atrophy (CONDBA) is progressive neurodegenerative disorder caused by toxic gain-of-function variants in *UBTF*. Despite its devastating nature, no disease-modifying treatments currently exist. We report results from an individual with CONDBA treated with an experimental Antisense Oligonucleotide (ASO).

METHODS: This is a first-in-human administration of allele-selective ASO therapy for CONDBA. Following dose escalation, the ASO is delivered intrathecally every 90 days. Primary endpoints include change in gross motor function and ataxia from baseline at 24 months as measured by the Brief Ataxia Rating Scale (BARS), wrist/ankle accelerometers, GMFM-88, Vineland-3, and home gait video assessments, and change in quality of life from baseline to 24 months as measured by the PedsQL. Secondary endpoints included safety/tolerability and change in feeding skills from baseline to 24 months. Exploratory endpoints include change in brain structure, atrophy, and myelination pattern measured by brain MRI.

RESULTS: A 15-year-old boy with developmental regression and severely impaired motor, language, and cognitive skills was enrolled and as of April 2026 has received 6 doses of study drug. After showing early signs of motor improvement, he experienced a fall and had subsequent decline in motor skills and progression of ataxia. These clinical changes correlated with declines in motor activity captured by wrist and ankle accelerometers. Despite this setback, he has had some improvement in social engagement. No adverse events have been deemed related to study drug.

CONCLUSIONS: This first-in-human, allele-selective ASO for CONDBA has been well-tolerated. Good correlation is seen between clinical assessments of motor function and ankle/wrist accelerometer data.

KEYWORDS: Experimental Therapeutics, Neurogenetics, Early Stage Investigator

136. Self-amplifying RNA (saRNA) produces high levels of survival motor neuron (SMN) protein, circumventing limitations of spinal muscular atrophy (SMA) disease-modifying therapies (DMTs): AAV9 viral vector & anti-sense oligonucleotides (ASOs)

Christian DeMoya, Sicheng Pang, Xue Han, Mark Grinstaff, Brian Snyder, Evan Snyder

OBJECTIVE: SMA is caused by deletion/mutation of the *SMN1*-gene that produces *SMN-protein*. *SMN-protein* deficiency results in α-motor neuron degeneration in the anterior horn of the developing spinal cord. *SMN2* "rescue" genes

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that produce mostly truncated *SMN-protein* and limited full-length *SMN2-protein* determine clinical severity. Of DMTs, ASOs target *SMN2* pre-mRNA to increase full-length *SMN-protein* production, but effectiveness depends on *SMN2* number (<3 is associated with profound weakness); AAV9 vector transfects cells with *SMN1-DNA*, enabling continuous *SMN-protein* production, but hepatotoxicity and immunotolerance limit 1x use. We developed an saRNA vector encoding an RNA-dependent RNA-polymerase to produce high levels of SMN-protein without these drawbacks.

METHODS: saRNA and mRNA constructs encoding *SMN-protein* were encapsulated into lipid nanoparticles (LNPs) and delivered to patient-derived SMA-fibroblasts. After 24-hours, *SMN-protein* was quantified by ELISA, normalized to the mass of DNA (pg SMN/ng DNA).

RESULTS: *SMN-protein* produced by saRNA increased in an saRNA dose-responsive manner: 13.67±9.09 pg/ng at 1ng saRNA dose; 65.29±43.20 pg/ng at 5ng; 112.82±34.98 pg/ng at 10ng. These levels were significantly higher than SMA-fibroblasts that were untreated (3.56±0.49 pg/ng), treated with empty LNPs (5.15±4.19 pg/ng), and treated with 10ng mRNA encoding *SMN-protein* (27.10± 5.75 pg/ng).

CONCLUSIONS: SMA-fibroblasts treated with saRNA resulted in higher *SMN-protein* expression than fibroblasts treated with an mRNA construct at the same dose. *saRNA* encoding *SMN-protein* enables continuous *SMN-protein* production without AAV9 toxicity and independent of SMN2 number, potentially offering SMA patients better prevention of motoneuron death and disease progression. Future studies will examine efficacy and safety of saRNA in SMA-hiPSC-derived motoneurons and animal models.

KEYWORDS: Experimental Therapeutics, Neurodevelopmental Disorders

Fetal Neurology

137. Expanding Phenotypic Characterization of Patients with COL4A1/2 Mutation

Mackenzie Buls, Usha Nagaraj, Charu Venkatesan

OBJECTIVE: Analyze MRI findings, clinical phenotypes and outcomes of patients with genetically confirmed COL4A1/2 mutations

METHODS: IRB-approved, retrospective chart review study of all cases of COL4A1/2 who had postnatal follow up data at Cincinnati Children's Hospital from 2010-2023.

RESULTS: Fourteen patients (age range: 3 to 31 years) with COL4A1 or COL4A2 mutations were identified (9: COL4A1 and 5: COL4A2 mutations). 4 had fetal MRI scans. Findings included germinal matrix hemorrhage (n=4; 2: hemorrhage; 2: porencephalic changes), vermian hypoplasia (n=2), cerebellar hemisphere anomalies (n=2), Blake Pouch Cyst (n=3), ventriculomegaly (n=3), suspected neuronal migration anomaly (n=1), white matter hyperintensity (n=1), and absent septum pellucidum (n=1). Importantly, none of the cases had findings suggestive of frontal lobe involvement as previously described in the literature. Post-natal imaging findings (n=14) included white matter gliosis, white matter volume loss, microhemorrhages, thin corpus callosum, delayed myelination, ventriculomegaly, cerebellar abnormality, and absent septum pellucidum. Epilepsy was present in 50% of patients (average age of onset: 14 months). 70% of patients were ambulatory and 30% were non-ambulatory. Language was appropriate in 46% and 54% of patients were fully independent with regards to performing activities of daily living.

CONCLUSIONS: Prenatal MRI findings suggestive of germinal matrix hemorrhage should raise suspicion for COL4A mutation. In addition to features classically described in the literature, our study found a higher prevalence of posterior fossa anomalies and white matter volume loss. Additionally, delayed myelination was observed postnatally, suggesting broader developmental white matter vulnerability. These results highlight a broader spectrum of structural abnormalities associated with COL4A1/2 mutations.

KEYWORDS: Fetal Neurology, Neuroimaging, Neurogenetics

138. Association of fetal cerebral growth and sulcal development with two-year neurodevelopmental outcome in children with prenatally diagnosed mild to moderate isolated ventriculomegaly

Sophie Reid, Patricia Lee, Neel Madan, HyukJin Yun, George Graham, Osamu Samura, Rie Kitano, Shizuko Akiyama, Emiko Takeoka, Alexa Craig, P Ellen Grant, Kiho Im, Tomo Tarui

OBJECTIVE: Isolated cerebral ventriculomegaly (IVM) is the most common fetal brain anomaly, yet prediction of neurodevelopmental outcomes remains challenging. We examined whether fetal regional brain growth and sulcal patterns are associated with postnatal neurodevelopment.

METHODS: Twenty-six fetuses with MRI-diagnosed IVM (atrial diameter 10–15 mm; 17.7–37.7 weeks' gestation) were prospectively recruited. Neurodevelopmental outcomes were assessed through medical record review at a mean age of 24.6 months. Post-acquisition MRI processing included regional volumetric and sulcal pattern analyses. For cases between 25 and 32 weeks' gestation, sulcal position similarity indices were calculated by comparison with normative template brains. Regional growth trajectories and sulcal patterns were compared between fetuses with delayed (n=9) and age-appropriate (n=17) neurodevelopment using nonlinear regression models and Mann–Whitney U tests.

RESULTS: Fetuses with delayed neurodevelopment had larger left and right cortical plates (p=0.020 and 0.012, respectively) and the right cerebellar hemisphere (p=0.017) than ones with age-appropriate neurodevelopment. Fetuses with delayed neurodevelopment had more atypical cerebral sulcal position patterns than those of ones with appropriate development in the left cerebral hemisphere analyzed in whole pattern (p=0.042), inter-sulcal relationship (p=0.042) and corresponding sulcal positions (p=0.042).

CONCLUSIONS: In fetal IVM, enlarged cortical and cerebellar volumes and abnormal sulcal positional patterns during

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the second to third trimester are associated with delayed neurodevelopment, suggesting that quantitative analyses may aid outcome prediction.

KEYWORDS: Fetal Neurology, Neuroimaging, Neurodevelopmental Disorders

139. Fetal MRI of Cortical Malformations of Development and Associated Postnatal Outcomes

Frances St George-Hyslop, Michelle Kasimov, Rhandi Christensen, Manohar Shroff, Shiri Shinar, Elka Miller

OBJECTIVE: Malformations of cortical development (MCDs) result from disrupted corticogenesis and are associated with neurodevelopmental morbidity. Fetal magnetic resonance imaging (MRI) plays a key role in the detection of these anomalies, yet diagnostic challenges and prenatal misclassification remain common. This study aims to characterize the spectrum of MCDs identified on fetal MRI, explore suspected etiologies, assess postnatal outcomes, and analyze cases misdiagnosed prenatally, with the goal of improving diagnostic accuracy and perinatal management.

METHODS: We conducted a retrospective cohort study of 1,809 fetal MRIs performed between 2012–2024 at a tertiary center. Cases with suspected or definitive MCDs on fetal MRI were identified, and correlated with prenatal ultrasound findings, genetic testing, postnatal MRI, and clinical outcomes extending to 12 years of age.

RESULTS: A total of 256 fetuses with suspected MCDs were identified; 126 (49%) had postnatal or post-mortem confirmation. The most common MCD subtypes were periventricular nodular heterotopia (36%) and polymicrogyria (27%). Fetal MRI demonstrated high concordance with postnatal diagnosis of MCDs (91%), though additional MCDs—especially polymicrogyria—were frequently detected only postnatally. Genetic aetiologies were most common (38%), with pathogenic variants returning in 50% of cases who underwent next generation sequencing. Mortality was 26%, with high rates of seizures (31%) and developmental delay (49%).

CONCLUSIONS: Fetal MRI is a critical and accurate tool for the prenatal detection and classification of MCDs, enabling early prognostication. However, limitations in detecting certain MCD types and incomplete etiologic characterization highlight the need for continued integration with postnatal imaging and genetic evaluation.

KEYWORDS: Fetal Neurology

140. A multi-center quality improvement initiative: use of imaging library to enhance communication in fetal neurology consultations

Amanda Summers, Riley Kessler, Sara Molisani, Dawn Gano, Charu Venkatesan, Sonika Agarwal

OBJECTIVE: The objective of this project is to create and implement an educational tool for fetal neurology consultations with the goal of facilitating family understanding of congenital brain differences during prognostic discussions. Additionally, the tool will serve as an educational resource for trainees and improve clinician comfort with fetal consultations.

METHODS: A practice survey from child neurologists and trainees established widespread interest in resources for improving fetal consultations. Reasons for neurologists' discomfort with fetal neurology consultation were analyzed using a Fishbone Diagram. We developed the Fetal Neurology Consultation Library, consisting of images of MRI findings and diagrams depicting neurologic differences encountered in fetal consultations. Prior to implementation, a needs assessment pre-survey was created and distributed to child neurologists across multiple centers. Clinicians will then use the library in clinical practice and complete a post-implementation survey. Outcome measures will be frequency of use and clinician-reported satisfaction with the tool. Feedback will be incorporated to improve the tool.

RESULTS: Fishbone diagram creation revealed several factors leading to clinician discomfort with fetal neurology consultations, including limited resources, adapting to a rapidly evolving field, lack of standardized practice guidelines, and counseling on conditions with uncertain prognoses. Based on this root cause analysis, the image library was created to address the needs of clinicians.

CONCLUSIONS: A structured, family-centered educational resource can enhance communication and support during fetal neurology consultations. Standardizing information delivery may improve both clinician experience and family understanding. Future work will focus on broader dissemination, accessibility, and evaluating long-term impacts on decision-making, family satisfaction, and patient outcomes.

KEYWORDS: Fetal Neurology, Neonatal Neurology, Education

141. Prenatally Diagnosed TUBB3 R262H Tubulinopathy with Congenital Absence of Cranial Nerves III and IV: A Case Report

Maren Heller, Tracy Gertler, Andrea Pardo

OBJECTIVE: Tubulinopathies are rare neurodevelopmental disorders caused by variants in genes encoding tubulin isotypes, resulting in abnormal neuronal proliferation, migration, and cortical development. These disorders present with a broad spectrum of prenatal imaging features and neurological outcomes. We present a neonate with prenatally diagnosed hand contractures, absent cavum septum pellucidum (CSP), and ventriculomegaly, found to have a TUBB3 mutation associated with a multisystem syndrome characterized by cranial neuropathies, joint contractures, brain malformations, and neurodevelopmental impairment.

METHODS: This single-patient case report describes a neonate evaluated at a tertiary fetal center. Prenatal and postnatal data were obtained by retrospective chart review, including maternal history, perinatal imaging, genetic testing, and neurodevelopmental assessments. A literature review of reported TUBB3 c.785G>A (p.Arg262His) cases was conducted.

RESULTS: Prenatal ultrasonography demonstrated hand contractures, absent CSP, and ventriculomegaly. Fetal MRI confirmed dysmorphic CSP. The neonate required early respiratory support and multidisciplinary care coordination due to facial diplegia, opthalmoplegia, and poor feeding. Postnatal MRI showed ventriculomegaly, callosal dysgenesis, and congenital absence vs. severe hypoplasia of cranial nerves

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(CN) III and IV. Trio genome sequencing revealed a de novo pathogenic TUBB3 (c.785 G>A; p.Arg262His) variant. At 2 months, neurodevelopmental evaluation demonstrated ptosis, impaired tracking, facial palsy, and hypotonia.
CONCLUSIONS: This case represents the 15th reported individual with TUBB3 R262H and notes the phenotypic spectrum to include possible congenital absence of CN III and IV, suggesting a severe manifestation of cranial dysinnervation. This also highlights the role of postnatal phenotyping when prenatal findings are uncertain, facilitating targeted genetic testing, multidisciplinary evaluation, and improved prenatal counseling.
KEYWORDS: Fetal Neurology, Neonatal Neurology, Neurodevelopmental Disorders

142. Preliminary Report of Neuroimaging and Infant Neurodevelopmental Outcomes Following Antenatal Lyme Disease Exposure (NCT06026969)

Sarah Mulkey, Meagan Williams, David Schwartz, Roberta DeBiasi

OBJECTIVE: To investigate the effects of Lyme disease (LD) on pregnancy and infant outcomes. The first prospective, neurodevelopmental outcome and neuroimaging study of infants exposed to LD during pregnancy is underway.
METHODS: Pregnant participants with acute LD or post-treatment Lyme disease syndrome (PTLDS) are prospectively enrolled. Pregnancy and early infant outcomes include infant biometry at birth compared to WHO Child Growth Standards, fetal and neonatal MRI and ultrasound, and neurodevelopmental assessment using the Ages and Stages Questionnaires-3 (ASQ-3), Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA), and the Alberta Infant Motor Scale (AIMS) through 6 months of age.
RESULTS: All 14 participants (7 with acute LD, 7 PTLDS) delivered liveborn term infants. Twelve infants had normal biometry for age and sex, one in the PTLDS group was small for gestational age, and one in the acute LD group was large for gestational age. One fetal MRI from the PTLDS group showed a small focal infarct which was not seen postnatally. All other fetal and newborn neuroimaging was normal. Participants' ASQ-3, WIDEA, and AIMS scores reflect normal early developmental milestones and no specific neurodevelopmental delays have been identified.
CONCLUSIONS: To date, no specific pattern of abnormalities in pregnancy or in early neurodevelopmental outcomes has been recognized in this pilot study. Further research is needed given the paucity of data on LD and the impacts of other congenital infectious exposures on early brain development. Our future studies include correlation with placental pathology and follow-up to older ages of child development.
KEYWORDS: Fetal Neurology, Neuroinfectious Disease

143. Defining developmental vectors and timepoints for prenatal intervention using a high resolution ultrasound atlas of primate brain development.

Rohan Soman, Margaret Fabiszak, Ali Brivanlou

OBJECTIVE: Clinically, large scale prenatal imaging is not easily accomplished. However, rodent and cell models don't adequately capture the spatiotemporal complexity of human brain development. We recently published the first comprehensive imaging atlas of marmoset development (*Soman 2024*), and in this study investigate brain development *in vivo* from neurulation to birth to establish a primate imaging model that can be used in comparative clinical studies.
METHODS: High resolution ultrasound was performed in the marmoset (Callithrix jacchus) over 14 pregnancies, 35 fetuses, and 100,000 images to create an atlas spanning every day of embryonic and fetal development. Obstetric measurements, Carnegie staging (C.S.), and analysis of neurologic features (biparietal distance, region morphology, ventricle size, cortical thickness and grey:white ratio) were performed. A deep convolutional neural network was trained to define developmental vectors with bootstrapping and nested cross validation, with blinded manual validation.
RESULTS: Marmoset brain development follows a strikingly similar developmental trajectory to humans, with two notable exceptions- an arrested gastrulation at C.S. 7, and a lissencephalic cortex. C.S. 7 is highlighted as a possible timepoint for genetic interventions. Biparietal distance and cortex:ventricle ratio proved reliable predictors of gestational age and developmental trajectory (8.4 day 95% C.I.). Predictive developmental vectors (5.4 day 95% C.I.) were validated for identification of orthogonal (pathologic) trajectories prior to events such as resorption or miscarriage.
CONCLUSIONS: The marmoset is a translational link between cell and rodent studies and obstetric imaging. Clinically relevant metrics define a generalizable progression of primate brain development, and highlight specific timepoints optimal for *in utero* genetic interventions.
KEYWORDS: Fetal Neurology, Neuroimaging

Global Neurology

144. The Impact of Climate Change on Pediatric Neurological Disorders: A Scoping Review of Current Evidence

Kirsten Sjonnesen, Bilal Rizvi, Jonathan Kuziek, Andrew Dhawan, Serena Orr

OBJECTIVE: The primary objective of this scoping review was to examine the impact of climate change and fossil fuel-related air pollution on the occurrence and health burden of neurological conditions in youth.
METHODS: The Embase, MEDLINE, PsycInfo, PubMed and Web of Science databases were searched for literature, including abstracts, published between January 1, 1990, and November 6, 2023. Systematic reviews were not eligible, but their citations were searched for additional sources. Sources reporting primary data or analyses specific to children and youth underwent data extraction.
RESULTS: Of the 105 studies included, case-control (37/105), ecological (37/105), and cohort (25/105) designs predominated. Most studies (75/105) included ≥1,000 participants. Commonly investigated conditions included

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congenital brain malformations, neuro-oncologic conditions, neuroinfectious diseases and seizure disorders, though investigations also spanned headache, stroke, tic disorders, neonatal encephalopathy and multiple sclerosis.
CONCLUSIONS: Changing and extreme weather conditions demonstrated consistent positive associations with rising neuroinfectious disease incidence. Short- and long-term exposure to air pollutants had heterogenous impacts on the burden of neurological conditions. Only one survey reported on the impacts of an extreme weather event on children with a neurological condition (epilepsy). Limited evidence was presented examining the odds of diagnosis for epilepsy, headache disorders, multiple sclerosis, and tic disorders, and favoured positive associations with exposure to air pollutants.
KEYWORDS: Global Neurology, Diversity, Equity, Inclusion, Early Stage Investigator

145. Pro bono genetics and neurology services on a low-income Caribbean nation

Shannon Shipley, Tomoki Nomakuchi, Trey Orndorff, Isabella Rhangos, Dominique Assing, Gaynel La Touche, Beverly Nelson, Aishwaria Gilkes, Sarah Elsea, Ruth Walker, Karla Figueroa, Dong Li, Andrew Sobering, Elizabeth Bhoj

OBJECTIVE: We describe how a medical genetics and neurodevelopmental outreach clinic in a small, resource-limited Caribbean nation helps the community. Many Caribbean nations lack specialty services due to geographic isolation, small population sizes, and socioeconomic disparities. Over 10 years, we organized *pro bono* medical genetics and neurology clinics 1-2 times annually.
METHODS: More than 250 consultations for >180 individuals were provided following referral by local physicians, with follow-up encouraged. *Pro bono* analyses of consented clinical samples were made possible through research protocols permitting result return, including genome sequencing (GS), exome sequencing (ES), microarrays, repeat expansion panels (for ataxia/chorea and FXS), epigenetic methylation profiling, metabolomic profiling, and karyotyping.
RESULTS: Completed ES of 60 individuals yielded 25 diagnoses (approximately 40%), similar to reported rates in well-resourced settings. Genes with causative variants identified by ES include *COL5A1*, *ASPM*, *SYNJ1*, *PHF8*, *NIPBL*, *ALG13*, *NALCN*, *KMT2A*, *TUBG1*, *SATB2*, *PAH*, *MECP2*, *USP7*, *EFNB1*, *DMAP1*, *KAT6B*, *PKD1*, *RFX7*, and *RAF1*. ES CNV analysis allowed 3 additional diagnoses. Karyotype, microarray, ES CNV analysis, or methylation profiling confirmed Down syndrome in 20 other individuals. Repeat expansion testing confirmed Huntington disease in two extended families and SCA3 in another. An additional 62 probands await analysis by ES or GS. Formal consultation notes written by an experienced geneticist or neurologist , including medical screening and management considerations, CME seminars, and teaching rounds build local capacity.
CONCLUSIONS: Although non-systematically obtained, parents, patients, and physicians unanimously expressed appreciation for our efforts. Despite limited availability, semi-annual visits from geneticists and neurologists benefit physicians, patients, families, and the community.
KEYWORDS: Global Neurology, Neurogenetics, Neurodevelopmental Disorders

146. Declining Mortality and Rising Disability in Neonatal Encephalopathy: Global Disparities by Socio-demographic Index

Shreya Tripathy, Joshua August

OBJECTIVE: To assess whether country socio-demographic index (SDI) is associated with changes in neonatal encephalopathy outcomes.
METHODS: We conducted retrospective ecological analysis using Global Burden of Disease data on deaths, disability-adjusted life years (DALYs), and years lived with disability (YLDs) per 100,000. Countries were stratified into SDI quintiles (Low–High). Average annual percent change (AAPC) and joinpoint regression summarized temporal trends. Linear regression evaluated associations between SDI and outcomes in 1990 and 2023.
RESULTS: Mortality declined across all SDI quintiles, with greater reductions in High SDI countries (−90.7%; AAPC −6.9%) than Low SDI countries (−56.4%; AAPC −2.5%). However, disparities widened, with Low-to-High SDI mortality ratio increasing from 10.4-fold to 49.0-fold. Strong negative association between SDI and mortality persisted in both 1990 ($\beta = -9.86$, $p = 0.006$) and 2023 ($\beta = -4.95$, $p = 0.017$). DALYs similarly had declining rates but widening disparity (9.5-fold to 22.1-fold) and sustained inverse association with SDI. YLDs increased across all quintiles, greatest in Low SDI countries (+507.1%; AAPC +5.6%), surpassing High SDI rates by 2018. Joinpoint analysis identified a period of accelerated YLD increase in Low and Low-middle SDI countries between 2013 and 2018, followed by stabilization, while High SDI rates remained stable. The positive SDI–YLD association observed in 1990 was absent by 2023.
CONCLUSIONS: Reductions in mortality outweigh increases in disability burden, reflecting improved survival but a growing population living with neurological sequelae. Rising YLDs and loss of an SDI gradient suggest increasing global burden of disability, emphasizing the need for expanded neurodevelopmental care, particularly in low-resource settings.
KEYWORDS: Global Neurology, Neonatal Neurology, Neurocritical Care

147. Challenges in analyzing GFAP in a clinical trial in individuals with Alexander disease

Belinda Cowling, Armand Soriano, Jinfeng Qi, Shane Doherty, Joel Mathews, Anne Smith, Abigail Collins

OBJECTIVE: Glial fibrillary acidic protein (GFAP) is a biomarker of astrocytic activation and causative protein of Alexander disease (AxD) pathophysiology. GFAP quantification in cerebrospinal fluid (CSF) and plasma is of interest for clinical trials. However, the analytical and biological behavior of GFAP in individuals with AxD has not been fully characterized.
METHODS: Human plasma and CSF samples were collected from individuals in the zilganersen AxD clinical trial,

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ION373-CS1 (NCT04849741). To quantify GFAP concentration, the Quanterix Simoa Discovery (plasma, CSF) and Advantage PLUS (plasma) immunoassays were validated. For CSF GFAP analysis, a novel mass spectrometry method was developed.

RESULTS: The Discovery and Advantage PLUS immunoassays met validation criteria. GFAP showed acceptable stability for two (CSF) or >four (plasma) freeze–thaw cycles. Despite acceptable replicate precision from a single aliquot, unacceptable analytical variability was observed between separate aliquots from the same CSF collection in trial samples. By mass spectrometry, CSF GFAP was stable for >five freeze-thaw cycles, with acceptable precision within and between aliquots. In individuals enrolled in ION373-CS1, biological variability was observed in absolute CSF and plasma GFAP concentrations between individuals at baseline, and within a subset of individuals longitudinally, consistent with Waldman et al, 2026, and confounding interpretation of individual profiles over time.

CONCLUSIONS: These findings identify analytical challenges in measuring CSF GFAP in samples from individuals with AxD by immunoassay, but not mass spectrometry, the latter warranting further investigation as an alternative for GFAP quantification. Despite variable GFAP concentrations within individuals, cohort-level reduction in GFAP concentration was observed post dosing, consistent with its mechanism.

KEYWORDS: Global Neurology

148. Functional scAAV vectors for rapid, cell-type specific tracing and functional manipulation of neurons in-vivo

Adam Lu, Lukas Bachmann, Yichen Lu, Yanyan Fang, Benjamin Temple, Samuel Pfaff, Jeffrey Moore

OBJECTIVE: Recombinase-dependent adeno-associated viruses (AAVs) are powerful tools for circuit mapping, yet conventional versions require 2-6 weeks for functional protein expression. This delay is incompatible with the ~21-day rodent pre-weaning period and the rapid maturation of neonatal neurons. We aimed to achieve faster expression to enable investigation of neural circuits in early postnatal development.

METHODS: We constructed and characterized a suite of recombinase-dependent self-complementing AAV (scAAV) vectors carrying effectors for neuronal labeling and axon tracing (GFP + tagged-synaptophysin), optogenetics (ReachR), ablation (diphtheria toxin fragment A; DTA, and intersectional recombinase-dependent scAAVs that use dual double-floxed inverse orientation (DDIO) technology to achieve Cre- and Flp-dependent specificity. Vectors were validated through neonatal brain and spinal cord injections in various transgenic mice to characterize expression speed and functional efficacy.

RESULTS: The scAAV vectors achieved functional expression within 2-3 days post-injection, outperforming single-stranded AAVs significantly. Our Cre-dependent scAAV construct expressing GFP had roughly 10-fold greater expression than an ssAAV benchmark vector after 2 days, and 5-fold after 10 days. Optogenetic stimulation of spinal motor neurons expressing ReachR enabled robust movements by P3. Rapid ablation via DTA significantly reduced tail-pinch-induced stepping within 3 days and abolished it by 6 days. Intersectional DDIO-scAAVs successfully labeled and ablated specific cortical interneurons within 14 days.

CONCLUSIONS: These DIO-scAAV and DDIO-scAAV vectors provide a high-speed toolkit for cell-type specific manipulation and tracing in the developing nervous system. By reducing incubation times to a few days, these tools facilitate the investigation of fast-paced developmental processes with superior temporal precision.

KEYWORDS: Global Neurology

149. Neurologic sequelae in Liberian pediatric Ebola survivors 10 years after infection

Hanalise Huff, John Tweh, Princess Lobbo, Victor Taryor, Joseph Dorbor, Rebecca Slewion, Gina Norato, Richa Duggirala, Leroy Yankae, Avindra Nath, Dehkontee Dennis, Kumblytee Johnson, B. Jeanne Billioux

OBJECTIVE: The 2014 West Africa Ebola Virus outbreak infected over 28,000 people throughout Liberia, Guinea, and Sierra Leone. This study aimed to characterize the neurologic sequelae following Ebola Virus Disease (EVD) in Liberian children ten years following infection.

METHODS: This cross-sectional observational study enrolled EVD survivors (cases) and their close contacts (controls) in Monrovia, Liberia between February and September 2025. A single visit included questionnaire, neurologic exam, and cognitive testing via NIH Toolbox-Cognition Battery (NIHTB-CB) and International Cognitive Assessment (ICA-P). Prevalence was compared using Fisher's exact test. Comparisons adjusting for age, sex and education for test scores used multiple linear regression.

RESULTS: Of the 153 cases and 175 controls, median age was 20 years (range 9-27) and 55% were female. Cases reported significantly more memory problems ($p<0.001$), confusion ($p=0.0012$), and vision problems ($p=0.0288$) than controls. On NIHTB-CB, attention was significantly worse for cases than controls ($p=0.01$). Scores did not differ significantly between groups on ICA-P. Affect ($p=0.0384$), receptive language ($p=0.0064$), facial strength ($p=0.0149$), tongue movement ($p=0.0475$), tone ($p=0.0209$), tremor ($p=0.0005$), reflexes ($p=0.0367$), and coordination ($p=0.0139$) were abnormal significantly more in cases. On Modified Rankin Scale, cases reported significantly more disability than controls ($p<0.0001$). On executive function assessment, survivors had significantly more trouble completing tasks independently ($p=0.005434$). On Patient Reported Outcome Measurement Information System cognition, survivors had significantly worse scores ($p<0.0001$).

CONCLUSIONS: At 10 years following infection, pediatric EVD survivors have significantly more neurologic and cognitive findings than controls and would therefore benefit from long-term follow up.

KEYWORDS: Global Neurology, Neuroinfectious Disease

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Headache

150. Elevated CSF IL-6 in an Adolescent with Reversible Cerebral Vasoconstriction Syndrome with Hemorrhagic Posterior Reversible Encephalopathy Syndrome

Darcy Engelhart, Ikroop Miglani, Naman Shah, Michael Kung, John Crawford, Rachel Pearson

OBJECTIVE: Reversible cerebral vasoconstriction syndrome (RCVS) is a rare cause of pediatric thunderclap headache. Posterior Reversible Encephalopathy Syndrome (PRES) is a known complication. Fewer than 10 pediatric cases of RCVS with PRES have been reported. We describe an adolescent with thunderclap headaches and vision loss diagnosed with RCVS complicated by PRES with elevated CSF IL-6.
METHODS: Case report.
RESULTS: A 14-year-old male developed severe post-tussive headache with vomiting that resolved within one hour. The following day, severe headache recurred with new bilateral vision loss which prompted presentation to the emergency department. Upon presentation he had hypertension (143/91 mmHg). Visual acuity was limited to light perception. Neurologic exam was otherwise unremarkable. Neuroimaging showed subarachnoid hemorrhage in the right temporal lobe. MR angiography (MRA) showed near-complete stenosis of the right posterior cerebral artery with segmental narrowing, concerning for vasospasm. Lumbar puncture revealed opening pressure >60cmH_2O and elevated CSF IL-6 (629.4pg/ml). Headache recurred on hospital day two; repeat CT showed bilateral occipital hemorrhages with edema, indicating hemorrhagic PRES. RCVS with PRES was suspected. Management included nimodipine for 21 days. Symptoms resolved by discharge. Follow-up MRAs at 3 and 10 months demonstrated gradual resolution of stenosis, supporting RCVS diagnosis.
CONCLUSIONS: RCVS is an underrecognized cause of thunderclap headache in children, and can be complicated by PRES. To our knowledge, we present the first pediatric report of CSF IL-6 elevation in RCVS, suggesting a neuroinflammatory component to the pathophysiology. Future studies may evaluate this possibility and clarify shared mechanisms and optimal management of pediatric RCVS complicated by PRES.
KEYWORDS: Headache, Neuroimaging, Neurocritical Care

151. Remote Electrical Neuromodulation (REN) Wearable Device is Safe for Multiple Treatments a Day and for Everyday Treatment in Pediatric Patients with Migraine

Klaus Werner, Reena Rastogi, Jason Santiago, Eden Mama, Alit Stark-Inbar, Alon Ironi

OBJECTIVE: Remote electrical neuromodulation (REN) wearable is an FDA-cleared, nonsignificant-risk, drug-free, non-invasive, prescribed therapy for migraine in ages ≥8 years, with a strong safety profile demonstrated in clinical trials and real-world studies. Although indicated for as-needed acute treatment and preventive use every-other-day, some patients use REN more frequently, multiple times/day or daily. This study assessed REN safety under such frequent-use patterns in pediatric patients.
METHODS: Frequent-use patterns were classified as multiple treatments per day (defined as ≥4 treatments within a single day), and daily use (defined as treatment on ≥25 of 28 consecutive days). Safety outcomes included device-related adverse-events (dAEs), classified by severity and seriousness, and the proportions of dAEs at both patient and treatment levels.
RESULTS: 313 pediatric patients (15.6±1.5 years-old; 81.2% female) used REN frequently, conducting 6,372 treatments: 286 patients performed multiple treatments/day, 35 used REN daily (8 met criteria for both patterns). Patients reported 4 dAEs in total, 3 in the multiple treatments per day group and 1 in the daily use group, reflecting dAEs in 1.28% of patients, 0.06% of treatments. All dAEs were mild and non-serious, with no treatment discontinuation. Pediatric dAE rates in a large real-world study (n=8,614 patients; 21 dAEs; 0.24% of patients; 0.03% of treatments) fell within the confidence intervals currently observed (0.03-2.52% in patients; 0.00-0.12% in treatments).
CONCLUSIONS: REN demonstrated a favorable safety profile even with frequent use, supporting its use in real-world clinical settings, particularly among pediatric patients with severe or highly frequent migraine.
KEYWORDS: Headache

152. Onabotulinumtoxin A is an effective preventative treatment of chronic and daily pediatric migraine

Lauren Vilardo, Elizabeth Pickup, Merve Aktop, Emily McCracken, Mrinmayee Takle, Raquel Langdon, Marc DiSabella, Alexandra Kornbluh, Jeffrey Strelzik

OBJECTIVE: Despite high efficacy and favorable safety profile in adults, Onabotulinumtoxin A (ONA) injections for migraines have not been Food and Drug Administration approved for children due to a lack of consistent data in children with chronic headaches.
METHODS: We prospectively surveyed 45 patients between 12-22 years of age with chronic migraine receiving ONA treatments using the Phase II Research Evaluating Migraine Prophylaxis Therapy (PREEMPT-2) protocol in our pediatric headache clinic. Subgroup analysis was performed on patients with daily chronic migraine. Headache frequency, pain scores, and disability were assessed at baseline and six weeks after each treatment.
RESULTS: 45 patients were included for analysis; median age was 17 years, and 36/45 (80%) were female. 12/45 (27%) patients had a greater than 50% reduction in headache days after one treatment ($p<0.005$). Of the patients with available data following two treatments, 8/24 (33%) patients had a greater than 50% decrease in headache days ($p=0.004$). In the subset of patients with daily chronic migraine, 6/27 (22%) patients with daily chronic migraine had a greater than 50% reduction in headache days after the first treatment ($p=0.016$). Mean headache disability as measured by the Headache Impact Test decreased after the first four treatments in the entire cohort and after the second and third treatments in the subset of patients with chronic daily migraine.
CONCLUSIONS: These results suggest that ONA is effective in decreasing headache frequency and disability in

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pediatric patients with both chronic migraine and daily chronic migraine, which may improve quality of life.
KEYWORDS: Headache

153. Redefining the Range of "Normal" Cerebrospinal Fluid Opening Pressure in the Pediatric Population

Maxime Munyeshyaka, Shalaka Indulkar, Gary Hsich

OBJECTIVE: To define normal range of lumbar puncture (LP) opening pressure (OP) in children through comparative analysis of OP between patients with or without papilledema, and effects of sedation, BMI, age, and sex on OP.
METHODS: A retrospective review of 593 LPs for patients aged 18 years or younger presenting for neurology evaluation between 1/2009-11/2025. The comparison groups were patients: 1) without papilledema and without headache; 2) without papilledema but with headache; 3) with papilledema and with headache; and 4) with papilledema but without headache. Patient demographics, including ophthalmological data, were collected. Exclusion criteria included fever, prior LP, or brain tumors. ANOVA and multivariate regression, to analyze mean differences of OP among groups and effect of factors on OP, respectively.
RESULTS: 212 LPs met our inclusion criteria. Pediatric patients with papilledema, with or without headache, had statistically significantly higher LP OP than those without papilledema, with or without headache (39.3 and 35.9 vs 24.1 and 20.6, respectively; P-value <0.0001). Among patients without papilledema, with and without headache, the multivariate regression model was statistically significant ($F(4,92) = 5.49$, $p < 0.0005$), with an adjusted R^2 of 0.19, indicating that 19% of the variance in OP was explained by the predictors with major contribution from age (beta=0.60, p=0.0001) and anesthesia (beta=6.43, p=.0007).
CONCLUSIONS: Our findings suggest that normal LP OP in the pediatric population ranges from 22 to 27 cm H2O, with moderate variation explained by age and anesthesia use. The higher OP in patients with papilledema is consistent with concerns for intracranial hypertension.
KEYWORDS: Headache

154. Primary Stabbing Headache in a Child with Chiari I Malformation and Hypophosphatasia: A Diagnostic Challenge

Lin Yao, Rachael Cheek, Nikita Malani Shukla, Aishwarya Venkataraman Pareek

OBJECTIVE: Background: Headaches in children with structural brain abnormalities such as Chiari I malformation are often attributed to the malformation. However, atypical features should prompt consideration of broader differential diagnosis including primary headache disorders.
METHODS: NA
RESULTS: Case Report: A 7-year-old girl with hypophosphatasia on enzyme replacement therapy presented with abrupt, severe stabbing headaches in the left temporal occipital region. Episodes lasted 5–10 seconds, recurred every few minutes, and were associated with head tilting. CT and MRI revealed Chiari I malformation with mild ventriculomegaly but no syringomyelia. Ophthalmologic evaluation was normal without papilledema. Despite her comorbidities, the headache phenotype was atypical for Chiari, as symptoms were not provoked by Valsalva, posture, or exertion. Occipital or nervus intermedius neuralgia were initially considered, but imaging was reassuring against neurovascular compression. Symptomatic treatment with acetaminophen, migraine cocktails, and initiation of a preventive regimen of riboflavin and gabapentin provided little relief. A meticulous pain-oriented examination revealed a sharply circumscribed tender scalp region behind the left ear, raising concern for primary stabbing headache. A diagnostic indomethacin trial led to complete resolution. She successfully weaned off indomethacin and gabapentin and remained headache-free at follow-up.
CONCLUSIONS: This case underscores the challenge of distinguishing primary headache syndromes from structural etiologies in children with other pain related comorbid conditions. The highly localized pain features and dramatic response to indomethacin supported a diagnosis of primary stabbing headache, an often overlooked and underdiagnosed headache in children. Recognition of this phenotype is critical to avoid misattribution to Chiari malformation and to guide effective, targeted therapy.
KEYWORDS: Headache, Practice Parameters, Education

155. Primary Headache in Children: Clinical Characteristics and Impact on School Functioning in a Low-Resource Country

Amal Abu Libdeh, Lara Alsubehat, Nada Tabbalat, Shahed Mraish, Noura Al-Nawaiseh, Nadine Arabiyat, Mustafa Elayyan, Mohammad Al-Daraghmeh, Hani Hussein, Mohammad Deameh, Lina Alshadfan, Amira Masri

OBJECTIVE: Objective: Primary headaches in children impair daily functioning, yet data from Jordan, particularly regarding their effect on school functioning, have not been systematically evaluated. We aim to assess the clinical characteristics of pediatric primary headaches in central Jordan and their association with school functioning.
METHODS: Methods: A cross-sectional study included children aged 5–18 years diagnosed with primary headaches at three public hospitals. Data were collected using a structured, culturally adapted questionnaire incorporating items from the validated Arabic PedsQL™ 4.0 school-functioning scale. Descriptive, univariable, and multivariable analyses were performed to identify factors associated with impaired school functioning.
RESULTS: Results: A total of 147 children were included (51% male; 61.2% aged 10–14 years). Migraine was most common (60.5%), followed by tension-type headache (23.8%). Common triggers included stress, noise, and sleep disturbance. Unfavorable lifestyle factors— increased screen time, skipped meals, low hydration, and limited physical activity—were prevalent. More than 92% of participants had impairment in at least one school-functioning domain. Poor academic performance and lower parental education were significantly associated with lower scores. In multivariable analysis, poorer academic performance and lower paternal education remained independently associated with worse school-functioning scores, while headache type and frequency

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were not significant predictors. Most patients used simple analgesics (paracetamol in 93%), whereas migraine-specific rescue medications and preventive therapies were rarely used.
CONCLUSIONS: Conclusion: Primary headaches in children are associated with substantial impairment in school functioning. Educational and family-related factors appear more influential than headache-specific variables. Addressing modifiable lifestyle and contextual factors may improve outcomes.
KEYWORDS: Headache, Global Neurology

156. Improving Access to Headache Care through eConsults

Abigail Turner, Christina Szperka, Alexander Fiks, Maura Powell, Gregory Lawton, Dustin Elliott, Kate Fuller, Donna Stephenson

OBJECTIVE: Headaches are the second most common neurology referral, resulting in high demand and long wait times for visits in Neurology. Electronic consultation (eConsult) enables primary care providers (PCPs) to get neurology advice through an asynchronous written consult, expediting neurology-guided care. We describe the implementation of this model in our high-volume headache program.
METHODS: An eConsult model for pediatric headache was implemented from July 2025 to March 2026. PCPs submitted headache related questions using a standardized formulary within the electronic medical record. A neurologist reviewed the clinical information and provided a written response within 5 business days. The eConsult could be declined by the Neurologist if deemed inappropriate.
RESULTS: 124 eConsults were placed. 73 (59%) were completed and 51 (41%) declined. The most common reasons to decline an eConsult were recommending an expedited neurology visit (24/51), asking a non-headache related question (10/51) or requiring additional information (8/51). Of the completed eConsults, the addition of preventive treatment with supplements was recommended in 59 (81%) and the addition or modification of rescue medications in 38 (52%; triptans alone 28/38, metoclopramide alone 3/38, combination of both 7/38). Nine eConsults (12%) recommended short-term treatments to break status migrainosus (bridge therapy) followed by expedited neurology visit if ineffective. An in-person neurology evaluation was required in 22 of 73 completed eConsults and 2 of 9 eConsults recommending bridge therapy.
CONCLUSIONS: eConsults are an effective strategy to improve timely care, support PCP headache management, and prioritize in-person neurology evaluations. Additional data is necessary to assess long-term outcomes and scalability.
KEYWORDS: Headache

157. Clinical Characteristics of pediatric patients with a Primary Headache in the ED, PPU and Inpatient settings: A Quality Improvement Study

Debra O'Donnell, Laura Fonseca, Cheyanne Harshman, Justin Stebbins, Annabel Almazan, Sargun Kahlon, Adriana Parella, Gogi Kumar

OBJECTIVE: To investigate clinical characteristics of patients with primary headache seen in the emergency department (ED), pediatric procedural unit (PPU) and inpatient settings at a tertiary pediatric hospital.
METHODS: Data was retrospectively abstracted from the hospital's internal Headache Dashboard from 1/1/2022 to 12/31/2025. Patients aged 8-21, who were seen in the ED, PPU and/or inpatient setting with primary diagnosis of headache were included. The Dashboard was created as an outcome of the Acute Primary Headache Clinical Pathway – an internal guideline for primary headache relief.
RESULTS: 5,191 encounters were identified (85.3% ED, 7.3% PPU and 7.4% inpatient). Majority were female (66.4%), white (67.8%), had public insurance (53.7%). The most common comorbidities in ED, PPU and inpatient were anxiety/stress disorders (47.3%, 28.6%, 52.8%). The average length of stay in hours was 3.0 for ED, 3.7 for PPU, 51.4 for inpatient. There was a trend across all years with the least admissions/discharges occurring during summer. Most common medication administered for headache relief was Toradol (23.2% ED, 23.3% PPU, and 29.2% inpatient). Average decrease in pain score between admission and discharge was significantly greater for PPU/inpatient (4.6/10) compared to ED (3.7/10). Rate of readmission at 14-, 30- and 90-days post-discharge gradually increased with a significant increase at 30- and 90-days in PPU/inpatient (9.8%, 19.3%) compared to ED (7.5%, 10.5%).
CONCLUSIONS: Patients discharged from PPU/inpatient had greater pain relief, but were more likely to be readmitted post-discharge compared to ED patients. These patients need close monitoring for management of comorbidities to prevent readmissions.
KEYWORDS: Headache

158. Comparative Prescription Patterns for the Treatment of Chronic Migraine in Pediatric Patients with Transplanted Solid Organs: Results from a Cross-Institutional Electronic Health Records Database

Benjamin Africk, Leon Moskatel

OBJECTIVE: We describe the differences in prescription patterns for pediatric patients with migraine and organ transplant compared to pediatric patients with migraine only.
METHODS: We searched Epic Cosmos database for pediatric patients with diagnosis of "Chronic Migraine without aura" between January 1, 2021 and December 31, 2025. We then filtered by organ transplant status. Demographic information was extracted. We then compared prescription rates of common acute and preventive headache medications. One way ANOVA was used to evaluate significance of average age. Chi squared tests were used to assess other demographics, while two-sided two sample proportion tests were used to assess prescription variations in transplant and non-transplant groups.
RESULTS: Our query yielded 27 heart transplant patients, 53 liver transplant patients, and 78 kidney transplant patients, along with 113,989 migraine patients without transplants. The average age between groups differed significantly,

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while females comprised the majority of patients. There were a higher proportion of Black patients with both chronic migraine and kidney transplantation compared to other subgroups, and similarly a higher proportion of Asian patients with both liver transplant history and chronic migraine compared to other subgroups. Transplanted patients showed lower rates of rizatriptan use compared to non-transplanted patients. With preventive medications, all three transplant subgroups utilized cyproheptadine at much higher rates compared to non-transplant patients. Injection-based medications were utilized at higher rates in certain transplant groups.
CONCLUSIONS: Pediatric patients with chronic migraine as well as a history of organ transplant utilize acute and preventive treatments at different rates compared to non-transplanted patients with chronic migraine.
KEYWORDS: Headache

159. Evaluating and Treating Headache in Individuals with Autism Spectrum Disorder (ASD)

Lanie Masset, Jennifer McVige, Virty Patel, Lily Anastasi

OBJECTIVE: There is a lack of diagnostic criteria and outcome measures to assess non-speaking individuals with ASD who experience headache. Sensory hypersensitivity is a common feature of both migraine and ASD. Differential diagnosis can be approached as head pain of unknown origin. With safe and effective disease-specific treatments for migraine, trialing medications to observe outcomes could clarify diagnoses. This study examines headache presentation, phenotypes, and treatment for patients with ASD and head pain, while highlighting diagnostic and treatment challenges in a predominantly pediatric cohort.
METHODS: Retrospective chart review examined the care of speaking and minimally/non-speaking patients with diagnoses of comorbid ASD and head pain, evaluated at one neurologic institute. History was obtained via patient and caregiver responses.
RESULTS: N=138 speaking (49.3%) and minimally/non-speaking (50.7%) patients with ASD and head pain. Head pain indicators (HPI): behavioral changes (47.8%), sleep disturbances (37.7%), self-injury to head (28.3%), aggression (26.8%), vocalized head pain (49.3%), and touching/motioning to head (15.2%). Headache diagnoses: migraine (55.1%), unspecified headache (37.7%), post-traumatic headache (13.0%), Chiari Malformation Type I headache (8.1%), tension-type headache (5.1%), and idiopathic intracranial hypertension (2.3%). Medication classes resulting in HPI improvement: CGRP inhibitors, medical cannabis, NSAIDs, triptans, and others. HPIs with the largest improvement: behavioral changes (56.1%) and self-injury to head (41.0%).
CONCLUSIONS: This study highlights the high incidence of head pain among individuals with ASD and suggests potential headache indicators in the form of altered behaviors and non-verbal communications. As clinicians, we have an obligation to better support this vulnerable population in a comprehensive, evidence-based manner.
KEYWORDS: Headache, Neurodevelopmental Disorders, Diversity, Equity, Inclusion

160. An 18 year old girl with headaches and altered mental status

Vihas Abraham, Maria Galardi, Anna Huguenard, Jennifer Griffith

OBJECTIVE: Cerebral venous sinus thrombosis (CVST) is an obstruction of the dural sinuses caused by a thrombus and increases risk for cerebral ischemia or hemorrhage. CVST is rare in the pediatric population and can present with non-specific symptoms which may complicate prompt diagnosis. While CVST is often primarily managed by anticoagulation, complicated cases may warrant endovascular intervention. This case describes an 18 year old female presents with PCOS and on estrogen-containing OCPs who presents after having 5 days of headaches followed by sudden onset altered mental status with lethargy, expressive and receptive aphasia and difficulty with ambulation on day of presentation and found to have occlusion of the deep venous system, straight sinus, bilateral transverse sinuses, torcula, and the posterior one-third of her superior sagittal sinus.
METHODS: Chart review
RESULTS: Given severity of symptoms, this patient was taken for emergent endovascular intervention with venous thrombectomy resulting in recanalization of superior sagittal sinus and right transverse sinus with residual occlusion in left transverse sinus, straight sinus, and deep venous system. This was followed by 48 hours of catheter-directed thrombolysis. Her exam after thrombectomy was significantly improved without any residual deficits. She was found to have an iron deficiency and a positive lupus anticoagulant. Thrombophilia workup was otherwise negative.
CONCLUSIONS: This case demonstrates the potential severity of CVST in a pediatric patient and the role of prompt multidisciplinary management, including consideration of endovascular intervention in critical and complex cases. Further research is needed to optimize and standardize therapies in pediatric patients with CVST.
KEYWORDS: Headache, Neuroimaging, Neurocritical Care

Lifespan Manifestations of Childhood Onset Conditions

161. PET-FDG in Subependymal Giant Cell Astrocytoma in Tuberous Sclerosis

Ne-Ron Loh

OBJECTIVE: Objective: PET-FDG in Subependymal Giant Cell Astrocytoma in Tuberous Sclerosis
METHODS: Method: PET-FDG imaging is sometimes used to assess metabolic activity in tumours like subependymal nodules (SEN) in tuberous sclerosis complex (TSC), with the assumption that metabolically active lesions may predict transformation to subependymal giant cell astrocytoma (SEGA). However, the predictive value of metabolically inactive lesions remains unclear.
RESULTS: Result: We present a female TSC patient with normal brain MRI at age 2 years, who developed an 8mm SEN by

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age 6 years, progressing to a 1.2cm SEGA by age 8 years. PET-FDG at age 8 years showed no metabolic activity in the lesion. The patient had no further neuroimaging for 9 years until presenting with blurred vision at age 17 years. Ophthalmological examination revealed papilloedema, prompting brain MRI which demonstrated a 5cm SEGA with associated hydrocephalus. Due to the large size primary resection was not possible. A ventriculoperitoneal shunt was inserted for hydrocephalus management, followed by mTOR inhibitor therapy to reduce tumour size prior to planned surgical resection.

CONCLUSIONS: Conclusion: This case demonstrates that metabolically inactive SEGAs on PET-FDG can undergo significant growth over time, leading to life-threatening complications requiring complex management strategies. PET-FDG appears to have limited negative predictive value for SEGA progression, suggesting that metabolically inactive lesions still require regular surveillance imaging regardless of metabolic activity.

KEYWORDS: Lifespan Manifestations of Childhood Onset Conditions, Neurogenetics, Neuro-oncology

162. Evaluating Adults with Long Standing Neurodevelopmental Disabilities at the Undiagnosed Diseases Program (UDP): The Role of Child Neurology

Maria Acosta, Ellen Macnamara, Lynne Wolfe, David Adams, Shanshan Chow, Colleen Howe, Margaret Delgado, Carolyn Allen, Jessica Chong, Danica Novacic, Camilo Toro, William Gahl

OBJECTIVE: Although pediatric and adult medical practice are traditionally distinct—with pediatric care centered on families and adult care emphasizing individual autonomy—the boundaries blur when adults with long-standing neurodevelopmental disabilities (NDD) seek evaluation in the Undiagnosed Diseases Program (UDP). Despite advances in transition models for childhood neurodevelopmental disabilities, UDP teams face unique challenges when older adults present with congenital or early-onset neurologic symptoms that have remained undiagnosed for decades. This study describes our experience evaluating such individuals and outlines the specific contributions of child neurologists.

METHODS: We reviewed adults over 18 years old who applied to or were accepted into our UDP over the past five years with an undiagnosed neurodevelopmental disability. Clinical documentation, multidisciplinary assessments, and diagnostic evaluations were examined to identify recurring clinical, communicative, and ethical challenges.

RESULTS: Twenty-six of 167 adults with NDD were evaluated or are pending evaluation. Challenges included missing developmental records, caregiver recall gaps, phenotypic changes obscuring congenital versus acquired features, and overlay of adult-onset chronic health conditions. Evaluations required balancing patient autonomy with the essential role of lifelong caregivers. Communication strategies had to address differing expectations and emotional responses to a late-life diagnosis. Legal considerations—consent, guardianship, decisional capacity, and familial genetic implications—were common and varied regionally.

CONCLUSIONS: Our experience underscores the need for lifespan-oriented diagnostic models, better preservation of early medical information, and ethically grounded communication. Child neurologists are essential in interpreting developmental histories and guiding accurate diagnosis in adults with longstanding neurodevelopmental disabilities.

KEYWORDS: Lifespan Manifestations of Childhood Onset Conditions, Neurodevelopmental Disorders, Neurogenetics

Movement Disorders

163. Chorea, epilepsy, and cyclic irritability crises due to a novel pathogenic variant in CAMK2B

Chaitanya Aduru, Lauren Blieden, Hongzheng Dai, Lisa Emrick, Monika Weisz-Hubshman, Pengfei Liu, Undiagnosed Diseases Network, Jill Rosenfeld, Ronit Marom, Mered Parnes

OBJECTIVE: Pathogenic variants in *CAMK2B*, encoding the calcium/calmodulin-dependent protein kinase II β subunit (CAMKIIB), are associated with an autosomal dominant neurodevelopmental disorder characterized by intellectual disability, impaired mobility, hypotonia, and epilepsy. We report a 7-year-old female with novel variant c.903G>A (p.Lys301=) that expands the phenotype.

METHODS: The patient presented with global developmental delay (non-verbal, non-ambulatory), seizures, marked hypotonia, persistent generalized chorea, cortical visual impairment, dysphagia, gastrointestinal dysmotility, and neurogenic bladder. Additionally, she exhibited episodes consisting of extreme irritability, apparent discomfort, inconsolable crying and sleep disturbance, which occurred at regular 1-month intervals and lasted days, since 10 months of age.

RESULTS: Brain magnetic resonance imaging (MRI) showed ventriculomegaly with progressive volume loss and atrophy of the cerebral hemispheres, cerebellum, and brainstem. Clinical genetic testing was non-diagnostic. Research genome sequencing revealed a synonymous variant, NM_001220.5: c.903G>A (p.Lys301=) in *CAMK2B* at exon/intron 11 junction that was predicted to cause splice changes and was not detected in mother. Splice-site variants in *CAMK2B* are thought to functionally disrupt the auto-regulatory domain in CAMK2 subunits via in-frame skipping of exon 11 with a gain-of-function (GOF) mechanism. Similar cyclic crises have been reported in two other affected children, one with a GOF variant and another with a dominant-negative variant. Chorea has not been previously described.

CONCLUSIONS: This case highlights a unique presentation due to a novel variant that is predicted to negatively impact splicing of *CAMK2B* and offers new insight into genotype-phenotype correlations in this disorder.

KEYWORDS: Movement Disorders, Neurodevelopmental Disorders, Neurogenetics

164. Mass Psychogenic Illness (MPI) and Mass Media: LeRoy, New York (NY)

Jennifer McVige, Lanie Masset, Virty Patel, Lily Anastasi, Laszlo Mechtler, Sophia McVige

OBJECTIVE: The world witnessed how modern media altered the evolution and treatment of a Functional

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Neurologic Disorder presenting as MPI in LeRoy, NY. The pediatric cohort included patients with abrupt onset tics who subsequently developed syncope, psychogenic nonepileptic seizures (PNES), and migraine. This study investigates the temporal association between symptom exacerbation and media events.

METHODS: Retrospective chart review (2011-2012) evaluated 16 patients diagnosed with MPI treated at one neurologic institute. Demographic information, symptom onset dates, exacerbation, and resolution were recorded. An extensive internet search documented media events related to LeRoy during the outbreak. Dates of symptom exacerbations and media events were evaluated for immediate and delayed temporal associations. Symptom exacerbations included: tics, syncope, psychogenic non-epileptic seizure (PNES), and migraine. Media events included: local television, national television, radio news, written news, and social media.

RESULTS: Numerous statistically significant temporal associations were found between media events and symptom exacerbations on the day of the media event and up to seven days following. The strongest same-day media associations were noted with worsening tics (OR:52.36 95% CI:10.89-251.67) and PNES (OR:90.46 95% CI:9.09-900.62). Delayed temporal associations were found for all media types involving at least one symptom type exacerbation.

CONCLUSIONS: This study presents evidence of a clear association between MPI exacerbation and exposure to all media types. The patients' symptoms included visibly prominent physical and/or auditory events (except for migraine), which may have strengthened this association. As media coverage subsided, MPI symptoms resolved. Further research is essential to understand this complicated and concerning connection, especially with pediatric patients.

KEYWORDS: Movement Disorders, Headache, Behavioral Neurology

165. Impaired Galectin-9 secretion in patient fibroblasts of AP-4-related hereditary spastic paraplegia

Tobias Brunnbauer, Neha Mohan, Habibah Agianda, Julian Alecu, Darius Ebrahimi-Fakhari

OBJECTIVE: Biallelic loss-of-function variants in adaptor protein complex 4 (AP-4) subunit genes (*AP4B1, AP4M1, AP4E1, AP4S1*) cause childhood-onset hereditary spastic paraplegia (AP-4-HSP). Therapeutic trials are emerging, yet biomarkers proximal to AP-4 function are lacking. A cellular hallmark of AP-4-HSP is impaired trafficking of ATG9A. ATG9A-positive vesicles were recently shown to mediate Galectin-9 secretion. We hypothesized that impaired ATG9A trafficking in AP-4-deficient patient fibroblasts reduces Galectin-9 secretion compared to healthy parental controls.

METHODS: Fibroblasts from three AP-4-HSP patients (2x $AP4B1^{LoF/LoF}$, 1x $AP4M1^{LoF/LoF}$) and their parental controls were cultured in serum-free medium for 48h to stimulate protein secretion. The conditioned medium was concentrated on 10 kDa MWCO filters, and Galectin-9 was detected by immunoblot. Loading was normalized to total protein. Cell viability was monitored by a colorimetric LDH assay. To test for causality, *AP4B1* was re-introduced into $AP4B1^{LoF/LoF}$ fibroblasts via lentiviral transduction.

RESULTS: Patient fibroblasts demonstrated significantly reduced Galectin-9 secretion into conditioned media compared to paired parental controls (FC: 0.26, paired t-test, $p < 0.001$, n=3). The secretion deficiency in $AP4B1^{LoF/LoF}$ fibroblasts was rescued by lentiviral re-introduction of *AP4B1*. LDH release was comparable between genotypes, confirming that differences were not driven by differential cell death. Intracellular Galectin-9 levels were unchanged, indicating a secretion-specific defect rather than reduced expression.

CONCLUSIONS: Impaired Galectin-9 secretion is a quantifiable cellular phenotype of AP-4 deficient patient fibroblasts, consistent with disturbed ATG9A-mediated trafficking. Ongoing validation in neuronal cell models, AP-4 mouse models and patient blood plasma will determine whether secreted Galectin-9 serves as a biomarker for emerging therapy trials.

KEYWORDS: Movement Disorders, Neurogenetics, Neurodevelopmental Disorders

166. Online CME Improved Neurologist Knowledge and Confidence in the Current and Emerging Approaches to the Management of Tourette Syndrome

Thomas Finnegan, Clinton Wright, Kelly Hanley, Irene Malaty

OBJECTIVE: The management of Tourette Syndrome (TS) is often complex due to the heterogeneity of symptoms, associated comorbidities, and limitations of current treatments. This study determined whether an educational program could improve the knowledge and confidence of neurologists related to the current and emerging management of TS.

METHODS: The online CME activity was a 40 minute video discussion between 3 expert faculty. Educational effect was assessed by comparing the pre-and post-education performance of a matched sample of neurologists' to 5 identical questions. A paired samples t-test was used for overall average number of correct responses, a McNemar's test was used to identify pre-post statistical significance, and Cohen's d was used to calculate effect size. Data were collected between February 5, 2026 and April 2, 2026.

RESULTS: Program participation resulted in a moderate educational effect size among neurologists (n=71; d=.72; $p<0.001$). Significant (P <.05) pre- vs post-educational improvements were seen for all questions: identification of the most common comorbidity associated with TS, the symptom of TS that should be the first treatment-related priority, and identifying the mechanism of action of 2 investigational agents being studied in TS. After participating in the intervention, 35% of neurologists reported an increase in their confidence to develop a treatment plan for TS.

CONCLUSIONS: This CME activity effectively bridged critical gaps in TS care. By enhancing knowledge of key comorbidities and emerging therapeutics, neurologists are better prepared to address the needs of patients. Future education should continue to address current and emerging approaches to the comprehensive management of TS.

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KEYWORDS: Movement Disorders, Education, Experimental Therapeutics

167. DBSMatchMaker: A Global Collaborative Platform for Deep Brain Stimulation in Rare Monogenic Movement Disorders

Kathryn Yang, Joshua Rong, Amy Tam, Katerina Bernardi, Darius Ebrahimi-Fakhari

OBJECTIVE: Rare monogenic movement disorders are individually uncommon but collectively substantial, yet evidence guiding deep brain stimulation (DBS) remains fragmented across isolated case reports and small institutional series. Scalable infrastructure for international data aggregation and clinician collaboration has been lacking. We developed DBSMatchMaker (https://dbsmatchmaker.com), a GeneMatcher-inspired platform to rapidly connect clinicians and unify global DBS experience in genetic movement disorders.

METHODS: DBSMatchMaker, launched publicly in December 2024, is a freely accessible web-based submission and matching system. Clinicians enter deidentified cases including genetic diagnosis, DBS target, and optional three-point outcome ratings (strong ≥50%, modest 25–49%, or no benefit <25% BFMDRS improvement). Automated queries match submitters sharing the same indication and notify them by email. Submissions through April 2026 were retrospectively aggregated and analyzed.

RESULTS: 219 cases have been submitted by 66 clinicians from 47 institutions across 22 countries, spanning 85 monogenic etiologies - most commonly GNAO1, KMT2B, PANK2, TOR1A, SGCE, THAP1, and ADCY5. The globus pallidus internus was the predominant target (90.1%; STN 4.0%, VIM 1.4%, other 4.5%). Among 159 cases with interpretable outcome ratings, 89.3% reported strong or modest therapeutic benefit. The platform generated over 600 clinician matches, catalyzing multicenter case series, informing individual management decisions, and surfacing previously undocumented genotype–target–outcome observations.

CONCLUSIONS: DBSMatchMaker provides scalable infrastructure to overcome geographic and institutional silos in rare genetic causes of movement disorders, accelerating evidence generation and clinical decision-making. Beyond bridging isolated experience, it supports earlier DBS consideration, clinical trial readiness, and offers a replicable model for other rare disease networks.

KEYWORDS: Movement Disorders, Neurogenetics, Global Neurology

168. Clinical and Molecular Phenotype of PTRHD1-associated Juvenile Parkinsonism

Bhavan Modi

OBJECTIVE: Although Parkinson's Disease is the most common movement disorder in adults, juvenile parkinsonism is rare. It is often dominated by rigidity, hypokinesia, and postural instability and less commonly features a resting tremor. Despite its rarity, several important scientific insights have come from studies of early-onset parkinsonism. We describe 6 previously unreported patients with mutations in *PTRHD1*, an orphan gene of unknown function. Although mutations in this gene have been reported in a few families with juvenile parkinsonism and intellectual disability, clinical phenotypes have been incompletely characterized. We sought to identify genotype-phenotype correlations in patients with mutations in *PTRHD1*.

METHODS: Each family provided written informed consent for participation according to local ethics guidelines. Clinical phenotypes, MRI images, patient photographs, and videos were collected from 6 patients with homozygous mutations in the *PTRHD1* gene. When possible, blood and/or skin punch biopsies were also performed for transcriptomic and proteomic analyses.

RESULTS: Clinical presentations included dysarthria, rigidity, postural instability, gait dysfunction, and mild intellectual disability. Anatomic MRI imaging was normal. Patients responded to carbidopa-levodopa but developed peak-dose dyskinesias and wearing-off effects early in the treatment course. RNA Seq outlier analysis revealed underexpression of *PTGR1* and *UFSP2*. Proteomics outlier analysis revealed decreased expression of the following proteins: ATP6V1C1, CNOT3, CPSF1, PTGR1, PTRHD1, SPC24, THUMPD3, and TSPAN10. These analyses highlight the genotype-phenotype correlations. Proteomic results suggest a potential role for the orphan protein, PTRHD1, in RNA metabolism and translational control.

CONCLUSIONS: Biallelic *PTRHD1* mutations represent a newly-recognized form of parkinsonism that should be considered in pediatric patients.

KEYWORDS: Movement Disorders, Neurogenetics

169. Childhood dystonia is associated with synchronous bursting in thalamus, basal ganglia, and brainstem

Terence Sanger

OBJECTIVE: The origins of childhood dystonia are unknown. We explore the firing patterns of neurons within deep brain regions that may be the origin of dystonic symptoms.

METHODS: We record from temporary depth electrodes placed in thalamus, basal ganglia, and brainstem during preoperative evaluation of targets for permanent deep brain stimulation (DBS) in children with genetic and acquired dystonias. 100 channels of high-impedance local field potentials (LFP) were recorded from 7 children during a one-week evaluation. Surface EMG, video, and kinematics are recorded to identify periods of dystonia.

RESULTS: All subjects showed widespread synchronous bursting in multiple brain regions during periods of dystonic muscle contraction. Bursts last from 50-400msec, are irregular, and are visible only across multiple channels. During bursts some units fire with sub-millisecond precise synchrony.

CONCLUSIONS: Synchronous bursts throughout multiple brain regions are associated with dystonic contractions in children. Further study is needed to determine if the bursts are a cause of dystonia or an associated biomarker. This finding suggests widespread dysfunction in motor systems in children with genetic or acquired dystonia.

KEYWORDS: Movement Disorders, Cerebral Palsy, Experimental Therapeutics

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170. Right PreSMA iTBS Acutely Engages Inhibitory Motor Physiology in Youth with Tourette Syndrome

Travis Larsh, Karlee Migneault, Weihong Yuan, Kim Cecil, Rana Elmaghraby, Ernest Pedapati, Donald Gilbert, Steve Wu

OBJECTIVE: Tourette syndrome (TS) is associated with impaired inhibitory control within cortico-basal ganglia motor circuits. The right pre-supplementary motor area (preSMA) is a key hub for motor inhibition, but it remains unclear whether intermittent theta burst stimulation (iTBS) targeting the preSMA can acutely engage inhibitory physiology in youth with TS.

METHODS: In a randomized, sham-controlled crossover study, 13 children and adolescents with TS (mean age 14.7 ± 2.4 years, 11 males) underwent active and sham accelerated iTBS, delivered as two sessions on the same day, targeting the right preSMA on separate visits. Cortical silent period (CSP) and preSMA-mediated inhibition of primary motor cortex (SMACI) were measured before and after stimulation. Exploratory multimodal biomarkers included diffusion MRI measures of basal ganglia-related output tracts and magnetic resonance spectroscopy-derived GABA levels within the supplementary motor complex. Baseline tic severity, premonitory urges, and comorbid symptoms were examined for associations with inhibitory biomarkers.

RESULTS: Active, but not sham, iTBS lengthened CSP and increased SMACI at 8-ms and 10-ms interstimulus intervals, consistent with strengthened inhibitory motor physiology. Exploratory diffusion analyses suggested active iTBS-related changes in basal ganglia-related pathways, most notably the ansa lenticularis and ansa subthalamica. Supplementary motor complex GABA showed a trend-level increase after active stimulation. At baseline, shorter CSP duration and weaker SMACI were associated with greater premonitory urge burden.

CONCLUSIONS: Right preSMA iTBS produced acute physiologic changes consistent with enhanced motor inhibition in youth with TS. CSP, SMACI, diffusion MRI, and MRS may provide complementary markers of target engagement and support biomarker-guided neuromodulation studies in TS.

KEYWORDS: Movement Disorders, Early Stage Investigator

171. Improving Early Recognition of Tic Disorders in Pediatric Practice: Utility of the DoTS Screener

Somayya Upal, Jennifer Vermilion, Morgan Main

OBJECTIVE: To assess the ability of the DoTS Parts I and II of DoTS to identify tics and tic disorders in children from a general pediatric setting. Analyses focused on determining sensitivity, specificity, AUC, and optimal cutoffs for different diagnostic thresholds.

METHODS: Participants (n=223) ages 6–17 were recruited from pediatric emergency department and primary care clinics at Golisano Children's Hospital. Parents/caregivers completed the parent-reported DoTS, and youth ≥8 years completed the child self-report version. A tic expert blinded to DoTS results evaluated each child to determine tic/tic disorder status. Logistic regression and receiver operating characteristic analyses assessed screening utility. Primary outcomes were presence of any tics and Tourette Syndrome (TS) diagnosis.

RESULTS: Parent Part I, which inquires about abnormal movements or sounds, was the strongest individual predictor of Tourette Syndrome (AUC = 0.92), achieving 100% sensitivity and 75% specificity at the optimal cutoff (≥5) with a positive predictive value (PPV) of 39% and a negative predictive value (NPV) of 100%. For tic detection, Parent Part I performed better (AUC = 0.87), than Parent Part II (AUC = 0.81). Self Part II (AUC = 0.84) outperformed Self Part I (AUC=0.69) for tic presence. Across all outcomes, parent-reported items consistently demonstrated stronger predictive ability than self-report.

CONCLUSIONS: The DoTS demonstrated favorable diagnostic performance for detecting tics and TS in a general pediatric population. These findings support its potential utility as a brief clinical screening tool to improve early recognition and referral for tic disorders.

KEYWORDS: Movement Disorders, Behavioral Neurology, Neurodevelopmental Disorders

172. What tics respond best to Comprehensive Behavioral Intervention for Tics (CBIT) in community practice?

Ashmitha Raja, Ngoc-Quynh Nguyen, Gwen Beard, Shalini Narayana, Madison Owens

OBJECTIVE: To identify tic characteristics associated with response to Comprehensive Behavioral Intervention for Tics (CBIT) in Tourette syndrome (TS).

METHODS: We retrospectively reviewed 12 patients (mean age 12.2 ± 3.5 years) with TS who received CBIT between 2020-2022. Inclusion criteria were children with ≥3 tics and completion of ≥5 CBIT sessions. Tics were treated sequentially from most to least bothersome. The primary outcome was change in tic-related distress for each targeted tic, measured using the Subjective Units of Distress Scale (SUDS). Changes in Yale Global Tic Severity Scale (YGTSS) scores were also measured. Paired Wilcoxon signed-rank exact tests were used to assess within-subject changes. Patient, tic, premonitory urge (PU), and treatment characteristics were evaluated using exploratory multivariable regression models with change in SUDS score as the dependent variable to identify factors associated with treatment response.

RESULTS: A statistically significant reduction in SUDS ratings was observed for the first and second targeted tics ($W = 64.0$, $p = 0.007$; $W = 48.5$, $p = 0.036$). We also noted a statistically significant decrease in YGTSS impairment and total severity scores ($W = 28$, $p = 0.019$; $W = 28$, $p = 0.016$). We did not find a statistically significant relationship between SUDS change and other variables of interest.

CONCLUSIONS: Only the first two tics targeted in CBIT demonstrated statistically significant reductions in distress. These early improvements were sufficient to produce clinically meaningful reductions in overall impairment. No associations were observed with patient or tic characteristics, though findings are limited by small sample size.

KEYWORDS: Movement Disorders

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173. Deep Brain Stimulation Reorganizes a Cortico-Pallidal State Linked to Muscle Activity in Pediatric Dystonia

Travis Larsh, Karlee Migneault, Sudhakar Vadivelu, Jesse Skoch, Rana Elmaghraby, Ernest Pedapati, Donald Gilbert, Steve Wu

OBJECTIVE: To test whether resting electroencephalography (EEG)-electromyography (EMG) and, when available, globus pallidus internus (GPi) local field potentials (LFPs) identify a deep brain stimulation (DBS)-responsive cortico-pallidal network state in pediatric dystonia linked to spontaneous muscle activity.

METHODS: We recorded 5 minutes of resting EEG with simultaneous EMG in 24 participants (median age 15.4 years [interquartile range 10.6-17.4]; 16 female): 6 children with dystonia without DBS, 6 with chronic GPi-DBS studied off and on, and 12 matched healthy controls. Simultaneous GPi LFPs were available in 5 DBS participants. Time-resolved spectra from dominant motor cortex, supplementary motor area, and GPi were parameterized into aperiodic and periodic components, and generalized additive mixed models captured nonlinear temporal dynamics.

RESULTS: DBS-On was associated with reciprocal aperiodic reorganization of the cortico-pallidal network: cortical spectral exponent and offset increased, whereas GPi spectral exponent decreased and GPi offset increased. Surface EMG covaried with concurrent cortical and pallidal aperiodic dynamics, and during DBS-On, GPi and dominant MC spectral offset covaried within the same time window. In 4-condition context models, healthy controls, non-DBS, and DBS-Off largely overlapped, whereas DBS-On showed the highest cortical aperiodic values and distinct time-varying trajectories across the recording, consistent with a stimulation-specific shift in network state rather than a static group difference. DBS-On was also associated with lower cortical beta power.

CONCLUSIONS: Resting EEG-EMG identified a DBS-responsive cortico-pallidal network signature linked to spontaneous muscle activity. These findings support aperiodic EEG measures as candidate biomarkers of circuit state and may help guide individualized treatment strategies in pediatric dystonia.

KEYWORDS: Movement Disorders, Early Stage Investigator

174. Bilateral GPi and PPN Deep Brain Stimulation for Secondary Dystonia After Hypoxic Brain Injury: A Case Report

Zachary LaJoie, Joshua Wong

OBJECTIVE: Deep brain stimulation (DBS) of the globus pallidus internus (GPi) is an established treatment for medication-refractory primary dystonia. Clinical outcomes in secondary dystonia remain highly variable. Stimulation of the pedunculopontine nucleus (PPN) has been explored for axial and non-motor symptoms of parkinsonism, but its use in dystonia remains unexplored. We present a case of bilateral GPi and PPN DBS for secondary generalized dystonia following hypoxic brain injury in a pediatric patient.

METHODS: We present a case of secondary generalized dystonia following hypoxic-ischemic brain injury at age 7 following cardiac arrest as a complication of an influenza infection.

RESULTS: Approximately 6 months after hypoxic injury, the patient developed whole-body dystonia with both fixed and hyperkinetic components. MRI demonstrated ischemic changes in the basal ganglia and spinal cord with diffuse petechial hemorrhages across the brain. After multiple medication and botulinum toxin trials, the patient underwent implantation of bilateral GPi and PPN DBS leads at age 14. At follow-up, GPi stimulation produced significant improvement in truncal dystonia and appendicular posturing. PPN stimulation was associated with improved alertness and motivation.

CONCLUSIONS: This case demonstrates the feasibility of combined bilateral GPi and PPN DBS for pediatric secondary dystonia with concurrent cognitive impairment following hypoxic brain injury. PPN stimulation may offer a complementary method to address non-motor symptoms when combined with standard DBS targets. Further study is needed to optimize dual-target programming strategies and characterize long-term outcomes in this population.

KEYWORDS: Movement Disorders, Traumatic Brain Injury

175. Characterizing the metabolomic profile of the synaptic space in children with unexplained neurotransmitter disorders.

Dakota Peacock, Danielle Lynch, Graham Sinclair, Grace Clarke, Nathania So, Meltem Omur, Gabriella Horvath

OBJECTIVE: Children with severe neurological impairment (SNI) often exhibit unexplained abnormal neurotransmitter concentrations in cerebrospinal fluid (CSF) for poorly understood reasons. We hypothesize that characterization of the synaptic metabolome of these children will generate rational mechanistic hypotheses, leading to therapeutic advancements.

METHODS: We conducted a retrospective study of patients who underwent CSF neurotransmitter analysis in British Columbia between 2009 and 2025 and had abnormal results. Clinical charts were reviewed. CSF samples underwent targeted quantitative metabolomic profiling. Metabolomic signatures were identified with hierarchical clustering; top-contributing metabolites were identified with partial least squares-discriminant analysis. Gene set enrichment analysis was then performed to identify affected pathways.

RESULTS: One hundred thirty-three CSF samples with abnormal neurotransmitter concentrations underwent secondary metabolomic analysis. Median age at CSF collection was 7 years (IQR 0–15); 49% were female. Sixty-four (44%) had no explanation for their neurological phenotype or neurotransmitter abnormality. Among these, 34 (53%) had epilepsy, 22 (34%) had movement disorders, and 22 (34%) had global developmental delay. Six hundred forty-five metabolites were quantified; 129 showed informative within-group variability. Preliminary analysis suggests patients can be divided into four distinct groups with signatures involving (1) branched chain amino acids, (2) aromatic amino acids, and (3), arginine and proline, among others.

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CONCLUSIONS: Children with SNI and abnormal CSF neurotransmitter profiles frequently exhibit unexplained seizures, movement disorders, and global developmental delay. Preliminary metabolomic analysis highlights the salience of amino acid metabolism as potential mechanisms of disease. Further analysis will explore associations between clinical phenotypes and CSF biochemical signatures to identify potential disease mechanisms.

KEYWORDS: Movement Disorders, Neurometabolic, Epilepsy

176. Explosive-Onset Orofacial Dyskinesia as the Initial Manifestation of Anti-NMDAR Encephalitis Following Suspected Subclinical HSV-1 Reactivation

Edward Poluyi, Dauda Olamiji, Abibat Odufowoke

OBJECTIVE: To raise awareness of anti-N-methyl-D-aspartate receptor encephalitis as a rare but treatable cause of pediatric status dystonicus and emphasise the importance of early recognition and immunotherapy.

METHODS: A 12-year-old previously well male (n=1) presented with rapidly progressive generalised dystonia evolving into status dystonicus requiring intensive care admission. Magnetic resonance imaging was unremarkable. Metabolic and genetic investigations were non-diagnostic. Electroencephalography demonstrated diffuse encephalopathy. Cerebrospinal fluid analysis revealed mild lymphocytic pleocytosis, and autoimmune testing identified anti-N-methyl-D-aspartate receptor antibodies.

RESULTS: The patient required intensive care support including sedation and ventilatory assistance. First-line immunotherapy with intravenous methylprednisolone and immunoglobulin resulted in partial improvement, necessitating escalation to rituximab. Supportive management for status dystonicus was continued. Dystonia gradually improved over several weeks. At 6-month follow-up, the patient demonstrated substantial functional recovery with mild residual motor impairment.

CONCLUSIONS: Anti-N-methyl-D-aspartate receptor encephalitis should be considered in unexplained pediatric status dystonicus. This case expands the differential diagnosis of a neurological emergency and highlights the importance of early immunotherapy to optimise outcomes when initial investigations for more common causes are unrevealing.

KEYWORDS: Movement Disorders, Neuroimmunology, Global Neurology

177. Holmes Tremor in Pediatrics: A Multicenter Case Series

Delia Rospigliosi, Jennifer Heim, Joseph Vithayathil, Andrea O'Brien, Kushala Shivaram, Laura Tochen, Michael Kruer, Alonso Zea Vera

OBJECTIVE: Holmes tremor (HT) is a low-frequency tremor with rest, postural, and intention components, typically resulting from brain lesions. The literature on HT is predominantly derived from adults, and the condition is rare in pediatrics. We aim to describe the clinical characteristics in a pediatric cohort with HT.

METHODS: Multi-institutional retrospective case series of pediatric patients with HT.

RESULTS: Seven patients (5 female) were included. The median age of onset was 12.5 years (range: 1-14). Tremor was unilateral in 5/7; upper extremities were involved in all and lower extremities in 3/7. All but one had additional neurological features: ataxia (5/7), dystonia (4/7), seizures (3/7), psychiatric symptoms (3/7), dysarthria (2/7), and hemiparesis (2/7). Brain MRI showed lesions in the thalamus (5/7), midbrain (4/7), basal ganglia (2/7), pons (1/7), and cerebellum (1/7). Etiologies included hemorrhage, trauma, demyelination, infection, tumor, genetic leukodystrophy, and presumed autoimmune leukoencephalopathy, each in a single patient. Latency from lesion to tremor onset, available in four patients, had a median of 9 months (range 0–17). The most common treatment was levodopa (3/7) followed by trihexyphenidyl, clonazepam, propranolol, and gabapentin (each 2/7). Levetiracetam, fluphenazine, tetrabenazine, primidone, and botulinum toxin were each used in one patient. Pharmacologic therapy was ineffective in 3/7 and partially effective in 4/7. One patient underwent unilateral Vim deep brain stimulation (DBS) with excellent response.

CONCLUSIONS: HT may present as early as infancy. In contrast to adult series, etiologies in this cohort were very variable. Pharmacologic response was limited. One patient had an excellent response to DBS.

KEYWORDS: Movement Disorders

178. Investigating Neurodevelopmental and Functional Alterations in AP-4-Deficient Mice as a Model for Hereditary Spastic Paraplegia

Franziska Hammar, Jonas Moghib, Hyo-Min Kim, Zoe Piccus, Darius Ebrahimi-Fakhari

OBJECTIVE: Adaptor protein complex 4 (AP-4) is a tetrameric complex at the trans-Golgi network (TGN) that transports cargo proteins to the neuronal periphery. Loss of any AP-4 subunit causes AP-4-related hereditary spastic paraplegia (AP-4-HSP), with developmental delay, progressive spasticity, and combined neurodevelopmental and neurodegenerative features. Using the well-established AP-4 cargo ATG9A, we examined early neurodevelopmental stages of AP-4 deficiency alongside motor function across the lifespan.

METHODS: *AP4B1*-knockout mice (C57BL/6J-*Ap4b1*^{em5Lutzy}/J, C57BL/6J-*Ap4b1*^{em2Lutzy}/J) were generated by heterozygous crosses and compared to wildtype littermates (n = 4–8 per group). Total ATG9A expression was assessed by western blot in forebrain and cerebellum at E18.5, P0, and P30, and in spinal cord at P0 and P30. Subcellular ATG9A localization was examined by immunofluorescence in cerebellum at E18.5, P0, and P30 and in P30 spinal cord. Motor function was tested by tail suspension at P30, P100, and P400.

RESULTS: By western blot, total ATG9A was significantly elevated in the forebrain at E18.5, P0, and P30 and in spinal cord at P0 and P30 (all $p \leq 0.01$). In cerebellum, elevation was significant at E18.5 but normalized by P30, consistent with developmentally restricted compensation. Immunofluorescence confirmed TGN retention of ATG9A in the cerebellum at all three timepoints and in P30 spinal cord (all $p \leq 0.004$). AP-

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4-deficient mice displayed impaired tail suspension responses compared to age-matched controls across all tested ages.
CONCLUSIONS: AP-4 deficiency causes ATG9A mislocalization at embryonic stages, supporting a neurodevelopmental component of the disease. Across multiple neuron populations including lower motor neurons, this early disruption manifests as a late-life motor phenotype.
KEYWORDS: Movement Disorders, Neurodevelopmental Disorders

179. Caregiver-Reported Health-Related Quality of Life and Sleep Disorders in GNB1/GNB2-Related Neurodevelopmental Disorders: Cross-Sectional Findings from a Prospective Natural History Study

Jonas Moghib, Siofra Carty, Joshua Rong, Julian Alecu, Kathryn Yang, Katerina Bernardi, Darius Ebrahimi-Fakhari

OBJECTIVE: Pathogenic variants in *GNB1* and *GNB2* cause neurodevelopmental disorders characterized by global developmental delay, movement disorders, and epilepsy. Existing knowledge derives primarily from retrospective case series, and data on health-related quality of life (HRQoL) and sleep, domains of critical importance to patients and families, are missing.
METHODS: Within a prospective longitudinal natural history study for epilepsy-dyskinesia syndromes, caregivers completed the Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD) and the Sleep Disturbance Scale for Children (SDSC) alongside standardized clinical assessments.
RESULTS: Twenty patients were enrolled (18 *GNB1*, 2 *GNB2*; 10 females; median age 5.7 years, IQR 4-8.4); 4 had epilepsy and 16 presented with at least one movement disorder. Median CPCHILD total score was 48.0 (IQR 43.0-62.6), with *Positioning, Transferring and Mobility* as the most impaired (median 34.7, IQR 26.4-64.6) and *Comfort and Emotions* as the highest-scoring domain (median 84.1, IQR 75.8-85.7). *Overall Quality of Life* had a median score of 50 (IQR 40-60). Clinically significant sleep disturbance (SDSC>39) was present in 9 of 16 patients (median SDSC 42, IQR 35.2–50.0). No significant differences in CPCHILD or SDSC scores were observed based on the presence of epilepsy or movement disorders. However, patients with ≥2 movement disorders had significantly lower CPCHILD scores than those with none or one (p=0.011, n=17).
CONCLUSIONS: Caregiver-reported HRQoL and sleep are markedly impaired in *GNB1*/*GNB2*-related disorders and account for significant disease burden. This highlights the importance of systematically capturing these domains to guide patient-centered care.
KEYWORDS: Movement Disorders, Epilepsy, Neurodevelopmental Disorders

180. Characterizing Pediatric Dystonia: Clinical Phenotypes and Diagnostic Yield of Genetic and Metabolic Testing

Cecilia O'Brien, Mariam Hull

OBJECTIVE: Pediatric dystonia represents a heterogeneous group of disorders with diverse genetic, metabolic, immunologic, and structural etiologies. Despite advances in neurogenetics, many patients remain undiagnosed, prolonging the diagnostic process and limiting targeted management. This study aims to characterize phenotypes of pediatric dystonia and evaluate the diagnostic yield of current genetic and metabolic testing modalities.
METHODS: We conducted a retrospective chart review of 398 patients diagnosed with dystonia. Data collected included clinical features, neuroimaging, and results of genetic and metabolic testing. Testing modalities included single-gene testing, gene panels, whole exome sequencing (WES), whole genome sequencing (WGS), mitochondrial next-generation sequencing (mitoNGS), and chromosomal microarray (CMA)/karyotype.
RESULTS: In a preliminary sample of 153 patients, diagnostic yield varied by modality. Single-gene testing identified a diagnosis in 9 out of 34 patients (26.5%). Gene panels yielded diagnoses in 10 out of 39 patients (25.6%). WES yielded a diagnosis in 24 out of 76 patients (31.6%). WGS yielded a diagnosis in 2 out of 11 patients (18.2%). No diagnostic findings were identified via mitoNGS (0/28). CMA/karyotype had a diagnostic yield of 2.5%, or 2/79 patients. A substantial proportion exhibited complex phenotypes, including intellectual disability or developmental delay (n = 119) and epilepsy (n = 60). Overall, a genetic diagnosis was achieved in 46 of 153 patients (30.1%).
CONCLUSIONS: Comprehensive genetic testing, WES in particular, demonstrates higher diagnostic yield in pediatric dystonia compared to targeted approaches. However, VUS findings remain a significant challenge in clinical interpretation.
KEYWORDS: Movement Disorders, Neurodevelopmental Disorders, Neurogenetics

181. Phenotypic Characterization and Natural History of Progressive Myoclonic Epilepsy Type 1 (EPM1/ Unverricht-Lundborg Disease): An International Registry Study

Zainab Zaman, Mohammed AlQahtani, Joshua Rong, Habibah Agianda, Julian Alecu, Katerina Bernardi, Mayank Verma, Berge Minassian, Darius Ebrahimi-Fakhari

OBJECTIVE: To characterize disease phenotype and progression, evaluate potential biomarkers, establish biorepositories, and support gene therapy development in the largest EPM1 cohort studied outside Finland.
METHODS: Twenty-one participants with molecularly confirmed CSTB mutations were enrolled internationally via online recruitment. Questionnaires assessed demographics, family history, seizure characteristics, medications, and functional status. Video-based examinations utilized the Unified Myoclonus Rating Scale (UMRS). Disability was assessed using the Gross Motor Function Classification System (GMFCS) and Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD). Medical records provided additional data. Neurofilament light chain (NFL) was analyzed as a potential biomarker. All data were entered into REDCap databases.
RESULTS: The cohort (65% male, mean age 25.4 years) included 59.1% heterozygous and 40.9% homozygous CSTB

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mutations. Median GMFCS was Level IV, with 46.7% reporting complete disability on the UMRS global severity scale. Mean action myoclonus score was 41.3 (range 0-80); negative myoclonus was reported as severe in 23%. Independent ambulation was lost at a mean age of 34.0±13.1 years. Progressive cognitive decline occurred in 31.8%. Neuropsychiatric symptoms were highly prevalent: anxiety (68.2%), depression (54.5%), sleep disturbance (45.5%). Higher GMFCS levels correlated strongly with myoclonus severity. NFL concentrations (2.5-13 pg/mL) showed no significant correlation with severity.

CONCLUSIONS: EPM1 causes progressive disability, with wheelchair dependency by the mid-30s and high neuropsychiatric burden. Substantial phenotypic variability exists. This registry, utilizing standardized UMRS assessments, quality-of-life measures, and biobanking, establishes infrastructure for clinical trials of emerging therapies including gene therapy. These natural history data provide essential baseline comparisons for future interventional studies.

KEYWORDS: Movement Disorders, Epilepsy

182. Atypical Episodic Hypotonia Responsive to Verapamil in a Child with RYR1 and GNAS Variants

Leslie Beltran, Casey Ryan, Nicholas Wu, Rachael Osaitile, Stephen Brown, Mariam Hull

OBJECTIVE: To present a pediatric patient with *RYR1* and *GNAS* variants and episodic hypotonia of unknown etiology responsive to calcium-channel blocker pharmacotherapy.

METHODS: N/A

RESULTS: We present a 19-month-old right-handed female with a medical history of *CFTR*-related metabolic syndrome, feeding difficulties, a monoallelic variant in *RYR1*, and a pathogenic variant in *GNAS*. She presented with recurrent, at times unilateral, episodes of hypotonia and weakness since one month of age. Initially, episodes were characterized by flaccidity with preserved awareness and visual tracking lasting 30 seconds to an hour and exacerbated by acute illnesses or physical exertion. Over time, the episodes progressed in severity, resulting in unresponsiveness and impaired tracking. Between episodes, the patient is developmentally appropriate with mild hypotonia. EEG did not show ictal correlates associated with the events, and there were no associated electrolyte abnormalities. Electrodiagnostic testing revealed decreased amplitude and slowed conduction in the motor median nerve. Muscle biopsy demonstrated nonspecific ultrastructural abnormalities, including sarcomeric disorganization, and mild mitochondrial pleomorphism. Given her *RYR1* variant, periodic paralysis was initially suspected. Albuterol and acetozolamide were prescribed without clinical improvement. She then developed suspected episodic dystonia and, given the unilateral nature of her episodes, treatment with Verapamil—reportedly used in a case of Alternating Hemiplegia of Childhood (AHC)—was initiated. Subsequent reduction in hypotonic episodes led to an increase in Verapamil and discontinuation of Albuterol and acetazolamide.

CONCLUSIONS: This case highlights a possible novel phenotype or overlap syndrome involving *RYR1* and *GNAS* variants with features reminiscent of AHC, expanding the differential diagnosis for episodic hypotonia in pediatric patients.

KEYWORDS: Movement Disorders, Neurogenetics, Neuromuscular

183. Non-Pharmacologic Management of PRRT2-related Paroxysmal Kinesigenic Dyskinesia

Darcy Engelhart, Adam Kalawi

OBJECTIVE: Paroxysmal Kinesigenic Dyskinesia (PKD) is a movement disorder characterized by recurrent involuntary movements triggered by sudden voluntary movements, typically managed with sodium channel blockers (SCB). We present a case of PRRT2-related PKD with improvement via self-implementation ketogenic diet.

METHODS: Case Report

RESULTS: 7-year-old male presented for a two-year history of abnormal involuntary movements. Movements were limited to the foot, however these progressed to involve both legs and, at times, other parts of the body. Episodes reached a peak of 2-to-4 brief episodes per day. Events were more noticeable during soccer practices and active periods at school. The patient remained conscious during episodes and could anticipate their onset, often sitting down to prevent falls. Outside EEG revealed sharply contoured centroparietal waves but no overt epileptiform discharges, and outside provider recommended treatment for focal seizures, however the family preferred non-pharmaceutical management with a self-imposed ketogenic diet (30-40 g/day), which resulted in a near-cessation of episodes. Episodes increased in frequency around "cheat" days with increased carbohydrate ingestion. Careful history called into question the given diagnosis of focal seizures. Genetic testing revealed a pathogenic variant in PRRT2. The family opted to continue non-pharmacologic management.

CONCLUSIONS: While PKD is typically managed with SCBs, some families prefer non-pharmacologic options. Ketogenic diet may function similarly to SCBs by elevating polyunsaturated fatty acids, shifting sodium channels towards inactivation. This case presents a natural experiment using ketogenic diet for PRRT2-related PKD, with modest preliminary efficacy. Patient will transition to a medically-supervised ketogenic diet to strengthen the evidence for this plausible treatment modality.

KEYWORDS: Movement Disorders, Experimental Therapeutics, Neurogenetics

184. Parent-Reported Functional Impairment in Youth with Tic and Other Movement Disorders: A Longitudinal EHR Study

Karlee Migneault, David Huddleston, Paul Horn, Travis Larsh, Steve Wu, Tara Lipps, Mallory Telles, Donald Gilbert

OBJECTIVE: Functional impairment is a clinically meaningful outcome in youth with movement disorders. Obtaining and analyzing longitudinal real-world data is hampered by clinic workflow time constraints. Our objective was to examine associations of movement disorder diagnostic category and psychiatric comorbidity with parent-rated functional impairment over time.

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METHODS: In 2021, our pediatric movement disorders program implemented a tablet-based questionnaire which included the mini-Child Tourette Impairment Scale (mCTIM) which captures movement-disorder related impairment assessed by the parent (CTIM-M-P). This questionnaire uploads continuously into EPIC to support point-of-care collaborative medical decision making. This retrospective longitudinal study combines clinical and questionnaire data extracted from EPIC for encounters from 1/1/2022 through 12/31/2025 for patients 10-17-years-old with ≥2 visits. Diagnoses were abstracted and collapsed into 4 categories: Tic-Disorders, Tremor-Disorders, Functional-Neurological-Disorders, and Other-Movement-Disorders. The presence of psychiatric symptoms or diagnoses of Anxiety/Obsessive Compulsive Disorder (Anx/OCD) and Attention Deficit/Hyperactivity Disorder (ADHD) were also extracted from EPIC. Changes in CTIM-M-P were analyzed.
RESULTS: 472 patients (65% male, median age 12.8 years) had ≥2 eligible visits. Anx/OCD was recorded in 76% and ADHD in 57%. CTIM-M-P scores improved over time (effect size 0.30, $p < 0.001$). First-visit CTIM-M-P scores were higher among children with co-occurring Anx/OCD and ADHD. After accounting for age, sex, Anx/OCD, and ADHD, comparable CTIM-M-P improvements occurred across movement diagnoses.
CONCLUSIONS: In this preliminary analysis, tablet-based questionnaires appear feasible for acquiring outcomes data, with potential to identify patients and groups with higher levels of impairment unfavorable clinical trajectories.
KEYWORDS: Movement Disorders, Neurodevelopmental Disorders

185. Establishing a Multidisciplinary Tic Clinic: Integrating CBIT, CBT, and ERP Into a Comprehensive Care Model at an Academic Pediatric Neurological Institute

Tammy Tarhini, Andrea Tabuenca, Vijay Vishwanath

OBJECTIVE: Tourette Syndrome (TS) and chronic tic disorders are complicated by high rates of comorbid obsessive-compulsive disorder (OCD) and anxiety. We aimed to develop a multidisciplinary clinic focused on delivering evidence-based therapies to children and adolescents with TS and chronic tic disorders, with co-morbid OCD and/or anxiety, using a comprehensive care model (COCM).
METHODS: We established a multidisciplinary tic clinic staffed by a pediatric neurologist and a psychologist trained in Comprehensive Behavioral Intervention for Tics (CBIT), Cognitive Behavioral Therapy (CBT), and Exposure and Response Prevention (ERP). The clinic model featured a single-intake process that included a thorough assessment of tics and standardized screening for OCD and anxiety. This is followed by directing patients to tailored treatment pathways involving CBIT, and when appropriate, followed by either ERP or CBT, with the neurology team coordinating pharmacotherapy simultaneously. We present data to evaluate clinical outcomes and feasibility, including care effectiveness, engagement, and patient/family satisfaction.
RESULTS: We provide an overview of the clinic model, including the referral process, initial operational metrics such as patient volume, rates of comorbidity, distribution among treatment options, and early outcome measures. We will discuss challenges in development, like workforce training and integrating behavioral health into a COCM, along with our solutions.
CONCLUSIONS: A COCM multidisciplinary tic clinic within a pediatric neurological institute offers a scalable model for delivering evidence-based care to children with TS and chronic tic disorders. By integrating CBIT, CBT, and ERP under a clinical umbrella, this model reduces care fragmentation, addresses high comorbid burden, and improves access to behavioral therapies.
KEYWORDS: Movement Disorders, Behavioral Neurology, Neurodevelopmental Disorders

Neonatal Neurology

186. Neurocognitive and Emotional Outcomes in Children with History of Perinatal Hypoxic-Ischemic encephalopathy and normal Magnetic Resonance Brain Imaging

Hui Li, Jonathan Mietchen, Qianqian Zhao, Jessica Kania, Jack vogel, Melissa Johnson, Dace Almane, Chrysanthy Ikonomidou

OBJECTIVE: This prospective cross-sectional study assessed neurodevelopment in patients with HIE and normal neonatal brain MRIs obtained within the first week of life. The objective was to establish a foundation for evidence-based prognostication to support pediatric neurologists during neonatal consultations
METHODS: 41 children with history of HIE and normal brain MRIs and 39 typically developing children (controls) were recruited. Pediatric neurologists performed all neurological examinations. Neurodevelopmental assessment was conducted using the Kaufman Brief Intelligence Test (KBIT-2), NIH Toolbox Cognition (NTCB) and Emotion Battery (NTEB) by pediatric neuropsychologists. A subset of 31 HIE patients underwent follow-up assessment approximately 2 years after initial evaluation.
RESULTS: Participants with HIE demonstrated normal but significantly lower composite (103.0 ± 15.66 vs. 112.2 ± 10.80, $p=0.0029$) and nonverbal IQ scores (94.93 ± 15.70 vs. 105.8 ± 13.98, $p=0.0016$) compared to controls, with notable improvement observed at 2-year follow-up (92.61 ± 14.16 vs. 102.22 ± 16.60, $p=0.0009$). NTCB showed overall normal cognition in HIE subjects, but significantly lower scores in picture vocabulary, list sorting, dimensional change card sorting, crystalized cognition and cognitive total composite domains, as well as lower emotional well-being scores in NTEB.
CONCLUSIONS: Children with history of HIE and normal neonatal brain MRI demonstrated normal cognition, neurological examination, and emotional well-being at 4- 12 years of

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age. Compared to controls, significantly lower performance in several cognitive and emotional domains was evident. Our findings suggest that early normal MRI findings are a valuable neuroprognostication tool for neonatal HIE consultations.

KEYWORDS: Neonatal Neurology, Neurodevelopmental Disorders, Neuroimaging

187. A case of severe neonatal hypotonia with IPEX myositis cured after hematopoietic stem cell transplantation

Zoe Labelle, Louis Marois, Benjamin Ellezam, Nicolas Chrestian

OBJECTIVE: IPEX is a rare, often fatal X-linked inherited disorder triggering immune dysregulation, polyendocrinopathies, and enteropathy. We present a case of a term infant born at 37 weeks, who, immediately after birth, exhibited severe neonatal hypotonia, pulmonary hypoplasia with respiratory distress requiring BIPAP support, and severe feeding difficulties.

METHODS: Throughout the initial evaluation and hospital course, he did not demonstrate the typical polyendocrinopathies, enteropathy, or characteristic skin manifestations seen in IPEX.

RESULTS: EMG was within normal limits despite severe hypotonia and myopathic facies. Clinical exome found a new hemizygous pathogenic variant (p.Ala261Valfs*36) in FOXP3 inherited from the mother. At 5 months of age, the patient was started on steroids and IVIG, followed by treatment with sirolimus. At 6 months of age, muscle biopsy showed perimysial and endomysial lymphohistiocytic nodules with overexpression of MCH1. The decision was made to consider a hematopoietic allograft at 15 months of age. Patient improved slowly. He was weaned of permanent ventilation, developed motor skills close to his developmental age at 4 yo and developed normal cognitive skills. A second muscle biopsy at 4 yo showed normal muscle.

CONCLUSIONS: Conclusion: This is the first case of neonatal IPEX myositis reported to be cured after a hematopoietic allograft. IPEX should be considered in severe cases of neonatal hypotonia with severe respiratory distress since it could be cured with early treatment.

KEYWORDS: Neonatal Neurology, Neurogenetics, Neuromuscular

188. Neurodevelopmental outcomes of infants with hypoxic ischemic encephalopathy and isolated abnormal MR spectroscopy

Michelle Machie, Heath Yancey, Khawar Nawaz, Ameera Sheikh

OBJECTIVE: Neonatal hypoxic ischemic encephalopathy (HIE) remains a major cause of neonatal mortality and morbidity. In neonates, quantitative assessment of cerebral lactate via MR spectroscopy (MRS) may be one of the most sensitive biomarkers of outcomes in neonatal HIE. Little is known regarding how isolated abnormal MRS lactate in the absence of visible parenchymal brain injury will impact neurodevelopmental outcomes.

METHODS: This is a retrospective cohort study of term babies born after 2010 who received therapeutic hypothermia (TH) for moderate/severe HIE. Infants were included if they were treated with TH and had a normal brain MRI with no parenchymal brain injury. Seventy-four infants met inclusion criteria of which 50 had normal MRS and 24 had abnormal MRS with lactate peak. Neurodevelopmental outcomes were assessed at 2 years of age via Bayley scale.

RESULTS: Infants with abnormal MRS (positive lactate peak) had lower Bayley language scale scores ($p = 0.009$), lower Bayley motor scale scores ($p = 0.03$), and a higher instance of cerebral palsy ($p = 0.04$).

CONCLUSIONS: Infants with abnormal MRS without evidence of any parenchymal injury had significantly lower language and motor scale scores at 2 years and a higher instance of cerebral palsy diagnoses as compared to infants with normal MRI/MRS. Overall, isolated abnormal MRS may represent a viable biomarker for neurodevelopmental prognostication and to identify those infants who should be referred for early interventions. More research is needed to validate this finding with future directions including correlation with quantitative ADC measurements.

KEYWORDS: Neonatal Neurology, Cerebral Palsy

189. A Decade of Neonatal Subpial Hemorrhages – Imaging characteristics, clinical risk factors and neurologic outcomes

Mia Chen, Makabongwe Tshuma, Elke Roland, Steven Miller, Thiviya Selvanathan

OBJECTIVE: To characterize the clinical presentation, pathophysiology, and long-term neurodevelopmental outcomes of neonatal subpial hemorrhage (NSH).

METHODS: We conducted a single-center retrospective cohort study of neonates diagnosed with NSH between January 2014 and December 2025. Medical records were reviewed for perinatal factors, clinical presentation, neuroimaging findings, and neurologic outcomes.

RESULTS: Thirty-nine infants were included; 62% were male, with a mean gestational age of 37 weeks (SD 4.1). Mean Apgar scores were 4.7 (SD 3.0) and 6.9 (SD 2.5) at 1 and 5 minutes, respectively. Perinatal fetal heart rate abnormalities were observed in 49%, and 36% required emergency cesarean delivery. NSH was predominantly unilateral (72%), commonly involved the temporal lobe (44%), and was frequently associated with adjacent cortical/subcortical infarction (56%) and venous congestion (59%). Head trauma (skull fracture, cephalohematoma or subgaleal hematoma) was identified in 38% of cases, with 83% occurring ipsilateral to the NSH. Hypoxic-ischemic encephalopathy (HIE) was present in 30%, and 62% of infants presented with seizures. Mortality was 8%. Among survivors, 86% had normal neurological examinations at NICU discharge. At follow-up (n=30), 13% developed cerebral palsy, particularly in those with frontal lobe involvement, and 27% exhibited developmental delay, notably among cases with cortical/subcortical infarction. Anti-seizure medications were prescribed in 42%; two required escalation, including ketogenic diet initiation. Four infants developed seizures beyond the neonatal period.

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CONCLUSIONS: NSH is a distinct entity often associated with adcjacent venous congestion. Cases with cortical/subcortical infarction may carry increased neurodevelopmental risk. Normal early examinations do not reliably predict long-term outcomes, underscoring the need for prolonged follow-up.

KEYWORDS: Neonatal Neurology, Neuroimaging

190. Preventing DHA oxidation using deuterated DHA ameliorates neonatal hypoxic ischemic brain injury.

Joseph Vithayathil, Baoyi Lin, Anjali Shankar, Frances Jensen, Mikhail Shchepinov, Delia Talos, Joshua Dunaief

OBJECTIVE: Polyunsaturated fatty acids (PUFAs), such as arachidonic acid (ARA) and docosahexaenoic acid (DHA), are highly susceptible to oxidative damage in neonatal hypoxic ischemic (HI) brain injury. While DHA supplementation is neuroprotective in rodent models of HI brain injury, it remains unclear whether this benefit is due to repletion of DHA damaged by oxidation or if it increases neuroprotective byproducts of DHA oxidation.

METHODS: Using the Vannucci model of neonatal HI in mice at post-natal day 9 (PND9), oxidation of DHA and ARA was assessed by measuring neuroprostanes and isoprostanes by mass spectrometry, which was confirmed by immunofluorescence staining for carboxyethylpyrrole (CEP) and 4-hydroxynonenal (HNE) and high throughput *in situ* staining (10X Xenium). To determine whether DHA oxidation contributes to neuronal injury, we utilized deuterated DHA (D-DHA) which decreases the rate of DHA oxidation. Pregnant dams were started on 0.25% D-DHA diet at conception with control mice receiving equivalent standard hydrogenated DHA (H-DHA) or standard diet with subsequent comparison of HI injury severity between different diets.

RESULTS: Mass spectrometry revealed selective elevation of neuroprostanes, but not isoprostanes, at 24 hours post-HI, indicating DHA-specific oxidation. CEP colocalization with TUNEL-positive cells confirmed that DHA oxidation products accumulate at sites of cell death. Pups preloaded with D-DHA achieved over 70% D-DHA incorporation into the brain by birth and demonstrated 31% and 48% reduction in injury severity compared to H-DHA ($p=0.012$) and regular diet ($p=0.0002$), respectively.

CONCLUSIONS: Preloading the developing brain with oxidation-resistant deuterated DHA reduces injury severity, establishing DHA oxidation as a significant driver of neuronal injury.

KEYWORDS: Neonatal Neurology, Cerebral Palsy, Early Stage Investigator

191. Temporal Lobe Measurements in Preterm Infants Receiving Standard Care versus Tailored Neurosensory Experiences in the Neonatal Intensive Care Unit

Alexandra Brooks, Katherine Bell, Yoonjoo Kim, Sophia Marogi, Terrie Inder, Carmina Erdei

OBJECTIVE: This study evaluated differences in temporal lobe length and related structures between a cohort of very preterm infants receiving standard care and those receiving tailored, structured neuro-promotive intervention (SENSE/SENSE-plus) while hospitalized in the NICU prior to term-equivalent age (TEA).

METHODS: Fifty-three very preterm infants (born <33 weeks' gestation) underwent TEA brain MRIs as part of a prospective cohort study. Twenty-six (9 high-risk, 17 low-risk without moderate-severe neurologic injury) received standard care, including 1-3 times/week PT. The remaining 27 received tailored neuro-promotive care: 19 low-risk infants received neurodevelopmental care (Supporting and Enhancing NICU Sensory Experiences "SENSE" program), while 8 high-risk infants received neuro-habilitative care (SENSE program plus 1-2 additional weekly sessions of targeted physical/occupational therapy). Temporal lobe length, extra-axial space, and temporal horn width were independently measured by three raters in TEA MRIs. Mean values of each metric were compared between standard care and SENSE/SENSE-plus groups, stratified by low/high neurologic risk, using t-tests.

RESULTS: Among low-risk infants, temporal lobe measures did not differ between those receiving standard care and those receiving SENSE. However, among high-risk infants, those exposed to SENSE-plus exhibited greater temporal lobe length than those in standard care group (mean 77.03 vs 73.54, mean difference -3.49, 95% CI -6.56 to -0.42).

CONCLUSIONS: These findings suggest that enhanced, tailored neuro-habilitative care may support temporal lobe development in high-risk preterm infants. Temporal lobe metrics are reliable and feasible to obtain on TEA MRI in preterm infants and thus may serve as practical neuroimaging marker for evaluating the impact of early habilitative interventions.

KEYWORDS: Neonatal Neurology, Neuroimaging

192. Etiology of Neonatal Seizures in the Pediatric Emergency Department

Kristen Bolte, Laura Armstrong, Richard Carozza, Kaylee Lynch, Robert Carson

OBJECTIVE: Existing data evaluating the etiology of seizure-like events in neonates typically focuses on patients admitted to the Neonatal Intensive Care Unit. This study aims to characterize the etiologies of seizure-like events in neonates presenting to the Emergency Department (ED).

METHODS: We retrospectively identified neonates less than 28 days old without a history of epilepsy who presented to the pediatric ED with a chief complaint of seizure-like events and were evaluated by our pediatric neurology service between December 2018 and March 2022. 94 patients met the inclusion and exclusion criteria. Charts were screened, data was collected by Pediatric Neurologists using REDCap, and descriptive statistics were used to identify the most common etiologies.

RESULTS: Of the 94 patients, 76.6% (n=72) were benign causes while 23.4% (n=22) were seizures. Of the seizures, the most common etiology was electrolyte abnormalities (n=8, 36.4%), specifically hypocalcemia (n=7) and hypoglycemia (n=1). The next most common etiologies were genetic epilepsy syndromes (n=7, 31.8%), ischemic/hemorrhagic events (n=3, 13.6%), and cryptogenic (n=3, 13.6%). Finally, a small percentage was secondary to intracranial infection (n=1, 4.5%).

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CONCLUSIONS: Seizure-like events in neonates presenting to the ED most commonly reflect benign causes. However, when the events are seizures, they are most commonly due to electrolyte abnormalities or genetic epilepsy syndromes. This is notably different than in neonates presenting in the NICU, where hypoxic ischemic encephalopathy is the predominant cause reported. Neonates presenting with seizures in the ED warrant prompt electrolyte evaluation as this is low-cost and can rapidly identify reversible causes of seizures.

KEYWORDS: Neonatal Neurology, Epilepsy, Neurocritical Care

193. Natural Course of Post-Hemorrhagic Ventricular Dilation in Neonates with High-Grade Intraventricular Hemorrhage

Natalia Fuenzalida, Jessica Klein, Michael Christian, Garrett Gianneschi, Onajovwe Fofah

OBJECTIVE: To determine the extent and average trend of post-hemorrhagic ventricular dilation and generate survival data using composite scoring for intraventricular hemorrhage grading in neonates.

METHODS: This study was designed as a retrospective cohort study using data collected from the hospital's electronic medical record. Data from 43 neonates was included using the following criteria: patient was admitted to the NICU between 01/2010 and 01/2025, and they must have a diagnosis of "Intraventricular hemorrhage," "IVH," "germinal matrix hemorrhage," or "periventricular hemorrhage." Lateral ventricles seen on cranial ultrasound were measured using ventricular index and anterior horn width per side, with a radiologist approving the measurements; if lumbar puncture or neurosurgical intervention was performed, measurements were stopped. Composite grading of both ventricles determined the total hemorrhagic burden. The association between IVH severity and survival past the neonatal period was determined by Wilcoxon rank-sum test.

RESULTS: Results showed an average anterior horn width growth rate of 0.219 mm/day, or 1 mm every 4.56 days, and an average ventricular index growth rate of 0.225 mm/day, or 1 mm every 4.44 days. These rates did not differ between Grade III & IV IVH. In addition, total hemorrhagic burden correlated better with dilation trends and survival rate ($p = 0.034$) when compared with standard IVH grading.

CONCLUSIONS: The results of this study help fill a research gap regarding trends in post-hemorrhagic ventricular dilation in neonates. In addition, using total hemorrhagic burden compared to standard IVH grading may give better insight into predicting survival past the neonatal period.

KEYWORDS: Neonatal Neurology, Neuroimaging, Neurocritical Care

194. Epigenetic regulation of neurogenesis by Gadd45β in response to hypoxic ischemic injury in neonatal mice

Vincent Shieh, Frances Northington, Ji Young Park, Thomas Robinson, Hongjun Song, Ryan Felling

OBJECTIVE: Hypoxic ischemic encephalopathy (HIE) remains the leading cause of neurological morbidity in neonates. Therapeutic hypothermia has improved mortality, but 48% of survivors develop moderate-to-severe neurologic sequelae. We sought to understand whether changes in DNA methylation regulate neurogenesis in response to this injury.

METHODS: We used a mouse model of perinatal hypoxic-ischemic brain injury to investigate changes in DNA methylation and Gadd45β, a protein important in active DNA demethylation, in a neurogenic niche within the subventricular zone (SVZ). P10 mice underwent right common carotid artery ligation or sham surgery followed by exposure to hypoxia. The SVZ was microdissected then processed for quantitative PCR and enzymatic methylsequencing. Immunofluorescence was performed on fresh frozen tissue. Proliferation studies were performed by pulse labeling of dividing cells with EdU.

RESULTS: We identified robust presence of 5-hydroxymethylcytosine, an intermediate of DNA demethylation, in SVZ neural progenitor cells. We then used enzymatic methylsequencing to quantify changes in 5-methylcytosine in the SVZ followed by pathway analysis, demonstrating that relatively demethylated regions were enriched in growth-promoting pathways important in neurogenesis. Then, we showed that Gadd45β expression is uniquely elevated compared to its homologs in response to hypoxic-ischemic injury. We also knocked out Gadd45β expression to find impaired SVZ cell proliferation following hypoxic-ischemic injury.

CONCLUSIONS: Growth permissive genes are actively demethylated within the SVZ in the subacute period following perinatal hypoxic-ischemic brain injury. This appears to be important for the increase in neurogenesis that follows injury. Active DNA demethylation offers a promising therapeutic target for modulating neuroplasticity following injury in the developing brain.

KEYWORDS: Neonatal Neurology, Stroke

195. Investigating brain volume in very preterm infants after arachidonic and docosahexaenoic acid supplementation

Gunnthorunn Gunnarsdottir, Oliver Geier, Tone Nordvik, Ivan Maximov, Anette Ramm-Pettersen, Tom Stiris, Helle Pfeiffer, Sissel Moltu

OBJECTIVE: To evaluate the impact of high dose supplementation of arachidonic acid (ARA) and docosahexaenoic acid (DHA) on regional brain volumes at term equivalent age in very preterm infants. We hypothesized that supplementation would increase brain volumes.

METHODS: This was a secondary analysis of a randomized controlled trial including infants born before 29 weeks' gestational age, who received enteral supplementation of either 0.4ml/kg Formulaid (100mg/kg of ARA and 50mg/kg of DHA) or MCT oil (medium chain triglycerides) from the 2nd day of life until 36 weeks postmenstrual age. Brain MRI was performed at term-equivalent age, and volumetric measures were obtained using automated anatomical segmentation. Group differences were analyzed using univariable and multivariable regression models.

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RESULTS: A total of 120 infants were included in the original trial; mean gestational age at birth (SD) was 26 weeks and three days (1.63). In total, 92 infants underwent MRI, 80 (ARA:DHA n = 43, MCT n = 37) scans were eligible for volumetric analysis. Mean (SD) postmenstrual age at scan was 41.1 weeks (1.26). In unadjusted analysis, infants in the ARA:DHA group had significantly larger cortical grey matter volume (β=11.1cm^3, 95%CI 1.7-2.1, p = 0.02) compared to the MCT-group and borderline larger total brain volume (β= 19.4cm^3, 95% CI -0.3-3,9, p=0.05); these differences were not significant after multivariable adjustment.
CONCLUSIONS: Our findings suggest that ARA and DHA supplementation may promote brain growth in very preterm infants, but observed effects were attenuated after adjustment for clinical covariates.
KEYWORDS: Neonatal Neurology

196. Novel Pathogenic Variant in MOCS2 Gene Leading to Molybdenum Cofactor Deficiency in a Neonate with Refractory Status Epilepticus

Rutvi Patel, Susan Duberstein, Elissa Yozawitz

OBJECTIVE: Molybdenum cofactor deficiency (MoCD) is a rare autosomal recessive disorder characterized by intractable seizures, progressive encephalopathy, and feeding difficulties. The MOCS2 gene is involved in molybdenum cofactor biosynthesis, with pathogenic variants in MOCS1, MOCS2, MOCS3, and GEPH disrupting this pathway. We report a neonate with a novel MOCS2 variant and a clinical phenotype consistent with MoCD.
METHODS: A two-week-old female with uncomplicated birth history presented with poor feeding and seizure-like activity. EEG confirmed refractory electroclinical and electrographic status epilepticus. Early brain imaging showed extensive reduced diffusion and edema suggestive of hypoxic-ischemic encephalopathy. Genetic testing identified a homozygous variant of uncertain significance (VUS) in the MOCS2 gene. Given the clinical presentation, further evaluation for molybdenum cofactor deficiency and a literature review were undertaken.
RESULTS: EEG revealed bilateral independent electrographic seizures refractory to multiple antiseizure agents, requiring escalation of care progressing to eventual burst suppression. MRI showed diffuse restricted diffusion in the left hemisphere, corpus callosum, and right subcortical white matter. Follow-up MRI in 3 weeks showed atrophy, cystic encephalomalacia, and new areas of active injury. Whole genome sequencing identified a homozygous VUS (c.422 C>T p.(S141L)) in the MOCS2 gene. Urine studies revealed elevated S-sulfocysteine and xanthine and decreased uric acid, confirming a biochemical diagnosis of MoCD.
CONCLUSIONS: MoCD is a rare autosomal recessive disorder. We describe a neonate with refractory status epilepticus, progressive MRI changes, and a characteristic biochemical profile harboring a homozygous MOCS2 VUS, supporting reclassification as a pathogenic variant consistent with MoCD.
KEYWORDS: Neonatal Neurology, Neurogenetics, Epilepsy

197. Post surgical decompensation in the NICU: A case presentation of ultra rare condition ABCC9-associated disease

Emily Garavatti, Brenda Rieger, Rahul Nikam, James Hammond, Simon Kayyal, Terrie Inder

OBJECTIVE: To present a case demonstrating the importance of rapid genetic testing in understanding vulnerabilities to drugs and therapies in the neonatal intensive care unit.
METHODS: A full-term male was diagnosed with ileal atresia at 32 hours of life. On day of life (DOL) 3, he developed focal seizures with electroencephalographic correlates and MRI evidence of multifocal diffusion restriction and T1 hyperintensities of unknown etiology, requiring phenobarbital and fosphenytoin. Following surgical correction on DOL 4, he experienced rapid clinical deterioration marked by refractory hypotension, lactic acidosis, coagulopathy, biventricular cardiac dysfunction, and recurrent seizures requiring the addition of levetiracetam. Rapid whole exome sequencing identified biallelic pathogenic ABCC9 variants, consistent with ABCC9-related Intellectual disability Myopathy Syndrome (AIMS), as well as an incidental G6PD deficiency that did not fully elucidate the decompensation. Extensive infectious and metabolic evaluations were unrevealing. The infant experienced a second episode a month later of near identical severe decompensation following surgical gastrostomy tube placement.
RESULTS: Collaboration with international researchers revealed ABCC9 associated cardiotoxicity in animal models from calcium channel blockers. This led to review of anesthetic agents in our patient and suspicion of propofol-induced cardiogenic shock related to ABCC9 mutation. Propofol's calcium channel–blocking properties and inhibitory effects on ATP-sensitive potassium (KATP) channels may exacerbate impaired metabolic stress responses in this patient population. This raises concern for heightened susceptibility to propofol-related cardiotoxicity or an exaggerated propofol infusion syndrome phenotype.
CONCLUSIONS: This case highlights the importance of rapid genomic diagnosis, multidisciplinary collaboration, and careful anesthetic selection in neonates with rare channelopathies.
KEYWORDS: Neonatal Neurology, Neurometabolic, Neurogenetics

198. Neurodevelopmental outcomes at two years corrected age for very preterm infants receiving neuropromotive care in the Neonatal Intensive Care Unit (NICU)

Carmina Erdei, YoonJoo Kim, Sara Cherkerzian, Bobbi Pineda, Terrie Inder

OBJECTIVE: Infants born very preterm (VP) experience neurodevelopmental impairment, yet evidence supporting the impact of early life interventions on long-term outcomes remains limited. This study examined the relationship between risk-stratified neuropromotive care for hospitalized

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VP infants before term-equivalent age and their neurodevelopmental outcomes at two years adjusted age.

METHODS: We prospectively enrolled 53 VP infants born <33 weeks gestation in a level-III NICU, stratified based on the degree of neurological injury at enrollment. Low-risk VP infants (without moderate-severe injury; n=19) were exposed to the Supporting and Enhancing NICU Sensory Experiences (SENSE) program from enrollment until term-equivalent; high-risk infants (n=8) were exposed to intensified habilitative support (SENSE-plus). A reference group (n=26) of low-risk and high-risk VP infants received standard care. Neurodevelopmental performance was assessed using the Bayley-4 at 18-24 months adjusted age.

RESULTS: Infants in the exposed (SENSE/SENSE-plus) vs reference group had comparable birth gestational ages (29.1±2.3 vs 28.6±2.5 weeks), birth weight (1224±418 vs 1204±363g), clinical and family-social characteristics. Among low-risk infants, the SENSE group demonstrated significantly higher scores than reference group in Expressive Communication (11.5[8.0-16.0] vs 9.0[6.0-10.0], p=0.016), Motor Composite (101.0[90.0-102.0] vs 90.0[84.0-94.0], p=0.023), and Fine Motor (11.0[10.0-12.0] vs 9.0 [9.0-10.0], p=0.018) domains. Language Composite scores showed a trend toward improvement in low-risk SENSE vs reference group (109.0[98.0-128.0] vs 100.0[72.0-108.0], p=0.094). No significant differences were observed among the exposed vs non-exposed high-risk infants.

CONCLUSIONS: Risk-stratified neuropromotive care leveraging the SENSE framework in the NICU is associated with improved expressive communication and motor performance at two years adjusted age in low-risk VP infants.

KEYWORDS: Neonatal Neurology, Neurodevelopmental Disorders, Neurocritical Care

199. The Role of DIP2A in Brain Development and Hydrocephalus: Insights from Xenopus Model

Deniz Elbizim, Stephen Viviano, Engin Deniz

OBJECTIVE: To investigate the role of DIP2A in brain development and its contribution to hydrocephalus using a Xenopus model, following identification of compound heterozygous variants in DIP2A in a family with two siblings affected by congenital hydrocephalus

METHODS: A family with two affected siblings presenting with congenital hydrocephalus was identified, and genetic testing revealed compound heterozygous variants in DIP2A. We performed loss-of-function studies using CRISPR/Cas9-mediated knockout in Xenopus embryos injected at the one-cell stage. Brain morphology was assessed using optical coherence tomography imaging. DIP2A expression patterns was further examined by whole-mount in situ hybridization.

RESULTS: Loss of DIP2A in Xenopus resulted in hydrocephalus phenotype, recapitulating the patient's presentation and suggesting a critical role in brain development. Mutant tadpoles displayed enlarged brain ventricles and aqueduct stenosis. Mutant tadpoles exhibited normal cerebrospinal fluid (CSF) circulation and flow, indicating that the underlying mechanism may differ from classical abnormal CSF circulation leading to hydrocephalus but suggesting impaired neurogenesis leading to hydrocephalus. In situ hybridization also revealed DIP2A expression during early forebrain development, further supporting its implication in hydrocephalus pathogenesis outside CSF homeostasis.

CONCLUSIONS: Loss of DIP2A function leads to hydrocephalus in a Xenopus model, suggesting a critical role in brain development independent of classical CSF circulation mechanisms. These findings provide novel mechanistic insight into DIP2A-associated neurodevelopmental disorders and establish its relevance to human congenital hydrocephalus.

KEYWORDS: Neonatal Neurology, Neurocritical Care, Neurogenetics

200. Clinical Outcomes and Safety of Intranasal Breast Milk in Preterm and Very-Low-Birth-Weight Infants With Intraventricular Hemorrhage: A Systematic Review and Meta-Analysis

Angel Godina-Sanchez., Camila Teran Hooper, Giselle Delgadillo-Veizaga, Crystal Ek-Góngora, Emilia Cabra Arellano, María Zavala Mejía

OBJECTIVE: Intraventricular hemorrhage (IVH) is a major cause of morbidity in preterm and very-low-birth-weight infants, with limited targeted therapies. We evaluated the efficacy and safety of intranasal breast milk (IBM) in preterm or very-low-birth-weight infants (VLBW) with IVH.

METHODS: We searched PubMed, Embase, and Cochrane Central through April 2026 for RCTs and cohort studies evaluating IBM in preterm and VLBW infants with IVH. Six reviewers, working in pairs, independently screened studies, extracted data, and assessed risk of bias. Each study was reviewed by two reviewers in duplicate, with disagreements resolved by discussion or by a third reviewer. Random-effects meta-analyses were performed using REML with Hartung-Knapp-Sidik-Jonkman adjustment. Bayesian normal-normal hierarchical models with weakly informative priors were used as sensitivity analyses.

RESULTS: Three studies met inclusion criteria: 1 RCT and 2 cohort studies. Compared with controls, IBM was not significantly associated with post-hemorrhagic ventricular dilatation (RR 0.91, 95% CI 0.09-9.50; I^2=81%), surgical intervention for PHVD/hydrocephalus (RR 0.79, 95% CI 0.22-2.81; I^2=0%), or all-cause mortality (RR 0.79, 95% CI 0.22-2.79; I^2=0%). Bayesian sensitivity analyses showed concordant estimates (PHVD 0.93; intervention 0.84; mortality 0.81). No serious adverse events attributable to IBM administration were reported.

CONCLUSIONS: IBM appears feasible and safe in preterm and VLBW infants with IVH. Available evidence suggests directionally favorable but statistically inconclusive effects on PHVD and neurosurgical intervention. Although effect estimates remain compatible with clinically meaningful benefit, the certainty of evidence is limited by the small number of studies and imprecision. Adequately powered randomized trials with standardized neurodevelopmental follow-up are needed before clinical adoption.

KEYWORDS: Neonatal Neurology, Neurocritical Care

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201. Prognostication for Neurocognitive Outcomes after Therapeutic Hypothermia for Hypoxic-Ischemic Encephalopathy

Kaitlyn Storm, Kathryn Elkins, Nathalie El Ters, Amit Mathur

OBJECTIVE: Perinatal hypoxic-ischemic encephalopathy (HIE) remains a major cause of neurodevelopmental disability despite therapeutic hypothermia (TH). MRI is widely used for prognostication, yet emerging data suggest structural imaging may underestimate subtle neurocognitive impairment. This study evaluates the utility of MRI and EEG in predicting Bayley outcomes following TH.

METHODS: We conducted a retrospective cohort study of 61 infants ≥35 weeks gestation treated with TH (June 2020–December 2024) who had Bayley-III/IV scores at 18–36 months. Data included Sarnat staging, EEG during TH, and MRI imaging. EEGs were classified by severity and temporal evolution.

RESULTS: At Bayley follow-up, 32/61 (52%) of infants had cognitive delay (<85 in ≥1 domain). MRI demonstrated poor predictive discrimination: HIE-type injury was present in 56% (18/32) of infants with abnormal outcomes and 48% (14/29) with normal outcomes. Notably, nearly half of infants with adverse outcomes had no MRI evidence of HIE-pattern injury. In contrast, EEG abnormalities were more predictive of abnormal neurodevelopment, though still imperfect. Moderate-to-severe EEG abnormalities during cooling occurred in 46% (15/32) of infants with abnormal neurodevelopment versus 24% (7/29) with normal neurodevelopment. Divergence between groups increased over time, with persistent EEG abnormalities more common among infants with adverse outcomes. However, overlap remained substantial, limiting predictive precision.

CONCLUSIONS: MRI alone performed poorly as a prognostic tool in this cohort. Serial EEG provided greater clinical signal, particularly when abnormalities persisted over time, but was not independently definitive. These findings challenge reliance on single-modality prognostication and support integrating EEG trajectory, imaging, and clinical assessment to better predict neurodevelopmental risk after HIE.

KEYWORDS: Neonatal Neurology, Neurodevelopmental Disorders, Neuroimaging

202. Clinical and radiographic characteristics do not differentiate etiology of echogenic foci on head ultrasound

Riley Kessler, Marcus Otavio Silva DeCampos Meneses, Mark Ramos, Alexander Gonzalez, Matthew Whitehead, Sara Reis Teixeira, Natalie Ullman

OBJECTIVE: "Echogenic foci" on head ultrasound (HUS) can represent ischemia, hemorrhage, or artifact, each with distinct clinical implications. Despite the high-stakes nature of this finding, there is limited evidence to differentiate between etiologies. We sought to identify sonographic and clinical features that help characterize "echogenic foci" on HUS.

METHODS: We identified HUS studies performed at the Children's Hospital of Philadelphia between 2014-2026 reporting a new "echogenic focus concerning for ischemia versus hemorrhage." Two blinded radiologists independently reviewed images to assess sonographic features. Follow-up MRI classified lesions as ischemia, hemorrhage, or artifact. Clinical data were obtained from medical records. Associations between variables and outcomes were analyzed using Fisher's Exact or Pearson's chi-squared tests.

RESULTS: Forty-seven patients met inclusion criteria with final diagnoses of ischemia in 24 (51%) hemorrhage in 10 (21%) and artifact in 13 (28%). 70% of patients had a change in medical management as a result of the HUS finding (change in anticoagulation goal or medication, blood product administration, obtaining additional imaging). Age, congenital heart disease, hypoxic ischemic encephalopathy, sepsis, coagulopathy, and ECMO were not associated with etiology. All patients with new EEG abnormalities (seizures or excessive sharps, n=5) had hemorrhage or ischemia (not artifact). Lesions with ill-defined margins were more likely to be ischemia and all hemorrhages had well-defined margins (p=0.03).

CONCLUSIONS: Despite intuitively assuming certain clinical characteristics may be associated with injury type, we found that clinical features do not differentiate etiologies of echogenic foci on HUS. New EEG changes and lesion margin characteristics may aid in interpretation on these findings.

KEYWORDS: Neonatal Neurology, Stroke, Neuroimaging

203. Evaluating CBC Declines as an Early Signal of Severe Neonatal Intraventricular Hemorrhage

Jessica Klein, Natalia Fuenzalida, Michael Christian, Garrett Gianneschi

OBJECTIVE: We tested whether severe IVH (intraventricular hemorrhage) produces a measurable acute CBC drop around HUS (head ultrasound) diagnosis and whether declines plausibly precede HUS detection of IVH.

METHODS: Retrospective cohort analysis compared NICU infants with severe IVH to non-IVH controls. t_0 = first HUS documenting grade ≥3 IVH. Acute CBC drop = max $[t_0-72h, t_0]$ − min$[t_0, t_0+24h]$ (windowed by DOL); controls indexed at pseudo-t_0 = DOL 4. A within-infant estimate compared the acute drop to expected 4-day decrease from post-t_0 CBC slope (≥3 CBCs at t_0+7d). One-sided Mann–Whitney U and Wilcoxon signed-rank tests used with Holm correction across Hgb, Hct, RBC, & Plt.

RESULTS: Among 14 severe IVH infants (median t_0 DOL 4.0, IQR 2.0–6.8), acute CBC drops exceeded controls (n=10) at t_0 ≤7d: Hgb 3.70 vs 2.20 g/dL, Hct 9.50 vs 6.00%, RBC 1.00 vs 0.40 $\times 10^6$/μL, Plt 95 vs 19 $\times 10^3$/μL (all Holm p<0.05). Within-infant drops far exceeded baseline fluctuations: Hgb 3.30 vs 0.08 g/dL, Hct 8.70 vs 0.26%, RBC 0.88 vs 0.01 $\times 10^6$/μL, Plt 75 vs 0 $\times 10^3$/μL (all Holm p<0.01). Temporal sequencing was confounded by transfusions: 79% (11/14) received RBC Tx prior to t_0; largest consecutive Hgb decrease occurred pre-t_0 in 50% and post-t_0 in 50%.

CONCLUSIONS: Severe IVH is associated with a reproducible acute CBC signature (Hgb/Hct/RBC/Plt) exceeding both control drops and baseline trends. Frequent pre-diagnosis

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transfusions and diagnostic lag limit causal inference, supporting association rather than a validated early screening signal.
KEYWORDS: Neonatal Neurology, Neuroimaging

Neurocritical Care

204. Cerebrospinal Fluid Leak Following Intense Weightlifting Workout: Injury or Self-Treatment of Intracranial Hypertension?

Gregory Anash, Yasemin Akinci, Aishwarya Aggarwal, Yevgeniya Shekhtman

OBJECTIVE: We aim to discuss a rare, challenging case of spinal cerebrospinal fluid (CSF) leak causing severe bilateral subdural hematoma (SDH) following intense weight lifting, presenting with double vision.
METHODS: This descriptive case study relied on structured physical exam, diagnostic testing, and literature analysis.
RESULTS: A 21-year-old male (5'7, 115 lb) with idiopathic intracranial hypertension presented with right 6th nerve palsy. Two weeks ago, while performing a barbell squat with 275 pounds, he heard a popping sound followed by pain in his lower back. Brain imaging showed subacute right and chronic left frontoparietal as well as right parafalcine SDHs with midline shift and osseous defect in the left connecting the frontal sinus with the frontal convexity (figure 1 and 2). Computed tomography (CT) myelogram showed contrast extravasation suspicious for CSF leak notably in the left L1-L2 foramen, and to lesser degree from T7 to L1 (figure 3). There was no rhinorrhea or headache. Beighton Scale score did not indicate generalized joint hypermobility. Two weeks after lumbar epidural blood patch, his 6th nerve palsy resolved, and a diagnostic CT myelogram with intrathecal microcatheter showed no signs of CSF leak. CT head at 3 months showed decreased SDH sizes (figure 4).
CONCLUSIONS: Dural tears causing CSF leak might occur during intense exercise (1). Additionally, heavy lifting can cause intracranial hypertension, and CSF leak might occur as a compensatory mechanism; this could explain the idiopathic systemic hypertension, frontal sinus defect, absence of the headache, and multilevel spinal CSF leak without obvious spinal trauma history (2-6).
KEYWORDS: Neurocritical Care

205. Marchiafava-Bignami Disease in an Adolescent: A Reversible Cause of Acute Neurological Deterioration After Metabolic Stress

Maria Sierra-Breton, Dagoberto Cabrera-Hemer

OBJECTIVE: To report a rare pediatric presentation of Marchiafava-Bignami disease (MBD) triggered by acute metabolic stress and micronutrient deficiency, highlighting the importance of early recognition of reversible causes of encephalopathy and prompt thiamine supplementation.
METHODS: We describe a 14-year-old female who presented with cardiorespiratory arrest after a near-drowning event, preceded by heavy alcohol intake. Clinical findings and nutritional history were reviewed. Brain MRI and thiamine levels were obtained.
RESULTS: Neurological examination revealed pyramidal signs, ophthalmoplegia, psychomotor agitation, and cerebellar dysfunction. Brain MRI demonstrated characteristic moth-eaten–like lesions involving the splenium and genu of the corpus callosum. Further history uncovered prolonged fasting, poor dietary habits, and recent heavy alcohol intake. Dextrose administration during initial resuscitation likely exacerbated an underlying thiamine deficiency. Based on clinical and radiological findings, MBD was suspected, and empiric thiamine and folic acid were started, leading to clinical improvement within 48 hours. Thiamine levels were within the low-normal range; although measured prior to treatment, results became available several days after supplementation and clinical improvement.
CONCLUSIONS: MBD can occur in pediatric patients under acute metabolic stress and nutritional deficiency. This case highlights a critical and potentially reversible cause of severe neurological impairment. Early thiamine supplementation should be considered in at-risk patients, particularly after alcohol consumption and glucose administration. These findings underscore the importance of nutritional assessment in critically ill children and the need for heightened clinical suspicion in emergency settings. Thiamine supplementation should be started based on clinical and radiological findings despite delayed laboratory confirmation.
KEYWORDS: Neurocritical Care, Neurometabolic, Early Stage Investigator

206. mTOR Signaling and Neuroinflammation in Refractory Status Epilepticus: Insights from mTORopathies

Max Goldberg, Yitao Ma, Matthew Kaminski, William Young

OBJECTIVE: Refractory status epilepticus (RSE) and super-refractory status epilepticus (SRSE) in mTORopathies are rare but critical neurological conditions with high morbidity and mortality. Currently, there is no consensus or treatment guideline available. This systematic review sought to assess current treatment approaches and identify associated challenges to enhance clinical outcomes.
METHODS: We followed the PRISMA framework. A systematic search was conducted for clinical trials, observational studies, case series, and case reports including patients with mTORopathies who presented with RSE/SRSE in PubMed, Embase and Web of Science from inception to December 2025. Their clinical presentation, treatment strategies, and outcomes were analyzed.
RESULTS: Three hundred and twenty-six records were initially identified, of which 16 case reports and one prospective observational study with total 23 cases were included for analysis. All except one patient were pediatric patients. Current treatment strategies include antiseizure medications, anesthetic agents, mechanistic target of rapamycin (mTOR) inhibitors, hemispherectomy, and immunotherapy. The treatment of RSE/SRSE is challenging, and traditional anti-seizure medications are often ineffective. Responses to mTOR

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inhibitors and hemispherectomy were mixed, whereas all four patients who had trials of immunotherapy responded well.
CONCLUSIONS: mTOR signaling and neuroinflammation are critical pathways activated in RSE/SRSE in mTORopathies. Simultaneous inhibition of both processes using mTOR inhibitors and immunotherapy may help terminate SE and improve epilepsy and neurodevelopmental outcomes. Future studies are needed to assess the value and adverse events of mTOR inhibitors and immunotherapy in the treatment of RSE/SRSE in patients with mTORopathies.
KEYWORDS: Neurocritical Care, Neurogenetics, Neuroimmunology

207. Incidence of neurologic complications in pediatric hemolytic uremic syndrome

Natasha Novoa, Tanner Hoke, Cybelle Can, Anna Scholz, Elizabeth Joyce, Lauren Mills, Kevin Barton, Rejean Guerriero, Shannon Agner

OBJECTIVE: Neurologic complications of pediatric hemolytic uremic syndrome (HUS) range from 10-30% of cases, including encephalopathy, seizures, strokes, or other acute neurologic deficits. Our objective was to describe the range of neurologic presentations in HUS and explore risk factors and outcomes in this patient population.
METHODS: We conducted a retrospective chart review of children aged up to 18 years old hospitalized at a single center between June 2018 and December 2022 with HUS. We defined neurologic complications as onset of any new neurologic symptom or condition, including seizures, stroke, CVST, PRES, encephalopathy, headaches, or new neurologic deficit. We excluded patients with preexisting neurologic, vascular, or coagulopathic diagnoses.
RESULTS: Fourteen of the sixty-eight patients with HUS developed neurologic complications. The most common complication was encephalopathy (9), followed by headache (5), generalized seizure (5), focal seizure (3), stroke (2), PRES (1), and other acute neurologic changes (3). Acute neurologic changes included abnormal movements (1), transient slurred speech with right facial droop (1), expressive and receptive aphasia (1), dizziness (1), and hallucinations (2). Eight patients had more than one neurologic complication.
CONCLUSIONS: In this study, the incidence of neurologic complications in pediatric patients with HUS was 20%. More than half (57%) of these patients had more than one neurologic complication. Additional data focusing on predisposing factors, neuroimaging, EEG, and functional outcomes could provide insight into prevention, acute treatment, and understanding long-term prognosis in patients with neurologic complication in HUS.
KEYWORDS: Neurocritical Care

208. Atypical Presentation of Pediatric Intracranial Abscess: Sudden Neurologic Deficits in an Infant

Andrea Kadima, Christy Daniel, Suzanne Strickland

OBJECTIVE: Background Pediatric intracranial abscesses are a rare but life-threatening condition that classically present as fever, headache and focal neurological signs. However, this triad may be absent in infants, and symptom presentation may vary, making careful clinical and diagnostic decision-making imperative.
METHODS: N/A
RESULTS: Case We present a case of a large intracranial abscess in a previously healthy 9-month-old male. He presented with one hour of altered consciousness, left facial twitching with left hemibody jerking which resolved after lorazepam. He returned to baseline within 10 minutes; however, had persistent left arm weakness at the time of neurological consultation. EEG revealed focal slowing and neuroimaging was recommended due to persistent weakness. MRI demonstrated a thick-walled rim-enhancing lesion measuring 3.8 $\times$ 3.1 $\times$ 3.8 cm within the right frontoparietal lobe with a 5.5 mm midline shift; mass effect and significant perilesional neovascularization were reported. The patient underwent emergent right burr hole drainage, and cultures grew Streptococcus pyogenes. He received treatment with intravenous ceftriaxone and metronidazole for 6 weeks and started levetiracetam for seizure prophylaxis.
CONCLUSIONS: Discussion Despite the significant size of the lesion, the patient remained largely asymptomatic until acute seizure and focal deficits developed. Prior literature suggests pediatric brain abscesses often present with fever and progressive neurologic symptoms, making this presentation atypical. This case highlights the importance of maintaining a high index of suspicion and obtaining prompt imaging in infants with new-onset seizures or continued focal deficits.
KEYWORDS: Neurocritical Care, Neuroimaging, Neuroinfectious Disease

209. Detecting Cognitive Motor Function in Children using Functional Near-Infrared Spectroscopy (fNIRS)

Stephanie Hassouneh, Anthony Zinos, Scott Beardsley, Raquel Farias-Moeller

OBJECTIVE: We aimed to develop a functional near-infrared spectroscopy (fNIRS) device that could ultimately be utilized in a pediatric critical-care setting to better phenotype consciousness. The first objective was to determine if our fNIRS device could reliably detect motor function in healthy children.
METHODS: We created an fNIRS device that is applied coronally. We recruited 20 typically developing children. The fNIRS device was placed on their head. We administered four task blocks and a rest period. Motor task required squeezing a ball repetitively. Focused motor imagery required imaging squeezing a ball. Diffuse motor imagery included imagining running. Somatosensory required a team member to scratch the surface of participant's palm. Rest task consisted of two minutes of rest with no prompted stimulus. Raw data was collected then converted to hemoglobin concentrations and analyzed to identify significance.
RESULTS: Individual channel responses over locations corresponding to tasks was identified as significant in all four task blocks with true positive rates of 94%, 83%, 83%, and 78% in motor, focused motor imagery, diffuse motor imagery, and somatosensory, respectively. Group block averages at the most significant channel amongst the participants was

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also significant in all four tasks. Rest block was used to identify false positives and showed a false positive rate of 11%.
CONCLUSIONS: Cognitive motor function can reliably be detected using our fNIRS prototype in children. Functional activity during motor imagery tasks was detectable at high rates. Motor imagery responses were spatially more variable than real motor tasks. This device can now be utilized in future consciousness research.
KEYWORDS: Neurocritical Care, Early Stage Investigator

210. When MOGAD Turns Malignant: A Fulminant Case of Bilateral Cortical Cytotoxic Edema

Claudia Francia, Nora Nikprelevic, Mikaela Camacho, Sayed Naqvi, Anuj Jayakar, Natanya Mishal

OBJECTIVE: We highlight a rare case with severe myelin oligodendrocyte glycoprotein (MOG)-IgG-associated cerebral cortical encephalitis (CCE) presenting as bilateral cytotoxic edema.
METHODS: Case Report
RESULTS: We present a 13 year-old male with prior ADEM who presented six years later with fever, headache, and encephalopathy after recent otitis media. Initial workup showed leukocytosis, CSF pleocytosis, negative infectious panel, and normal CT brain. He was treated empirically for meningitis vs. recurrent encephalomyelitis with antibiotics, IVIG and steroids. During his clinical course, he developed seizures and became obtunded. Repeat CT brain revealed diffuse cerebral edema and MRI brain revealed severe bilateral cortical edema with diffusion restriction, concerning for cytotoxic edema. He was intubated and treated with hyperosmolor therapy. CSF encephalitis panel returned negative. Serum MOG antibody returned positive (1:320). He received 5 sessions of PLEX, cyclophosphamide, and tocilizumab and was eventually extubated; however his overall neurological improvement was marginal.
CONCLUSIONS: MOG-IgG-associated cerebral cortical encephalitis is a rare but severe neurological presentation. Early recognition and MOG antibody testing are critical, as infectious studies are frequently negative. It presents clinically with fevers, seizures, encephalopathy, and bilateral cortical edema. Fulminant cases may progress to malignant cerebral edema. Aggressive immunotherapy with steroids, IVIG/PLEX and second-line agents are often required. Early treatment may improve outcomes, although prognosis depends on disease severity and relapse risk.
KEYWORDS: Neurocritical Care, Neuroimmunology, Pediatric Demyelinating Disease

211. Hyperactive Delirium as a Potential Trigger for Malignant Hemorrhagic Transformation in Pediatric Stroke: A Case Report and Call for Standardized Management

Maria Molinaro, Ryan Felling

OBJECTIVE: Post-stroke delirium (PSD) affects ~25% of patients and signals a poor prognosis. While documented in adults, pediatric data regarding PSD and secondary complications remain limited. Evidence suggests that hyperactive delirium-induced emotional outbursts can trigger sympathetic activation, raising blood pressure (BP) by 25–40%. In pediatric large-volume arterial ischemic stroke (AIS) under anticoagulation, these physiological spikes may trigger malignant hemorrhagic transformation (HT).
METHODS: -
RESULTS: A 14-year-old with steroid-dependent nephrotic syndrome presented with a right MCA infarction (proximal M1 occlusion). Following unsuccessful thrombectomy (TICI 0, NIHSS 17), aspirin was initiated. Therapeutic heparin began on day six, transitioning to enoxaparin on day nine. A post-anticoagulation MRI showed no HT. Delirium emerged on day four, requiring risperidone and restraints. Agitation became refractory to redirection, necessitating escalated analgesics and twice-daily risperidone by day eleven. On day thirteen, the patient developed severe agitation (BP 208/84, HR 175), followed by a focal seizure and pupillary nonreactivity. MRI revealed large hemorrhagic conversion with midline shift and herniation. Despite an emergency hemicraniectomy and a 49-day hospitalization, the patient was discharged with muteness, quadriparesis, and impaired command-following.
CONCLUSIONS: This case illustrates how hyperactive delirium-induced autonomic surges can trigger catastrophic secondary complications. It underscores the need for pediatric-specific guidelines for PSD identification and management. In large-volume infarcts requiring anticoagulation, rigorous delirium screening and aggressive intervention may be vital to preventing malignant HT and improving functional outcomes.
KEYWORDS: Neurocritical Care, Stroke, Behavioral Neurology

212. Recurrent Hypoxic Episodes as a Presenting Manifestation of COL4A1-Related Cerebral Vasculopathy in an Infant

Deniz Elbizim, Sarah Rehman, Jennifer Zuccaro

OBJECTIVE: COL4A1 mutations cause a rare cerebral small-vessel vasculopathy associated with intracranial hemorrhage, ocular abnormalities, and severe neurologic impairment. Respiratory instability and recurrent hypoxic episodes are increasingly recognized but underappreciated manifestations. We report an infant with a pathogenic COL4A1 mutation presenting with recurrent hypoxia and severe neurologic decline.
METHODS: We describe a 3-month-old female (born at 36 weeks' gestation) with a complex neonatal course including bilateral grade IV intraventricular hemorrhage, severe hydrocephalus, bronchopulmonary dysplasia requiring home oxygen, congenital cataracts status post repair, bilateral hydronephrosis, patent foramen ovale, and gastrostomy tube dependence. She was readmitted after recurrent hypoxic episodes following NICU discharge. Initial ED evaluation, including chest radiograph and respiratory viral panel, was unremarkable; however, persistent desaturations prompted hospital admission. Due to worsening clinical status, she was transferred to the PICU for further evaluation, including continuous EEG and brain MRI, along with genetic testing.

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RESULTS: The patient developed recurrent hypoxic episodes requiring escalation to intensive care, where EEG demonstrated subclinical status epilepticus with burst suppression and reduced cortical activity. MRI revealed extensive prior hemorrhagic injury with cystic encephalomalacia, porencephaly, and severe ventriculomegaly. Genetic testing confirmed a pathogenic COL4A1 mutation. Multidisciplinary discussions led to transition to comfort-focused care, and the patient subsequently died after DNR status was established.
CONCLUSIONS: COL4A1-related vasculopathy should be considered in infants with severe IVH and unexplained recurrent hypoxia. Neurologic dysfunction, including subclinical seizures and autonomic instability, likely contributes to respiratory failure. Early genetic diagnosis is critical for prognostication, guiding management, and informing timely goals-of-care discussions.
KEYWORDS: Neurocritical Care, Neurogenetics, Lifespan Manifestations of Childhood Onset Conditions

Neuro-Cutaneous Disorders

213. Case Series: The Presentation of Peripheral Nerve Sheath Tumors in Six Pediatric Patients without a Diagnosis of Neurofibromatosis Type 1 or Schwannomatosis

Tena Rosser, Rachelle Manookian, Nathan Robison, Ashley Margol, Anat Epstein

OBJECTIVE: Identification of a peripheral nerve sheath tumor raises concern for a diagnosis of neurofibromatosis type 1 (NF1) or schwannomatosis (SWN). However, *KRAS* and *ERBB2* pathogenic variants may also be associated with these lesions and with mosaic cases.
METHODS: Six patients with a nerve sheath tumor who had negative germline NF1 and SWN testing were identified in our institutional NF database. Their clinical presentations, radiographic findings and genetic testing results were reviewed.
RESULTS: An 11-year-old presented with a large café au lait spot across the lumbosacral region and progressive myelopathy due to a T11-12 paraspinal mass compressing the spinal cord. A variant of potential clinical significance in *KRAS* within the tumor and associated overlying hyperpigmented skin was identified. A 10-year-old presented with a myelopathy after a fall and a lobulated homogeneously enhancing extradural mass with T11-L1 intraspinal and extraspinal components was found. Genetic testing on the tumor revealed an in-frame duplication/insertion in *ERBB2*. A third patient was found to have innumerable enhancing lesions throughout the cervical and thoracic spine on neuroimaging as a young child. A *KRAS* variant at a variant allele consistent with a somatic mosaic *KRAS*-associated RASopathy was found after a cervical mass was resected. Three adolescents were found to have nerve sheath tumors of the brachial plexus with no diagnosis made.
CONCLUSIONS: These six pediatric cases illustrate that a variety of underlying pathogenic variants can be associated with nerve sheath tumors and with mosaic cases. Correctly identifying the genetic etiology is critical for management and possible medical treatment.
KEYWORDS: Neuro-Cutaneous Disorders

214. Steroids for Drug-Resistant Seizures and Prolonged Stroke-Like Episode in Sturge-Weber Syndrome: A Case Report and Retrospective Case Series Review

Fabiola Morales-Vias, Brenna Keam, Siddharth Gupta, Doris Lin, Anne Comi

OBJECTIVE: Sturge-Weber syndrome (SWS) is a rare neurovascular disorder characterized by capillary malformations in the brain, skin and eyes. SWS brain involvement is associated with blood-brain barrier (BBB) impairments and cortical microglial activation. Common neurological crises include prolonged episodes of seizures, stroke-like episodes, and headaches; we aimed to provide via case report, case ascertainment and medical record review, new data on high-dose steroids for prolonged neurologic crises in SWS.
METHODS: Case ascertainment and a medical record review conducted between 2019-2025 through Epic, identified 3 patients who were treated for neurologic symptoms with corticosteroids (IRB #NA_00043846).
RESULTS: A 13-year-old-male with known unilateral SWS involvement presented with fever, headache, seizures and right-sided hemiparesis. He was placed on continuous electroencephalogram that showed status epilepticus; his hospital course was complicated by refractory seizures. A follow up brain MRI demonstrated significantly increased leptomeningeal enhancement with associated gyral edema and sulcal effacement. After treatment with high-dose corticosteroids, he showed rapid marked improvement in hemiparesis and resolution of seizures. Medical record review identified 2 additional patients with prolonged SWS acute neurological crises in whom high-dose corticosteroid therapy was associated with return to baseline, although less clinical detail was available.
CONCLUSIONS: This case and small cohort, though limited by potential confounding factors, suggests a potential role for high-dose steroid therapy in patients with SWS who present with prolonged acute neurological crises. Their clinical improvement following high-dose corticosteroids supports the need for future clinical and preclinical research to validate this approach, and highlights the complex neuroinflammatory, BBB, and neurovascular mechanisms in SWS.
KEYWORDS: Neuro-Cutaneous Disorders, Stroke, Epilepsy

215. Activated mTOR Signaling Without Angiogenesis in an Infant with Congenital Hemangiomas: A p-S6–Positive Case Responding to Sirolimus

Laura Swanson, M. Luisa Iruela-Arispe, Tracy Gertler

OBJECTIVE: To share the case of a 7-month-old female with numerous craniofacial proliferative vascular lesions suspected congenital hemangiomas found to have a significant presence of phosphorylated ribosomal protein S6 (p-S6) via vascular staining of the lesion and a favorable response to sirolimus.

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METHODS: Given the location and aggressive nature of patient's vascular malformations, further diagnostic evaluation was performed with both lesional genetic testing and vascular staining as well as chromosomal microarray.
RESULTS: Patient underwent IR guided needle biopsy of her large intra-orbital lesion with histopathological findings consistent with a hemangioma. Notably GLUT-1 staining was negative, indicating congenital rather than infantile hemangiomas. Biopsied tissue was sent for the next generation sequencing somatic overgrowth panel, with no pathogenic mutation identified. Chromosomal microarray without copy number variants detected. Extended histological evaluation of the lesion with inflammatory, vascular, proliferative markers, proliferative markers as well as mTOR and STAT signaling was completed. GLUT-1 negative was confirmed. Delta-like ligand (Dll4), Ki-67, and ETS-related gene (ERG) were all negative, suggestive of a lack of angiogenesis or on-going vascular proliferation. There was also no evidence of increased inflammation with lack of STAT activation. Despite lack of evidence for vascular proliferation, phosphorylated ribosomal protein S6 production remained increased, indicating PI3K/Akt/mTOR pathway activation.
CONCLUSIONS: The above findings of increased production of pS6 suggest significant activation of the mTOR pathway despite no evidence of ongoing proliferation or angiogenesis. Given these findings, the patient was started on the mTOR-inhibitor sirolimus. Initiation of sirolimus resulted in near resolution of vascular proliferation.
KEYWORDS: Neuro-Cutaneous Disorders, Neurogenetics

216. Race representation in Tuberous Sclerosis care: A need for outreach or epidemiological reassessment?

Emily Walsh, Derek Bauer

OBJECTIVE: To understand Tuberous Sclerosis Complex (TSC) health care utilization and access across racial groups in a large academic center.
METHODS: SlicerDicer function within Epic EMR was utilized to retrospectively review patients with a diagnosis of TSC. Data was sliced to determine the proportion of patients self-identified as white or black. Comparison was made to patients receiving care through the Neurology Department and Epilepsy Center. Patients without identified race were excluded. Chi-Square analysis was performed to assess differences in proportions.
RESULTS: 143 TSC patients were identified from a total population of 3,220,831, resulting in estimated period prevalence of 4.44:100,000. Race was self-identified in 122 patients, with 114 (93.4%) identifying as white and 8 (6.6%) identifying as black. 494,007 patients had ≥1 visit with neurology. Race was self-identified in 440,274 patients. 378,677 (86%) identified as white and 61,597 (14%) identified as black. 40,654 patients had ≥1 visit with epilepsy. Race was self-identified in 36,260 patients. 31,530 (87%) identified as white and 4,730 (13%) identified as black. Chi-Square analysis revealed a significant difference in health care utilization for black patients with TSC compared to black patients receiving general neurology (6.6 vs 14%, p=.02) or epilepsy (6.6 vs 13%, p=.03) care.
CONCLUSIONS: TSC prevalence in this population resembles previous reports. Rates of epilepsy and general neurology care mirror Rochester metropolitan area's population demographics, however utilization of TSC care does not. Fewer black TSC patients received care, which was not accounted for by bottlenecking to subspecialty care, and reflects reports from multicenter databases.
KEYWORDS: Neuro-Cutaneous Disorders, Diversity, Equity, Inclusion

Neurodevelopmental Disorders

217. Tolerability of Leucovorin in Autism Spectrum Disorder in Clinical Practice

Sanjana Palakodeti, Mark Mintz, Madeline Chadehumbe

OBJECTIVE: To describe the clinical utility and tolerability of leucovorin in people with autism spectrum disorder (ASD)
METHODS: A retrospective review of medical records was conducted at a community-based neurology clinic specializing in autism lifespan care over five years (2020–2025). All patients prescribed leucovorin were included. Basic demographics and other details were extracted from records. Patients were considered lost to follow-up (LTFU) if no visits or refills occurred for ≥6 months. Reported benefits and side effects were based on subjective caregiver or patient reports.
RESULTS: Of 150 patients with confirmed leucovorin prescriptions, 144 initiated treatment; 126 with formal ASD diagnoses were analyzed. Mean age was 10.66 years; 96 were male and 30 female. Follow-up visits or refills were recorded for 121 patients, while 5 were LTFU. At last assessment, 99 continued leucovorin and 22 discontinued, including 3 without a recorded stop date. Discontinuation was attributed to lack of perceived benefit or side effects. Reported benefits included improved attention, speech, eye contact, social participation, and appetite. Side effects included hyperactivity, sleep disturbances, and irritability. Mean treatment duration was 254.18 days at analysis.
CONCLUSIONS: These findings should be interpreted cautiously as benefits were subjective but risks were minimal. Moreover, the American Academy of Pediatrics (AAP) and Child Neurology Society (CNS) emphasize that evidence is insufficient to support routine use of leucovorin for ASD, particularly in those with undocumented folate-pathway abnormalities. This underscores the need for well-designed, prospective randomized controlled trials with standardized outcomes to establish efficacy, safety, patient selection, and long-term impact before broader adoption.
KEYWORDS: Neurodevelopmental Disorders, Behavioral Neurology, Behavioral Neurology

218. In children with tuberous sclerosis complex, keratan sulfate proteoglycan defines transmantle dysplasias and adheres to dysplastic neurons and balloon cells

Harvey Sarnat, Weiming Yu, Laura Flores-Sarnat

OBJECTIVE: This study addresses cerebral keratan sulfate (KS) proteoglycan in tuberous sclerosis complex (TSC). Extracellular KS is secreted by astrocytes, but not radial glia..

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KS adheres to neuronal membranes except dendritic spines in normal fetal brain, repelling glutamatergic and facilitating GABAergic axons during synaptogenesis. KS forms a template for axonal fascicles and a nonstructural chemical pathway for tangential migratory neuroblasts without a structural scaffold such as radial glia. Pathogenesis of transmantle dysplasias in TSC also might involve KS.

METHODS: Surgical resections of epileptogenic cortical foci were performed in 4 children, ages 2-4 years, with TSC and refractory epilepsy, and 1 neonatal autopsy. Specimens included cortical tubers with adjacent cortex and white matter. Paraffin-embedded sections were prepared for multiple immunocytochemical neuronal and glial reactivities including KS.

RESULTS: Tubers, adjacent cortex, and subcortical heterotopia within transmantle dysplasias contained many megalocytic dysmorphic neurons and glial cells. Balloon cells were confirmed with vimentin, nestin and αBcrystallin. Dysmorphic and morphologically normal neurons and some balloon cells exhibited granular KS reactivity at their membranes. Some balloon cells exhibited cytoplasmic without surface membrane KS. Extracellular KS was demonstrated within transmantle dysplasias but not adjacent white matter. Cytoplasmic KS appeared in astrocytes but not neurons.

CONCLUSIONS: As with tangential migratory pathways, KS defines transmantle dysplasias from subventricular zone to base of cortical tubers and but continues postnatally and may be primary in their pathogenesis. KS also adheres to somatic membranes of megalocytic dysplastic neurons and some balloon cells in TSC, similar to normal neuronal adhesion.

KEYWORDS: Neurodevelopmental Disorders, Epilepsy, Fetal Neurology

219. Evaluating the effect of verbal skills on associations between social-communicative and adaptive functions in children with autism and ADHD

Celina Cerf, Alyssa DeRonda, Rachel Reetzke, Stewart Mostofsky

OBJECTIVE: The goal is to examine how language skills for individuals with ASD and ADHD impact associations between social-communicative and adaptive function. Symptoms of ADHD and ASD overlap, with underlying cognitive processes contributing to poor verbal skills, which can impact adaptive outcomes.[1] It remains unclear, in the context of autism and ADHD, how verbal skill mediate the impact of core autistic social communicative features on adaptive function.[2]

METHODS: Participants included children ages 8-12 years diagnosed with either ASD, ADHD, comorbid ASD + ADHD, or were typically developing (TD). The parent report Social Responsiveness Scale (SRS) social-communicative and related behavioral functions core to ASD; the Adaptive Behavior Assessment System-General Adaptive Composite (ABAS-GAC) assessed adaptive function. The Verbal Comprehension Index (VCI)s from the Wechsler Intelligence Scale for Children (WISC) was used to assess verbal skills. ANOVA evaluated group differences; mediation models evaluated the effect of verbal skills on the relationship between autism severity and adaptive functioning.

RESULTS: VCI significantly mediated the relationship between SRS and ABAS-GAC (0.002, 5.3%). Follow up analyses examining associations with specific ABAS subscales revealed the mediation effect of VCI was observed across several specific adaptive functions (social: <0.001, 5.88%; practical: 0.003, 7.47%; functional academics: <0.001, 16.5%, community use: 0.001, 9.08%).

CONCLUSIONS: Individuals with ASD and ASD +ADHD have the lowest performance across all verbal IQ measures. This suggests that autism is a predictor of lower verbal IQ scores with or without ADHD. Furthermore, language skills appear to significantly moderate associations of core ASD features with several adaptive outcomes, especially academic and social.

KEYWORDS: Neurodevelopmental Disorders

220. CSF Dynamics and Glymphatic Function in Down Syndrome-Associated Alzheimer's Disease: Implications for Pathogenesis and Biomarker Development

Jennifer Marte Jimenez, Gurjit Nagra

OBJECTIVE: Down syndrome (DS) is the most common genetic cause of Alzheimer's disease (AD), with near-universal amyloid pathology by age 40. While APP triplication on chromosome 21 drives amyloid accumulation, the contribution of CSF dynamics and glymphatic dysfunction to DS-associated AD (DS-AD) remains poorly characterized. This review examines convergent evidence implicating impaired brain waste clearance as an accelerant of DS-AD pathogenesis.

METHODS: A narrative literature synthesis was performed integrating findings from DS genetics, glymphatic biology, sleep medicine, neuroimaging, and astrocyte pathophysiology, drawing on key longitudinal cohort data and recently published primary studies.

RESULTS: Three converging mechanisms were identified. First, Pcp4 overexpression on the trisomic chromosome 21 segment causes ependymal ciliary dysfunction and ventriculomegaly, impairing CSF circulation from early development. Second, AQP4 water channels exhibit age-dependent mislocalization from astrocytic endfeet in DS frontal cortex, with expression positively correlated with amyloid burden. Third, obstructive sleep apnea — affecting up to 88% of DS adults — reduces sleep-dependent glymphatic clearance and upregulates amyloidogenic secretases. Neuroimaging further reveals enlarged perivascular spaces and cerebrovascular changes emerging in the early 30s, preceding amyloid and tau deposition. A "triple hit" model is proposed wherein these genetic, sleep-pathological, and molecular insults converge to accelerate amyloid accumulation beyond APP triplication alone.

CONCLUSIONS: Glymphatic dysfunction is a modifiable and underrecognized contributor to DS-AD. Priority interventions include OSA treatment, sleep optimization, and glymphatic-targeted therapies. Imaging biomarkers of glymphatic function should be integrated into future DS-AD longitudinal studies.

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KEYWORDS: Neurodevelopmental Disorders, Neuroimaging, Neurogenetics

221. A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of NNZ-2591 in Children With Phelan-McDermid Syndrome

Ann Neumeyer, Kimberly Farrand, Nancy Jones, Jessica Kardish, Liza Squires, Alexander Kolevzon

OBJECTIVE: Phelan-McDermid syndrome (PMS) is a rare neurodevelopmental disorder characterized by developmental delay, impaired communication, and intellectual disability. No therapies are currently approved to treat PMS. The investigational drug NNZ-2591 is a synthetic analog of cyclic glycine-proline that modulates insulin-like growth factor-1 bioavailability to restore synaptic function. In a 13-week (wk) phase 2 open-label study, NNZ-2591 treatment was well tolerated and associated with improvements in PMS symptoms. This phase 3 study will evaluate the efficacy and safety of NNZ-2591 vs placebo in children with PMS.
METHODS: This double-blind, placebo-controlled, multicenter study (NCT07281079) will enroll ~160 participants aged 3–12 years at screening with genetically confirmed PMS defined by *SHANK3* haploinsufficiency. Participants will be randomized 1:1 to NNZ-2591 or placebo for 13 wks. NNZ-2591 will be administered orally twice daily, with titration from 4mg/kg (wk1) to 8 mg/kg (wk2) to 12.5mg/kg thereafter for those weighing 10–49kg, and from 200mg (wk1) to 400mg (wk2) to 600mg thereafter for those ≥50kg. Key eligibility criteria include PMS Assessment of Severity score ≥3, controlled concomitant medications, and stable seizure management. Co-primary endpoints at wk 13 are the PMS Assessment of Change score and change from baseline on the Vineland Adaptive Behavior Scales-3 receptive communication subdomain raw score. The key secondary endpoint is Caregiver Impression of Change overall score at wk 13. Safety and tolerability will be assessed.
RESULTS: Enrollment is ongoing.
CONCLUSIONS: This phase 3 study will assess the efficacy and safety of NNZ-2591 and its potential to improve clinically relevant symptoms in children and adolescents with PMS.
KEYWORDS: Neurodevelopmental Disorders, Experimental Therapeutics

222. Real-World Utilization and Treatment Patterns of Trofinetide among Children Aged 2-4 with Rett Syndrome in the United States

Nazia Rashid, Vinod Yakkala, Krithika Rajagopalan

OBJECTIVE: To describe the real-world use and treatment patterns of trofinetide (TROF) among individuals with RETT syndrome (RTT) aged 2-4 years old in the United States.
METHODS: A retrospective cohort study was conducted using linked medical and pharmacy claims from 01/01/2021–09/30/2024. Individuals aged 2–4 years with RTT diagnosis who initiated TROF during 04/01/2023–03/31/2024 were included (index date=first TROF RX). Continuous enrollment of ≥6 months pre- and post-index was required. Outcomes included baseline characteristics, prescriber specialty, TROF persistence, dosing patterns, time on treatment, and restarts among non-persistent individuals. Continuous and categorical variables were summarized descriptively as means, SD, counts and percentages. Kaplan-Meier survival curve was assessed to evaluate time to treatment.
RESULTS: A total of 159 individuals aged 2-4 years at index were included: 65.4% (n=104) persistent and 34.6% (n=55) non-persistent; 14.5% (n=8) of non-persistent individuals restarted TROF. Mean (SD) age was 3.2 (0.8) vs 3.3 (0.7) years in persistent vs non-persistent groups. Females comprised 95.2% vs 87.3%, respectively. Child neurology was the most common prescriber specialty (54.8% vs 63.6%). Median (IQR) time on treatment was 13.3 (6.1–17.2) months for the persistent group and the Kaplan–Meier analysis showed >87.5% remained on TROF beyond 3 months.
CONCLUSIONS: Two-thirds of children aged 2–4 years initiating TROF remained persistent, with sustained use beyond 1 year and a subset restarting after discontinuation. These findings provide real-world evidence on TROF persistence and dosing patterns in this young RTT population.
KEYWORDS: Neurodevelopmental Disorders

223. Brain on Wheels: Advancing Pediatric Neurodevelopmental Care Through Mobile Clinics

Lyra Seaborn, Chaitanya Aduru, Madeleine Allocco, Madeleine Heliste, Mariana Carretero-Murillo, Allison Stephens, Mikael Guzman-Karlsson, Sarah Risen

OBJECTIVE: This study aims to assess barriers to accessing child neurology and neurodevelopmental disabilities (CN/NDD) care among underserved pediatric populations in Houston and evaluate the need and feasibility of integrating CN/NDD evaluations into a pre-existing pediatric mobile clinic program.
METHODS: A descriptive cross-sectional needs assessment was conducted among caregivers of children receiving pediatric care at pre-existing mobile clinics. Surveys assessed demographics, neurologic and developmental concerns, awareness and use of community resources, barriers to specialty care, and perceived usefulness of mobile CN/NDD services. Medical students administered in-person surveys in English and Spanish. Responses were entered into REDCap and analyzed using descriptive statistics. At analysis, 31 surveys were completed.
RESULTS: Among respondents (n=31), 81.5% of caregivers were born outside the U.S. and 70.4% identified as Hispanic or Latino, with most reporting annual incomes below $40,000. The most common barriers to care were cost (64.3%), transportation (57.1%), and immigration-related concerns (21.4%). Most caregivers indicated that integrating neurodevelopmental services within the mobile clinic would be helpful (63.0% extremely helpful, 33.3% very helpful), suggesting strong community interest in accessible, community-based specialty care.

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CONCLUSIONS: Families served by pediatric mobile clinics in Houston face significant barriers to pediatric neurology and neurodevelopmental care. Integrating CN/NDD services into mobile clinics may improve early identification and access to specialty evaluation for underserved pediatric populations.

KEYWORDS: Neurodevelopmental Disorders, Diversity, Equity, Inclusion

224. Adult and Pediatric Outcomes with Levacetylleucine in Niemann-Pick Disease Type C: 36-Month Data from the Phase 3 Trial Extension Phase

Marc Patterson, Kyriakos Martakis, Jorgji Kerthi, Bethany Zanrucha, Janelle Raymond, Taylor Fields, Ian Billington, Michael Strupp, Tatiana Bremova-Ertl

OBJECTIVE: Niemann-Pick disease type C (NPC) is a rare, autosomal-recessive lysosomal storage disorder. IB1001-301 is a Phase 3, double-blind, placebo-controlled, crossover trial encompassing a Parent Study and an ongoing Extension Phase (EP) evaluating the long-term effects of levacetylleucine (N-acetyl-L-leucine) in adults and children with NPC.

METHODS: Follow-up analysis of the EP was conducted to evaluate levacetylleucine treatment outcomes in adult (≥18 years) and pediatric (<18 years) participants with NPC. The primary endpoint of the EP is the modified 5-domain NPC Clinical Severity Scale (5-D-NPC-CSS). Exploratory endpoints include 15-domain and 4-domain NPC-CSS, and the Scale for the Assessment and Rating of Ataxia. Comparison was made to the expected annual trajectory of decline established in a natural history study.

RESULTS: Thirty-nine participants completed Visit 13 (36-months) of the EP, 22 adults and 17 pediatric participants. The mean (±SD) baseline score on the 5-D-NPC-CSS in the full participant cohort that completed 36 months' treatment was 10.38±4.46. After 36 months, full cohort mean (±SD) change from baseline in the 5-D-NPC-CSS was -0.28 ±2.76 with levacetylleucine vs +4.50±9.48 in the historical cohort; mean difference between the cohorts: -4.78; 95% CI, -7.96 to -1.61; P=0.0037. After 36 months, the mean (±SD) change from baseline in the 5-D-NPC-CSS was -0.18±2.32 in adults and -0.41±3.32 in pediatric participants. Exploratory endpoint findings are supportive with primary endpoint findings. Levacetylleucine was well tolerated, and no serious adverse events were reported.

CONCLUSIONS: Extended treatment with levacetylleucine resulted in clinically meaningful improvements in adult and pediatric participants, consistent with outcomes observed in the full cohort.

KEYWORDS: Neurodevelopmental Disorders, Neurogenetics

225. Integrating Multidisciplinary Medical Collaboration with Applied Behavior Analysis to Address Medically-Driven Challenging Behaviors in Autism Spectrum Disorder

Sanjana Palakodeti, Mark Mintz, Sandra Lewis, Adriana Neumann, Matan Mintz, Madeline Chadehumbe

OBJECTIVE: Children and adults with autism spectrum disorder (ASD) frequently present with medical comorbidities that influence behavioral presentation and response to intervention. These conditions are often underrecognized due to limited verbal abilities, resulting in severe behaviors driven by pain or discomfort. We describe an integrated, multidisciplinary model combining medical evaluation with Applied Behavior Analysis (ABA) to identify and treat medically driven challenging behaviors, and to clarify limitations of stand-alone behavioral interventions.

METHODS: This descriptive analysis examines an integrated care model implemented in Pennsylvania and New Jersey. The framework incorporates neurologists, developmental-behavioral pediatricians, psychiatric practitioners, neuropsychologists, psychologists, and ABA clinicians. Core components include interdisciplinary case conferences, physician consultation hours, shared electronic health records, and joint evaluations. Functional behavior assessments are paired with longitudinal, data-driven behavioral tracking using quantified metrics and graphical analyses. Clinicians review these data to assess behavioral function; deviations from expected patterns or lack of response to interventions prompt focused medical evaluation. This structure enables rapid interdisciplinary communication and iterative, real-time assessment of treatment impact.

RESULTS: Across five cases, severe behaviors resistant to conventional ABA (self-injury, tantrums, self-scratching, focal hitting, feeding difficulties) were linked to underlying conditions including cluster headaches, gastrointestinal disorders, and a dental abscess. Data-guided identification enabled targeted medical treatment, resulting in resolution or substantial reduction of behaviors.

CONCLUSIONS: Medically driven behaviors in ASD are underrecognized in fragmented systems, leading to ineffective care. This data-driven, integrated model improves diagnostic precision, enables timely medical inquiry, and rapid evaluation of outcomes. Broader implementation requires investment in care coordination, cross-disciplinary training, and reimbursement reform.

KEYWORDS: Neurodevelopmental Disorders, Behavioral Neurology, Behavioral Neurology

226. Use of a Digital Autism Diagnostic Application to Improve Efficiency of Autism Spectrum Disorder Diagnosis in Outpatient Developmental Pediatrics

Sinan Turnacioglu, Jenna Resnik, Rebecca Lane

OBJECTIVE: To evaluate the accuracy and clinical utility of a digital autism diagnostic application (Canvas Dx) when incorporated into an outpatient developmental pediatrics workflow.

METHODS: This quality improvement project assessed use of an FDA-authorized digital autism diagnostic application in an outpatient developmental pediatrics clinic. Children aged 18–72 months with caregiver or provider concern for developmental delay completed the assessment as part of routine clinical care. Diagnostic outputs were compared with specialist clinical diagnoses. Clinician and caregiver feedback was collected to assess usability and perceived efficiency.

RESULTS: A total of 28 children were included (mean age 52.2 months, SD 12.8; 25% female), with an autism

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prevalence of 67.9% (19/28) based on specialist diagnosis. The device generated a determinate result for 22 participants (78.6%). Among participants with determinate device results, sensitivity was 94.1% (95% CI 73.0–99.0) and specificity was 80.0% (95% CI 37.6–96.4%). Positive predictive value was 94.1% (95% CI 73.0–99.0), and negative predictive value was 80.0% (95% CI 37.6–96.4%), indicating strong agreement with specialist diagnostic determinations. Test accuracy and determinate result rates did not differ significantly by sex or race/ethnicity. 56% of participating families and 66.7% of providers completed the post-assessment feedback survey. Clinicians reported improved efficiency and insights during evaluation visits, and caregivers reported high satisfaction with the assessment process. Use of the tool supported timely diagnostic decision-making within routine outpatient workflows.

CONCLUSIONS: Incorporation of a digital autism diagnostic application into outpatient developmental pediatrics practice appears feasible and may improve diagnostic efficiency while maintaining diagnostic accuracy.

KEYWORDS: Neurodevelopmental Disorders

227. The Financial Impact of Down Syndrome Regression Disorder

Katherine Chow, Bryan Lei, Jonathan Santoro

OBJECTIVE: This study aimed to examine and quantify the annual economic impact of caregiving for individuals with Down Syndrome Regression Disorder (DSRD).

METHODS: In this cross-sectional study, caregivers completed a survey assessing multiple DSRD-related costs, including household expenses, caregiver health costs, employment impacts, and lost leisure time. Productivity changes were measured using the validated Work Productivity and Activity Impairment questionnaire. Data were analyzed using descriptive statistics, cost-of-illness analysis, and Spearman correlation.

RESULTS: 104 surveys were completed. The cohort was predominantly composed of female caregivers (94.1%). Individuals with DSRD had a median age of 22.0 years, symptom onset in late adolescence (mean 18.0 years), and mean disease duration of 28.4 months. Median grand total annual cost was $58,144 (mean $89,460), with 100% of caregivers incurring some cost. The greatest burden was indirect, with annual salary lost averaging $57,522 (SD $51,214). Total recurring out-of-pocket costs averaged $39,898 (SD $72,950), followed by total one-time costs at $12,899 (SD $30,978) and lost leisure time at $2,417 (SD $1,010). Grand total cost correlated significantly with DSRD duration ($\rho=0.222$, $p=0.023$), as did one-time ($\rho=0.205$, $p=0.037$) and recurring costs ($\rho=0.214$, $p=0.030$). Salary lost and leisure cost were not significantly associated with duration.

CONCLUSIONS: The financial burden of DSRD caregiving is substantial and multimodal, driven primarily by lost caregiver income. Direct costs increase with disease duration, reflecting growing management complexity, while income and leisure disruption occur early, consistent with symptom severity peaking near onset and subsequent family adaptation. These findings underscore the need for early caregiver support to reduce familial impact.

KEYWORDS: Neurodevelopmental Disorders

228. Beta-Propellor Protein-Associated Neurodegeneration (BPAN), a genetic cause of autism spectrum disorder: behavioral and developmental profile

Laura Adang, Vanessa Smith, Todd Levy, Anjana Sevagamoorthy, Nivedita Thakur, S. Russo, Samuel Pierce, Joseph Vithayathil, Isabella Barcelos, Sarah Woidill

OBJECTIVE: We sought to characterize the developmental-behavioral phenotype of Beta-Propellor Protein Associated Neurodegeneration (BPAN).

METHODS: Patients with molecularly confirmed BPAN were enrolled. Medical records were reviewed for medical events. Three trained providers administered the Childhood Autism Rating Scale (CARS-2), a 15-item battery, as a standardized measure of autism-related behavior as well as severity. Each CARS-2 item is assigned a score 1 to 4, with higher scores representing more abnormal behavior.

RESULTS: The study included 88 individuals with BPAN with a median age at diagnosis of 3.89 years [Inter-quartile range, IQR: 1.86, 6.52]. Early developmental delay was common (n=72 with available records): 18/72 (25%) of individuals never achieved independent ambulation, and 46/69 (66.7%) did not obtain two-word phrases. Among those who achieved these developmental milestones, delayed acquisition was also common, 72.2% for ambulation and 82.6% for two-word phrases. Of the 51 participants with data available, 41/51 (80.4%) of individuals experienced seizures with a median age of onset of 1.6 years [95% Confidence Interval (CI): 1.2, 2.1]. 39 individuals (76.5%) scored within the ASD range on the CARS-2, which was typically severe (61.5%, 24/39). The most impacted symptoms were verbal (mean score of 2.94; Standard deviation, SD 0.81) and non-verbal communication (mean 2.5; SD 0.69).

CONCLUSIONS: We found that children with BPAN have symptoms of Autism Spectrum Disorder and abnormal early development. A better understanding of the developmental-behavioral phenotype of this population can support better anticipatory guidance to families, the addition of targeted services to support their development and behavior, and inform future clinical trial design.

KEYWORDS: Neurodevelopmental Disorders, Neurogenetics, Behavioral Neurology

229. Resting-state functional brain network alterations and cognitive-behavioral associations in young children with autism and language impairment, Down syndrome, and Fragile X syndrome

Grace Kromm, Haerin Chung, Wenkang An, Meagan Tsou, Carol Wilkinson

OBJECTIVE: Atypical neural synchronization is a feature of many neurodevelopmental disorders, yet disorder-specific patterns of early brain functional connectivity (FC) remain poorly understood. We characterized EEG FC and cognitive-behavioral outcomes in young children (2–6 years) with

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autism spectrum disorder and language impairment (ASD-LI), Down syndrome (DS), and Fragile X syndrome (FXS) compared to typically developing (TD) peers.

METHODS: Continuous resting-state 128-channel EEG was collected across ASD-LI (N=38), DS (N=35), FXS (N=34), and TD (N=68). Global and regional FC were computed in theta (3–7 Hz), alpha (7–11 Hz), and high beta (25–35 Hz) bands as EEG coherence on current source density-transformed signals. Verbal and nonverbal developmental quotients (VDQ, NVDQ) and adaptive behavior composite standard scores (ABC SS) were derived. Linear mixed-effects models controlled for age and sex, with multiple comparison correction following significant omnibus effects ($p<0.05$).

RESULTS: Relative to age- and sex-matched TD, ASD-LI showed reduced global FC in theta and alpha, and DS showed reduced global FC in alpha. ASD-LI, DS, and FXS exhibited distinct regional patterns of hypo- and hyperconnectivity. Within DS, stronger language (VDQ) was associated with reduced global FC in all bands. Within FXS, stronger cognition (NVDQ) was associated with increased temporal–posterior FC in theta, and stronger adaptive behavior (ABC SS) was associated with reduced central–temporal FC in high beta.

CONCLUSIONS: We identify frequency- and region-specific alterations in functional brain network architecture across young children with ASD-LI, DS, and FXS. Network signatures in DS and FXS are associated with cognitive-behavioral outcomes, capturing early EEG biomarkers that may inform precision neurointervention targets.

KEYWORDS: Neurodevelopmental Disorders, Neuroimaging

230. Ecopipam—Evidence for Its Lack of Abuse Potential Based on Evaluation in an 8-Factor Analysis

Stephen Wanaski, Timothy Cunniff, George Karkanias, Sharon Smith, Jane Gosden, David Heal

OBJECTIVE: To evaluate the abuse potential of ecopipam, a selective dopamine D1 receptor (D1R) antagonist in development for Tourette syndrome (TS), using an 8-Factor Analysis.

METHODS: Chemical structure/pharmacological/nonclinical/clinical studies (published/unpublished) were reviewed. Evidence for Factor 1 (“actual or relative potential for abuse”) and Factor 7 (“psychic or physiological dependence liability”) is presented.

RESULTS: Ecopipam is not structurally related to any compounds scheduled under the Controlled Substances Act. Ecopipam exhibits >100-fold selectivity for D1Rs versus dopamine D2 receptors and has no pharmacologically/clinically relevant affinity for any other abuse-related molecular targets. Published nonclinical studies showed ecopipam competitively reduced the discriminative and reinforcing effects of cocaine. In individuals with a cocaine use disorder, ecopipam dose-dependently decreased the desire for cocaine and its subjective effects (eg, feeling “high”). A pooled analysis in healthy volunteers (N=253) identified somnolence, anxiety, and restlessness as the only adverse events (AEs) of interest related to abuse potential, occurring in >5% of ecopipam-treated individuals; high-level abuse signals (ie, euphoric mood, feeling drunk, feeling relaxed) each occurred only once. In individuals with TS (N=475), somnolence (9%) was the most frequent AE of interest, with single reports of psychomotor hyperactivity, visual hallucination, and auditory hallucination. Treatment discontinuation in individuals with TS did not produce any withdrawal symptoms indicative of physical/physiological dependence.

CONCLUSIONS: Nonclinical and clinical studies consistently showed that ecopipam reduced the psychoactive effects of abused stimulants. Results from ecopipam trials in healthy volunteers and individuals with TS complement these findings. Collectively, the evidence demonstrates that ecopipam has no meaningful potential for human abuse or dependence.

KEYWORDS: Neurodevelopmental Disorders, Movement Disorders, Experimental Therapeutics

231. Behavioral Clustering and Resting-state EEG signatures of Neurodevelopmental Profiles Using Machine Learning

Emmanuelle Coutu-Nadeau, Vardan Arutiunian, Charles-Olivier Martin, Valérie Fontaine, Anne-Marie Bélanger, Khadidje Jizi, Inga Sophia Knoth, Anthony Hosein, Saeideh Davoudi, Mayada Elsabbagh, Baudoin Forgeot D’Arc, Sebastien Jacquemont, Sarah Lippé

OBJECTIVE: ASD and ADHD show significant clinical heterogeneity and overlapping symptoms that challenge traditional diagnostic boundaries. This study adopted a transdiagnostic approach using unsupervised machine learning (ML) to identify data-driven behavioral profiles and determine if these clusters correlate more closely with neurophysiological biomarkers (EEG) than standard categorical diagnoses.

METHODS: We analyzed a multi-site sample (N=237; ages 4–18; 40.5% female) from the Q1K and Brain Canada cohorts (ASD, ADHD, comorbid, and neurotypical profiles). An unsupervised Self-Organizing Map (SOM) clustered participants based on five dimensions: social responsiveness, social cognition, social communication, ADHD traits, and non-verbal IQ. Subsequent EEG analysis compared clusters based on the Hurst exponent, Higuchi (complexity), and periodic power bands (delta, theta, alpha, beta, gamma).

RESULTS: The SOM identified four groups transcending categorical labels: Cluster 2 (N=85) was primarily neurotypical, Cluster 3 (N=49) was ADHD-dominant, and Clusters 1 (N=49) and 4 (N=54) were highly heterogeneous with no dominant diagnosis. EEG analysis validated these clusters, revealing significantly higher Hurst exponent values and increased periodic high-gamma power for Cluster 4 compared to Cluster 2 ($p < 0.05$), suggesting distinct underlying neural dynamics.

CONCLUSIONS: These findings demonstrate that behavioral profiling through ML reveals meaningful neurobiological differences that categorical labels overlook. This supports a shift toward personalized interventions based on a child’s specific symptomatic and physiological profile over traditional diagnostic labels.

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KEYWORDS: Neurodevelopmental Disorders, Behavioral Neurology, Neuroimaging

232. Size and breakpoint matter: clinical heterogeneity in males with terminal MECP2 duplications

Davut Pehlivan, Claudia Carvalho, Miguel Del Campo, Lynne Bird, Cary Fu, Sarika Peters, Jeffrey Neul, Seth Berger, John Harting, Jill Madden, Paymaan Jafar-nejad, Christine Coquery, Paul Malik

OBJECTIVE: MECP2 Duplication Syndrome (MDS) is a rare, X-linked neurodevelopmental disorder characterized by global developmental delay, severe intellectual disability, epilepsy, recurrent respiratory infections and early mortality. Duplications including the terminus of Xq are typically associated with a more severe phenotype and shorter survival. This case series evaluates an unexpectedly mild phenotype in 3 terminal duplication males from a prospective observational study (NH00006).

METHODS: NH00006 (NCT06014541) is a recently completed prospective observational study in males with MDS; 29 participants were enrolled and underwent genetic testing. Development and adaptive functioning were evaluated using standard scales (Vineland, Bayley). We validated observations from NH00006 using clinical, genomic and survival data from a separate MDS cohort at Baylor (Pehlivan et al. 2024; PMID 39696717).

RESULTS: Four out of 29 (13.8%) NH00006 participants were found to have terminal duplications, and 3 of those 4 had greater-than-expected cognition (16-27 months age-equivalent) with sustained ambulation after age 10. In contrast, no participants in NH00006 with simple/tandem duplications walked independently after age 10. The 3 higher-functioning participants had duplications with breakpoints distal to 151.8 Mb (hg19, duplication size < 3.4 Mb). These findings were reproduced in the Baylor registry, where independent walking was only observed for terminal duplication males when duplication size was < 3.4 Mb. Survival curves showed separation between terminal duplications ≥3.4 Mb and < 3.4 Mb. Translocation events were not explanatory.

CONCLUSIONS: Terminal *MECP2* duplications are further divided into two subgroups and smaller terminal duplications have a milder presentation. Breakpoint and duplication size have prognostic value in this group.

KEYWORDS: Neurodevelopmental Disorders, Neurogenetics, Lifespan Manifestations of Childhood Onset Conditions

233. Case Report of a Toddler with ODLURO Syndrome: A Rare Neurodevelopmental Disorder

Gregory Anash, Manisha Bandari, Yasemin Akinci, Andrew Liu, Savitra Bandari

OBJECTIVE: O'Donnell-Luria-Rodan (ODLURO) syndrome is a recently defined neurodevelopmental disorder (NDD) due to de novo or autosomal-dominant inherited heterozygous mutations in the N-methyltransferase 2E (KMT2E) gene on chromosome 7q22 (1,2). It is characterized by intellectual disability, autism spectrum disorder (ASD), epilepsy, macrocephaly, microcephaly, hypotonia, gastrointestinal abnormalities, and dysmorphic features (1-4). Here, we present a case of this rare condition to highlight the importance of awareness.

METHODS: This descriptive case study relied on a structured physical exam, diagnostic tests and imaging, and a literature analysis.

RESULTS: A 2-year-8-month-old male was referred for evaluation of macrocephaly and found to have dysmorphic facial features, hypotonia, gross motor development and speech delay, and level II ASD. Family history was positive for macrocephaly. Brain magnetic resonance imaging revealed supratentorial atrophy, including the corpus callosum and brainstem. A diagnosis of ODLURO syndrome was established based on clinical findings and whole-exome sequencing that identified a maternally inherited pathologic variant in KMT2E gene, specifically c.2904+2 a splice site variant which is predicted to result in an in-frame loss of the adjacent exon. The patient's mother was without any obvious symptoms.

CONCLUSIONS: Since the first publication, 80 patients with ODLURO syndrome have been reported, highlighting it as a common single-gene cause of NDD and ASD, though many cases remain undiagnosed. The disease has a variable presentation, with some individuals with mutations, especially parents, being asymptomatic or exhibiting very mild symptoms. Improved recognition is likely to enhance accurate diagnoses, allowing early intervention and family planning options through prenatal and preimplantation genetic testing.

KEYWORDS: Neurodevelopmental Disorders, Neurogenetics, Behavioral Neurology

234. Real-World Benefits and Tolerability of Trofinetide in Rett Syndrome Patients Categorized as Atypical, Males, and Adults: the LOTUS Study

Veeral Gohil, Mubeen Rafay, Arthur Beisang, Jenny Downs, Loan Robinson, Louise Cosand, Ryan Bucco

OBJECTIVE: Trofinetide is approved for the treatment of Rett syndrome (RTT) in patients aged ≥2 years in the US. The trofinetide phase 3 clinical trial program enrolled female patients, aged 5-20 years, with classical RTT. Here we report the real-world benefits and tolerability of trofinetide in patients with atypical RTT, male patients with RTT, and adult patients (aged ≥20 years) with RTT.

METHODS: LOTUS is an ongoing, prospective study of patients with RTT prescribed trofinetide in real-world clinical practice. Caregivers of patients who are prescribed trofinetide under routine clinical care are eligible to participate. Assessments include the Behavioral Improvement Questionnaire, the Quality-of-Life Inventory-Disability Questionnaire, and the Gastrointestinal Health Questionnaire. Data are reported to 12 months since the initiation of trofinetide.

RESULTS: Overall, 227 patients were included in this follow-up; 56 patients had atypical RTT, 7 patients were male, and 77 patients were adults aged ≥20 years. In all groups, clinicians tended to individualize trofinetide dosing.

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Across all groups at any given time point, at least 70% of caregivers reported improvements in the symptoms of RTT since trofinetide initiation. The most common behavioral improvements in all populations were nonverbal communication, alertness, and social interaction/connectedness. Modest improvements in all patients' quality of life were reported. Caregivers mostly reported formed/normal stools or diarrhea contained inside the diaper throughout the follow-up for all patients.
CONCLUSIONS: The real-world benefits and tolerability of trofinetide in subpopulations of LOTUS not included in the phase 3 trofinetide clinical program followed similar trends to the overall LOTUS study population.
KEYWORDS: Neurodevelopmental Disorders

235. In-depth analyses of cognition, motor, communication, and adaptive natural history disease course in participants with MPSIIIB

Ilyas Okur, Fatih Ezgu, Yin-Hsiu Chien, Cara O'Neill, Roberto GIUGLIANI, Can Ficicioglu, Igor Nestrasil, Irene Chang, Elizabeth Jalazo, Martha Solano, Saba Sile, Richard Kim, Kirk Ways, Nicole Muschol

OBJECTIVE: MPS IIIB is an ultra-rare genetic disease characterized by a deficiency of the NAcetyl-Alpha-Glucosaminidase (NAGLU) enzyme resulting in the accumulation of glycosaminoglycans (GAGs) and impaired neurodevelopment. Urinary GAGs, cognitive functions, and adaptive skills were assessed in a prospective, long-term, longitudinal natural history study in non-attenuated MPS IIIB patients (NCT03227042).
METHODS: Participants up to 18 years of age with deficient NAGLU activity underwent urinary GAG determination. Bayley's Scale of Infant and Toddler Development-III (BSID-III), Vineland Adaptive Behavior Scale-II (VABS-II), Sanfilippo Behavioral Rating Scales, Children's Sleep Habits Questionnaire, Infant Toddler Quality of Life questionnaire (ITQOL) and PedsQL Family Impact Module were assessed over 5 years
RESULTS: At baseline (N=41), mean age was 6.82 years, 53.7%male, and 26.8% Hispanic or Latino. BSID-III cognition, gross motor, and receptive communication age-equivalent (AEq) were 1.14, 1.45 and 0.75 years, respectively. VABS-II was AEq 1.29 years and urine GAG/Creatinine 8.9 mg/mmol/creatinine. BSID-III cognition AEq increased to 1.1 years at week 72, plateaued between 46 to 72 months of age, and declined from 72 to 96 months to an AEq nadir of 12 months. BSID-III motor and communication domains and VABS-II composite and socialization, motor and daily living domains followed similar age-dependent trajectories as did cognition. Changes from baseline in cognition and VABS-II scores were highly correlated. Other than responses to ITQOL, none of the questionnaire responses showed the same age-dependent trajectories as did cognition. Urine GAG/Creatinine levels remained relatively constant.
CONCLUSIONS: These findings highlight the urgency for earlier recognition, diagnosis, and need for treatment.
KEYWORDS: Neurodevelopmental Disorders, Lifespan Manifestations of Childhood Onset Conditions, Neurometabolic

236. Barriers to Genetic Testing in Children With Autism Spectrum Disorder

Minaal Zahid, Nicol Awadalla-Bacon, Naterra Walker, Sinan Turnacioglu, Davut Pehlivan

OBJECTIVE: Despite American College of Medical Genetics and Genomics and American Academy of Pediatrics recommendations for genetic testing in all children with autism spectrum disorder (ASD), completion rates remain low, and where families fall out of the testing pathway is not well studied. This study aimed to identify modifiable points of failure in the genetic testing pipeline for children with ASD.
METHODS: This study was conducted via cross-sectional survey of 81 caregivers across multiple neurodevelopmental clinics of a tertiary care center. We analyzed referral-to-completion rates and patient-reported barriers. Stakeholder interviews with policy makers, clinical faculty, advocacy group leaders, and laboratory representatives provided systems-level context.
RESULTS: Only 28% of all surveyed children completed genetic testing. Three sequential gaps emerged: 27% were never offered testing; 44% of referred families never obtained a genetics appointment; 30% of those seen and recommended testing did not complete it due to insurance denials, lost kits, or communication failure. Stakeholder interviews revealed no centralized referral pathway or tracking, a payer philosophy questioning the value of genetic testing in ASD, and underutilized resources like in-office sample collection that could bypass logistical failures. Despite these barriers, 65% of caregivers reported that genetic testing would or has helped them better understand their child's health.
CONCLUSIONS: The genetic testing pipeline in children with ASD fails at three modifiable points: provider referral, referral navigation, and testing logistics. Targeted interventions at each gap such as provider education, centralized referrals and tracking, payer advocacy, and in-office collection offer a roadmap to improve diagnostic equity for children with ASD.
KEYWORDS: Neurodevelopmental Disorders

237. Epilepsy as a Comorbidity with Autism Spectrum Disorder

Sailaja Golla, Mary Pionk, Hitha Amin, Jonathan Megerian, Elissa Kaustinen

OBJECTIVE: To explore the prevalence, clinical implications, and impact on quality of life of epilepsy as a comorbid condition in individuals with Autism Spectrum Disorder(ASD), and to identify potential shared etiological mechanisms and therapeutic considerations.
METHODS: A review of recent literature and clinical studies was conducted, focusing on epidemiological data, neurobiological mechanisms, and quality of life assessments in patients diagnosed with both ASD and epilepsy. Studies included retrospective cohort analyses, meta-analyses, and clinical phenotype investigations.
RESULTS: •Epilepsy occurs in ~20–30% of individuals with ASD; prevalence rises from childhood to adolescence/adulthood. •Risk strongly correlates with cognitive level: ~40% (severe ID), ~24% (moderate ID), ~8–12% (no ID). •Bimodal peak: early childhood (2–5 years) and adolescence (10–15 years). •Common seizure types: focal

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(40–60%), generalized tonic–clonic(20–30%), absence (10–20%); infantile spasms ~6–8%. •EEG abnormalities present in up to ~60% of ASD even without clinical seizures.
CONCLUSIONS: The co-occurrence of epilepsy and ASD necessitates integrated diagnostic and therapeutic approaches. Early identification and tailored interventions can improve outcomes and quality of life. Further research into shared pathophysiological mechanisms may inform future treatment strategies and enhance clinical care for affected individuals.
KEYWORDS: Neurodevelopmental Disorders, Epilepsy

238. Design of a Pediatric Low Motor Function Item Battery in Leukodystrophies

Francesco Gavazzi, Sarah Woidill, Anjana Sevagamoorthy, Abbas Jawad, Russell D'Aiello, Jamie Bradford, Miriam Lerner, Peter Hong, Aaliyah White, Zarrin Tashnim, Stacy Cusack, Allan Glanzman, Ann Harrington, Amy Waldman, Adeline Vanderver, Laura Adang

OBJECTIVE: Leukodystrophies are rare genetic disorders disrupting myelin in the central nervous system, causing neuromotor impairment. Standard tools like Gross Motor Function Measure-88 (GMFM-88) focus on higher-level skills, lacking sensitivity for early developmental skills. In populations with limited gross motor skills, sensitive assessments are needed to detect motor changes across the spectrum.
METHODS: This study describes the development and preliminary evaluation of the Pediatric Low Motor Function Item Battery (P-LoMo), designed to extend sensitivity into the lowest ranges of ability. Items were selected from validated assessments, including the Test of Infant Motor Performance, the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, the Bayley Scales of Infant and Toddler Development-4th Edition, the Mullen Scales of Early Learning, and the Early Clinical Assessment of Balance, through expert consensus.
RESULTS: The P-LoMo and the GMFM-88 were administered to 168 leukodystrophy patients. Median GMFM-88 performance was 17.5%, with a skew to low performance (52% of scores within the bottom 20%). The P-LoMo median score was 71 out of 84 potential points. There was a strong correlation between assessments (Spearman's R=0.94, p<0.0001) across the total cohort as well as among individuals in the lowest register of performance on the GMFM-88 (Spearman's R=0.90, p<0.0001).
CONCLUSIONS: The P-LoMo can enhance capturing neurologic function in children with leukodystrophies and severe motor impairments. It offers a sensitive, feasible, caregiver-aligned outcome assessment, potentially improving trial readiness, functional measurement, and therapy evaluation in low motor function pediatric populations.
KEYWORDS: Neurodevelopmental Disorders

239. Diagnostic Accuracy of an Autism Screening Questionnaire Compared with ADOS: An Age-Stratified Analysis

Ram Kairam, VIJAYA DEEPIKA INTI

OBJECTIVE: To evaluate the utility of an Autism Screening Questionnaire based on the Childhood Autism Rating Scale (CARS) by comparing it with ADOS, with a focus on age-related variation.
METHODS: In this diagnostic accuracy study, all participants completed both the screening questionnaire and the ADOS assessment. Participants were stratified into children under 4 years and those aged 4 years or older. Positive predictive value (PPV) was calculated, and false-positive and false-negative results were analyzed by age.
RESULTS: Among participants who screened positive, 312 were confirmed by ADOS, yielding a positive predictive value of 78.9%. Age-stratified analysis showed that 67.6% of ADOS-positive cases were children under 4 years, compared with 32.3% in those aged 4 years or older. Among ADOS-negative cases (n = 83), 39.8% (33/83) were under 4 years and 60.2% (50/83) were 4 years or older, suggesting variation in screening performance by age.
CONCLUSIONS: The autism screening questionnaire demonstrates good overall predictive value, particularly in children under 4 years of age. Age-related differences highlight the need for cautious interpretation of screening results, especially in older children. Incorporating age-specific considerations may enhance the clinical utility of screening tools and support earlier and more accurate identification of ASD.
KEYWORDS: Neurodevelopmental Disorders

240. Neurodevelopmental Outcomes Following Prenatal SARS-CoV-2 Exposure: The Role of Caregiver Stress and Mental Health

Malavika Mahendran, Manuela Iglesias, Daniella McCausland, Heather Gordish-Dressman, Lora Jackle, Jessica Harkness, Robin Baker, George Maxwell, Gianluca Ursini, Sarah Mulkey

OBJECTIVE: To describe how caregiver stress and mental health influence neurodevelopmental outcomes in children with prenatal SARS-CoV-2 exposure.
METHODS: 130 parent-child dyads with laboratory-confirmed or self-reported SARS-CoV-2 infection during pregnancy were prospectively enrolled. Child neurodevelopment was evaluated at 24-42 months of age using the Bayley Scales of Infant and Toddler Development (BSID-III). Caregiver stress and mental health were assessed using the Depression, Anxiety, and Stress Scale (DASS-21), COVID-19 Exposure and Family Impact Scales (CEFIS), WHO Disability Assessment Schedule (WHODAS), and Parenting Stress Index (PSI-4). Spearman correlations were performed for non-normally distributed data.
RESULTS: Most caregivers who completed questionnaires (96.6%) were mothers. Median (IQR) BSID-III percentile scores were 37 (25) for cognition, 27 (45) for language, and 50 (24) for motor function. Lower language scores were associated with greater exposure to traumatic events (r_s=-0.22, p=0.048) and family stress (r_s=-0.25, p=0.02) due to the pandemic, and higher caregiver anxiety related to the child's behavior problems (r_s=-0.19, p=0.047). Cognitive scores were positively correlated with caregiver anxiety (r_s=0.23, p=0.03), stress (r_s=0.26, p=0.01), and disability (r_s=0.29, p=0.02). Motor scores were positively correlated with caregiver depression (r_s=0.22, p=0.04), anxiety (r_s=0.26,

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p=0.01), stress (r_s=0.22, p=0.03), and disability (r_s=0.27, p=0.03).

CONCLUSIONS: Higher child neurodevelopmental scores were associated with lower parenting stress and family stress related to the pandemic, yet with poorer caregiver mental health. Neurodevelopment in children with prenatal SARS-CoV-2 exposure may be affected by home factors such as caregiver stress and mental health, and vice versa, but additional unmeasured factors likely contribute to this relationship.

KEYWORDS: Neurodevelopmental Disorders, Behavioral Neurology

241. Family Impact of Adult Angelman Syndrome: Caregiver Perspectives

Abigail Lore, Heidi Blackburn, Daphne Davis, Pia Manzi, Lesley McCullough McCallister, Theresa Parenteau, Sally Sansom, Robin Wilkerson, Manpreet Sidhu

OBJECTIVE: Angelman syndrome (AS) is a rare neurodevelopmental disorder characterized by severe cognitive/speech impairment, sleep disorders, motor dysfunction, and hyperactivity/noncompliance. There are no approved therapies for AS. This study aimed to characterize the impact caring for a person with AS into adulthood has on caregivers and family members.

METHODS: Seven current and future caregivers were recruited globally for individual, one-hour interviews.

RESULTS: Five parents and two siblings of adults with AS (18-37 years old) were interviewed. Caregivers reported that individuals with AS require constant supervision and support for basic activities of daily living. Sleep disturbances, communication issues, anxiety, and limited ambulation were noted as difficult symptoms to manage. A majority of caregivers described leaving the workforce to care for their child with AS, limiting earning potential. Most caregivers who discontinued gainful employment outside the home never returned to the workforce. Caregivers of adults with AS must facilitate transition from pediatric to adult healthcare providers, make financial and medico-legal arrangements, and find day habilitation programs to replace school. Many facilities for adults closed during the COVID-19 pandemic and never reopened, impacting nearly all caregivers. Most individuals with AS were covered under a complex combination of government-funded programs and private insurance that varied from state to state within the U.S. and from country to country outside the U.S.

CONCLUSIONS: Caregivers of individuals with AS reported substantial and persistent caregiving burden that extends across the lifespan of an individual with AS and impacts all aspects of family life.

KEYWORDS: Neurodevelopmental Disorders

242. Dissociation Between Tone Perception and Production in Mandarin-Speaking Taiwanese Children with Neurodevelopmental Disorders

Jung Chieh Du, Suk Yin Ho, Jung Yueh Tu

OBJECTIVE: Language abnormalities in neurodevelopmental disorders (NDDs) are often attributed to global deficits, yet tone processing in Mandarin remains underexplored. We aimed to delineate whether tone perception and production differ across NDD subtypes and to identify underlying neurocognitive mechanisms relevant to clinical practice.

METHODS: We conducted a cross-sectional study of 46 Mandarin-speaking children (26 NDD; 20 typically developing [TD]; mean age 8.4 years). NDD diagnoses included ADHD, tic disorders/Tourette syndrome (TD/TS), autism spectrum disorder, and learning disorders. Participants completed three Paradigm-based tasks: tone discrimination, tone identification (mono- and disyllabic), and tone production. Accuracy and reaction time (RT) were analyzed, with tone production rated by trained linguists. Nonparametric statistics and correlation analyses were applied.

RESULTS: Tone perception accuracy and RT did not differ significantly between NDD and TD groups. In contrast, tone production revealed subtype-specific abnormalities: TD/TS showed significantly elevated error rates (33∼42%), whereas ADHD showed lower error rates (7∼14%). ADHD participants demonstrated increased fast-response bias and a pronounced speed–accuracy tradeoff, consistent with impaired response regulation. TD/TS participants exhibited greater RT variability and absence of syllable position effects, suggesting unstable motor–cognitive coupling. Across all groups, age positively correlated with accuracy and inversely with RT, confirming developmental maturation.

CONCLUSIONS: Tone perception is relatively preserved in NDDs, but tone production deficits are selectively prominent in TD/TS. ADHD-related differences reflect regulatory control rather than phonological impairment. These findings challenge deficit-based models and support a mechanism-based framework distinguishing "regulatory" versus "stability" dysfunctions. Clinically, this paradigm may refine language assessment and guide targeted interventions in pediatric neurology.

KEYWORDS: Neurodevelopmental Disorders, Behavioral Neurology, Early Stage Investigator

243. Intravenous and Intrathecal Onasemnogene Abeparvovec for Presymptomatic and Symptomatic Spinal Muscular Atrophy: Long-Term Follow-Up

Anne Connolly, Michelle Farrar, Eugenio Mercuri, Kevin Strauss, John Day, Yin-Hsiu Chien, Riccardo Masson, Roberto Bernardo Escudero, Iulian Alecu, Nigel Dodd, Lesa Mehl, Basil Darras

OBJECTIVE: In clinical trials, intravenous (IV) or intrathecal (IT) onasemnogene abeparvovec (OA) safety and efficacy were demonstrated. LT-002 evaluates the long-term safety and efficacy of OA.

METHODS: Long-term safety was assessed by medical history/record review, serious adverse events (SAEs), adverse events of special interest (AESI), physical/laboratory evaluations, pulmonary/cardiac analyses. Efficacy was assessed by developmental motor milestones and HFMSE (change from baseline).

RESULTS: As of June 30, 2025, 86 patients (IV, n=68; IT, n=18) were enrolled (mean [range] follow-up: IV, 6.3 [2.8–

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7.7]; IT, 5.7 [2.9–7.4] years). 82 patients (95.3%) were alive without permanent ventilation; three in the symptomatic IV cohort required permanent ventilation. Most frequently reported AE (>10%) was pneumonia. AESI included hepatotoxicity (n=2), new incidence of neurologic disorders (n=6; tremor, balance disorder, hypotonia, seizure, migraine), and new incidence of autoimmune disorders (n=1; seasonal allergy). None were considered related to OA. New motor milestones were achieved in LT-002 (presymptomatic IV, 23.1%; symptomatic IV, 53.7%; IT, 38.9%). Mean improvements from baseline HFMSE were 9.1 (range –5 to 36) and 5.7 (range –5 to 34) points in the IV and IT cohorts, respectively. No patient required invasive ventilatory support; most did not require any ventilatory support as of last visit (presymptomatic IV, 96.2%; symptomatic IV, 48.8%; IT, 83.3%). Most patients did not require feeding support at data cutoff (presymptomatic IV, 96.2%; symptomatic IV, 78.0%; IT, 100%).

CONCLUSIONS: OA demonstrated efficacy with no new safety signals for up to 7.7 and 7.4 years post-dose in the IV and IT cohorts, respectively.

KEYWORDS: Neurodevelopmental Disorders, Neuromuscular, Movement Disorders

244. Functional abilities in a POLR3-related disorders cohort: a step towards clinical trial readiness

Francesco Gavazzi, Miriam Lerner, Sarah Woidill, Anjana Sevagamoorthy, Giulia Porcari, Russell D'Aiello, Adamo Ghezzo, Adam Le, Laura Lentini, Monica Chan, Chi-Lan Tran, Nicole Grant, Elizabeth Ballance, Jamie Bradford, Jessica Costagliola, Tracy Kornafel, Emma McKenzie, Lindsay Busarello, Stacy Cusack, Michelle Fitzgerald, Ann Harrington, Nicole Wolf, Davide Tonduti, Laura Adang, Adeline Vanderver, Geneviève Bernard

OBJECTIVE: POLR3-related disorders are a rare group of disorders characterized by dental anomalies, hypogonadotropic hypogonadism, and neurological impairment. Despite advances in therapeutic development, no standardized clinical outcome assessments (COAs) have been validated for this population. We hypothesized that established pediatric COAs capturing motor, cognitive, and adaptive functioning would be feasible and informative across this heterogeneous disease spectrum.

METHODS: Four COAs [Gross Motor Function Measure-88 (GMFM-88), Peabody Developmental Motor Scale-2 (PDMS-2), Leiter-3, and Vineland Adaptive Behavior Scale-3 (VABS-3)], selected via expert consensus were administered to 71 individuals (age range 0.82-48.1 years) with molecularly confirmed POLR3-related disorder, enrolled in IRB-approved registries. Performance was summarized using descriptive statistics and compared using Spearman correlations, Wilcoxon rank-sum tests, and linear mixed-effects models .

RESULTS: All four COAs were successfully administered (median age 10.8 years, IQR 6.7-19.5). Gross motor performance (n=60) was highly variable (median GMFM-88 68.5%, IQR 44.5–90.9) and age-independent (r=0.08, p=0.56), with deficits in single-leg and static balance. Fine motor skills (n=32) were relatively preserved [median Grasping 47.5 (IQR 42-51) and VMI 126 (IQR 101–137)], and correlated moderately with age (r=0.50, p=0.003). Nonverbal IQ (n=28) had a median of 70.5 (IQR 59-93.8) with no failed administrations, and declined with age (r=-0.64, p=0.0002). Adaptive functioning (n=49) was most impaired in motor domain (mean 64.3) relative to Socialization (mean 76.1) and Communication (mean 69.4).

CONCLUSIONS: These COAs are feasible and capture heterogeneous functional profiles in POLR3-related disorders. Longitudinal studies are needed to establish responsiveness and meaningful change thresholds for clinical trial readiness.

KEYWORDS: Neurodevelopmental Disorders

245. Clinical Characterization and Disease Trajectory in EPRS1-Related Disorder

Alexandra Chapleau, Reza Maroofian, Mahi Zaki, Anne-Michèle Laperriere, Luis Alejandro Rodriguez Torres, Felipe Villa Tobon, Stephanie Efthymiou, Wolfgang Köhler, Hanna Mierzewska, Marcelo Kauffman, Vernet Machado Matheus, Vincent Michaud, Aboulfazl Rad, Anju Shukla, Mariko Bennett, Henry Houlden, Geneviève Bernard

OBJECTIVE: EPRS1-related disorder (EPRS1-RD) is an ultra-rare neurodevelopmental disorder (NDD) caused by biallelic pathogenic variants in *EPRS1* encoding an aminoacyl-tRNA synthetase (aaRS) responsible for proline and glutamate tRNA charging. EPRS1-RD has an expanding clinical spectrum, including hypomyelinating leukodystrophy (HLD), early-onset epileptic encephalopathy (EOEE), and a milder NDD. Emerging evidence in ARS-RD suggests amino acid supplementation and ISR modulation may provide therapeutic benefit. However, the natural history of EPRS1-RD remains poorly defined, hindering clinical management and trial readiness. This study aims to characterize its clinical trajectory.

METHODS: We assembled an international cohort of >30 individuals with genetically confirmed EPRS1-RD (HLD n=20; EOEE n=5; NDD n=5). Data were retrospectively extracted from medical records and included developmental milestones, functional scores, time-to-event outcomes, and survival.

RESULTS: Median age of onset was 1 year (range: birth-14y), with presenting features of developmental delay or regression, and/or epilepsy (EOEE). Age of onset correlated with disease severity. Developmental trajectory correlated with disease subtype: no EOEE patients achieved independent ambulation, whereas all NDD patients did (mean 2.25y, median 2y). In HLD, 30% never walked, and those who did walked at a mean age of 1.76y (median 1.5y). Among the ambulatory HLD group, 50% lost ambulation by age 10, while all with NDD retained independent/assistive ambulation. Four (4/20) individuals with HLD have died (mean 12.5y, median 9y), whereas no EOEE cases have died to date, likely reflecting that all are currently very young (<2y).

CONCLUSIONS: Better characterization of EPRS1-RD and its subtypes will improve clinical management, guide targeted interventions, and support future therapeutic trials.

KEYWORDS: Neurodevelopmental Disorders, Neurogenetics

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246. Corticostriatal Microstructure Relates to Fine Motor Function in Autism: Diagnosis-Dependent Brain-Behavior Associations

Monica Duran, Jose Guerrero-Gonzalez, Nagesh Adluru, Doug Dean, Greg Kirk, Andy Alexander, Brittany Travers

OBJECTIVE: Fine motor challenges are highly prevalent in autism and are linked to functional outcomes. Corticostriatal pathways, connecting cortical motor-cognitive regions with the striatum, play a key role in refining fine movements and represent a promising system for understanding motor function in autism. Here, we examined associations between fine motor performance and corticostriatal white matter microstructure in autistic and non-autistic children.

METHODS: Participants included 40 autistic and 40 non-autistic children (ages 6-11). Fine motor ability was assessed using the BOT-2. Diffusion MRI data were acquired (3T). White matter microstructure was assessed using fractional anisotropy (FA), proxy of tissue integrity. FA was examined across three corticostriatal pathways (prefrontal, premotor, and primary motor) segmented with TractSeg. Group differences and brain-behavior relationships were evaluated using general linear models.

RESULTS: Autistic children demonstrated lower fine motor performance than non-autistic children ($d = 1.36$, $p < 0.001$). Small but consistent reductions in FA were observed in the autistic group across pathways ($d = 0.40$–0.44, all $p < 0.05$), without tract-specific effects. In non-autistic children, higher FA was associated with better motor performance ($r = 0.32$, $p < 0.05$), whereas this relationship was absent in autistic children.

CONCLUSIONS: Despite modest group differences in white matter microstructure, brain–behavior relationships differed across groups. These findings suggest that fine motor function may rely on distinct neural mechanisms in autism, highlighting differences in how brain structure relates to behavior. Understanding the systems underlying motor differences is critical for expanding our understanding of the neurobiology of autism.

KEYWORDS: Neurodevelopmental Disorders, Neuroimaging, Behavioral Neurology

247. Reduction in frequency of all-cause hospitalizations from the ION373-CS1 clinical trial of zilganersen in the treatment of individuals with Alexander disease

Steven Kymes, Montserrat Vera-Llonch, Chen Chen, Amy Waldman, Norma Ruiz-Santiago, Abigail Collins

OBJECTIVE: Alexander disease (AxD) is a rare, genetic, progressive astrocytopathy. Zilganersen is an investigational antisense oligonucleotide evaluated for treatment of people living with AxD. Approximately one-third of individuals with AxD are hospitalized annually, which substantially burdens patients, families, and payers. We evaluated hospitalization frequency in the zilganersen vs control groups of the ION373-CS1 trial to determine the effect of treatment on all-cause hospitalization.

METHODS: The zilganersen pivotal trial (ION373-CS1; NCT04849741) was an international phase 1-3 trial that enrolled 53 participants at database lock; 41 were in the full analysis set (zilganersen 50 mg, n=24; control, n=17). Hospitalization was not a prespecified endpoint but was captured in serious adverse event data. The frequency of all-cause hospitalizations during the double-blind treatment period was compared between the zilganersen and control groups by estimating the rate ratio with negative binomial regression including age and sex as covariates.

RESULTS: There were 12 hospitalizations among 7 participants in the zilganersen group and 15 hospitalizations among 7 participants in the control group. The estimated rate of all-cause hospitalization was 43.7 per 100 patient-years with zilganersen vs 78.5 per 100 patient-years with control. Treatment with zilganersen was estimated to reduce all-cause hospitalizations by 60% vs control (adjusted rate ratio, 0.4; 95% confidence interval, 0.12-1.33).

CONCLUSIONS: In post hoc analyses of data from a pivotal AxD trial, participants treated with zilganersen experienced numerically fewer all-cause hospitalizations vs those receiving control. Despite the small sample size, findings indicate a trend toward potential benefits of zilganersen in reducing hospitalizations and related health care costs.

KEYWORDS: Neurodevelopmental Disorders

248. Psychometric Evaluation of the 10-Meter Walk Test in Alexander Disease (AxD): Findings from the ION373-CS1 study

Aaron Yarlas, Stephen Maher, Montserrat Vera-Llonch, Steven Kymes, Tanguy Vilcot, Abigail Collins, Amy Waldman, Elizabeth Berry-Kravis

OBJECTIVE: Alexander disease (AxD) is a rare astrocytic leukodystrophy caused by pathogenic *GFAP* variants that is frequently associated with impaired gait and mobility. Using clinical trial data, we assessed psychometric properties of 10-Meter Walk Test (10MWT) speed in ambulatory patients with AxD aged 5–65 years.

METHODS: Patients were administered the 10MWT in a global randomized phase 1-3 (ION373-CS1) study at Screening, Baseline, and Week 61. Test–retest reliability of 10MWT was assessed using intraclass correlations (ICC) for within-visit and screening-to-baseline trials. Construct validity was assessed through cross-sectional correlations at Baseline and Week 61 with gross motor function (GMF) measures - GMF Classification System-Expanded and Revised (GMFCS-E&R), GMF item on the AxD Patient Domain Impression of Severity, Vineland-3 Motor Skills – and measures of more distal concepts, including quality-of-life, adaptive behavior, and disease severity. Known-groups validity used ANCOVA (age as covariate) comparing 10MWT speed across clinician-rated (GMFCS-E&R) severity groups, and between groups with caregiver-/self-reported most bothersome symptom (MBS) being GMF vs. other symptoms.

RESULTS: Thirty-six participants were included. Test–retest reliability was high (ICCs ranged from 0.82–0.91). Convergent validity was supported using GMF measures (rs from $|0.33|$–$|0.73|$); correlations with more distal constructs were generally weaker. Known-groups validity was supported for clinical severity and MBS (all ps<0.05) with moderate-to-large effect sizes (0.69 to 1.40).

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CONCLUSIONS: Findings support reliability and construct validity of the 10MWT in AxD. The 10MWT should be considered reliable and valid for capturing gross motor function in ambulatory patients with AxD.
KEYWORDS: Neurodevelopmental Disorders

249. Temporal Evolution of EEG Biomarkers in Rett syndrome and MECP2 Duplication syndrome

Carole Linda Djagang Nguignang, Siyan Wang, Marie Le Roux, Aboubacrine Mahamane Touré, Inga Sophia Knoth, Enora Jeuland, charles-olivier Martin, Myriam Moutawakil, Sarah Lippé, Elsa Rossignol

OBJECTIVE: Rett syndrome (RTT) is a rare neurodevelopmental disorder caused by loss-of-function mutations in *MECP2*, while *MECP2* duplication syndrome (MDS) results from gene duplication. Despite distinct clinical phenotypes, both conditions are severe and currently lack effective disease-modifying therapies. Preclinical studies in RTT models showing symptom reversibility following *MECP2* re-expression highlight the need for objective biomarkers to evaluate treatment efficacy. This study aims to identify and to track longitudinally various electroencephalographic biomarkers in RTT and MDS.
METHODS: Patients with RTT or MDS followed in our institution were recruited along with age- and sex-matched neurotypical controls. Demographic, genetic and clinical data were collected. Clinical severity was assessed using the CGI-S and Vineland scales. Participants underwent high-density EEG recordings (Magstim EGI, 128 channels) at baseline and at one-year follow-up. The acquisition protocol included visual evoked potentials (VEPs), auditory evoked potentials (AEPs), an auditory Oddball task for mismatch negativity, and resting-state EEG recordings. Evoked responses were analyzed using Brain Vision Analyser and quantitative resting-state EEG metrics were analysed using a Python-based customized pipeline to extract power spectral density, multiscale entropy, and phase–amplitude coupling.
RESULTS: We enrolled 27 RTT patients, 5 MDS patients, and 34 sex-matched controls. VEP analyses revealed reduced P1 amplitude and increased N2 latency in RTT patients compared with controls. Resting EEG was characterized by increased delta power in both Rett and MDS patients compared to controls.
CONCLUSIONS: Longitudinal recordings will help clarify how these electrophysiological biomarkers evolve over time, supporting their use as objective outcome measures in future therapeutic trials.
KEYWORDS: Neurodevelopmental Disorders, Neurogenetics, Practice Parameters

250. Respiratory Burden in MECP2 Duplication Syndrome Determined from Retrospective Medical Records

Katie Wester-Neal, Marianna Sockrider, Cary Fu, Gudrun Gröppel, Masayuki Itoh, Amitav Parida, Sarika Peters, Courtney Bisbee, Eric Marsh, Davut Pehlivan, Paul Malik

OBJECTIVE: MECP2 Duplication Syndrome (MDS) is a rare, X-linked neurodevelopmental disorder associated with severe intellectual disability, often drug-resistant epilepsy, recurrent respiratory illness, and early mortality. We characterized respiratory burden in a retrospective medical record-based cohort of genetically confirmed MDS.
METHODS: This study used secondary longitudinal data from Citizen Health, a patient-facing platform that extracts and standardizes variables from U.S. medical records from first medical contact through data cut. Respiratory morbidity was assessed from hospitalization records (primary admission reason, significant intercurrent events) and clinical diagnoses. First serious respiratory event was defined as the earliest non-neonatal hospitalization for a respiratory-related reason, respiratory failure/insufficiency, or pleural effusion. Associations with age at diagnosis, prematurity, microcephaly, epilepsy, and documented immunologic diagnoses were evaluated through univariable analyses.
RESULTS: Sixty participants from 1-33 years old (median 7 years) were included. Overall, 42/60 experienced at least one serious respiratory event. The respiratory-related hospitalization rate was 47.6 events per 100 person-years, and the median age at first serious respiratory event was 1.2 years. Acute respiratory failure was diagnosed in 22 participants. In univariable analyses, microcephaly was associated with earlier serious respiratory events (HR 2.04, 95% CI 1.09–3.84). Documented immunologic diagnoses were infrequent (6/60) and were not associated with earlier serious respiratory events (HR 0.87, 95% CI 0.31–2.47). Across diagnosis years, first serious respiratory event often preceded genetic diagnosis. Prematurity and epilepsy were not explanatory.
CONCLUSIONS: Serious respiratory morbidity in MDS is common, begins early, and extends beyond the small subgroup with documented immunologic diagnoses.
KEYWORDS: Neurodevelopmental Disorders, Lifespan Manifestations of Childhood Onset Conditions

251. Online CME Encourages Clinical Practice Changes Associated with the Diagnosis and Comprehensive Care of Patients with Rett Syndrome Among Pediatricians, Neurologists, and Family Medicine Providers

Thomas Finnegan, Pakinam Aboulsaoud, Kelly Hanley, Timothy Feyma

OBJECTIVE: This study assessed the ability of an online continuing medical education (CME) program to improve healthcare provider (HCP) performance in talking action to improve screening, diagnosing, and managing of Rett syndrome (RTT). Barriers to optimal care were also identified.
METHODS: The CME activity was a 60-minute video discussion between three expert faculty. The impact of the education on performance outcomes was measured with an intent to change survey, emailed to learners 30-60 days after participation in the activity. Learners were asked to complete a survey about the type of changes they made in practice based on the education and to identify any barriers that prevented them from integrating changes into practice. Survey data were collected between August 2025 and March 2026.
RESULTS: 69 learners from the target audiences (pediatrics, neurology, and family medicine) completed the survey.

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Overall, 66% of learners reported modifying or implementing new practices. The most commonly reported actions were: looking for a period of regression followed by stabilization when assessing a patient for RTT (74%); improved referral to specialty care if red flag associated with RTT is identified (70%); and improve evaluation of multisystem symptoms associated with RTT (68%). The most frequently (25%-35%) selected barriers were limited access to genetic counseling; limited time to comprehensively evaluate patients with RTT; and difficulty securing specialty referral for patients with RTT.

CONCLUSIONS: Online CME prompted essential practice changes to improve diagnostic accuracy, comprehensive patient evaluation, and multidisciplinary care. Future education should prioritize strategies to overcome time constraints and access to specialty providers.

KEYWORDS: Neurodevelopmental Disorders, Education

252. Examining seizure-free days with fenfluramine in children and adults with CDKL5 deficiency disorder: a post hoc analysis of a phase 3, randomised, double-blind, placebo-controlled trial

Melinda Martin, Ángel Aledo-Serrano, Scott Demarest, Heather Olson, Eric Marsh, Sam Amin, Nadia Bahi-Buisson, Amanda Jaksha, Patrick Healy, Brian Moseley, Nicola Specchio

OBJECTIVE: To assess changes in seizure-free days with fenfluramine in patients with CDKL5 deficiency disorder (CDD).

METHODS: Post hoc analysis of a randomized placebo-controlled trial (EP0216/NCT05064878) in children/adults (1-35 years) with confirmed/likely pathogenic *CDKL5* mutation, clinical CDD diagnosis, and ≥4 countable motor seizures (CMS)/week, who received fenfluramine 0.7 mg/kg/day (maximum 26 mg/day) or placebo over 14 weeks (2-week titration [T]; 12-week maintenance [M]).

RESULTS: At baseline, patients receiving fenfluramine/placebo (n=42/44) had a median of 5.4 (range:0-17)/3.9 (0-17) CMS-free days/month, and 2.6 (0-17)/1.0 (0-13) all-seizure-free days/month. From baseline to T+M, patients receiving fenfluramine/placebo had median increases of 6.4 (range:−6-28)/0.1 (−14-10) CMS-free days/month (estimated median difference: 6.7 [95% CI:4.1-10.7]), and 5.7 (−2-24)/0.3 (−12-7) all-seizure-free days/month (estimated median difference: 5.5 [95% CI:2.8-9.1]). Median longest intervals of seizure-free days during T+M with fenfluramine/placebo were 8.5/3.0 days for CMS (estimated median difference: 6 days [95% CI:3.00-11.00]), and 7.0/2.0 days for all-seizures (estimated median difference: 4 days [95% CI:2.00-6.00]). During T+M, 71.4/31.8% of patients receiving fenfluramine/placebo had >7 CMS-free days/month (baseline: 42.9/27.3%) and 59.5/6.8% had >14 CMS-free days/month (baseline: 14.3/6.8%); 66.7/18.2% of patients receiving fenfluramine/placebo had >7 all-seizure-free days/month (baseline: 28.6/13.6%) and 45.2/2.3% had >14 all-seizure-free days/month (baseline: 2.4/0%). Among fenfluramine-treated patients, responders (change from baseline to T+M of ≥7 CMS-free days) were more often rated 'much/very much improved' on the investigator-assessed Clinical Global Impression-Improvement scale than non-responders (11/19 [57.9%] vs.5/23 [21.7%]; odds ratio 5.2 [95% CI:1.3-20.6]).

CONCLUSIONS: In this post hoc analysis, fenfluramine provided marked increases in seizure-free days and longest seizure-free intervals vs. placebo in children/adults with CDD.

KEYWORDS: Neurodevelopmental Disorders, Experimental Therapeutics, Epilepsy

253. A Real-World Assessment of Functional Abilities and Assistance Level in People with Niemann-Pick Disease Type C, GM2 Gangliosidoses, and Ataxia Receiving Levacetylleucine

Jorgji Kerthi, Marc Patterson, Bethany Zanrucha, Janelle Raymond, Megan Grosso, Jake Caines, Susan Rounds

OBJECTIVE: A need exists for the generation of real-world patient reported outcome (PRO) data in therapies for rare, neurodegenerative disorders. The Functional Independence Measure for Children (WeeFIM® [1]) is one of the most respected pediatric outcomes management tools in the market that may also be applied to adults. Developed from the World Health Organization bio-psycho-social model, the WeeFIM is a validated tool assessing functional independence. Utilizing a validated, well recognized assessment provides standardized real-world insight into the treatment journey for people with NPC, GM2 gangliosidoses, and ataxia taking levacetylleucine.

METHODS: The 18-item questionnaire is administered telephonically to the caregiver or person with NPC, GM2 gangliosidoses, or ataxia assessing self-care, mobility, and cognition on a 7-level ordinal scale, categorized as "Complete Dependence" (1-2), "Modified Dependence" (3-5), or "Independence" (6-7). Total WeeFIM scores range from 18 to 126.

RESULTS: A total of 56 participants had a baseline and follow-up assessment of which 42 were people with NPC, 8 with GM2 gangliosidoses, and 6 with ataxia. Among the 56 participants, approximately 70% (39/56) showed either functional improvement or stability, with 48% (27/56) demonstrating total functional improvement.

CONCLUSIONS: Real-world functional improvement observed in 48% of participants both aggregately and across one or more domains is compelling. A further 21% (12/56) of participants reported disease stabilization. The ongoing collection of PRO data will provide valuable insights into long-term treatment effectiveness of levacetylleucine. [1]WeeFIM and WeeFIM II are trademarks of Uniform Data System for Medical Rehabilitation, a division of UB Foundation Activities, Inc.

KEYWORDS: Neurodevelopmental Disorders, Neurogenetics, Movement Disorders

254. Leveraging Rett Syndrome Natural History and Caregiver Input to Assess Treatment Effects in Embolden™ Pivotal Trial of NGN-401

Jeffrey Neul, Tim Benke, Eric Marsh, Bernhard Suter, Cara Mayfield, Andrew Mulberg, Christine Mikail, Julie Jordan

OBJECTIVE: Rett syndrome (RTT) is a rare neurodevelopmental disorder defined by a period of seemingly

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normal early childhood development followed by regression of developmental milestones and severe impairment of hand and gross motor function, and communication. We conducted analyses to identify developmental milestones that, if acquired, would be clinically meaningful and not expected at ≥3 years of age, to evaluate treatment effects of NGN-401 gene therapy in the Embolden™ pivotal trial.

METHODS: Caregivers of female RTT patients were asked to assess clinical meaningfulness of developmental milestones from the Rett Syndrome Natural History Study (RNHS). Incidence rates for acquisition/reacquisition of these milestones were analyzed in the RNHS over a one-year post-baseline period in a population matched to the Embolden trial: females aged ≥3 years with post-regression classic RTT, and baseline Clinical Global Impression-Severity (CGI-S) scores of 4–6 (n=135)

RESULTS: Twenty-eight developmental milestones across the core domains of RTT were identified as clinically meaningful and demonstrated low incidence of acquisition/reacquisition at ≥3 years of age, the age at which regression is typically complete and the lower age of eligibility in the Embolden trial. Among patients meeting Embolden inclusion criteria, acquisition of one or more milestones was uncommon and acquisition of multiple milestones was rare. Overall, acquisition/reacquisition of these 28 milestones is uncommon in RTT patients aged ≥3 years.

CONCLUSIONS: The clinical meaningfulness of these 28 developmental milestones and the rarity of acquisition in RTT beyond ≥3 years of age support their selection for evaluation in the Embolden pivotal trial.

KEYWORDS: Neurodevelopmental Disorders

255. Assessing neurofilament light chain (NfL) as a surrogate outcome measure in GM2 gangliosidoses

Marc Patterson, Kyriakos Martakis, Taylor Fields, Ian Billington, Jorgji Kerthi, Janelle Raymond, Bethany Zanrucha, Michael Strupp, Tatiana Bremova-Ertl

OBJECTIVE: GM2 gangliosidoses (GM2) are a group of inherited neurodegenerative disorders. Neurofilament light chain (NfL) is a sensitive marker of axonal injury and has been extensively investigated as a biomarker in a range of neurodegenerative disorders, including GM2. The clinical utility of NfL was evaluated in individuals with GM2 in a Phase 2b trial of levacetylleucine.

METHODS: The Phase 2b trial (IB1001-202) encompassed a Parent Study and an Extension Phase (EP). Blood samples were obtained from participants at Visit 2 (baseline), Visit 4 (after 6 weeks), and Visits 9 and 12 of the EP. NfL plasma levels were assessed using a validated assay at Medpace Reference Laboratories. Ordinary Least Square regression was used to test the null hypothesis of no relationship between NfL and clinical outcome measures.

RESULTS: Viable samples for NfL analysis were obtained from 19 participants during the Parent Study and 10 during the EP. During the Parent Study, NfL levels declined by a mean of -8.9% (SD 13.1%; P=0.008), followed by a rebound of +9.2% (SD 16.1%; P=0.022) during the post-treatment 6-week washout. In the EP, participants showed a mean NfL reduction of -16.9% after one year (SD 15.0%; P=0.010) and -30.5% after two years (SD 12.8%; P<0.001) of continuous levacetylleucine therapy. Changes in the NfL correlated with meaningful changes captured in clinical outcomes.

CONCLUSIONS: These results provide evidence supporting the use of NfL as a surrogate outcome measure for GM2, demonstrating treatment response to levacetylleucine, and supporting the observed clinical efficacy.

KEYWORDS: Neurodevelopmental Disorders, Neurogenetics

256. Functional Near-Infrared Spectroscopy Reveals Working Memory–Related Cortical Activation During an N-Back Task in Individuals with MSUD

Benjamin Agyemang, Kosar Khaksari, Andrea Gropman

OBJECTIVE: To investigate cortical activation associated with working memory and learning during an N-back task in children with MSUD using fNIRS.

METHODS: Children with MSUD and age-matched healthy controls completed a standardized N-back task with increasing cognitive load (1-back and 2-back). fNIRS was used to measure changes in oxygenated and deoxygenated hemoglobin over prefrontal cortical regions. Behavioral performance (accuracy and reaction time) was recorded. Changes in cortical activation across task conditions and groups were analyzed, along with associations between activation patterns and task performance.

RESULTS: Children with MSUD demonstrated altered prefrontal activation compared to controls during higher working memory load conditions. Specifically, reduced and/or less efficient recruitment of dorsolateral prefrontal regions was observed during the 2-back condition. Behavioral performance showed trends toward lower accuracy and longer reaction times in the MSUD group, though variability was noted. In some participants, increased activation in adjacent regions suggested possible compensatory mechanisms.

CONCLUSIONS: fNIRS reveals differences in cortical activation during working memory tasks in children with MSUD, even when behavioral performance differences are subtle. These findings suggest that fNIRS may serve as a sensitive tool for detecting early neurocognitive alterations and could inform monitoring and intervention strategies in pediatric metabolic disorders.

KEYWORDS: Neurodevelopmental Disorders, Early Stage Investigator, Behavioral Neurology

257. Pharmacological Interventions for Sleep and Behavior Co-morbidities of Smith-Magenis Syndrome: A Literature and Database Review.

Ben Litvak-Hinenzon, Samantha Vanderslice, Ann Neumeyer

OBJECTIVE: Smith–Magenis syndrome (SMS) is a genetic condition associated with severe behavioral dysregulation and circadian disruption, yet pharmacologic management remains largely trial-and-error. This study synthesizes published literature and analyzes real-world registry data to characterize medication use, effectiveness, and tolerability in SMS.

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METHODS: A mixed-methods design combined a systematic literature review (PubMed, Google Scholar, 1982–2024) with analysis of caregiver-reported data from an SMS patient registry (N = 107). Included studies examined psychiatric medication use in genetically confirmed SMS. Registry data included medication use, caregiver-reported effectiveness, and side effects across multiple timepoints. Medications were categorized by class and tracked longitudinally.
RESULTS: Across the literature and registry data, medication response was highly variable, with frequent polypharmacy and regimen instability over time. Atypical antipsychotics and stimulants demonstrated inconsistent effectiveness and were commonly associated with side effects, including sedation and irritability. In contrast, sleep-related therapies, particularly melatonin, were the most frequently used and perceived as effective by a majority of caregivers, with comparatively fewer reported side effects. However, melatonin also showed high rates of discontinuation and reinitiation across timepoints. Exploratory analyses suggested reduced perceived effectiveness and increased side effects of melatonin among individuals with pathogenic RAI1 mutations compared to those with chromosomal deletions.
CONCLUSIONS: Pharmacologic treatment in SMS is characterized by substantial heterogeneity, frequent medication changes, and reliance on trial-and-error prescribing. Sleep-targeted therapies show the most consistent benefit but are not reliably sustained. Preliminary genotype-related differences in melatonin response highlight the potential for more individualized, mechanism-informed treatment approaches.
KEYWORDS: Neurodevelopmental Disorders, Sleep, Early Stage Investigator

258. Characterization of Behavioural Outcomes at School-Age using Child Behavioural Checklist in Children Born Preterm

Colleen Haughey, Rhandi Christensen, Tricia Williams, Vann Chau, Mehmet Cizmeci, Linh Ly, Helen Branson, Ting Guo, Ruth Grunau, Steven Miller

OBJECTIVE: Children born preterm are at heightened risk for behavioural concerns. We aim to characterize behavioural outcomes at 4 years of age in a prospective preterm cohort using the Child Behaviour Checklist (CBCL) and to identify predictors of either internalizing or externalizing behaviour via univariate and multivariate models.
METHODS: Participants were selected from a prospective cohort of children born 24-32 weeks' gestation (N=171). Behavioural outcomes were assessed on the CBCL at 4 years, comprising internalizing and externalizing behaviours. We calculated the proportion of children with clinically significant scores for behaviour outcomes. We completed both univariate and multivariate logistic regression for possible predictors of behaviour (e.g gestation, sex, maternal education, brain injury).
RESULTS: The study sample included 171 children, with a median gestational age of 27.9 weeks. Neonatal morbidities included bronchopulmonary dysplasia (22%), retinopathy of prematurity (36%) and multiple infections (19%). Brain injury included: intraventricular hemorrhage (45%), white matter injury (30%), and cerebellar hemorrhage (16%). We observed a large proportion with behavioural problems in externalizing (8%) and internalizing (15%) behaviours. Univariate models described increased odds for behavioural problems in those with bronchopulmonary dysplasia (BPD) (3.4; 95%CI 1.5, 7.8), corrected to 3.0 (95% 1.2, 8.0) in multivariate analysis.
CONCLUSIONS: Behavioural concerns were reported among 8-15% of children born preterm. Children with BPD had three times increased odds of developing behavioural problems, which may be related to multiple factors (e.g. hypoxia, brain development, prolonged hospitalization).
KEYWORDS: Neurodevelopmental Disorders, Behavioral Neurology, Neuroimaging

259. X-Linked Coffin-Lowry Syndrome Phenotype differrences by Sex

Mary Hames, Jin Lee, Lauren Beach, Brian Leonard

OBJECTIVE: Current literature on Coffin-Lowry Syndrome (CLS) is reported as aggregate data of males and females. When phenotype is vastly different between the sexes, averaged data becomes inaccurate for all patients. We aimed to analyze early gender-based differences in growth parameters, musculoskeletal features, systemic complications, functional independence, and educational needs using data from a CLS natural history and patient registry.
METHODS: Survey data from 43 of 62 registered CLS patients were analyzed. Demographic, clinical, musculoskeletal, neurological, functional, and educational variables were stratified by sex. Descriptive statistics were used to evaluate patterns and differences.
RESULTS: Males demonstrated higher rates of musculoskeletal abnormalities, spinal deformities (particularly scoliosis), respiratory complications, earlier gastrointestinal involvement, earlier wheelchair dependence, and greater functional dependence. Spinal deformities were markedly more prevalent in males (scoliosis: 14 males vs. 1 female). Males required more intensive educational supports, including full-time one-on-one assistance. Females demonstrated comparatively greater functional independence and later onset of systemic complications. Certain features, including dental issues and vision abnormalities, occurred at comparable rates.
CONCLUSIONS: Early registry data suggest that males with CLS experience greater clinical severity and earlier progression across multiple domains. These findings underscore the importance of gender-stratified monitoring protocols and support the need for longitudinal investigation to better understand disease progression and inform anticipatory clinical management.
KEYWORDS: Neurodevelopmental Disorders, Neurogenetics, Diversity, Equity, Inclusion

260. Post-Launch Interviews with Caregivers of Patients from the Trofinetide Clinical Trial Program: Assessing Real-World Experiences for Individuals with Rett Syndrome

Nazia Rashid, Amy Barrett, Oyebimpe Olayinka-Amao, Dilesh Doshi, Alyssa Peckham

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OBJECTIVE: A qualitative study was conducted with caregivers of individuals with RTT who participated in the trofinetide (TROF) clinical trial program and subsequently received TROF for approximately 2.5 years after launch to obtain insight about long-term use of TROF in the real-world setting.
METHODS: Independent researchers conducted 60-minute interviews with primary caregivers of TROF clinical trial participants (patients) who were still receiving TROF approximately 2.5 years post-launch. Caregivers were asked about the patient experience with RTT and TROF since the end of the clinical trial, including any change in RTT symptoms they observed following the trial, whether they noticed the change for the first time during or after the trial, and the meaningfulness of each change. Transcripts were created from audio recordings of the interviews, and a thematic analysis approach was used to generate themes and summarize the reported changes.
RESULTS: Eight caregivers participated in the study; the mean age of patients was 16.7 years. The caregivers reported 36 instances of new improvements and 72 of further improvement in RTT after the trial ended. All caregivers reported improvement in the patient's nonverbal and device-facilitated communication, awareness of their environment, and social engagement, and all expressed a high level of satisfaction ("very satisfied") with TROF since the trial ended.
CONCLUSIONS: New and continued long-term improvements in RTT that are important to patients and caregivers continue to occur for ≥2.5 years after clinical trial follow-up. These insights support additional and continued benefit of long-term TROF for individuals with RTT.
KEYWORDS: Neurodevelopmental Disorders

261. Infections and Underlying Immune Status in MECP2 Duplication Syndrome

Christine Coquery, Chen Chen, Davut Pehlivan, Jeffrey Neul, Eric Marsh, Miguel Del Campo, Timothy Feyma, Lynne Bird, Paul Malik

OBJECTIVE: Characterize serious infections in MECP2 duplication syndrome (MDS) and explore contributors to infection risk, a major source of morbidity and mortality in this population.
METHODS: Infection history, longitudinal assessment of infection frequency, serious infections and changes from baseline in leukocyte subsets, lymphocytes, and serum immunoglobulins were evaluated in participants enrolled in a prospective natural history study NH00006 (NCT06014541). Associations between serious infections and clinical features (age, motor function, eating, chewing, swallowing impairment) were assessed by correlation and subgroup analyses. Functional immune competence was not directly assessed.
RESULTS: Twenty-nine males with genetically confirmed MDS, aged 2-22.5 years, were enrolled (follow-up 0.38-1.94 years). Interstitial duplications were present in 82.8% (24/29), and 41.4% (12/29) had epilepsy. Eighteen serious infections (moderate or severe) were reported in 11 participants. Leukocyte and lymphocyte subsets were within normal range at ≥1 timepoint during follow-up except one participant with elevated monocytes at all timepoints. One participant (3.4%) showed an IgA/IgG2 deficiency phenotype associated with recurrent serious urinary tract infection and acute respiratory failure; this pattern was not broadly observed among participants with serious infections. Serious infections were more common in non-ambulatory and older participants and were associated with impairment in eating, chewing, and swallowing.
CONCLUSIONS: In this small cohort, baseline immune measures were generally intact; only one male showed IgG/IgA2 deficiency with associated infection susceptibility. Other males appeared generally immunocompetent and still experienced recurrent serious infections. Together, especially with greater functional impairment, these findings support investigation of non-immune drivers of infection risk, including aspiration, alongside immune contributors in MDS.
KEYWORDS: Neurodevelopmental Disorders, Lifespan Manifestations of Childhood Onset Conditions

262. The Developmental Plateau in Rett Syndrome: New Insights from the Natural History Study Inform Novel Interventional Study Designs

Minna Montgomery, Tessa Clarkson, Alexa Bowie, Patrick O'Keefe, Craig Mallinckrodt, Suku Nagendran, Eric Marsh, Bernhard Suter, Rumana Haque-Ahmed, Elizabeth Berry-Kravis, Jeff Neul

OBJECTIVE: Heterogeneity of Rett syndrome (RTT) poses challenges for well-controlled, ethical interventional gene therapy trials. We analyzed U.S. Rett Natural History Study (RNHS) data to define the developmental plateau and inform responder thresholds for single-arm Patient-as-own-control (PAOC) trial design to address these challenges.
METHODS: RNHS data (N=1,191; 2006–2021) was analyzed using criteria aligned with the interventional trial (female, typical RTT, MECP2 mutation). Caregiver-reported gain, loss, and regain across 28 milestones were modeled using cumulative incidence and multivariable Cox proportional hazards (CPH). Repeated simulations assumed cohorts of N=15 and a 6.7% null hypothesis (1 spontaneous gain/regain per cohort) in participants ≥6 years.
RESULTS: Spontaneous first-time milestone gain at ages 1-<6 ranged from 0-54% (lowest at age 5; highest at ages 2-3). A clear developmental plateau emerged at age 6, after which spontaneous milestone gain/regain was rare (∼0-3% across milestones). In CPH models, no prognostic factors beyond age and time since loss predicted gain/regain. Across 150,000 patient simulations, <2% (n<3000) spontaneously gained/regained milestones. Simulations support "≥1 gain/regain" as a responder threshold and indicate a feasible PAOC sample size of ∼15 in the ≥6 years population.
CONCLUSIONS: RNHS provides a robust external benchmark for milestone gain/regain and supports an ethical single-arm PAOC study in the plateau population, with ≥1 gain/regain as a primary endpoint. These findings support the FDA-aligned REVEAL pivotal trial enrolling patients aged 6-<22, a population with stable baseline function and low spontaneous improvement rates.
KEYWORDS: Neurodevelopmental Disorders, Experimental Therapeutics, Neurogenetics

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263. ATTUNE: Preliminary Blinded Safety, Tolerability, and Pharmacokinetics of ION440 in Males with MECP2 Duplication Syndrome

Eric Marsh, Davut Pehlivan, Lynne Bird, Gudrun Gröppel, Timothy Feyma, Constance Smith-Hicks, Cary Fu, David Lieberman, Timothy Benke, Laurence Faivre, Paul Malik, Tanya Watanabe, Shirley Li, Arthur Wu, Roger Lane, Christine Coquery

OBJECTIVE: *MECP2* Duplication Syndrome (MDS) is a rare and severe X-linked neurodevelopmental disorder caused by copy number gain of the *MECP2* gene resulting in MeCP2 overexpression. Manifestations include severe intellectual disability, often drug-resistant epilepsy, recurrent respiratory infections, and early mortality. ION440 is an antisense oligonucleotide designed to target *MECP2* pre-mRNA being investigated for the treatment of MDS. Preliminary blinded safety and tolerability data from the first-in-human study (NCT06430385) are presented.

METHODS: ATTUNE is a Phase 1/2, multicenter, double-blind, sham-controlled (3:1), multiple ascending dose study of intrathecal ION440 in males with MDS. Six sequential subcohorts evaluate three dose levels across two age groups (8–65 years and 2 to <8 years) guided by an independent safety monitoring committee. The primary endpoint is safety and tolerability, assessed by adverse events and changes from baseline in laboratory measures, vital signs, electrocardiogram, and physical and neurologic examinations. Secondary endpoints include CSF concentrations and plasma pharmacokinetic parameters.

RESULTS: Preliminary blinded data indicate that multiple dosing of ION440 is generally well tolerated in males with MDS. As of 26APR2026, 24 participants were enrolled and eight entered the open label part. There were no dose-limiting toxicities or discontinuations due to adverse events. Adverse events were mostly mild-to-moderate in severity, consistent with the experience of MDS and similar to those observed in the prospective observational study (NH00006). Observed Cmax and AUC mean values were within the predicted values based on preclinical data.

CONCLUSIONS: ION440 is in development as a potential first-in-class treatment for MDS. ATTUNE may support future studies in this population.

KEYWORDS: Neurodevelopmental Disorders, Experimental Therapeutics

264. Multi-Domain Functional Gains Following TSHA-102 Gene Therapy Across the Rett Syndrome Lifespan: Safety and Efficacy Results from the REVEAL Part A Phase 1/2 Trial of TSHA-102 in Pediatric and Adolescent/Adult Cohorts

Elsa Rossignol, Elizabeth Berry-Kravis, Robert Haas, Robin Ryther, Tim Feyma, Inge Meijer, Colleen Buhrfiend, Tessa Clarkson, Rumana Haque-Ahmed, Laura Pisani, Jason Cataldo, Minna Montgomery, Suku Nagendran

OBJECTIVE: Rett syndrome (RTT) is a rare neurodevelopmental disorder with no approved therapies targeting its genetic root. A clear developmental plateau begins at age 6, resulting in lost/missed developmental milestones (DMs) across fine/gross motor function, communication and causes autonomic dysfunction (breath holding, sleep disturbances, seizures) impacting activities of daily living. Here we present safety and efficacy data from REVEAL Part A evaluating TSHA-102 gene therapy in RTT designed to optimize MECP2 expression and address the underlying genetic cause.

METHODS: A single dose of TSHA-102 (low-dose [LD], 5.7×10^{14} vector genomes [vg]; or high-dose [HD],1.0×10^{15}vg) was administered intrathecally to participants 6-21 years old. Assessments included safety evaluation and gain/regain of predefined DMs was assessed by multiple independent central raters through video evidence.

RESULTS: 100% of participants gained/regained ≥1 DM with a <6.7% likelihood of being achieved after age 6 (LD, n=4; HD, n=6; 05/2025 data cut-off). Participants achieved 22 DMs and 165 additional skills/improvements across the core RTT domains: communication (use of phrases, improved communication), fine motor (purposeful hand use, finger feeds), gross motor (improved mobility), and additional autonomic/other improvements (absent/reduced breath holding/hyperventilation, seizure reduction), improving core RTT features with meaningful impact on activities of daily living. TSHA-102 was well-tolerated with no treatment-related SAEs or DLTs (05/2025 data cut-off).

CONCLUSIONS: TSHA-102 was generally well-tolerated. Contrary to natural history expectations, both cohorts showed early, multi-domain functional improvements that deepened over time across measures, supporting the disease-modifying potential of TSHA-102. Additional sub-analyses reflecting therapeutic impact on neurological function will be presented at CNS 2026.

KEYWORDS: Neurodevelopmental Disorders, Experimental Therapeutics

265. Early and Sustained Gross Motor Improvements in a Phase 1/2 Study of NGN-401, a Novel Regulated AAV9 Gene Therapy, in Rett Syndrome

Julie Jordan, Jenny Downs, Melissa Licari, Bernhard Suter, Tim Benke, David Lieberman, Elizabeth Berry-Kravis, Aleksandra Jacobs, Carolyn Ellaway, Jeffrey Neul, Stuart Cobb

OBJECTIVE: Impaired gross motor function and loss of developmental milestones are defining features of Rett syndrome (RTT). Complex skills (e.g., climbing stairs unassisted) are rarely acquired. NGN-401 is an investigational AAV9 gene therapy delivering full-length human *MECP2* transgene, incorporating EXACT™ transgene regulation technology, and is administered intracerebroventricularly to target RTT pathophysiology in the brain and spinal cord.

METHODS: The Phase 1/2 open-label trial (NCT05898620) in females with classic RTT, age ≥4, with baseline CGI-S 4–6, is evaluating safety, tolerability, and efficacy of NGN-401 (1E15 vg). Gross motor function is assessed through acquisition of developmental milestones and the Rett Syndrome Gross Motor Scale (RSGMS), each with independent central rating.

RESULTS: As of October 30, 2025, 10 participants received 1E15 vg NGN-401 (n=8, age 4–10 cohort; n=2, age ≥11

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cohort). Five of eight pediatric participants (follow-up ~6-24 months) showed increased RSGMS scores and three achieved clinically meaningful improvement (≥4-point increase). The greatest improvement was observed in a participant with more severe baseline impairment, who required markedly less assistance for multiple motor tasks over time. Six of eight pediatric participants achieved 10 gross motor developmental milestones and other functional gains, including complex skills unexpected in RTT patients ≥3 years. Safety (n=10, follow-up ~3–24 months) demonstrated mild-to-moderate treatment-related AEs consistent with known AAV risks.

CONCLUSIONS: NGN-401 (1E15 vg) was well tolerated and produced clinically meaningful improvements in gross motor function, including increased mobility and acquisition of developmental milestones. Emergence of complex motor skills is unexpected in RTT natural history, supporting potential disease modification in RTT.

KEYWORDS: Neurodevelopmental Disorders

266. NGN-401, a Novel Regulated AAV9 Gene Therapy, Demonstrates Clinically Meaningful Improvements in Hand Function in a Phase 1/2 Study in Rett Syndrome

Julie Jordan, Jenny Downs, Melissa Licari, Bernhard Suter, Tim Benke, David Lieberman, Elizabeth Berry-Kravis, Aleksandra Jacobs, Carolyn Ellaway, Jeffrey Neul, Stuart Cobb

OBJECTIVE: Rett syndrome (RTT) is a neurodevelopmental disorder where loss of purposeful hand use has substantial impact on patients and caregivers. NGN-401 is an investigational AAV9 gene therapy delivering full-length human *MECP2* transgene, incorporating EXACT™ transgene regulation technology and is administered intracerebroventricularly to target RTT pathophysiology in the brain and spinal cord.

METHODS: The Phase 1/2 open-label trial (NCT05898620) in females with classic RTT, age ≥4 years and baseline CGI-S 4–6, is evaluating safety, tolerability, and efficacy of 1E15 vg NGN-401. Hand function is assessed through acquisition of developmental milestones and the Rett Syndrome Hand Function Scale (RSHFS), each with independent central rating.

RESULTS: As of October 30, 2025, 10 participants received 1E15 vg NGN-401 (n=8, age 4-10 cohort; n=2, age ≥11 cohort). Seven of eight pediatric participants (follow-up ~6-24 months) showed objective improvements, including increased RSHFS total scores ranging from 1-6 points on the 8-point scale, reflecting measurable functional improvement. Acquisition of pincer grasp and bilateral hand skills (e.g., transferring objects) were attained, irrespective of baseline hand function. Seven of eight pediatric participants achieved 15 durable hand function developmental milestones and other functional gains, including finger feeding and unassisted utensil use - outcomes unexpected per RTT natural history in females ≥3 years. Safety (n=10, follow-up ~3-24 months) data demonstrated mild-to-moderate treatment-related AEs consistent with known AAV risks.

CONCLUSIONS: NGN-401 (1E15 vg) was well tolerated and produced durable, clinically meaningful improvements in hand function, including complex skills where acquisition is uncommon in RTT patients ≥3 years, supporting potential disease modification.

KEYWORDS: Neurodevelopmental Disorders

267. Giardia-Associated Gut Inflammation in Down Syndrome Regression Disorder: Neurobehavioral Improvement After Multimodal Intervention

Gabriela Guimaraes, Douglas Barret, Farzad Salehpour, Jordan Schwartz, Francisco Gonzalez-Lima

OBJECTIVE: Down syndrome regression disorder (DSRD) is a rare neuropsychiatric condition marked by loss of previously acquired cognitive, language, behavioral, and adaptive skills. We report a pediatric case of severe DSRD associated with Giardia duodenalis infection, intestinal inflammation, and dysbiosis, emphasizing investigation of treatable medical triggers.

METHODS: An 11-year-old girl with Down syndrome developed regression at age five, with loss of continence, expressive language, comprehension, sleep regulation, and motor coordination, plus behavioral agitation. Brain MRI was unremarkable, and folate receptor autoantibodies were negative. Gastrointestinal evaluation identified Giardia duodenalis, elevated fecal calprotectin and secretory IgA, and microbial imbalance. She received single-dose tinidazole, folinic acid, and daily transcranial and abdominal photobiomodulation for 90 days. Outcomes were followed using caregiver-reported functional changes, CARS-2-QPC, ABC, and ATEC.

RESULTS: After 90 days, stool testing confirmed Giardia clearance and normalization of inflammatory markers: fecal calprotectin decreased from 234 to 12 μg/g and secretory IgA from 2320 to 42.5 mg/dL. Microbial findings shifted toward a more favorable profile, including Bacteroides, Bifidobacterium, and Lactobacillus. Clinically, she regained nocturnal continence, developed new words and short phrases, improved motor coordination, and became calmer and more socially engaged. Scores improved on CARS-2-QPC (106 to 91), ABC (63 to 31), and ATEC (62 to 57). No adverse events occurred.

CONCLUSIONS: This case highlights DSRD associated with a treatable gastrointestinal infectious-inflammatory trigger. The temporal association between Giardia eradication, biomarker normalization, and neurobehavioral improvement supports further study of gut–brain axis mechanisms in DSRD. Given the single-patient, multimodal design, causality cannot be established.

KEYWORDS: Neurodevelopmental Disorders, Neurometabolic, Early Stage Investigator

268. A Pilot Telehealth Model for Autism Spectrum Disorder Diagnosis

Sarah Wilson, Pauline Filipek

OBJECTIVE: With the increasing ASD prevalence of 1 in 31 (Shaw et al, 2025), the gap between children needing an ASD evaluation and diagnostician availability continues to widen, and even more so in rural locations. Routine telehealth cannot narrow the gap due to ineffective behavioral

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observation with parental phones/tablets. We report a novel telehealth approach for ASD diagnosis that can be generalized to other neurology conditions, with the following Objectives: (1) Perform telehealth ASD evaluations with specified hardware including on-site 360° pan/tilt/zoom and eye-glass cameras *controlled by the remote clinician*. (2) Evaluate the feasibility and accuracy of this telehealth method by comparing scores of the diagnostic tests.

METHODS: Patients: Aged 24-68 months with ASD symptoms who failed routine screening, referred from PCP and Early Intervention in rural Texas. Procedures: (1) A standardized telehealth visit with administration of the *Brief Observation of Symptoms of Autism* (BOSA) and *Childhood Autism Rating Scale-2nd Edition* (CARS-2) followed by completion of *Vineland Adaptive Behavior Scale, Third Edition*; (2) A subsequent on-site administration by a blinded team member of the *Autism Diagnostic Observation Schedule–Second Edition* (ADOS-2) and *Mullen Scales of Early Learning* (MSEL).

RESULTS: Analysis of telehealth scores obtained by the two instruments performed remotely (BOSA, CARS-2) relative to onsite scores from the ADOS-2 will be without significant differences based on diagnostician location.

CONCLUSIONS: This study design explores a novel telehealth approach to increase accessibility to children in low resource settings for a timely diagnosis of ASD.

KEYWORDS: Neurodevelopmental Disorders, Behavioral Neurology

269. Medical Decision-Making Capacity in a Nonverbal Young Adult with Acquired Neurodevelopmental Disability: A Case Report

Laxhmi Ramjit, Zeynep Salih

OBJECTIVE: Medical capacity and legal competency are distinct constructs that frequently conflict in patients with neurodevelopmental disabilities (NDD). Capacity is a clinical, task-specific determination requiring understanding, appreciation, reasoning, and communication of a decision. Competency is a global legal designation established by a court. Patients with motor impairment and communication barriers are at particular risk of having capacity underestimated and autonomy consequently denied.

METHODS: An 18-year-old male with acquired NDD following resection of a posterior fossa pilocytic astrocytoma, complicated by anoxic brain injury, critical illness polyneuropathy, tracheostomy, and gastrostomy dependence, was admitted with pseudomonal pneumonia following inadequate placement at an adult rehabilitation facility. Despite profound motor impairment and nonverbal status, he communicated reliably via eye movements. A contentious guardianship dispute, partially supported by an unrevised postoperative note documenting "altered mental status," threatened his right to participate in placement decisions. He exhibited marked behavioral deterioration when informed of the guardianship outcome.

RESULTS: A structured interdisciplinary approach involving psychiatry, ethics, legal counsel, and the primary team established decision-making capacity through adaptive binary questioning, serial assessments, and cross-session consistency verification. The ad litem attorney presented this documentation in court to advocate for competence. The patient's expressed preference to return home to his mother was honored by the court.

CONCLUSIONS: This case demonstrates that capacity can be meaningfully assessed in nonverbal patients with NDD through adaptive, individualized methods. Clinicians must not conflate communication barriers with cognitive incapacity, nor medical capacity with legal competency. Interdisciplinary collaboration, corrected medical documentation, and disability-informed advocacy are essential to preserving autonomy in this population.

KEYWORDS: Neurodevelopmental Disorders, Ethics, Diversity, Equity, Inclusion

270. CNTN4: A Possible Candidate Gene for Microbiota-Gut-Brain Axis in Autism Spectrum Disorders and Attention-Deficit/Hyperactivity Disorder

Yin Li, Wei Liu

OBJECTIVE: The gut microbiota plays a significant role in Autism Spectrum Disorders (ASD) and Attention Deficit/Hyperactivity Disorder (ADHD), though findings vary substantially across studies.

METHODS: Using gut microbiome data from a GWAS of 5,959 participants and summary statistics from 46,351 ASD and 55,374 ADHD cases, we conducted bidirectional Mendelian randomization (MR) analyses with inverse variance weighting as the primary method. Reverse MR analysis assessed potential reverse causality. We annotated single nucleotide polymorphisms with SNP-nexus to identify associated genes, followed by GO and KEGG enrichment analyses to characterize their functional roles.

RESULTS: Seventeen gut microbial taxa showed causal associations with ASD risk, while 27 were linked to ADHD. Reverse MR analysis revealed associations between ASD and species *Desulfovibrio piger* as well as species *Bacillus U*, but no reverse causality was detected for ADHD. Biological annotation identified five novel conserved genes in host-microbiome interactions shared by ASD and ADHD, with *CNTN4* emerging as a common candidate gene.

CONCLUSIONS: These findings support a potential causal relationship between gut microbiota and ASD/ADHD risk while uncovering novel conserved genes implicated in host-microbiome interactions for both disorders.

KEYWORDS: Neurodevelopmental Disorders, Neurogenetics

271. Mechanisms for the Treatment of Autism Spectrum Disorders with Verbascoside: Based on Network Pharmacology, Molecular Docking and Molecular Dynamics

Yin Li, Wei Liu

OBJECTIVE: To analyze the potential therapeutic targets and mechanism pathways of verbascoside (VB) in treating autism spectrum disorder (ASD) through network pharmacology, molecular docking, and molecular dynamics simulations.

METHODS: Potential therapeutic targets for ASD were screened while identifying VB's targeted effects.

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Subsequently, drug-disease shared targets were selected to construct a protein-protein interaction network. Biological functions and signaling pathways were explored through GO and KEGG enrichment analyses. Molecular docking was performed using AutoDockTools, and molecular dynamics simulations were conducted with GROMACS 2022 software.
RESULTS: Seven potential key target genes for VB in ASD treatment were identified: STAT3, PPARG, FGF2, BRAF, PTPN11, NTRK1 and MAPK1. Subsequent GO analysis revealed enriched biological processes, cellular components, and molecular functions. KEGG pathway analysis demonstrated VB's therapeutic targets, including neurotrophin and Ras signaling pathway. Molecular docking results indicated that VB's active components generally exhibited favorable binding affinity with macromolecular target proteins encoded by core target genes. Molecular dynamics simulations further confirmed the stable binding of PPARG-, PTPN11-, STAT3-, MAPK1-, FGF2-, and BRAF-ligand complex systems, with robust hydrogen bond interactions observed across all complexes, suggesting strong target protein engagement.
CONCLUSIONS: This study revealed the multi-target and multi-pathway mechanisms underlying VB's therapeutic effects in ASD, constructing a comprehensive "drug-target-disease" network, which advance understanding of traditional Chinese medicine's pharmacological actions in ASD treatment and support VB's clinical development.
KEYWORDS: Neurodevelopmental Disorders

272. Establishing the Rett Syndrome Developmental Milestone Assessment (RS-DMA) as a Primary Endpoint for Interventional Studies

Tessa Clarkson, Megan Quarmley, Minna Montgomery, Chris Jones, Robin Ryther, David Lieberman, Elizabeth Berry-Kravis, Suku Nagendran, Kristin Phillips, Emily McGinnis

OBJECTIVE: Trial design in Rett syndrome (RTT) is complicated by heterogeneity in baseline function and progression. Existing assessments may not detect individual change in single-arm patient-as-own-control (PAOC) studies. We developed the RS-DMA, an individualized endpoint enabling rigorous evaluation of treatment-associated efficacy. RS-DMA milestones were derived from the U.S. Rett Natural History Study and filtered to prioritize high-utility, activities-of-daily-living–linked skills while excluding low-sensitivity milestones.
METHODS: RS-DMA evaluates 28 milestones across communication, gross and fine motor domains statistically unlikely to show spontaneous gain/regain without intervention in the developmental plateau population (≥6 years). Milestone eligibility is individualized based on historical gain/loss and confirmed at baseline through standardized video-recorded RS-DMA that can be blinded and centrally rated using binary scoring to enable a responder analysis. To evaluate the RS-DMA psychometrics and trial-readiness we conducted assessments in a non-interventional study (RESUME; n=13) in individuals with classic RTT. Psychometric data was evaluated from site assessors, stakeholder feedback, and eight independent central raters with 100% overlap.
RESULTS: RS-DMA demonstrated excellent psychometric properties with above psychometric thresholds for feasibility, fidelity, and inter-rater reliability. Stakeholder feedback supported the validity, feasibility, and clinical meaningfulness of RS-DMA milestones, confirming milestone gain/regain reflects outcomes meaningful to caregivers.
CONCLUSIONS: Findings provide the statistical and methodological foundation for RS-DMA as an individualized, PAOC-anchored endpoint in the FDA-aligned REVEAL pivotal trial enrolling patients aged 6–<22, a plateau population with stable baseline function and low spontaneous improvement.
KEYWORDS: Neurodevelopmental Disorders, Experimental Therapeutics, Practice Parameters

273. A Domain-Based Severity Scoring System and Natural History Analysis of TBCD Neurodegenerative Disorder

Jackson Mittlesteadt, Allison Bradbury, Margie Ream

OBJECTIVE: To develop a severity scoring system to describe the natural history of patients with biallelic variants in *TBCD*, which cause Progressive Early-onset Brain Atrophy with Thin Corpus callosum (PEBAT).
METHODS: Retrospective natural history study of 12 patients with TBCD-related neurodegenerative disorder. A novel domain-based severity scoring system was developed to quantify neurologic involvement across seven domains: seizures, tone abnormalities (hypotonia and spasticity), language, vision, gross motor function, and feeding. Each patient was scored at initial and last clinical encounters using predefined criteria. In parallel, we constructed a clinical timeline dataset capturing age at first symptoms, seizure onset, and developmental milestone attainment. Descriptive analyses were performed to evaluate patterns of early disease presentation and longitudinal progression.
RESULTS: Initial clinical manifestations included tone abnormalities and motor delay, with additional early features including visual impairment and microcephaly. Symptom onset typically occurred within the first year of life, consistent with prior reports of early neurodegenerative presentation. Severity scoring demonstrated heterogeneity in disease burden across patients, with disease progression most frequently observed in motor and language domains. Some patients exhibited early severe phenotypes with persistent high disease burden, while others demonstrated milder or domain-specific progression. Temporal analysis revealed that developmental regression often followed or coincided with seizure onset.
CONCLUSIONS: This study introduces a structured severity scoring system and integrated clinical timeline framework for TBCD-related neurodegenerative disorder. These tools enable standardized assessment of disease burden and progression, highlight phenotypic heterogeneity, and provide a foundation for future natural history studies and therapeutic trials.
KEYWORDS: Neurodevelopmental Disorders, Epilepsy

274. Clinical, Radiological, and Genetic Features in a Cohort of 94 Patients with Schizencephaly

Emma Rodriguez, Andrea Accogli, Nassima Addour, Ferruccio Romano, Antonella Riva, Nikita Neale, Yumi Dille, Valeria Capra, Patrizia De Marco, Marina Martinez Popple, Gabrielle

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Lambert, Elisabeth Simard-Tremblay, Chantal Poulin, Kenneth Myers, Domenico Tortora, Christine Saint-Martin, Emmanouil Rampakakis, Michael Shevell, Elana Pinchefsky, Mariasavina Severino, Myriam Srour

OBJECTIVE: This study aims to characterize the clinical, radiological, and genetic features of schizencephaly, a rare brain malformation characterized by a grey-matter-lined cleft extending from the lateral ventricle to the pial surface, and to identify imaging predictors of developmental, motor, and epileptic outcomes

METHODS: A multicentre retrospective review of 94 pediatric and adult patients with radiologically confirmed schizencephaly was conducted. Clinical, radiological, and genetic data were collected. Imaging was systematically reviewed and classified per Griffiths' 2018 criteria: transmantle heterotopia (Type I), closed-lip (Type II), and open-lip clefts (Type III). Whole-exome sequencing was performed in 15 individuals. Logistic regression identified imaging predictors of clinical outcomes.

RESULTS: Transmantle heterotopia was the most common subtype (52.1%), followed by open-lip (30.9%) and closed-lip (17.0%). Additional cortical anomalies were present in 79.8%. Neurodevelopmental impairment occurred in 71.6% and motor impairment in 53.3%, with severity associated with cleft type and laterality. Transmantle and unilateral cases had lower odds of developmental delay. Basal ganglia anomalies, cystic clefts, and hemosiderin or calcium deposition were associated with worse motor and cognitive outcomes. Seizures occurred in 50%; subtype did not predict epilepsy overall, though transmantle cases were more often drug-resistant. Perinatal risk factors, including young maternal age, substance use, and prenatal infections, were common, while genetic yield was low (2.1%).

CONCLUSIONS: This largest cohort to date expands the clinical and radiological spectrum, emphasizing the prognostic value of detailed imaging. Low genetic yield and prevalent prenatal risk factors suggest vascular and environmental contributions to pathogenesis

KEYWORDS: Neurodevelopmental Disorders, Neurogenetics, Epilepsy

275. Early evidence of an emerging NPC treatment paradigm: adrabetadex use alongside arimoclomol and/or N-acetyl-L-leucine

Brian Tumminello, Elizabeth Berry-Kravis, Laurence Keller, Lixia Jiao, Jason Camm, Natasa Rajicic, David Huang, Cary Harding, Jasmine Knoll, Sookyong Koh, Nicola Longo, Randal Richardson, Ian Rossman, Natasha Shur, Joseph Lasky, Forbes Porter

OBJECTIVE: Niemann-Pick disease type C (NPC) is a lethal, rare, progressive, neurodegenerative genetic disorder caused by accumulation of unesterified cholesterol in late endosomes and lysosomes. Approved treatments for neurologic manifestations include arimoclomol in combination with miglustat and N-acetyl-l-leucine (NALL; levacetylleucine). Arimoclomol is a heat shock protein co-inducer and increases proper NPC1 protein folding and NALL restores metabolic dysfunction by acting on mitochondrial function. Adrabetadex is an intrathecal injection in development for infantile-onset NPC. It is a well-characterized 2 hydroxypropyl-β-cyclodextrin proprietary mixture designed to reversibly bind accumulated cholesterol and increase its redistribution from late endosomal and lysosomal compartments, directly targeting the underlying pathophysiology of NPC. Combination use of adrabetadex with arimoclomol and/or NALL has not been described previously.

METHODS: Individuals with infantile-, juvenile-, or adult-onset NPC were eligible to participate in an expanded access program (EAP) for intrathecal adrabetadex. Enrollment in the EAP was initiated in 2013 and required that participants be ineligible for all currently enrolling clinical trials. The program permitted concomitant use of other NPC therapies, arimoclomol, or NALL, which became commercially available in 2024, allowing evaluation of adrabetadex administered alongside arimoclomol, NALL, or both.

RESULTS: At the data cutoff of March 1, 2026, 33 participants had received combination therapy: 6 participants received adrabetadex with arimoclomol, 12 received adrabetadex with NALL, and 15 received all three. Additional participant-level data will be presented.

CONCLUSIONS: This analysis will provide the first description of adrabetadex use in combination with other approved NPC therapies. These observations may help inform clinicians when considering combination therapy.

KEYWORDS: Neurodevelopmental Disorders, Experimental Therapeutics, Neuromuscular

276. In-trial interviews to explore the experience of individuals with Alexander disease in the zilganersen phase 3 clinical trial

Steven Kymes, Anna Roberts, Amy Waldman, Kate Williams, Abigail Collins, Jacqui Bernarde, Elina Matter, Sara Saver, Geneviève Bernard, Stephanie Keller, Chloe Cunningham, Florian Eichler, Yael Hacochen, Jacinda Sampson, Wendy Currlin, Susan Hazel, Lonnie Lee, Montserrat Vera-Llonch

OBJECTIVE: Alexander disease (AxD) is a rare, genetic, progressive astrocytopathy. Zilganersen is the first investigational treatment to demonstrate potential for disease modification in AxD. This in-trial study explored caregivers' perspectives on the experience of participants in the zilganersen trial (ION373-CS1; NCT04849741), including perceived treatment effects and effect on health-related quality of life (HRQoL).

METHODS: Qualitative semistructured video interviews were conducted with caregivers of participants in ION373-CS1 in English-speaking countries (US, UK, Canada, Australia). Participant experiences were recalled separately for the double-blind period (placebo and zilganersen treatment) and the open-label zilganersen treatment periods. Interviewers and analysts were blinded to treatment assignment during coding and analyses.

RESULTS: Of 26 eligible caregivers, 15 (58%) completed the interview, 11 (73%) described perceived change consistent with treatment benefit (ie, improvement or stability with

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zilganersen), and 4 (36%; all with zilganersen) reported worsening. Improvement was most frequently reported in gross motor function, expressive and receptive communication skills, and cognitive function. Caregivers considered improvement (n=4/14; 27%), stability or delayed progression (n=9/14; 64%), or both improvement and stability (n=1/14; 7%) during the double-blind period as a successful treatment outcome. Most caregivers (n=7/8; 86%) reporting improvement described a positive effect on at least 1 aspect of the participant's HRQoL; all 7 perceived the combined improvement in AxD and HRQoL as meaningful.

CONCLUSIONS: This study provides unique insights into the zilganersen treatment experience in AxD. Despite the potential for selection bias, this qualitative report provides important context for ION373-CS1 study results, showing a perceived favorable treatment effect across key AxD symptoms.

KEYWORDS: Neurodevelopmental Disorders, Movement Disorders

277. A Phase 3, Multinational, Randomized, Placebo-Controlled, Double-Blind, Crossover Trial (IB1001-304) Evaluating Levacetylleucine in CACNA1A-Related Neurodevelopment Disorder

Bethany Zanrucha, Tatiana Bremova-Ertl, Michael Strupp, Marc Patterson, Jorgji Kerthi, Janelle Raymond, Taylor Fields, Kyriakos Martakis

OBJECTIVE: CACNA1A-related neurodevelopment disorder (CACNA1A-NDD) refers to a range of rare disorders with pathogenic mutations in the *CACNA1A* gene. This gene plays a critical role in calcium-ion signaling and release of neurotransmitters. Levacetylleucine enters enzyme-controlled pathways to correct metabolic dysfunction, improve energy production, and normalize lysosomal calcium levels, thereby stabilizing inter-ion calcium signaling. IB1001-304 is a planned Phase 3 trial to assess the efficacy and safety of levacetylleucine in CACNA1A-NDD.

METHODS: IB1001-304 will enroll participants ≥4 years with a genetically confirmed diagnosis of CACNA1A-NDD and with manifest cerebellar ataxia based on the Scale for the Assessment and Rating of Ataxia (SARA). Participants will be assessed during three study periods: a baseline period, Treatment Period 1 and Treatment Period 2. Participants will be randomized 1:1 to receive levacetylleucine or placebo for 12-weeks and will crossover to receive the opposite treatment for 12-weeks. An Extension Phase will be planned to assess long-term effects of levacetylleucine. Treatment will be administered orally for a total daily dose of 2-4 g/day based on weight-tiered doses.

RESULTS: The primary efficacy endpoint will be the SARA. Secondary endpoints include Spinocerebellar Ataxia Function Index, quality of life (EQ-5D-5L and EQ-5D-Y), Neurology Quality of Life-Upper Extremity Function, and Clinical Global Impression of Improvement. Safety assessments include adverse event incidence and severity.

CONCLUSIONS: CACNA1A-NDD are a group of neurological disorders with no approved treatments. IB1001-304 will evaluate the efficacy and safety of levacetylleucine in improving neurological symptoms, functioning, and quality of life in people with this disorder.

KEYWORDS: Neurodevelopmental Disorders, Neurogenetics, Movement Disorders

278. Paradoxical Improvement in Social-Communication Behaviors Following a Generalized Seizure in a Child With Autism Spectrum Disorder: A Case Report

Samantha Maguire, Olivia Pavin, Garrett Gianneschi

OBJECTIVE: Autism spectrum disorder (ASD) is frequently associated with epilepsy. In patients with ASD, seizures have been linked to transient neurologic impairment or regression. We describe a pediatric case of paradoxical improvement in communicative and social behaviors following a generalized seizure.

METHODS: We performed a retrospective review of the clinical course of a 5-year-10-month-old male with ASD, global developmental delay, and nonverbal baseline who presented after a seizure. Clinical history, caregiver observations, and video EEG findings were analyzed.

RESULTS: The patient experienced a 30-second generalized seizure characterized by behavioral arrest, upward eye deviation, perioral cyanosis, emesis, bowel incontinence, and tonic-clonic movements. Postictal confusion resolved prior to emergency department arrival. A prior febrile seizure at age 4 was noted. A video EEG was completed a month later, demonstrating frequent sleep-potentiated generalized spikes and polyspikes consistent with a generalized epilepsy pattern. Following the seizure, the patient's parents reported improvement in certain ASD symptoms. At baseline, the patient demonstrated minimal eye contact and nonverbal status. After the seizure, the patient demonstrated increased eye contact, improved attention to speakers, and a new ability to repeat words during speech therapy. These sustained changes were observed over six weeks and corroborated by speech therapy documentation.

CONCLUSIONS: This case highlights improvement in social-communication behaviors following a generalized seizure, suggesting that seizure-related changes in brain network activity may influence behavioral function. Further study is needed to clarify mechanisms and determine whether this phenomenon may inform understanding of network dysfunction in ASD.

KEYWORDS: Neurodevelopmental Disorders, Epilepsy

279. "How Old Does My Child Act?" A Novel Application of the General Movement Assessment Motor Optimality Score-Revised as a Clinical Marker of Developmental Age in Infants with Critical Congenital Heart Disease

Tara Johnson, Alexa Escapita, Heather Watson, Jenny Carr, Dala Zakaria

OBJECTIVE: Infants with critical congenital heart disease (cCHD) are disproportionately impacted by developmental motor delay. Structural neuroimaging studies in this population demonstrate brain dysmaturity, with brain volumes and myelination patterns often lagging 4 weeks behind healthy

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peers. The General Movement Assessment (GMA) and accompanying Motor Optimality Score-Revised (MOS-R) are predictive of neurodevelopmental disabilities, with "fidgety" movements and optimal MOS-R scores indicating low risk for neurodevelopmental disabilities. Our objectives were to (1) present GMA outcomes in infants with cCHD and (2) determine the developmental ages of "fidgety" infants without "age-adequate" movement patterns.

METHODS: In a retrospective cohort study, an advanced reader interpreted "fidgety age" GMA videos in cCHD infants from an outpatient cardiac neurodevelopmental program. We reported the proportion with "fidgety" movements. In "fidgety" infants without "age-adequate" movement patterns, we determined the median age at which their movements would be "age-adequate."

RESULTS: We identified 29 infants with cCHD. 16 (55%) had normal "fidgety" movements. However, 10 (62%) of "fidgety" infants did not demonstrate "age-adequate" movement patterns. Of these, 8 (80%) met criteria for "age-adequate" movement patterns if the infant were 4 weeks younger.

CONCLUSIONS: In infants with cCHD, only 21% had both "fidgety" and "age-adequate" movement patterns, suggesting increased risk of adverse neurodevelopmental outcomes in the remainder. In "fidgety" infants without "age-adequate" movement patterns, their clinical dysmaturity was commensurate with expected structural dysmaturity. Our study is the first to quantify age-specific maturity of cCHD infants' movements with the MOS-R, supporting its application as a potential clinical marker of brain dysmaturity in these high-risk infants.

KEYWORDS: Neurodevelopmental Disorders, Neonatal Neurology

280. Study Design of ROCKET and ORBIT and Initial Insights into Disease Trajectory in Pelizaeus-Merzbacher Disease

Katrina Moore, Joshua Bonkowsky, Stephanie Keller, Amy Waldman, Candice Junge, Garrett Miller, Nicole Wolf

OBJECTIVE: Pelizaeus-Merzbacher Disease (PMD) is a rare X-linked hypomyelinating leukodystrophy, caused by duplications (most common phenotype) or pathogenic variants in the *PLP1* gene, affecting a major myelin protein. PMD typically presents in infancy or early childhood with nystagmus, hypotonia and cognitive impairment. PMD is clinically heterogenous, with limited longitudinal natural history and therapeutic approaches. ION356 is an investigational modified antisense oligonucleotide (ASO) drug that selectively targets *PLP1* pre-mRNA, reducing *PLP1* mRNA, which encodes PLP1 protein.

METHODS: Two complementary clinical studies are underway to address critical gaps in PMD research. ROCKET (NCT05659901) is a non-interventional prospective and retrospective study enrolling up to 32 male participants with PMD and genetically confirmed *PLP1* duplication, aged 6 months to 17 years. Participants undergo longitudinal collection of fluid biomarkers (cerebrospinal fluid and blood), neuroimaging, and standardized clinical assessments over approximately 26 months. ORBIT (NCT06150716) is a Phase 1b, open-label, multiple-ascending dose (MAD) study evaluating ION356 in approximately 24 male pediatric participants with genetically confirmed *PLP1* duplication. The study includes a 48-week MAD period followed by a 109-week long-term extension. ROCKET and ORBIT enrollment is ongoing.

RESULTS: Early longitudinal observations from ROCKET provide initial insights into disease trajectory in PMD, reflecting a disease course characterized by profound developmental arrest and widening divergence from age-appropriate milestones.

CONCLUSIONS: ROCKET and ORBIT collectively establish a foundation for clinical trial readiness in PMD by defining disease trajectory, enabling biomarker development, and advancing interventional research.

KEYWORDS: Neurodevelopmental Disorders, Experimental Therapeutics

281. Outcomes in participants with infantile-onset Niemann-Pick disease type C receiving prompt and sustained treatment with adrabetadex

Jameson Korb, Elizabeth Berry-Kravis, Laurence Keller, Lixia Jiao, Natasa Rajicic, David Huang, Nicola Longo, Kristina Julich, Jean-Baptiste Le Pichon, Randal Richardson, Jasmine Knoll, Sookyong Koh, Young-Min Kim, Leigh Ramos-Platt, Eugene Kim, Ian Rossman, Paula Schleifer, Natasha Shur, Joseph Lasky

OBJECTIVE: Niemann-Pick disease type C is a lethal, rare, progressive, neurodegenerative genetic disorder caused by impaired cholesterol trafficking. Infantile-onset NPC (IO-NPC) (neurological onset <6), is associated with rapid neurodegeneration and premature mortality with mean (SD) ages of death of 5.6 (2.0) years (<2 years onset) and 13.4 (6.7) years (2 to <6 years onset). Adrabetadex is an investigational treatment designed to transport accumulated cholesterol out of the lysosome and restore intracellular trafficking, targeting the underlying disease. Prior analyses demonstrated improved survival and reduced neurological progression with adrabetadex in IO-NPC compared with matched controls.

METHODS: Individuals with IO-NPC participated in an expanded access program (EAP) initiated in 2013. Intrathecal adrabetadex was administered every 2 weeks with age-based starting doses and protocol-specified titration, with dose adjustments permitted. Outcomes included change from baseline in the Rescored 4-domain NPC Clinical Severity Scale (R4DNPCCSS). Participants with sustained treatment ≥5 years were stratified by treatment initiation <1 year (prompt) or ≥1 year (delayed) after neurological onset.

RESULTS: Twenty-five participants were included (prompt: n=9; delayed: n=16). Baseline R4DNPCCSS scores were lower in the prompt group (median [Q1, Q3] 1.5 [0.5, 2.5]) than in the delayed group (5.0 [2.0, 10.0]). Over 1–6 years of follow up, median changes from baseline were stable or improved in the prompt group, whereas the delayed group showed greater variability over time.

CONCLUSIONS: Adrabetadex treatment was associated with slowed disease progression relative to published natural

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history. Initiation within 1 year of neurological symptom onset may maximize benefit, warranting future studies.

KEYWORDS: Neurodevelopmental Disorders, Experimental Therapeutics, Neuromuscular

282. From Development to Early Real-World Use: Clinical and Formulation Rationale for DAYBUE® Stix in Rett Syndrome

Alyssa Peckham, Mona Darwish, Ravi Tejwani, Louise Cosand

OBJECTIVE: Trofinetide is the first approved treatment for Rett syndrome (RTT). The efficacy and safety of the ready-to-use oral solution of trofinetide (DAYBUE®) was established in clinical trials, yet real-world experience revealed challenges in some patients regarding excipient sensitivity, taste, large dose volume, dietary restrictions, and refrigerated storage/portability. DAYBUE® Stix, a trofinetide powder for oral solution, was designed to address these challenges. Here, we summarize the data supporting DAYBUE® Stix development and present early learnings on the real-world use of DAYBUE® Stix.

METHODS: A randomized, Phase 1 study evaluated the bioequivalence of DAYBUE® Stix and DAYBUE®. A separate, open-label assessment of taste and compatibility with beverages was performed by trained sensory panelists. Formulation and ingredient comparisons were conducted to characterize formulation differences. Qualitative, real-world insights of DAYBUE® Stix were collected with pharmacy data and in advisory boards.

RESULTS: DAYBUE® Stix is bioequivalent to DAYBUE® based on pharmacokinetic analysis, supporting 1:1 dosing interchangeably. Compared with DAYBUE®, DAYBUE® Stix excludes maltitol, preservatives, and red dye; it reduces sucralose and carbohydrate burden, alongside dose volume flexibility. Taste assessments showed that the flavor quality of DAYBUE® Stix varied by beverage and reconstitution volume, with increased dilution and viscous vehicles mitigating sourness and astringency. Early real-world insights from pharmacy data and advisory boards will be presented at the congress.

CONCLUSIONS: DAYBUE® Stix addresses real-world administration needs in RTT. The integration of bioequivalence, formulation, taste, and early real-world insights support the role of DAYBUE® Stix as a flexible and patient-centered treatment option for RTT.

KEYWORDS: Neurodevelopmental Disorders

283. Survival outcomes by baseline disease burden in participants with infantile-onset Niemann-Pick disease type C treated with adrabetadex

Elizabeth Berry-Kravis, Laurence Keller, Lixia Jiao, John Winnike, Natasa Rajicic, David Huang, Forbes Porter

OBJECTIVE: Niemann–Pick disease type C is a lethal, rare, progressive neurodegenerative genetic disorder caused by impaired cholesterol trafficking. Infantile-onset NPC (I-NPC) is the most severe, rapidly progressive phenotype associated with premature mortality. Adrabetadex has been shown to improve overall survival in I-NPC compared with matched external controls (HR [95% CI]: 0.289 [0.141–0.593]; $P<0.0001$). This analysis evaluated overall survival by baseline disease severity, assessed using a rescored 4-domain NPC Clinical Severity Scale (R4DNPCCSS; ambulation, fine motor function, speech, rescored swallowing) in adrabetadex-treated individuals with I-NPC.

METHODS: Individuals with I-NPC (neurological onset <6 years) treated with adrabetadex in clinical studies or the Expanded Access Program were included. Baseline R4DNPCCSS scores (0–5 per domain; higher scores indicate greater impairment) were used to stratify participants into disease burden tertiles: low (≤4), medium (>4–≤9), high (>9). Overall survival was estimated using Kaplan–Meier methods.

RESULTS: Seventy-six participants were included in the analysis stratified by low (n=29), medium (n=23), and high (n=24) baseline R4DNPCCSS scores. Participants received adrabetadex treatment for up to 10 years. At 5 years, Kaplan–Meier–estimated overall survival was 100% (95% CI: 100%, 100%) in the low R4DNPCCSS group, 82% (95% CI: 55%, 94%) in the medium group, and 71% (95% CI: 46%, 86%) in the high group.

CONCLUSIONS: Individuals treated with adrabetadex with the lowest baseline severity demonstrated the longest survival observed, (100% survival at 5 years), supporting the importance of initiating adrabetadex treatment before advanced disease progression.

KEYWORDS: Neurodevelopmental Disorders, Experimental Therapeutics, Neuromuscular

284. Case Report of Siblings With Infantile-Onset Niemann-Pick Type C (I-NPC) Initiating Adrabetadex at Different Ages and Intervals From Disease Onset

Kristina Julich, Lance Trainor, Laura Schmelz, Irene von Hennigs, Pam Andrews, Elizabeth M Berry-Kravis

OBJECTIVE: Niemann–Pick disease type C (NPC) is a rare, progressive, neurodegenerative genetic disorder. The infantile-onset form (I-NPC) is the most severe phenotype, typically fatal before age 6. This report describes the impact of early diagnosis and adrabetadex initiation, an investigational therapy targeting the underlying cholesterol trafficking defect, in siblings with I-NPC.

METHODS: Parents and the treating physician summarized disease progression before and after intrathecal adrabetadex treatment through an expanded access program (EAP).

RESULTS: Sibling A exhibited neurological onset at age 3 with ataxia, gross motor decline, and tremors/dysmetria. Sibling B exhibited onset at 13 months with inability to stand or walk without assistance. Both were diagnosed with I-NPC in early 2016; Sibling A at age 6, Sibling B at 21 months. Following diagnosis, Sibling A enrolled in a clinical trial and was randomized to placebo for 10 months. Due to progression, she initiated rescue therapy with adrabetadex via EAP at age 6.75. Sibling B initiated adrabetadex via EAP at 23 months. Sibling A (now 16) shows no progression after 9 years of treatment, but symptoms persist. Sibling B (now 12), treated earlier in the disease course, remains minimally symptomatic with no evidence of disease progression after 10 years.

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CONCLUSIONS: Despite the rapid progression of I-NPC, both demonstrated preservation of neurological function with adrabetadex. Sibling B, treated earlier, remains minimally symptomatic, whereas Sibling A, who initiated treatment years after symptom onset, shows stabilization with residual symptoms. These observations support early diagnosis and timely treatment initiation to optimize outcomes in I-NPC.
KEYWORDS: Neurodevelopmental Disorders, Experimental Therapeutics, Neuromuscular

285. Evaluating Agreement Between Clinical and Caregiver-Reported Neurodevelopmental Outcomes in Early Childhood Following Prenatal SARS-CoV-2 Exposure

Elyse Lanquaye, Manuela Iglesias, Ruth Olujobi, Heather Gordish-Dressman, Lora Jackle, Jessica Harkness, Lauren Patterson, Samantha Mattern, Robin Baker, Gianluca Ursini, Sarah Mulkey

OBJECTIVE: To evaluate the relationship between direct child developmental evaluation and parent-completed questionnaires at age 3 for a cohort of children, both antenatally exposed and unexposed to SARS-CoV-2.
METHODS: To understand child outcomes following antenatal SARS-CoV-2 exposure, children were evaluated by the Bayley Scales of Infant and Toddler Development (BSID-III) at age 3, while mothers completed the Child Behavior Checklist (CBCL), Behavior Rating Inventory of Executive Function: Preschool Edition (BRIEF-P), and Vineland-3 questionnaires. Normality of cognitive and language BSID-III outcomes was verified, followed by linear regression analysis between BSID-III cognition and Vineland-Adaptive Behavior Composite (ABC) percentile, CBCL autism and ADHD problems t-scores, and BRIEF-P Global Executive Composite (GEC) percentile to assess relationship strength and direction. BSID-III language and Vineland-3 communication percentile, and CBCL autism, ADHD, internal, and external problems t-scores underwent regression analysis. Each model included covariates of infant age at assessment, maternal education and ethnicity, gestational age at birth, McNeil severity score of 5, and SARS-CoV-2 status.
RESULTS: We evaluated 212 children, 140 (66%) of whom had prenatal SARS-CoV-2 exposure. BSID-III language scores were related ($p < 0.001$) to all parental questionnaire domains. BSID-III cognition and corresponding questionnaire domains, excluding CBCL ADHD problems, demonstrated similar significance. Maternal education was significant ($p < 0.001$) across regressions, and subsequent post-hoc analyses correlated higher maternal education to improved neurodevelopmental outcomes. Additionally, children unexposed to SARS-CoV-2 demonstrated improved cognitive outcomes ($p \leq 0.048$).
CONCLUSIONS: Scores on direct child developmental evaluations and parent-completed child development questionnaires are related, with maternal education and SARS-CoV-2 status being significant predictors of neurodevelopmental outcomes.
KEYWORDS: Neurodevelopmental Disorders, Behavioral Neurology

286. Study Design and Rationale of the ASCEND Study in Patients with Dravet Syndrome

Tara Skarpaas, Steven Kymes, Vidhi Mody, Aaron Yarlas, Dennis Dlugos, Kelly Knupp, Eric Marsh, Takashi Saito, Christine Coquery

OBJECTIVE: Dravet syndrome (DS) is a rare, severe, developmental epileptic encephalopathy mostly caused by loss-of-function variants in the sodium channel gene *SCN1A*, causing $Na_V1.1$ haploinsufficiency. Affected individuals experience early-onset, drug-refractory epilepsy and severe neurodevelopmental comorbidities (cognitive, behavioral, motor impairment). Approved therapies do not address underlying molecular etiology, leaving a substantial unmet need for disease-modifying treatments. ION337 is an investigational, novel splice-switching antisense oligonucleotide with next-generation 2′-O-[2-(methyl-amino)-2-oxoethyl] and mesyl-phosphoramidate modifications designed for durable, robust increases in *SCN1A* mRNA and $Na_V1.1$ expression. ION337 specifically and potently upregulates productively spliced *SCN1A* transcripts with a long duration of action in healthy animals and in a DS mouse model supporting a mechanistically targeted approach to restoring $Na_v1.1$ function. We describe the design and rationale for ASCEND, a first-in-patient study evaluating ION337 as a potential disease-modifying therapy for individuals with DS.
METHODS: ASCEND is a global Phase 1–2 open-label, single- and multiple-ascending-dose study evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of ION337 administered intrathecally every six months in patients with DS aged 2–12 years and a confirmed *SCN1A* variant. The 26-week open-label single-dose period is followed by a 104-week open-label multiple-dose period. The primary objective is safety and tolerability; secondary objectives include pharmacokinetics and antiseizure activity. Exploratory objectives assess patient- and caregiver-relevant outcomes, including functional and neurodevelopmental measures.
RESULTS: Study enrollment is ongoing in 2026.
CONCLUSIONS: ION337's novel chemistry is designed to enhance ASO performance, potentially enabling sustained $Na_V1.1$ restoration with infrequent dosing without the need for a loading dose.
KEYWORDS: Neurodevelopmental Disorders, Epilepsy, Experimental Therapeutics

287. Phenotypic Expansion of the ERF Gene

Connolly Steigerwald, Jullianne Diaz, Shannon Terek, Becky Milewski

OBJECTIVE: As exome and genome sequencing (ES/GS) become standard in clinical practice, the value of robust phenotypic delineation becomes crucial. While ERF variants were initially identified in craniosynostosis cohorts, the disease spectrum rapidly evolved with additional case descriptions. As such, craniosynostosis, previously a hallmark feature, was demonstrated to have more variable expressivity compared to other common features. Utilizing an internal cohort of patients with ERF variants, we sought to further define the associated phenotype.

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METHODS: We performed a retrospective review of 12 ES cases with ERF pathogenic, likely pathogenic, and variants of uncertain significance. Human phenotype ontology (HPO) terms were assigned to features in published cohorts and compared to those provided for internal cases.
RESULTS: Speech delay and facial dysmorphism were consistently observed between internal and published cases (>50%). Global developmental delay, absent from the original cohort, and short stature, identified in 3% of the original cohort, were observed in 50% of internal patients, consistent with recent publications. The internal cohort demonstrated a higher frequency of autism (42% vs 6%) and behavioral issues (67% vs 19%). Craniosynostosis was observed/inferred in 33% of internal cases compared to 75% in the original cohort. Other features only observed internally included axial hypotonia, gastroesophageal reflux, and sleep apnea.
CONCLUSIONS: Although a limited series of cases, our data support the emergence of a broader ERF-related neurodevelopmental phenotype in which craniosynostosis is not a requisite feature. This highlights the value of leveraging laboratory datasets to refine disease spectrums for improved ES/GS filtering and guidance of patient care.
KEYWORDS: Neurodevelopmental Disorders

288. From Baseline Impairment to Progressive Developmental Gains Across Motor and Communication Domains After Treatment with NGN 401 in Phase 1/2 Trial for Rett Syndrome

Bernhard Suter, Timothy Benke, David Lieberman, Jeffrey Neul, Jenny Downs, Melissa Licari, Alana Salvucci, Julie Jordan, Christine Mikail

OBJECTIVE: Rett syndrome is associated with limited acquisition and subsequent loss of hand use, gross motor skills, and communication. We evaluated whether NGN-401-treated participants acquire milestones in a developmentally ordered, progressive manner, similar to typical developmental trajectory.
METHODS: Milestone acquisition across fine motor, gross motor, and communication was assessed longitudinally in four participants treated with NGN-401 with longest follow-up (through 24 months) in the Phase 1/2 trial. Milestones were assessed by an independent central rater based on video review and interpreted within a hierarchical developmental ladder.
RESULTS: All four participants (age 4-7 years) demonstrated post-treatment step-wise acquisition of developmentally higher skills relative to baseline, with durability across follow-up. Fine motor milestones advanced from absent hand use/early prehension patterns to pincer, self-feeding, utensil use, cup holding/drinking, and bimanual transfer (subject-dependent). Gross motor improvements included progression from limited or assisted standing/mobility to pull-to-stand, dynamic balance tasks requiring motor planning, and stair negotiation with or without assistance (subject-dependent). Communication gains included emergence of receptive command-following without gestural cueing, intentional expressive gestures and spoken words with meaning (subject-dependent).
CONCLUSIONS: Across four NGN-401-treated participants with longest follow-up, milestone acquisition patterns showed developmentally ordered, progressive gains across fine motor, gross motor, and communication domains with durability up to 24 months. The sequencing of observed milestone acquisition contrasts with natural history patterns in Rett syndrome, which is typically characterized by limited new milestone attainment and loss of purposeful hand and complex motor skills. Moreover, emergence of early prehension patterns suggest improvements in fine motor function may precede broader functional gains.
KEYWORDS: Neurodevelopmental Disorders

289. Association Between Gestational Age and Cognitive Delay based on the Bayley Cognitive Growth Scale

Blake Windham, Edgard Andrade

OBJECTIVE: This study aims to evaluate the association between gestational age (GA) and the Cognitive Growth Scale (CGGS) of the Bayley Scales of Infant and Toddler Development with the goal to determine whether GA is associated with cognitive delay based on the CGGS.
METHODS: This study included 30 subjects ($N = 30$) with available GA and CGGS data. Both GA and CGGS scores were treated as continuous variables. The relationship between GA and CGGS values was assessed using scatter plot and Pearson correlation analysis. Statistical significance was defined as $p < 0.05$. The null hypothesis stated that GA is not associated with CGGS values.
RESULTS: The mean GA was 35.70 weeks (SD 4.43), and mean CGGS value was 490.80 (SD 18.40). Interpretation of the scatter plot demonstrated no clear linear relationship between GA and CGGS scores. Pearson correlation analysis revealed a weak positive correlation that was not statistically significant ($r = 0.137$, $p = 0.469$). Hence, non-parametric statistics using Kendall's tau and Spearman's rho correlations were performed which revealed p values of 0.913 and 0.983, respectively, confirming initial findings.
CONCLUSIONS: There was no statistically significant association between GA and CGGS scores in this cohort. Hence, the null hypothesis cannot be rejected, and it can be concluded that GA is not associated with CGGS values. Limitations of this study include it may be underpowered as well as being a single-variable analysis without adjustment for confounders such as birth weight or NICU complications. This conclusion should be followed with further studies to better evaluate this association.
KEYWORDS: Neurodevelopmental Disorders

290. Maternally Inherited Variant in the FLG gene in Two Siblings with Autism Spectrum Disorder: Case Report

Julia Totten, Nilaksa Sivanenthiran, Tuba Rashid Khan

OBJECTIVE: Autism spectrum disorder (ASD) is a neurodevelopmental disorder with a multifactorial genetic architecture. With the emergence of whole exome sequencing as a first-tier genetic test, understanding of the genes involved has evolved to encompass dozens of single gene disorders and hundreds of gene variants. This case report of a multiplex family with ASD explores variants in the FLG gene in the context of ASD.

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METHODS: Two siblings with ASD underwent clinical and diagnostic evaluations, whole exome sequencing, and family history analysis. Existing literature was reviewed for associations between FLG and ASD.
RESULTS: Whole exome sequencing revealed distinct de novo pathogenic variants in each sibling. One sibling has a mutation in GRIA2, while the second sibling has a heterozygous duplication within 1q21.1q21.2. Both siblings also shared a maternally inherited FLG frameshift mutation, a variant typically associated with atopic conditions. Notably, the mother was diagnosed with attention deficit/hyperactivity disorder (ADHD) but does not exhibit autistic features.
CONCLUSIONS: The co-occurrence of the FLG variant with established ASD-related pathogenic variants supports the need for further investigation into FLG's role in ASD. This report highlights the value of genetic testing in ASD evaluation and its role in advancing understanding of the condition's genetic structure.
KEYWORDS: Neurodevelopmental Disorders, Neurogenetics, Behavioral Neurology

291. Delayed Recognition of Epilepsy in Children with Autism Spectrum Disorder: A Systematic Quantitative Review of Prevalence, Diagnostic Delay, and Associated Factors

Ayush Tripathy, Shreya Tripathy

OBJECTIVE: To characterize the prevalence of epilepsy in pediatric ASD, synthesize data on diagnostic delay in children with epilepsy, and identify factors associated with under-recognition of epilepsy.
METHODS: PubMed and PsychINFO were searched using terms including "autism spectrum disorder," "epilepsy," "seizure," "diagnostic delay," "comorbidity," and "pediatric." Twenty-four studies were included (k=24; N≈380,000), comprising systematic reviews, population-based cohorts, and clinical cross-sectional studies reporting prevalence, delay, or risk factor data.
RESULTS: Pooled epilepsy prevalence in pediatric ASD ranged from 8–30% across studies (median 12.1–12.5%), rising to 26% in children ≥13 years. In general pediatric epilepsy cohorts, diagnostic delay ≥1 month occurred in 41% of children with early-onset epilepsy; when delay exceeded 1 year, median time-to-diagnosis was 4.4 years—findings applicable to ASD populations given shared phenotypic complexity. Delay ≥1 month was associated with FSIQ reductions of 8–14 points at 8–9-year follow-up. Intellectual disability was the most consistently identified epilepsy risk factor in ASD (prevalence 8% without ID vs. 20–40% with ID). Female sex conferred disproportionate epilepsy risk (male-to-female ratio narrowing from 3:1 in ASD broadly to <2:1 in ASD-epilepsy cohorts). Lower socioeconomic status was independently associated with delayed epilepsy treatment by >6 months. Phenotypic overlap—stereotypies mimicking automatisms, staring spells resembling absence seizures—was identified as a primary driver of clinical misattribution across multiple studies.
CONCLUSIONS: Epilepsy affects a substantial proportion of children with ASD and shares diagnostic barriers with pediatric epilepsy broadly, compounded by ASD-specific communication and behavioral factors. Systematic epilepsy screening within ASD care pathways is warranted to reduce preventable delay.
KEYWORDS: Neurodevelopmental Disorders, Epilepsy, Behavioral Neurology

292. A Call for More Inclusive, Patient-Centered Nomenclature for Antipsychotics in the Treatment of Autism Spectrum Disorder

Nilaksa Sivanenthiran, Julia Totten, Navneet Kaur, Tuba Rashid Khan

OBJECTIVE: Risperidone and aripiprazole are the only FDA-approved medications for the treatment of irritability and aggression associated with autism spectrum disorder (ASD). Despite their established role in managing behavioral symptoms, these medications are classified as "antipsychotics," a term that does not reflect therapeutic intent. This nomenclature may contribute to misunderstanding, stigma, and hesitancy among patients and caregivers. The objective of this work is to examine the implications of antipsychotic nomenclature in ASD.
METHODS: A literature review was conducted examining the evolution of antipsychotic nomenclature, use of these medications in ASD, and terminology changes in neurologic conditions. Studies assessing patient and caregiver perceptions of antipsychotic labeling in psychotic and non-psychotic disorders were reviewed. In addition, perspectives from caregivers of patients with ASD and physicians treating patients with ASD were collected to explore terminology perceptions.
RESULTS: The literature review identified concerns regarding the stigmatizing, misleading nature of the term "antipsychotic." Prior studies demonstrated negative emotional reactions, reduced self-esteem, and delayed treatment initiation. In the current clinical sample, most caregivers and physicians felt the antipsychotic label was misleading, indicated it affected treatment decisions, and supported alternative terminology. Historical precedent from epilepsy care illustrates how revised nomenclature can improve patient understanding.
CONCLUSIONS: The term "antipsychotic," when applied to medications used to manage irritability and aggression in ASD, may contribute to stigma and barriers to care. Adopting patient-centered nomenclature that reflects therapeutic intent may enhance shared decision-making and facilitate inclusive care. Further engagement with individuals with ASD, families, clinicians, and professional societies is warranted to advance precise, respectful terminology.
KEYWORDS: Neurodevelopmental Disorders, Behavioral Neurology, Diversity, Equity, Inclusion

293. Antibody responses to UX111 gene therapy and impact on cerebrospinal fluid (CSF) heparan sulfate (HS) and neurodevelopment in mucopolysaccharidosis IIIA (MPS IIIA)

Heather Lau, Eines Monteagudo, Maria de Castro, Maria Couce, Nicholas Smith, Kaushik Patra, Melissa Wolf, Barbara Sullivan

OBJECTIVE: MPS IIIA (Sanfilippo type A) is a progressive neurodegenerative disease characterized by developmental

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arrest, regression, and early death. UX111 (rebisufligene etisparvovec) is an investigational intravenous AAV9 gene therapy that delivers human *SGSH* for MPS IIIA. In clinical trials, UX111 reduced CSF HS and stabilized or improved neurodevelopmental outcomes. Here we describe antibody responses to SGSH and the impact on CSF HS levels and neurodevelopmental function.

METHODS: UX111 safety and efficacy are being assessed across two open-label studies (NCT02716246, NCT04088734) and an ongoing long-term follow up (NCT04360265). Data snapshot: 22Sept2025.

RESULTS: Thirty-three children received UX111. While all developed anti-SGSH antibodies, two demonstrated rapid, high, and sustained serum and CSF anti-SGSH antibodies followed by a rebound in CSF HS to ≥50% of baseline. Both had received $3x10^{13}$ vg/kg UX111 and demonstrated initial rapid reductions in CSF HS with subsequent initial improvement or stabilization in neurodevelopmental functions. The first participant showed a rebound in CSF HS between Months 6-18 with subsequent declines in neurodevelopmental function beginning ∼1 year later. The second showed a rebound in CSF HS at Month 24. This participant began adjuvant immunomodulation (bortezomib, rituximab, and sirolimus) at Month 36. Immunomodulation was followed by a decrease in serum and CSF anti-SGSH antibodies and eventual reduction of CSF HS back to 50% of baseline. This participant tolerated adjuvant IM with no serious adverse events. Throughout, neurodevelopmental function was maintained.

CONCLUSIONS: These preliminary observations are consistent with a potential role for adjuvant immunomodulation in supporting immune tolerance to the transgene protein SGSH.

KEYWORDS: Neurodevelopmental Disorders

294. A case of GRIN2B-related neurodevelopmental disorder presenting with white matter abnormalities concerning for leukoencephalopathy

Gabrielle Herman, Shailly Jain, Natarie Liu

OBJECTIVE: We describe a case of an infant with white matter changes initially concerning for progressive leukodystrophy, who was ultimately found to have a *GRIN2B* loss of function variant.

METHODS: Case report.

RESULTS: A 9 month old male presented with developmental delays since 5 months of age and concerns of dysphagia. On examination, he was hypotonic with brisk reflexes. While awaiting neuroimaging, the patient's developmental progress and feeding abilities declined, and he developed recurrent dystonic posturing of his arms and legs. MRI brain at 14 months of age found biposterior-predominant T2 hyperintense white matter lesions suspicious for leukodystrophy or metabolic encephalopathy. A trio whole exome found a pathogenic heterozygous loss of function variant in *GRIN2B* (c.2512del) in the C-terminal domain. He was started on L-serine supplementation at a dose of 500 mg/kg/day and started rehabilitation therapies. Repeat MRI at 35 months showed stable white matter. Clinically, the patient is making developmental gains at age 3 years, functioning at a level of 18-24 months of age.

CONCLUSIONS: *GRIN2B*-related disorder is characterized by developmental delay and intellectual disability, and commonly also includes epilepsy, movement disorders, and feeding problems. More rarely, disorders of cortical development have been described. To our knowledge this is the first *GRIN2B* patient described with white matter changes. This report not only highlights the broad phenotypic spectrum of this rare disorder but also adds to the growing literature of l-serine supplementation as a therapeutic agent for *GRIN* related neurodevelopmental disorders.

KEYWORDS: Neurodevelopmental Disorders, Neurogenetics

295. Expanding Reality: A Systematic Review of XR Interventions for Social and Functional Outcomes in Children with Autism

Chelcie Puetz, Georgia Barbayannis, Sinan Turnacioglu

OBJECTIVE: Extended reality (XR) interventions offer immersive, interactive environments that may enhance engagement and skill development in children with autism spectrum disorder (ASD). This review systematically evaluates the effectiveness of virtual reality, augmented reality, and mixed reality interventions for children and adolescents with ASD. Outcomes examined include DSM-5 core domains, social communication deficits and restricted or repetitive behaviors, as well as functional domains such as motor skills, executive functioning, and adaptive independence.

METHODS: A systematic search of PubMed, Scopus, and Web of Science identified peer-reviewed studies published between 2015 and 2026. Eligible studies included participants aged 2-18 years with ASD who received a VR, AR, or MR intervention and reported quantitative pre- to post-intervention outcomes in at least one relevant clinical domain. Two independent reviewers conducted screening and selection. Data extracted included study characteristics, participant demographics, intervention details, outcome measures, and statistical findings. Risk of bias in randomized trials was assessed using RoB 2. Findings were qualitatively synthesized by outcome domain.

RESULTS: Nineteen studies (n=640-1,165 participants) were included. Most reported significant improvements in social communication, emotion recognition, and joint attention following XR interventions. Several randomized trials demonstrated greater gains in adaptive behaviors, executive functioning, and motor skills compared to controls. Improvements in anxiety and vocational readiness were also noted. Engagement and feasibility were consistently high, though heterogeneity in intervention design and outcome measures limited comparability.

CONCLUSIONS: XR interventions show promise for improving social and functional outcomes in youth with ASD, though larger trials are needed to confirm efficacy and long-term impact.

KEYWORDS: Neurodevelopmental Disorders, Experimental Therapeutics

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296. Behavioral Phenotypes of Autism in Tuberous Sclerosis Complex Reveal Distinct Connectivity Patterns Using Lesion Network Mapping

Jorge Ortega-Márquez, Alberto Castro Palacin, Alexander Li Cohen

OBJECTIVE: Autism Spectrum Disorder (ASD) is highly prevalent in individuals with Tuberous Sclerosis Complex (TSC), yet its clinical heterogeneity remains poorly understood. Leveraging TSC as a lesion-defined model, this study aimed to identify data-driven behavioral phenotypes and determine whether lesion-derived functional connectivity profiles map to clinically meaningful subgroups.

METHODS: A cross-sectional analysis was performed in individuals with TSC from the TSC Autism Centers of Excellence Research Network (TACERN) (n=114), integrating structural MRI with multidimensional behavioral assessments (ADOS-2, Mullen Scales of Early Learning, language measures). Unsupervised clustering approaches (k-means, hierarchical clustering with Ward's D2 linkage) were applied to identify behavioral phenotypes. Lesion network mapping was used to estimate functional connectivity profiles associated with lesion locations. Phenotype-specific and between-group connectivity analyses were conducted with appropriate correction for multiple comparisons.

RESULTS: Three clinically interpretable phenotypes were identified: (1) severe impairment with high ASD burden and low adaptive functioning, (2) moderate impairment with intermediate symptom severity, and (3) relatively preserved functioning with low ASD symptom burden.Lesion network mapping revealed distinct connectivity patterns across phenotypes. The severe phenotype showed distributed connectivity involving cerebellar, thalamic, and dorsal frontoparietal networks, whereas intermediate and preserved phenotypes demonstrated more focal subcortical–cerebellar patterns. Between-group comparisons indicated a graded increase in network disruption, with cerebellar vermis and deep gray nuclei emerging as key differentiating regions.

CONCLUSIONS: Data-driven phenotyping in TSC identifies distinct, circuit-level substrates of ASD heterogeneity beyond traditional diagnosis. These findings support a network-based framework linking focal lesions to distributed functional systems and clinical phenotypes, with implications for biologically informed stratification and therapeutic targets.

KEYWORDS: Neurodevelopmental Disorders, Neuroimaging, Behavioral Neurology

297. Incorporation of an FDA-Authorized Eye-Tracking Diagnostic Device for Autism Evaluation into a Multi-provider Neurology Clinic

Abigail Ley, Isabela Iglesias

OBJECTIVE: To address barriers in the timely diagnosis of autism spectrum disorders in toddlers, an FDA-authorized eye-tracking (FDA 510(k): K230337) diagnostic device was integrated into the autism evaluation process in a multi-provider child neurology practice.

METHODS: Following a standardized comprehensive diagnostic evaluation of children 16-30 months old, those with borderline symptoms of autism undergo assessment with the eye-tracking device. The total evaluation typically takes no more than 1 hour. In cases where the device and clinical assessment provide ongoing equivocal results, a referral is placed for secondary evaluation through psychology or a board-certified neurodevelopmental specialist.

RESULTS: The device was administered to 140 toddlers; 15 (10.7%) were administration failures due to insufficient or invalid data. Of the 125 children who completed a valid session, 60 (48%) had true positive and 31 (24.8%) had true negative results; 9 (7.2%) had definitive false negative results; 20 (16%) had questionable false negative results and 5 (4%) had questionable false positive results with secondary evaluation pending.

CONCLUSIONS: Findings support eye-tracking as an effective tool for rapid autism identification or rule-out in toddlers, facilitating earlier and appropriate community referrals and intervention access. However, three key limitations exist: 1) Lack of third-party reimbursement restricts use of the device to children with unclear neuro-behavioral profiles, which may impact program-wide accuracy of the test; 2) limited secondary evaluation access in suspected cases of false positive or false negative device results; and 3) a 10.7% administration failure rate. Despite these challenges, the model offers significant operational and diagnostic benefits for multi-provider neurology programs.

KEYWORDS: Neurodevelopmental Disorders, Behavioral Neurology

298. Clinical Genetic Testing Findings in Autism Spectrum Disorder With and Without Developmental Regression

Advika Ventrapragada, Deanna Streck, Mainul Hoque, Ryan Martin, Garrett Gianneschi, Milind Mahajan

OBJECTIVE: Developmental regression in autism spectrum disorder (ASD) is sometimes attributed clinically to environmental or physiologic triggers. Whether children with regressive ASD have a lower burden of diagnostic genetic findings than children with non-regressive ASD remains uncertain. We reviewed clinical genetic testing results in pediatric patients with ASD with and without regression.

METHODS: We performed a retrospective review of 55 pediatric patients evaluated with genetic testing, including 40 patients categorized as ASD without regression and 15 patients categorized as developmental regression. Available testing included chromosomal microarray, prior next-generation sequencing, and additional variant review. Results were categorized as diagnostic, inconclusive, or nondiagnostic based on reported pathogenicity and clinical relevance.

RESULTS: Among 40 patients in the ASD/non-regression group, 4 had diagnostic findings and 4 had inconclusive findings. Among 15 patients in the regression group, 2 had diagnostic findings and at least 1 had an inconclusive finding. Diagnostic yield was therefore 10.0% in the ASD/non-regression group and 13.3% in the regression group. The regression group did not show an absence or reduction of clinically significant genetic findings compared with the non-regression ASD group.

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CONCLUSIONS: In this exploratory cohort, developmental regression was not associated with a lower rate of diagnostic genetic findings. These results do not support the assumption that regressive ASD is primarily non-genetic or environmentally caused. Larger cohorts with standardized regression definitions, parental testing, and systematic review of antecedent events are needed to clarify whether regression reflects genetic susceptibility, environmental modification, or gene-environment interaction.

KEYWORDS: Neurodevelopmental Disorders

299. Optimizing the MCHAT-R for Autism Screening

Joshua Ewen, Sean McWeeny

OBJECTIVE: Early screening for autism is essential to earlier identification and subsequent access to evidence-based interventions. However, the available screening tools have low sensitivity to detect autism. The predictive power of the individual items have not been fully described nor incorporated into the risk algorithm. The goal of the present study was to understand which Modified Checklist for Autism in Toddlers – Revised (MCHAT-R) items best predicted diagnostic outcomes.

METHODS: Using electronic health record data, we pulled the MCHAT-R scores from all children ($n = 11{,}232$) who were seen at Lurie Children's Primary Care clinics since 2019. 2.2% of the children ($n = 244$) went on to receive an autism diagnosis, in line with current incidence rates. We tested a one-factor confirmatory factor analysis model, which indicated it was sufficiently unidimensional for an item response theory (IRT) model (CFI/TLI = .96, RMSEA = .026, SRMR = .065). We conducted both a two-parameter IRT model and a cross-validated random forest (RF) classification model to extract item discrimination/difficulty and importance metrics, respectively.

RESULTS: The best performing items according to both IRT and RF importance sampling-derived metrics were "point to show" and "point to request" (IRT model), and "joint attention" and "pretend play" (RF model). Four items were particularly uninformative in the IRT model: "wondered if deaf," "unusual finger movements," "noise sensitivity," and "likes movement activities."

CONCLUSIONS: There is the potential to further revise the MCHAT-R to increase efficiency (decrease the number of items) and perhaps increase sensitivity/specificity.

KEYWORDS: Neurodevelopmental Disorders, Behavioral Neurology

300. Gesture Imitation with Simultaneous Movement Elements Challenging for Autistic Children

Joshua Ewen, Sean McWeeny

OBJECTIVE: Imitation plays a critical role in enhancing social-communicative reciprocity and social skill learning. Autism-related imitation differences are thought to have a multifactorial origin in social, motor, cognitive, and representational domains. However, these domains share many overlapping processes, and there is preliminary evidence that simplifying gesture imitation by presenting components sequentially—as opposed to simultaneously, as is done in most naturalistic gestures—may alleviate these differences. If this is the case, there is substantial clinical relevance for teaching children to imitate or learn other skills in sequential fashion. The primary goal of the present study was to understand the extent to which sequential presentation could alleviate autism-associated difficulties with imitation.

METHODS: We assessed 7–12-year-old children with FSIQ≥80 with (n=50) and without autism (n=66) on a novel-gesture imitation task. The task comprised 20 novel hand/arm gestures, each with 4-6 movement elements, presented via video. All gestures were presented in sequential and simultaneous conditions across four blocks, counterbalanced across participants. Mixed effects models were utilized, with age and sex included as covariates.

RESULTS: Non-autistic children performed significantly more accurately than autistic children on novel gesture imitation (p<0.001, d=0.98), with sequential gestures performed more accurately than simultaneous gestures across groups (p<0.001, d=0.45). A significant interaction was found, such that the autistic group benefitted more from sequential presentation than did the non-autistic group (p=0.04, d=0.22).

CONCLUSIONS: Sequential (versus simultaneous) presentation of gesture elements improves imitation accuracy, particularly for autistic children. Simplifying complex processes temporally may help autistic individuals learn new social and motor skills.

KEYWORDS: Neurodevelopmental Disorders, Behavioral Neurology

301. Understanding the Medical Experience of families of patients with Angelman Syndrome: A qualitative study

Maya Ayoub, Krithika Praveen, Gianna Karkafi, Gery Ryan, Elana Evan, Rajsekar Rajaraman, Rujuta Wilson

OBJECTIVE: Angelman Syndrome (AS) is a genetic neurodevelopmental disorder presenting with developmental delays, ataxia, and speech difficulties. Despite major research initiatives, there remains little work on understanding factors that affect AS medical experiences. Many patients are minimally speaking, which complicates understanding of needs during clinical encounters. This study explores themes affecting AS individuals' and families' experiences in medical encounters.

METHODS: This single-center, qualitative study recruited participants through clinics and national organizations. Virtual semi-structured interviews and focus groups were conducted, with a follow-up survey for demographics. The data is in the process of being coded with a reflexive thematic analysis approach.

RESULTS: 20 caregivers of AS individuals completed focus groups/ interviews, and 17 completed surveys. 59% were fathers of AS individuals; the majority of participants (47%) were Black or African American. Questions were directed at signals of comfort and anxiety in AS individuals, tools for preparation for medical visits, and use of Augmentative and Alternative Communication (AAC) and visual supports in medical encounters. Emerging codes focus on communication being demonstrated in alternative ways by AS individuals, and comfort of medical experiences being affected by wait time, appointment pace, providers' level of listening to caregivers' concerns, and direct communication with the AS individual themselves.

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CONCLUSIONS: This study provides deep qualitative data on key aspects of care for minimally-speaking individuals. Thematic analysis around the data are being analyzed; themes will inform an intervention informing clinic supports with AS and other genetics conditions with communication difficulties and will be presented at the time of the meeting.

KEYWORDS: Neurodevelopmental Disorders, Neurogenetics, Diversity, Equity, Inclusion

302. The Developmental Plateau in Rett Syndrome: New Insights from the Natural History Study Inform Novel Interventional Study Designs

Minna Montgomery, Tessa Clarkson, Alexa Bowie, Patrick O'Keefe, Craig Mallinckrodt, Suku Nagendran, Eric Marsh, Bernhard Suter, Rumana Haque-Ahmed, Elizabeth Berry-Kravis, Jeffrey Neul

OBJECTIVE: Heterogeneity of Rett syndrome (RTT) poses challenges for well-controlled, ethical interventional gene therapy trials. We analyzed U.S. Rett Natural History Study (RNHS) data to define the developmental plateau and inform responder thresholds for single-arm Patient-as-own-control (PAOC) trial design to address these challenges.

METHODS: RNHS data (N=1,191; 2006–2021) was analyzed using criteria aligned with the interventional trial (female, typical RTT, MECP2 mutation). Caregiver-reported gain, loss, and regain across 28 milestones were modeled using cumulative incidence and multivariable Cox proportional hazards (CPH). Repeated simulations assumed cohorts of N=15 and a 6.7% null hypothesis (1 spontaneous gain/regain per cohort) in participants ≥6 years.

RESULTS: Spontaneous first-time milestone gain at ages 1-<6 ranged from 0-54% (lowest at age 5; highest at ages 2-3). A clear developmental plateau emerged at age 6, after which spontaneous milestone gain/regain was rare (∼0-3% across milestones). In CPH models, no prognostic factors beyond age and time since loss predicted gain/regain. Across 150,000 patient simulations, <2% (n<3000) spontaneously gained/regained milestones. Simulations support "≥1 gain/regain" as a responder threshold and indicate a feasible PAOC sample size of ∼15 in the ≥6 years population.

CONCLUSIONS: RNHS provides a robust external benchmark for milestone gain/regain and supports an ethical single-arm PAOC study in the plateau population, with ≥1 gain/regain as a primary endpoint. These findings support the FDA-aligned REVEAL pivotal trial enrolling patients aged 6-<22, a population with stable baseline function and low spontaneous improvement rates.

KEYWORDS: Neurodevelopmental Disorders, Experimental Therapeutics, Neurogenetics

303. Early-Life Cadmium and Arsenic Exposure and Neurodevelopmental Outcomes: Clinical Implications for Pediatric Risk Identification

Aryana Wadhwani

OBJECTIVE: To characterize neurodevelopmental outcomes associated with prenatal and early childhood cadmium and arsenic exposure and evaluate implications for pediatric risk identification and developmental surveillance.

METHODS: A systematic scoping review was conducted using PRISMA and PICO frameworks. Literature searches of PubMed, Scopus, and Web of Science (2015–2025) identified 33 eligible studies examining cadmium and arsenic exposure from the prenatal period through early childhood. Data were synthesized to assess neurodevelopmental outcomes, exposure biomarkers (e.g., blood, urine, maternal matrices), and study design characteristics, with emphasis on clinical interpretability.

RESULTS: Across studies, early-life cadmium and arsenic exposure was consistently associated with adverse neurodevelopmental outcomes, particularly in domains of attention, cognition, and behavioral regulation. Substantial heterogeneity in exposure assessment, biomarker selection, and outcome measurement limited cross-study comparability and clinical translation. Few studies incorporated co-exposure modeling or longitudinal follow-up sufficient to inform pediatric risk stratification, and populations from low- and middle-income settings were underrepresented despite higher exposure burdens.

CONCLUSIONS: Evidence supports an association between early-life cadmium and arsenic exposure and adverse neurodevelopmental outcomes; however, gaps in standardization and longitudinal data limit clinical application. Improved exposure assessment and diverse, long-term studies are needed to inform pediatric screening, environmental risk assessment, and early intervention strategies.

KEYWORDS: Neurodevelopmental Disorders, Global Neurology, Diversity, Equity, Inclusion

304. Establishing the Rett Syndrome Developmental Milestone Assessment (RS-DMA) as a Primary Endpoint for Interventional Studies

Tessa Clarkson, Megan Quarmley, Minna Montgomery, Chris Jones, Robyn Ryther, David Lieberman, Elizabeth Berry-Kravis, Kristin Phillips, Emily McGinnis, Rumana Haque-Ahmed, Suku Nagendran

OBJECTIVE: Trial design in Rett syndrome (RTT) is complicated by heterogeneity in baseline function and progression. Existing assessments may not detect individual change in single-arm study designs. We developed the RS-DMA, an individualized endpoint enabling rigorous evaluation of treatment-associated efficacy. RS-DMA milestones were derived from the U.S. Rett Natural History Study and filtered to prioritize high-utility, activities-of-daily-living–linked skills while excluding low-sensitivity milestones.

METHODS: RS-DMA evaluates 28 milestones across communication, gross and fine motor domains statistically unlikely to show spontaneous gain/regain without intervention in the developmental plateau population (≥6 years). Milestone eligibility is individualized based on historical gain/loss and confirmed at baseline through standardized video-recorded RS-DMA that can be blinded and centrally rated using binary scoring to enable a responder analysis. To evaluate the RS-DMA psychometrics and trial-readiness we conducted assessments in a non-

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interventional study (RESUME; n=13) in individuals with classic RTT. Psychometric data was evaluated from site assessors, stakeholder feedback, and eight independent central raters.

RESULTS: RS-DMA demonstrated excellent psychometric properties with above psychometric thresholds for feasibility, fidelity, reliability, and validity. Stakeholder feedback supported the clinical meaningfulness of RS-DMA milestones, confirming milestone gain/regain reflects outcomes meaningful to caregivers.

CONCLUSIONS: Findings provide the statistical and methodological foundation for RS-DMA as an individualized, PABA-anchored endpoint in the FDA-aligned REVEAL pivotal trial enrolling patients aged 6–<22, a plateau population with stable baseline function and low spontaneous improvement.

KEYWORDS: Neurodevelopmental Disorders, Experimental Therapeutics, Neurogenetics

305. BASC-3 Profiles in DDX3X Syndrome: Associations with Adaptive Functioning and Sensory Symptoms

Tamar Caceres, Jordan Norris, Fiona Biondic

OBJECTIVE: Evaluate BASC-3 profiles in a cohort of individuals with DDX3X syndrome and assess the relationships between behavior, adaptive functioning, and the impact of sensory symptoms.

METHODS: Parents of 24 individuals with DDX3X syndrome between the ages of 2-23 years completed the Behavior Assessment System for Children (BASC-3), Short Sensory Profile-2 (SSP-2), and Vineland Adaptive Behavior Scales-3 (Vineland-3). We examined correlations between BASC-3 composite indices and Vineland-3 adaptive behavior composite (ABC). Linear regression was conducted to examine whether sensory related behaviors predicted variance in BASC-3 composite indices.

RESULTS: BASC-3 Behavioral Symptom Index (BSI) (rho = -.562, $p = .01$) and Externalizing Problems (EP) (rho = -.423, $p = .05$) negatively correlated with the BASC-3 Adaptive Skills composite (AS); correlations were driven by AS subdomains of daily living and functional communication. AS was closely correlated with Vineland-3 ABC (rho= .638, p=.01). Significant regressions were found between SSP-2 sensory raw score and AS ($R^2 = 0.48$, p<.001), BSI ($R^2 = 0.37$, p=.002), and EP ($R^2 = 0.38$, p=.001).

CONCLUSIONS: Individuals with DDX3X syndrome demonstrate adaptive skill strengths in adaptability and social skills and relative weaknesses in functional communication and daily living skills. Greater behavioral symptoms are associated with poorer adaptive functioning. Sensory processing differences predict variance in both behavioral symptoms and adaptive skills, suggesting that sensory-related symptoms may significantly impact functioning. These findings highlight the importance of comprehensive assessment and interventions targeting functional communication in addition to sensory processing and adaptive skill development in this population.

KEYWORDS: Neurodevelopmental Disorders, Neurogenetics, Behavioral Neurology

Neurogenetics

306. SMC1A-related Developmental and Epileptic Encephalopathy: A Clinically Heterogenous Cohesinopathy

Abhik Banerjee, Isabelle Whetsel, Piret Saagpakk, Matthew Deardorff

OBJECTIVE: The cohesin complex is responsible for organizing chromosomal organization in all living organisms. One of the most well-characterized Cohesinopathies is Cornelia de Lange Syndrome (CdLS), caused by mutations in *NIPBL, SMC3*, and *SMC1A*. Several studies have reported *SMC1A* variants associated with severe epilepsy and developmental delay termed SMC1A-related Developmental and Epileptic Encephalopathy (SMC1A-DEE, OMIM # 301044). This study aims to characterize the clinical heterogeneity of SMC1A-DEE and compare CdLS- and DEE-associated missense variants to speculate mechanistic differences between the conditions.

METHODS: The present study used a combination of 1) prospectively collected data per Institutional Review Board protocol; 2) patients recruited via referral to the study team by clinicians or word-of-mouth from other participants; and 3) clinical information voluntarily shared to the SMC1A Foundation. 43 previously published participants were included in our analysis. *SMC1A* mutations were identified via clinical exome sequencing, next-generation focused-exome sequencing panels, or extracted from published reports.

RESULTS: Of our total cohort of 102 individuals, we report 59 newly identified individuals with *SMC1A* loss-of-function variants. The top five reported features of SMC1A-DEE include developmental delay, seizure, microcephaly, muscular problems, and ataxia. Hierarchical clustering of anti-seizure interventions identified three subclusters of patients. Structural analysis demonstrated that CdLS- and DEE-variants localize to distinct domains of SMC1A, which we speculate preferentially alters cohesin complex DNA loop capture and loop extrusion.

CONCLUSIONS: By reviewing the natural history of SMC1A-DEE and comparing the localization of DEE- to CdLS-variants, our study challenges the paradigm that these conditions are distinct Cohesinopathies but rather exist on a continuous spectrum.

KEYWORDS: Neurogenetics, Epilepsy

307. A Rare Case of Early Onset Brain Calcification in a Child with Biallelic JAM2 Variants

David Toupin, Amanda Rentas, Kayla Horne, Yuri Zarate

OBJECTIVE: Primary familial brain calcification (PFBC) caused by biallelic variants in *JAM2* is rare and is believed to account for ~2% of PFBC cases. Pathogenic biallelic *JAM2* variants disrupt blood-brain barrier integrity and are associated with extensive brain calcifications and gradually progressive neurological symptoms. We report a girl with *JAM2*-associated PFBC with calcifications first noted on imaging at 4 years, with focal epilepsy and speech delay.

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METHODS: Consent was obtained. We reviewed clinical records, serial neuroimaging, neuropsychological testing, and genetic testing results.
RESULTS: Speech delays and gait imbalance were noted at age 2 years. At 3.5 years, she developed focal-onset seizures. Serial head imaging at ages 4, 7, and 10 years showed bihemispheric, subcortical, and deep white matter calcifications with interval progression from 4–7 years with relative stability from 7–10 years. At 11 years, seizures were well-controlled, neurologic examination was normal, and WISC-V full-scale IQ was 66. Family history was notable for two paternal relatives with seizures but no known history of intracranial calcifications. Duo genome sequencing identified a homozygous *JAM2* c.55del (p.Val19Serfs*19) variant and a heterozygous 2.79-Mb 16p13.11 duplication. The 16p13.11 duplication is a neurodevelopmental risk-factor copy number variant not known to be associated with brain calcifications.
CONCLUSIONS: We describe a girl with early-onset brain calcifications due to *JAM2* loss-of-function variants. The calcifications observed on imaging are, to our knowledge, the youngest reported in *JAM2*-related PFBC. This case underscores that progressive, symmetric brain calcifications in young children should prompt consideration of recessive PFBC genes.
KEYWORDS: Neurogenetics, Neuroimaging

308. Beyond the Triad: An Unusual Non-Uniform Motor-Predominant Axonal Neuropathy Unmasked as Triple A Syndrome

Michelle Tram, Stella Deng

OBJECTIVE: Triple A syndrome is an extremely rare autosomal recessive disorder characterized by the triad of alacrima, achalasia, and adrenal insufficiency, with neurologic manifestations typically emerging later in life. We describe a pediatric patient presenting with gait abnormalities who was found to have an unusual non-uniform motor-predominant axonal neuropathy that eventually led to a genetic diagnosis of Triple A syndrome in absence of known achalasia or adrenal insufficiency.
METHODS: We conducted a retrospective chart review of a single pediatric case.
RESULTS: A 7-year-old boy with history of speech delay presented with a 2-year history of falls and leg pain with walking. Examination revealed a pronated gait, mild distal extremity weakness, difficulty toe-walking, and decreased distal vibratory sensation. Nerve conduction studies demonstrated a non-uniform motor predominant axonal polyneuropathy with more selective ulnar and tibial motor nerve involvement. Initial genetic testing with a comprehensive neuropathies gene panel was non-diagnostic and evaluation for acquired causes of neuropathy was also negative. Whole exome sequencing was subsequently performed and identified two pathogenic *AAAS* variants (c.355C>T, p.R119*; c.464G>A, p.R155H) in trans, confirming a diagnosis of Triple A syndrome. At diagnosis, there was no definitive clinical evidence of adrenal insufficiency or achalasia, and alacrima was only elicited retrospectively.
CONCLUSIONS: This case expands the pediatric phenotype of Triple A syndrome by highlighting neuropathy as a possible presenting symptom. Early consideration of *AAAS* sequencing and screening for typical triad symptoms in unexplained or atypical childhood axonal neuropathy can facilitate timely diagnosis.
KEYWORDS: Neurogenetics, Neuromuscular

309. Divergent Kinesinopathies: A Comparative Analysis of KIF11-Related Structural Malformation and KIF1A-Related Neuroregression

Angelica Montilla, Alina Rivadeneira-Limongi, Alcy Torres

OBJECTIVE: Kinesin family genes are critical for intracellular transport and mitosis, yet mutations yield vastly different neurological outcomes. We aimed to compare the clinical and neuroimaging phenotypes of KIF11 (implicated in spindle assembly) and KIF1A (critical for axonal transport) to improve clinical recognition.
METHODS: A retrospective comparative analysis was performed on two pediatric patients with molecularly confirmed pathogenic variants in KIF11 and KIF1A. Longitudinal clinical data, dysmorphology exams, and serial neuroimaging were reviewed.
RESULTS: Patient 1 (KIF11) is a 9-year-old female with microcephaly, global developmental delay, and significant dysmorphism (peripheral retinal pigmentary changes, upslanting palpebral fissures, micrognathia, and high-arched palate). Neurologically, she remained stable but exhibited lower extremity hypotonia. Brain MRI revealed a severe malformation of cortical development with lissencephaly and pachygyria. Patient 2 (KIF1A) is a 3-year-old female who achieved early milestones (walking at 13 months, single words at 14 months) followed by significant language and motor regression. Her course was complicated by seizure onset at 12 months and autism spectrum disorder. Examination showed lower extremity hypermobility and an abnormal "crouched" gait. Genetic testing identified a 2q37.3 deletion encompassing KIF1A. In contrast to Patient 1, her brain MRI was unremarkable.
CONCLUSIONS: These cases demonstrate the divergent paths of kinesin mutations. KIF11 disruption can present as a primary disorder of neurogenesis and migration (expanding the spectrum to include lissencephaly), whereas KIF1A manifests as a functional "transport" defect characterized by epilepsy and neuroregression despite preserved initial brain structure. This comparison underscores the need for genomic testing in both malformative and regressive pediatric encephalopathies.
KEYWORDS: Neurogenetics, Neurodevelopmental Disorders, Neuroimaging

310. Clinical Utility of Exome Sequencing in a Large Real-World Autism Cohort

Sophia Ceulemans, Michelle Morrow, Kendall King, Sarah Poll, Bobbi McGivern, F. Kyle Satterstrom, Mark Daly, Michael Talkowski, Heather McLaughlin, Krystal Brown

OBJECTIVE: We demonstrated the potential utility of exome sequencing (ES) for autism in a real-world cohort of over 65,000 individuals.

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METHODS: We analyzed de-identified data from individuals with autism or autistic behavior who received ES as part of standard care from 2015-2026 (N=68,629). Molecular diagnoses were classified as definitive (pathogenic/likely pathogenic (P/LP) variant in a validated disease gene consistent with the reported phenotype) or possible (P/LP/variant of uncertain significance (VUS) in a validated disease gene possibly associated with the reported phenotype). Diagnostic yield was calculated as the proportion of individuals with a definitive or possible diagnostic finding within the overall cohort and stratified by phenotype complexity (autism ± multiple congenital anomalies (MCA)). Medically actionable findings were those in genes with treatments per the Rx-Genes database and/or medical actionability per a recent publication (Stafford et al. 2022).

RESULTS: The overall molecular diagnostic yield was 48.1% (17.5% definitive, 30.6% possible). Medically actionable findings were observed for 12.4% of individuals with a definitive diagnostic finding. Diagnostic yield was higher in individuals with autism plus MCA than those without MCA (50.8% vs 39.8%, respectively; $p<0.01$).

CONCLUSIONS: ES identified molecular diagnoses in nearly half of individuals with autism tested in this large, real-world cohort, 12.4% of whom had definitive diagnostic findings in genes with management implications. Although diagnostic yield was highest among those with complex phenotypes, meaningful yield and medical actionability extended across all presentations, supporting exome sequencing as a foundational diagnostic tool for individuals with autism.

KEYWORDS: Neurogenetics, Neurodevelopmental Disorders, Practice Parameters

311. Distinguishing Miller Fisher Syndrome from Kearns-Sayre Syndrome: Diagnostic Insights

Agilda Dema, Moon Hee Hur

OBJECTIVE: Miller Fisher syndrome (MFS), a rare variant of Guillain-Barré syndrome, is an immune-mediated neuropathy associated with anti-GQ1b antibodies. Kearns–Sayre syndrome (KSS) results from large-scale mitochondrial DNA deletions impairing oxidative phosphorylation. Despite distinct pathophysiology, both conditions can present with overlapping features, including ophthalmoplegia, ataxia, and areflexia. Albuminocytologic dissociation—elevated cerebrospinal fluid (CSF) protein without pleocytosis—is characteristic of MFS but may also occur in KSS due to blood–CSF barrier dysfunction and white matter degeneration. This overlap can obscure diagnosis and delay appropriate management. We present a case illustrating the diagnostic overlap between MFS and KSS in an adolescent.

METHODS: This is a retrospective case review of an adolescent patient, including analysis of clinical features, cerebrospinal fluid studies, neuroimaging, and comprehensive genetic testing with whole-exome and mitochondrial genome sequencing.

RESULTS: A 16-year-old male with migraines, ADHD, speech delay, and growth hormone deficiency developed progressive ataxia, areflexia, and ophthalmoplegia over three months. CSF showed elevated protein (104 mg/dL) with normal cell count. MRI revealed diffuse T2/FLAIR white matter abnormalities and cerebral volume loss, which were atypical for MFS. Despite this, he received IVIG and plasma exchange for presumed MFS. Lack of clinical improvement and atypical features prompted genetic testing, which identified a pathogenic mitochondrial DNA deletion (m.6130_15656del), confirming KSS. He was started on mitochondrial supplements and multidisciplinary care.

CONCLUSIONS: KSS can closely mimic MFS both clinically and diagnostically. Mitochondrial disease should be considered in patients with subacute progression, treatment resistance, or atypical neuroimaging. Early genetic testing is essential for accurate diagnosis, prognostication, and management.

KEYWORDS: Neurogenetics

312. Beyond Cryptogenic NORSE: Rapid Genomic Diagnosis of POLG Mutation in an Infant

Morgan Young, Brittany Gerald, Connor Gatewood

OBJECTIVE: We aim to report a case of an 8-month-old female with new onset refractory status epilepticus (NORSE) who was found to have a POLG mutation.

METHODS: Single case report with an abbreviated literature review.

RESULTS: Patient was a previously healthy 8-month-oldfemale who presented in new onset refractory status epilepticus (NORSE). She was treated with multiple benzodiazepine boluses, and loading doses oflevetiracetam, lacosamide, and phenobarbital. Care was escalated to continuous infusions of ketamine, lorazepam, and pentobarbital to achieve burst suppression. When weaned, frequent electrographicseizures returned. Treatment progressed to include high dose steroids, IVIG, and tocilizumab, and a trial of pyridoxine. Ketogenic diet was considered but not initiated. Initial imaging was normal, howeverrepeat MRI brain demonstrated extensive diffusion restriction of bilateral temporal, parietal lobes. CSF studies were notable for elevated protein. Rapid sequence whole genome sequencing identifiedbiallelic pathogenic POLG mutations, as well as heterozygous KCNQ1 variant. With this information, we were able to alter her clinical course by enabling discussion with family of her disease prognosis and open goals of care discussions. Her family chose palliation with ptimal quality of life. Despite best efforts of all teams, the patient died secondary to respiratory failure 52 days from initial presentation andbefore discharge.

CONCLUSIONS: This case supports the literature regarding POLG progression and severity. More severe, and rapidly progressive cases are seen with younger age of presentation, and with genetic homozygosity. Rapid whole genome sequencing can significantly alter the clinical course and allow families to make informed decisions about their child's care.

KEYWORDS: Neurogenetics, Neurocritical Care, Epilepsy

313. Language-Aware Reranking Improves Gene Prioritization in Pediatric Neurologic Rare Disease Diagnosis

Lin Yao, Jaeyeon Lee, Lisa Emrick, Zhandong Liu, Hyunhwan Jeong

OBJECTIVE: Pediatric neurologic rare diseases often present with complex neurodevelopmental, epileptic, and

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multisystem phenotypes, while genomic testing frequently yields many candidate genes requiring time-intensive interpretation. We evaluated whether a language-aware reranking framework could improve causal gene prioritization in pediatric neurologic rare disease diagnosis.

METHODS: We developed LA-MARRVEL, a two-stage framework that applies large language model–based reranking after high-recall candidate retrieval. The system integrates diagnostic inputs, including patient phenotypes, disease phenotypes, inheritance patterns, and variant annotations, and combines repeated outputs using deterministic ranked voting to improve stability. Performance was evaluated in 367 diagnosed pediatric rare disease cases from 3 independent cohorts and compared with established gene-prioritization tools and prompt-only large language model ranking.

RESULTS: Prompt-only large language model ranking showed poor recovery of causal genes. In contrast, LA-MARRVEL achieved the highest Recall@K across cohorts, with the largest gains at the most clinically relevant top ranks. Recall@1 approached 78%, outperforming Exomiser (∼50%) and LIRICAL (∼31%). By Top-10, recall reached approximately 90%–95% while preserving overall coverage. Removal of patient phenotype information caused the greatest decline in performance, supporting the importance of phenotype-rich clinical context for neurologic diagnosis. Ranked voting improved stability over single-run inference. In representative pediatric neurodevelopmental cases, the framework corrected major ranking errors and generated interpretable evidence traces linking phenotype concordance, inheritance, and variant features.

CONCLUSIONS: Language-aware reranking improves causal gene prioritization in pediatric neurologic rare disease diagnosis, particularly at the top of the ranked list where clinical interpretation is most consequential. Phenotype-grounded, clinician-interpretable AI tools may strengthen genomic decision support in child neurology.

KEYWORDS: Neurogenetics, Neurodevelopmental Disorders, Neurometabolic

314. An Atypical SCN8A Mutation Phenotype with Congenital Anomalies and Myopathy: Implications for Missed Molecular Diagnosis

Priya Raju, Stacey Adams, Nathaniel Wooten, Yael Shiloh-Malawsky, Katelyn Bricker

OBJECTIVE: To report a neonate with SCN8A-related epileptic encephalopathy with a rare phenotype not previously well described, expanding the phenotypic spectrum of the disorder, and highlighting the diagnostic challenges of molecular testing in the setting of a rare phenotypic presentation.

METHODS: A case report with clinical, electrophysiological, neuroimaging, and initially negative genomic data reviewed retrospectively. We describe the process leading to molecular diagnosis.

RESULTS: A term neonate presented with multiple congenital anomalies including macrocephaly, bell-shaped thorax, clinodactyly, single palmar crease, urethral atresia, inguinal hernias, severe hypotonia, weakness and knee contractures. He had choreoathetoid movements, pulmonary hypertension, and respiratory failure. Initial head ultrasound and EEG were normal and whole genome sequencing was negative. Evaluation for congenital myopathy showed imaging evidence of diffuse muscle atrophy and suggested extensive fatty infiltration or fibrosis. At one month of age, multifocal refractory seizures emerged. Genomic reanalysis, with the addition of new epilepsy, identified a likely pathogenic heterozygous SCN8A mutation, (c.1225G>A, p.V409M), confirming SCN8A-related developmental and epileptic encephalopathy. The common phenotype includes intellectual disability, global developmental delay, movement disorder, and intractable epilepsy. Literature review identified only one prior report of neonatal hypotonia and congenital anomalies without report of specific neuromuscular findings. The patient was compassionately extubated per family goals of care and died at 3 months of age.

CONCLUSIONS: The first reported case of congenital anomalies and myopathy in SCN8A-related epileptic encephalopathy, expanding the phenotypic spectrum. Vigilance for evolving clinical findings and awareness of rare phenotype of SCN8A is essential for analyzing genomic data and establishing molecular diagnosis.

KEYWORDS: Neurogenetics, Epilepsy, Neuromuscular

315. The Role of Genetic Testing in Pediatric Expressive Language Delay: Evidence from The National Brain Gene Registry

Shivani Waghmare, Alexa Taylor, Cecilia Bouska, Ana Chaza, Andrea Gropman

OBJECTIVE: Expressive language disorder, a subset of common childhood speech-language delay, frequently appears alongside neurodevelopmental conditions. This study examines genetic testing yield, result-return timing, and several genes commonly associated with expressive language disorder.

METHODS: We conducted a retrospective analysis using the National Brain Gene Registry (BGR), a multi-site database of rare neurodevelopmental disorders. Participants with an ICD-10 diagnosis of ELD (F80.1) were identified through electronic health records. Demographic characteristics, comorbidities, genetic findings, inheritance patterns, age at diagnosis, and timing of genetic testing were analyzed.

RESULTS: Among 687 participants in the BGR, 32 (4.7%) had documented ELD. Participants ranged from 3 to 19 years and commonly exhibited comorbid developmental delay, ASD, epilepsy, and hypotonia. Genetic analysis identified 49 unique variants across 42 genes, including 26 pathogenic or likely pathogenic variants, 22 variants of uncertain significance, and one benign variant. Seventeen variants were de novo, and 10 individuals harbored multiple variants. Most participants (75%) were diagnosed with ELD prior to undergoing genetic testing, with results returned an average of 1.5 years after diagnosis.

CONCLUSIONS: Children with ELD frequently harbor genetic variants and neurodevelopmental comorbidities; however, genetic testing is often delayed and does not currently influence early clinical management. These findings highlight the need for evidence-based guidelines to better define the role and optimal timing of genetic testing in ELD evaluation.

KEYWORDS: Neurogenetics, Neurodevelopmental Disorders

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316. From Despair to Hope: A Family's Journey From Natural History to AAV9-Gene Therapy Treatment of GM1 Gangliosidosis in Three Siblings

Maria Acosta, Hera Akmal, Precilla D'Souza, Jean Johnston, Connor Lewis, Cynthia Tifft

OBJECTIVE: GM1 gangliosidosis (GM1) is an autosomal recessive neurodegenerative disorder that is uniformly fatal with no approved therapies. We describe three siblings with juvenile-onset GM1—one untreated and two treated with AAV9-GLB1 gene transfer—to illustrate differential outcomes within a single family

METHODS: Three male siblings with identical *GLB1* variants were followed longitudinally. Sibling 1, diagnosed at age 9, participated in a natural-history study (NCT00029965). Siblings 2 and 3 received AAV9-gene therapy (NCT03952637) at 3 years 9 months and 2 years of age. Evaluations included neurological exams, neuropsychology, EEG, MRI, and diffusion tensor imaging analyzed with differential tractography

RESULTS: Sibling 1 had normal early development until age 3, followed by progressive loss of speech, fine motor skills, gait, and continence. By age 17, he had severe scoliosis, bilateral femoral head necrosis, was gastrostomy-dependent, non-verbal, and wheelchair-dependent. Sibling 2 was mildly symptomatic at treatment and remains in a regular classroom with an IEP, showing no major neurological decline five years later, though articulation, fine motor, and attention deficits persist. Mild progressive cerebral and cerebellar atrophy appeared after Year 4. Sibling 3, treated presymptomatic, has demonstrated normal development through Year 1. Differential tractography a novel biomarker, used by our group (Lewis 2026, NEJM) showed extensive white-matter loss in Sibling 1, whereas both treated siblings exhibited widespread net gains despite isolated losses.

CONCLUSIONS: This within-family comparison highlights AAV9-GLB1 gene therapy's potential to stabilize juvenile GM1, especially with presymptomatic treatment. Differential tractography may enable early visualization of therapeutic brain changes preceding clinical benefit.

KEYWORDS: Neurogenetics, Neuroimaging, Experimental Therapeutics

317. Juvenile-Onset Progressive Ataxia: A Novel Phenotype and Mutation of CACNA1A

Jaclyn Martindale, Avery Wright, Aubrey Hite, Robert Goodrich, Jennifer Harmon

OBJECTIVE: To describe a case of juvenile-onset progressive ataxia associated with a previously unpublished, novel, likely pathogenic in-frame deletion of the *CACNA1A* gene, and to expand the phenotypic spectrum of *CACNA1A*-related disorders.

METHODS: A single-patient case report was conducted with clinical evaluation, laboratory testing, neuroimaging, and genetic analysis. Neurological and neuro-ophthalmologic examinations were performed. A non-contrasted head CT and a brain MRI with and without contrast were obtained. Genetic testing included an expanded ataxia panel and repeat expansion testing.

RESULTS: A 17-year-old male presented after two years of progressive clumsiness and whole-body tremors. Examination demonstrated postural and kinetic tremor of the head and bilateral upper and lower extremities, limb and truncal ataxia, postural instability, and abnormal gait. Neuro-ophthalmologic findings included ptosis and mixed nystagmus. MRI brain with and without contrast revealed marked cerebellar vermis atrophy with lesser hemispheric involvement. Extensive laboratory evaluation was largely unremarkable. Genetic testing identified a de novo heterozygous likely pathogenic *CACNA1A* variant (c.5110_5112del; p.F1704del). Repeat expansion testing for spinocerebellar ataxia type 6 (SCA6) was negative.

CONCLUSIONS: This case describes a novel *CACNA1A* in-frame deletion associated with juvenile-onset progressive ataxia, expanding the known phenotypic spectrum of *CACNA1A*-related disorders. The findings highlight the clinical heterogeneity of *CACNA1A* mutations and demonstrate the importance of comprehensive genetic testing in pediatric patients with ataxia, even in the absence of classic episodic features.

KEYWORDS: Neurogenetics, Lifespan Manifestations of Childhood Onset Conditions

318. Non-missense ATP1A3 mutations in Children: Genotype-Phenotype Correlations and Molecular Modeling

Mohamad Mikati, Ashley Lin, Vijaykumar Pillalamarri, Praveen Ramani, Jad Kourany, Vandana Shashi, Andrew Landstrom, David Mueller

OBJECTIVE: Test the hypothesis that non-missense *ATP1A3* variants, which are known to be very rare and so far of uncharacterized phenotype-genotype correlation, result in a single consistent phenotype.

METHODS: We studied sequential non-missense mutations cases identified in our prospective ATP1A3-Alternating Hemiplegia of Childhood (AHC) and Related Disorders Registry. Clinical phenotyping as performed by two specialists in in AHC and epilepsy. Variant pathogenicity, reported by the testing lab, was confirmed by our analyses using the Franklin-Genoox, ClinVar, ClinGen, gnomAD, OMIM, GeneCC platforms and were classified based on American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) guidelines. Structural modeling was performed using ClustalW, Aline, PyMOL and Post-Albers models/platforms.

RESULTS: Phenotyping: 6/143 consecutive registry patients had non-missense variants. Their phenotypes ranged from mild or moderate AHC (c.2755_2757del-p.Val919del, c.2542+1G>A, c.388_390delGTG-p.Val130del, c.1297_ 2542del-exons 9-23del) to severe developmental and epileptic encephalopathy-DEE (c.2562_2565delTGGCinsG-p.Gly855del, c.2570_2572delTCT-p.Phe857del). Molecular modeling: In-frame deletions localized to transmembrane domains critical either to Na^+ binding or to conformational transitions. The other two, splice-site and multi-exon deletion, variants were assessed to result in truncation and, thus, in haploinsufficiency. This indicated that haploinsufficiency can result in AHC, a novel finding, given that a dominant negative mechanism has been suspected to be required for an AHC phenotype.

CONCLUSIONS: Non-missense variants cause phenotypes ranging from AHC to DEE, so prognostication should be

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based on the phenotype and specific variant, rather than on variant class alone. The in-frame deletions demonstrate that even small structural disruptions impair pump function. Splice-site and exon deletion variants indicate that haploinsufficiency can cause AHC.

KEYWORDS: Neurogenetics, Epilepsy, Neurodevelopmental Disorders

319. Clinical utility of whole exome sequencing (WES) and whole genome sequencing (WGS) in the diagnostic assessment of children with global developmental delay (GDD) and autism spectrum disorders (ASD)

Sailaja golla, Mary Pionk, Hitha Amin, Jonathan Megerian, Adrienne Moore

OBJECTIVE: To evaluate the clinical utility of whole-exome sequencing (WES) and whole-genome sequencing (WGS) in the diagnostic assessment of children with global developmental delay (GDD) and autism spectrum disorders (ASD)

METHODS: A focused literature review was conducted using recent systematic reviews, meta-analyses, large cohort studies, and the AAP 2025 clinical report on genetic evaluation in neurodevelopmental disorders. Studies assessing diagnostic yield, clinical impact, and comparative effectiveness of WES and WGS were prioritized.

RESULTS: WES consistently demonstrated a diagnostic yield of 25–40% in unexplained GDD and ASD, outperforming chromosomal microarray (10–15%) (Srivastava et al., 2019; Miller et al., 2021). WGS provided an additional 10–15% diagnostic increase by identifying non-coding variants, structural variants, and complex rearrangements not captured by WES (Clark et al., 2018; Lionel et al., 2020). The 2025 AAP report emphasized WES or WGS as preferred first-tier tests for children with GDD/ASD when no clear etiology is identified, citing improved diagnostic efficiency and reduced time to clinical decision-making. Trio-based sequencing further enhanced variant interpretation accuracy (Wright et al., 2018). Molecular diagnoses frequently informed targeted management, surveillance, and recurrence-risk counseling

CONCLUSIONS: Current evidence, reinforced by AAP 2025 recommendations, supports early integration of WES or WGS in the evaluation of children with GDD and ASD. Their superior diagnostic yield and broad variant detection enable precise etiologic identification and guide personalized care, improving long-term clinical outcomes. REFERENCES AAP Clinical Report, 2025; Clark et al., 2018; Lionel et al., 2020; Miller et al., 2021; Srivastava et al., 2019; Wright et al., 2018.

KEYWORDS: Neurogenetics, Neurodevelopmental Disorders

320. Characterizing the spectrum of RAB1A-related hereditary spastic paraplegia

Ashira Edelheit-Rice, Kristhen Atala, Suzanne Baxter, Daralyn Fulton, Prasanna Gangishetti, Daniel Gonzalez, Sydney Hubbard, Naama Orenstein, Chanika Phorphutkul, Maria Guillen Sacoto, Linsley Smith, Catherine Thompson, Efrat Sofrin-Drucker, Michelle Christie, Jonathan Rios, Daniel Calame

OBJECTIVE: *RAB1A*, a gene involved in ER-Golgi trafficking, autophagy, and neuronal morphogenesis, has been recently implicated as a cause of autosomal dominant hereditary spastic paraplegia (HSP). We sought to better characterize the spectrum of *RAB1A*-related HSP through deep phenotyping of new and previously reported cases.

METHODS: Retrospective case series. Patients were identified through clinical practice, diagnostic laboratories, or GeneMatcher.

RESULTS: We identified four unrelated individuals and one set of twins (ages 2.5-28 years old) with the previously reported pathogenic nonsense *RAB1A* variant: c.523C>T; p.(R175*). *RAB1A* p.(R175*) occurred *de novo* in three cases and was inherited in two cases. One case had unknown inheritance. All individuals presented with delayed walking by age four. Notable clinical features included lower extremity spasticity (n=6), hyperreflexia (n=6), positive Babinski sign (n=5), motor delays (n=6), speech delays (n=5), and intellectual disability (n=5). Spasticity was progressive in four cases. One case had elevated plasma neurofilament light chain. The patients' MRIs had typical HSP-related findings: corpus callosum thinning (n=4) and the "ears of the lynx" sign (n=4). *RAB1A* p.(R175*) should escape nonsense-mediated decay (NMD) and yield a nonfunctional C-terminal truncated protein. In contrast, published cases with chromosome 2p14-p15 microdeletions encompassing *RAB1A* and *RAB1A* NMD-triggering loss-of-function variants rarely exhibited spastic paraplegia.

CONCLUSIONS: Our findings confirm that the recurrent *RAB1A* last exon nonsense variant c.523C>T; p.(R175*) causes a slowly progressive, complicated childhood-onset HSP. Together with our literature review of cases with chromosome 2p14-p15 microdeletions encompassing *RAB1A* and *RAB1A* NMD-triggering loss-of-function variants, this may suggest that *RAB1A* p.(R175*) acts through mechanisms beyond haploinsufficiency.

KEYWORDS: Neurogenetics, Neuromuscular, Movement Disorders

321. Comparative Phenotypic Profiles of RAI1-Related Disorders: A Retrospective Analysis of Smith-Magenis and Potocki-Lupski Syndromes

Davut Pehlivan, Walter Williamson, Sukru Aras, Diane Treadwell-Deering, Kevin Kaplan, Lorraine Potocki

OBJECTIVE: Smith–Magenis syndrome (SMS) and Potocki–Lupski syndrome (PTLS) are allelic neurodevelopmental disorders caused by haploinsufficiency or duplication of the dosage-sensitive *RAI1* gene, respectively. Although these conditions share overlapping features, systematic comparative phenotyping remains limited, hindering accurate diagnosis and informed therapeutic development.

METHODS: We performed a single-center retrospective chart review of 112 genetically confirmed individuals evaluated over 25 years, including 44 with SMS and 68 with PTLS. Clinical, laboratory, and imaging data were systematically analyzed to identify shared and distinguishing phenotypic features. Group differences were assessed using appropriate statistical tests.

RESULTS: Both syndromes showed high prevalence of developmental delay, neurobehavioral features, and sleep-

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disordered breathing; however, statistically significant differences emerged. SMS was associated with progressive weight gain, self-injurious behavior, insomnia with multiple nocturnal awakenings, constipation, hyperlipidemia, frequent infections, hearing loss, and short stature. In contrast, PTLS was characterized by failure to thrive or underweight status that usually resolved with aging, chewing and swallowing difficulties in the early childhood, subclinical central and/or obstructive sleep apnea, periodic limb movements during sleep, hypothyroidism, and aortic root dilation. While many features were present in both conditions, their frequency and severity differed significantly, revealing syndrome-specific phenotypic traits.

CONCLUSIONS: Comprehensive comparative phenotyping of *RAI1*-related disorders reveals distinct clinical signatures that differentiate SMS and PTLS despite involving the same dosage-sensitive gene. These findings support the concept of dosage-dependent "mirror traits" and have important implications for diagnostic precision, clinical management, and future gene-based therapeutic strategies.

KEYWORDS: Neurogenetics, Neurodevelopmental Disorders

322. Deep Behavioral and Clinical Phenotyping of DDX3X Syndrome in a Cohort of 213 Individuals

Ruiji Jiang, Emanuela Argili, Carolyn Le, Elizabeth George, Elliott Sherr

OBJECTIVE: *DDX3X* is an X-linked gene which encodes a DEAD-box RNA helicase with broad roles in RNA metabolism. Pathogenic variants in *DDX3X* are linked to DDX3X Syndrome (OMIM:300958), a disorder that predominantly affects females and characterized by intellectual disability, structural brain anomalies, abnormal muscle tone, and neurodevelopmental and behavioral features. These variants are estimated to be responsible for 1-3% of unexplained intellectual disability in females. Here, we present the most complete genotype-phenotype characterization of *DDX3X* syndrome based on the largest cohort assembled to date.

METHODS: We performed a retrospective analysis of 213 individuals with 156 unique likely pathogenic/pathogenic DDX3X variants. Clinical, neuropsychiatric, and neuroimaging data were systematically collected. Brain MRIs were centrally reviewed by a neuroradiologist using a standardized protocol.

RESULTS: Structural brain abnormalities were present in most individuals, with findings of agenesis/dysgenesis of the corpus callosum(70.4%), generalized white matter loss(43.6%), hypoplastic brainstem(11.4%), abnormal myelination(12.7%), polymicrogyria(12.1%), and microcephaly(26.1%). Global developmental delay was common, with median age at independent walking of 24 months (95% CI:15-26 months) and a median age at first word of 36 months(95% CI:24-48 months); 31.2% of individuals were non-verbal. Vineland behavioral state scores were consistent with these findings, with median percentile scores below the 5th percentile across all domains. Other clinical findings included hypotonia(57.6%), seizures(26.6%), hypertonia (28.1%), sleep issues(29.5%), congenital cardiac defects(10.4%), and scoliosis(13.3%). Less common findings included osteopenia, precocious puberty, optic nerve hypoplasia and three cases of neuroblastoma.

CONCLUSIONS: We present the largest single cohort of *DDX3X* syndrome individuals and the most complete clinical description of DDX3X syndrome to date.

KEYWORDS: Neurogenetics, Neurodevelopmental Disorders

323. Novel CACNA1A mutation associated with paroxysmal tonic up-gaze and ocular apraxia without seizures

Francis DiMario

OBJECTIVE: Mutations in the gene *CACNA1A* are commonly associated with epilepsy, episodic ataxia and severe forms of hemiplegic migraine. There have been rare reports of ocular motor abnormalities other than nystagmus. We report a child who had paroxysmal tonic up-gaze, ocular apraxia, hypometric saccades and gaze directed nystagmus associated with a novel mutation in *CACNA1A* (c.835 C>T p.(R279C).

METHODS: After IRB approval, the clinical course and evaluation were abstracted from chart review

RESULTS: She presented at 8 months with paroxysmal tonic up-gaze and depressor anguli oris hypoplasia. An MRI revealed a small pituitary pars intermedia cyst. By 2 years, she developed head tilt and gait unsteadiness, saccadic pursuit movements, and ocular apraxia with head thrust to redirect gaze. MRI now revealed a 1-1.5 cm T2 hyperintense pineal cyst and the pituitary cyst. She received PT and OT. Her truncal instability improved with stable head tilt and oculomotor findings. At 3 years she underwent an inferior oblique recession for CN IV palsy. By age 9 years, serial MRI remained unchanged with static truncal coordination, oculomotor movement and gaze-directed nystagmus. There was diminished head thrust but eye-blink before eye movement and a reduced right head tilt at rest. WES identified a pathogenic, heterozygous, dominant *CACNA1A* mutation (c.835 C>T p.(R279C). Prior laboratory and genetic testing were normal or negative.

CONCLUSIONS: We describe a novel dominant *CACNA1A* mutation associated with congenital paroxysmal tonic up-gaze, depressor anguli oris hypoplasia, head tilt with CN IV palsy, gait unsteadiness, saccadic pursuit movements, and ocular apraxia.

KEYWORDS: Neurogenetics, Movement Disorders, Neurodevelopmental Disorders

324. The impact of an iterative points-based framework on variant classification outcomes for neuromuscular disorders (NMDs)

Hannah White, Yi-Lee Ting, Christopher Tan, Marjorie Westbrook, Yuya Kobayashi, Dan Swartzlander, Sarah Klemm, Alexander Wahl, Karen Ouyang, Robert Daber

OBJECTIVE: Panel-based NMD genetic testing results in molecular diagnosis in 13-70% of cases. Diagnostic yield variability may be partially attributed to variant classification (VC) practices, making robust, agile VC critical. In 2016, we

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developed a points-based VC framework based on ACMG/AMP guidelines that has undergone iterative refinement to expand utility and incorporate new evidence over time. Here, we evaluate the impact of these changes on VC outcomes across a large set of NMD genes.

METHODS: We evaluated the classification of 68,550 variants in 210 NMD-associated genes using framework version v7.1 (2024) and simulated the effect of removing criteria added since v4.2 (2016). Evidence categories included variant effect, AI-based models, indirect evidence, and paired DNA-RNA evidence.

RESULTS: The number of evidence criteria increased from 134 to 300 over 18 versions (v4.2-v7.1), incorporating new data sources, refining existing criteria, and expanding variant type support. In framework v7.1, 6,415 NMD variants were classified as P/LP (9.4%), 15,134 as B/LB (22.1%), and 47,001 as VUS (68.6%). Simulation analysis showed that of the 21,549 definitively classified variants (P/LP, B/LB), 13,433 (62.3%) would have remained VUS without the additional evidence introduced over time. AI-based models contributed to most reclassifications.

CONCLUSIONS: VC systems must continuously adapt to incorporate new evidence types and better leverage existing data. Our iterative approach, especially the addition of AI-based modeling, resulted in more variants reaching clinically impactful classifications for NMDs. These results underscore the importance of flexible, continuously updated frameworks to advance the accuracy and utility of VC in clinical practice.

KEYWORDS: Neurogenetics, Neuromuscular

325. Autism and Epilepsy: An Unusual Initial Presentation of Neimann-Pick Type C

Hallie Shpack, Chris Barton, Jaime Shoup

OBJECTIVE: Childhood-onset Niemann-Pick C (NPC) is a slowly progressive lysosomal storage disorder that typically presents with ataxia and vertical supranuclear saccadic palsy with global cognitive impairment, regression and seizures as later manifestations. We report a case of NPC diagnosed in a child with autism, epilepsy, and moderate developmental delay without many of the typical early findings of childhood-onset NPC.

METHODS: A 6-year-old boy with a past medical history of non-verbal autism presented to the emergency department with new-onset seizure-like activity. Video EEG confirmed focal epileptiform discharges from the bilateral frontal and frontotemporal head regions as well as background with delta/theta slowing. On exam, he had mildly low muscle tone, intact extraocular movements without nystagmus, and normal balance and gait.

RESULTS: An epilepsy gene panel was ordered which revealed two pathogenic mutations in NPC1 (c.1436G>A and c.3019C>G); variants were confirmed to be biallelic after parental testing. Abdominal ultrasound showed mild splenomegaly. Oxysterol profile showed elevated cholestane-3β,5α,6β-triol (0.107nmol/mL) and 7-ketocholesterol (0.233nmol/mL) consistent with NPC. He was started on a therapeutic dose of miglustat. At the time, he had a NPC clinical severity score of 7 with moderate developmental delay. He has not had any appreciable progression of symptoms to date.

CONCLUSIONS: This case documents an unusual presentation of NPC in a child with autism, moderate developmental delay, and epilepsy without the typical findings of ataxia or vertical gaze palsy. We hypothesize that our patient may have underlying multifactorial genetic risk for autism outside of NPC that may have contributed to a more severe early neurodevelopmental phenotype.

KEYWORDS: Neurogenetics, Neurodevelopmental Disorders, Epilepsy

326. Comparative Genomic Architecture and Diagnostic Yield of WGS for Pediatric Movement Disorders in Underserved Populations

Enrique Gonzalez Saez-Diez, Amy Tam, Joshua Rong, Luca Schierbaum, Kathryn Yang, Zainab Zaman, Monica Ferrer Socorro, Beril Ay, Matt Danzi, Stephan Züchner, Daniel Calame, Salma Zouari Mallouli, Farah Ben Lakhal, Chahnez Charfi Triki, Katerina Bernardi, Vicente Quiroz, Darius Ebrahimi-Fakhari

OBJECTIVE: Reference databases remain dominated by European ancestry, biasing variant interpretation. We compared the genomic architecture and diagnostic yield of pediatric movement disorders in two underrepresented cohorts with contrasting population histories and health-care resources from Sfax, Tunisia, and Valparaíso, Chile.

METHODS: Trio-short-read whole genome sequencing was performed in children with suspected genetic movement disorders (21 Sfax, 22 Valparaíso probands) assessed via remote case review and multidisciplinary team discussion. Variants were prioritized via segregation, gnomAD frequencies, and *in silico* predictors, then classified per ClinGen/SVI-refined ACMG criteria. Cases were classified as Solved (P/LP), Candidate Variants (VUS in established disease genes with concordant phenotype and segregation), or Unsolved. Genomic architecture was assessed via autozygosity mapping (F_ROH ≥3 Mb).

RESULTS: Self-reported consanguinity differed markedly (47.6% in Tunisia vs. 4.5% in Chile; p=0.0015). F_ROH was significantly higher in Sfax (median 2.3% vs. 0.03%; p=0.0004); parental F_ROH was concordantly elevated, indicating multi-generational endogamy. The predominant phenotype was spasticity in the Chilean cohort (63.6%) and dystonia in the Tunisian cohort (42.9%). A molecular diagnosis (P/LP) was established in 57.1% of Tunisian and 50.0% of Chilean probands. Including candidate variants, preliminary yields reached 66.7% and 63.6%, respectively. Among diagnostic cases, homozygous variants were more frequent in the Tunisian cohort (42.9% vs. 21.4%), while heterozygous variants were more frequent in the Chilean cohort (50.0% vs. 35.7%).

CONCLUSIONS: Pediatric movement disorders cohorts from different geographic, ethnic and health-care backgrounds display distinct genomic architectures shaping diagnostic strategy. Systematic inclusion of non-European populations is essential to advance equitable genomic medicine and accurate variant interpretation.

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KEYWORDS: Neurogenetics, Movement Disorders, Diversity, Equity, Inclusion

327. Improving Care and Outcomes for Neurological Issues in Children

Heather Davies, Ken Dyson, Ariel Hinkson, Myriam Srour, Maryam Oskoui

OBJECTIVE: Development of the ICONIC program (Improving Care and Outcomes for Neurological Issues in Children) to improve the process of genetic disorder testing for children and their families.

METHODS: All children and families seen in the neurology clinic at the Montreal Children's Hospital who required genetic testing enrolled in the ICONIC program from January to April 2026. An administration lead was trained to coordinate genetic testing and to liaise with internal and external laboratories. A database was generated to track genetic testing—from the time the sample was drawn to when results were received—as well as the harmonization of results among family members.

RESULTS: Two hundred seventy-two children and parents registered in the ICONIC program in the first from January to April 2026. In comparison to the four months preceding the introduction of the ICONIC program, there was a reduction in lost specimens (three lost specimens vs twelve) resulting in a reduction in repeated specimen procurement and , improved harmonization in obtaining family specimens, and subsequent fewer hospital visits for the family. The appropriate completion of requisitions for genetic testing (90% appropriately vs 45%) ameliorated. The database improved the tracking of genetic testing; specimens and results are easily traceable.

CONCLUSIONS: The ICONIC program improved the process of genetic testing for children and families through the creation of a database that allows comprehensive tracking of specimens in addition to facilitating their procurement. This initiative will allow improved parental satisfaction and experience and early diagnosis of genetic disorders, reducing the diagnostic odyssey.

KEYWORDS: Neurogenetics, Neurodevelopmental Disorders, Epilepsy

328. Expanding the Neurologic Phenotype of Vici Syndrome: Non-epileptic Hyperkinetic Movements and Ketogenic Diet Response

Katherine Bailey, Ahsan Moosa Naduvil Valappil, Sara Bewley, Abigail Kacpura, Moises Auron, Elia Pestana-Knight

OBJECTIVE: To describe previously unreported non-epileptic hyperkinetic and stereotyped movements in Vici syndrome captured on EEG without ictal correlate and to highlight the effectiveness of ketogenic diet therapy in treating refractory infantile spasms in this patient population.

METHODS: Vici syndrome [OMIM 242840] is a rare, severe multisystem genetic disorder caused by autosomal recessive mutations in the *EPG5* gene on chromosome 18q12.3. It is classically characterized by agenesis of the corpus callosum, oculocutaneous hypopigmentation, cataracts, cardiomyopathy, and combined immunodeficiency. This case report describes a 2-year-old male with agenesis of the corpus callosum, global developmental delay, immune dysfunction, ocular abnormalities, and mild cardiac findings.

RESULTS: Whole exome sequencing with mtDNA analysis identified biallelic pathogenic variants in *EPG5* (c.1435_1438del and c.3044C>T). The patient developed infantile spasms, with electroencephalography confirming hypsarrhythmia. He also exhibited multiple distinct episode types, including left tonic upgaze, hemiballismus-like flinging, choreoathetoid limb movements, and repetitive head rocking, all occurring without corresponding EEG changes, consistent with an extrapyramidal movement disorder. Following initiation of the ketogenic diet, seizure frequency decreased by 80–90%, with sustained improvement at one year.

CONCLUSIONS: This case expands the neurologic phenotype of Vici syndrome by characterizing non-epileptic hyperkinetic and stereotyped movements captured on EEG without an ictal correlate and demonstrates a sustained, clinically meaningful response of infantile spasms to ketogenic diet therapy.

KEYWORDS: Neurogenetics, Movement Disorders, Epilepsy

329. Early-onset ALS2-Related Motor Neuron Disease: A Case Report of Two Siblings from a Consanguineous Pakistani Family

Ayesha Ali, Shahnaz Ibrahim

OBJECTIVE: Mutations in the ALS2 gene cause a spectrum of autosomal recessive upper motor neuron predominant disorders, including infantile ascending hereditary spastic paraplegia (IAHSP), juvenile primary lateral sclerosis (JPLS), and juvenile amyotrophic lateral sclerosis (JALS). JALS accounts for less than 0.1% of all ALS cases.

METHODS: Case Report

RESULTS: Two siblings from a consanguineous Pakistani family presented with early-onset progressive spastic paraplegia with bulbar involvement. The older brother, aged 5 years, presented with the inability to walk or stand independently, with symptom onset at 1.5 years of age. Examination revealed bilateral lower limbs spasticity, ankle clonus, hyperreflexia (3+), reduced power, upgoing plantar responses, speech delay, dysphagia, scoliosis, scissoring posture, and left ankle contracture. Brain MRI demonstrated bilateral posterior periventricular white matter signal abnormalities. Whole Exome Sequencing (WES) identified a homozygous likely pathogenic variant in the ALS2 gene (c.1438C>T; p.-Arg480Ter). The younger brother, aged 2.5 years, presented with an inability to ambulate without support and speech delay. Examination revealed microcephaly, slurred speech, scissoring posture, increased lower limb tone, and hyperreflexia (3+). Both were managed by a multidisciplinary team including neurology, genetics, and physiotherapy.

CONCLUSIONS: This case emphasizes the importance of considering ALS2-related disorders in patients with early-onset spastic paraplegia. The occurrence in two siblings from a consanguineous family highlights the role of genetic testing,

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including WES, in establishing the diagnosis and guiding counselling in a resource-limited setting. The presence of periventricular white matter abnormalities in one sibling represents an atypical neuroimaging finding that broadens our understanding of ALS2-related disease manifestations.
KEYWORDS: Neurogenetics, Neuromuscular

330. CARELeuko: A National Network for Leukodystrophy Care, Research, and Innovation

Alexandra Chapleau, Adamo Ghezzo, Sunita Venkateswaran, Justin Simo, Adam Le, Thomas Durcan, Roberta La Piana, Geneviève Bernard

OBJECTIVE: Rare diseases face significant challenges, including limited expertise, fragmented care, and relatively slow progress in research and therapy development. Collaborative research networks have emerged as an effective strategy to address these gaps by uniting stakeholders, increasing awareness, and accelerating discovery. We applied this model to leukodystrophies (LDs), a group of rare, typically progressive genetic disorders affecting the cerebral white matter, through the establishment of the Canadian Association for Research Excellence in Leukodystrophy (CARELeuko), a national network aimed at improving clinical care and fostering research collaboration and participation across Canada.
METHODS: To identify national priorities, we convened a multidisciplinary group of stakeholders, including clinicians, researchers, and patient advocates, at two consecutive CARELeuko symposia. Presentations and discussions were used to identify and prioritize gaps in LD care and research.
RESULTS: CARELeuko successfully established a national, multidisciplinary network and identified key gaps specific to Canada. These included limited access to specialized expertise and absence of national guidelines, challenges related to Canada's large geographic distribution affecting care access, limited newborn screening for treatable LDs, and barriers to accessing newly approved therapies. Higher incidence LD subpopulations within Canada were also identified, highlighting opportunities for targeted research and care strategies.
CONCLUSIONS: The CARELeuko network provides a coordinated national framework to address gaps in LD care and research. These findings will guide targeted initiatives to improve access to care, advance research, and ultimately improve outcomes for affected individuals and families.
KEYWORDS: Neurogenetics

331. Pediatric-onset neurological and neuropsychiatric involvement in adult subjects investigated for leukodystrophies

Annamaria Del Boca, Justin Simo, Abbe Lai, Mayra Aldecoa, Pablo Iruzubieta Agudo, Bernard Brais, Simona Orcesi, Roberta La Piana

OBJECTIVE: Leukodystrophies (LDs) are genetic disorders primarily affecting the central nervous system white matter. While many forms appear in infancy, milder phenotypes or specific entities emerge in adulthood. Adult LDs are still underrecognized and understudied, also due to the frequent confounding comorbidities. We aimed to investigate the presence of neurological and/or neuropsychiatric symptoms presenting before age 16 in adult patients assessed for adult-onset LD.
METHODS: We conducted a retrospective observational study on the 172 adult subjects enrolled in the research study on genetic white matter diseases at our Institution. Inclusion criteria were: (i) molecularly confirmed diagnosis of LD, or clinical-neuroradiological picture highly suggestive of LD, (ii) being ≥16 years old at the time of assessment, (iii) positive personal and/or family history for neurological and/or neuropsychiatric symptoms with onset before the age of 16, (iv) sufficient clinical data available for review.
RESULTS: We identified a history of pediatric-onset neurological or neuropsychiatric involvement in 78 subjects (78/172; 45.3%). Of these, 62 (79.5%) presented a positive pediatric personal history: neurological signs were the most common (72.6%), followed by neuropsychiatric symptoms (61.3%). In 16/78 subjects (20.5%) we documented a positive pediatric family history.
CONCLUSIONS: Our study showed that a considerable proportion of adults investigated for late-onset LDs presented a history of pediatric-onset signs. The identification of early-onset red flags can reduce the diagnostic delay of subjects with adult LDs. These findings lay the foundation to further investigate the presence of a continuum between pediatric and adult leukodystrophies.
KEYWORDS: Neurogenetics

332. A Heterozygous NRXN3 Missense Variant in a Patient With Autism Spectrum Disorder and Developmental Regression: A Case Report

Nesrin Mohamed Dar Hamed, Simon Carlo

OBJECTIVE: To describe the clinical presentation of a patient with severe autism and developmental regression found to have a heterozygous NRXN3 missense variant of uncertain significance.
METHODS: Clinical data were obtained from a detailed caregiver interview, medical record review, and physical examination. Prior neuroimaging and electroencephalography results were reviewed. Genetic findings were obtained through whole-genome sequencing.
RESULTS: We report a 14-year-old male with autism spectrum disorder level 3, intellectual disability, and behavioral dysregulation. Early development was largely typical until 4–5 years of age, when he developed regression in language, social interaction, and toileting skills. He is currently nonverbal and exhibits persistent stereotyped behaviors and episodes of agitation with hyperventilation and tremulousness. Brain MRI (n=4) and prior EEG were unremarkable. Physical exam showed hypotonia and mild joint hyperextension without dysmorphic features. Whole-genome sequencing identified a heterozygous NRXN3 missense variant classified as a variant of uncertain significance.
CONCLUSIONS: This case highlights the clinical variability associated with NRXN3 variants and the challenges in interpreting variants of uncertain significance. Careful clinical correlation remains important, particularly in patients with developmental regression and severe neurodevelopmental phenotypes.

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KEYWORDS: Neurogenetics, Neurodevelopmental Disorders, Behavioral Neurology

333. A Novel Frameshift Variant in TRRAP in a Child with Autism and Global Developmental Delay

Nesrin Mohamed Dar Hamed, Stephanie Diaz Rodriguez, Simon Carlo

OBJECTIVE: To describe a pediatric patient with neurodevelopmental delay and autism spectrum disorder carrying a novel frameshift variant in TRRAP and to expand the phenotypic spectrum associated with truncating variants.

METHODS: We conducted a retrospective review of clinical, developmental, and genetic data of a single patient (n=1) evaluated for global developmental delay. Data were obtained from medical records and caregiver interview. Clinical exome sequencing was performed.

RESULTS: A 6-year-old female presented with autism spectrum disorder (level 3), global developmental delay, hypotonia, dysphagia, microcephaly, and poor growth. Developmental concerns began at 2 years with absent speech, limited eye contact, and toe walking. She achieved independent walking at 15 months but demonstrated persistent gait instability. Language was limited to single words without progression to phrases. She exhibited stereotyped behaviors, sensory sensitivities, and social communication deficits. Family history was notable for developmental delay and autism. Exome sequencing identified a heterozygous novel frameshift variant in TRRAP (c.6197_6198del; p.Leu2066Glnfs*6), classified as a variant of uncertain significance.

CONCLUSIONS: This case highlights a novel TRRAP frameshift variant in a patient with features consistent with TRRAP-associated neurodevelopmental disorder. Our findings support the need for further investigation into the pathogenic role of truncating variants in TRRAP.

KEYWORDS: Neurogenetics, Neurodevelopmental Disorders, Behavioral Neurology

334. Rare Paternal Transmission of a Novel KDM6A Variant in Kabuki Syndrome Type 2: A Father–Daughter Case

Abigail Rasch, Asma Azam, Susanna O'Kula, Suman Ghosh

OBJECTIVE: We describe a father-daughter pair with Kabuki syndrome type 2 harboring a previously unreported *KDM6A* missense variant (c.4160A>G; p.Tyr1387Cys). Reports of paternal *KDM6A* transmission are exceedingly rare. We provide detailed clinical characterization of one such case and highlight the role of familial segregation analysis in variant interpretation.

METHODS: Clinical evaluation, neuroimaging, video-EEG, and whole-exome sequencing were performed on a 3-year-old female with seizures, autism spectrum disorder, feeding difficulties, and poor weight gain, and her 31-year-old father with epilepsy and intellectual disability. Both had dysmorphic facial features consistent with Kabuki syndrome. Targeted parental testing assessed variant segregation. In silico pathogenicity prediction tools were applied.

RESULTS: Exome sequencing identified a heterozygous missense variant of uncertain significance in exon 28 of *KDM6A* in the proband. The same variant was found hemizygous in the affected father and absent in the unaffected mother, consistent with X-linked inheritance and familial segregation. In silico analysis supported a deleterious effect on protein function. Both patients had epilepsy with focal semiology but differed in age of onset, seizure burden, and associated features, reflecting the phenotypic variability expected with partial *KDM6A* escape from X-inactivation and incomplete UTY compensation.

CONCLUSIONS: Although most *KDM6A* variants are de novo or maternally inherited, paternal transmission remains largely undocumented.This case represents one of the few reported instances of father-to-daughter transmission and underscores the diagnostic value of familial segregation analysis in establishing variant pathogenicity. These findings expand the genotypic and clinical spectrum of KS2 and highlight the importance of considering familial inheritance patterns in atypical presentations.

KEYWORDS: Neurogenetics, Epilepsy, Neurodevelopmental Disorders

335. Title: Delineation of Gross Motor Function in PLP1-related Disorders

Giulia Porcari, Francesco Gavazzi, Miriam Lerner, Kaleb Kelley, Sarah Woidill, Anjana Sevagamoorthy, Ylenia Vaia, Russell D'Aiello, Nivedita Thakur, Jennifer Orthmann-Murphy, Danielle deCampo, Laura Adang, Adeline Vanderver

OBJECTIVE: Proteolipid protein 1 (PLP1)-related disorders are rare X-linked hypomyelinating leukodystrophies caused by pathogenic variants in *PLP1*. While motor function is prominently impacted across patients, there is a wide severity spectrum which poses measurement challenges for emerging clinical trials. We evaluated the feasibility of administering scales of motor function, specifically the Gross Motor Function Measure-88 (GMFM-88), Gross Motor Functional Classification System-Expanded and Revised (GMFCS-ER), and Gross Motor Function Classification-Metachromatic Leukodystrophy (GMFC-MLD). We assessed their ability to stratify patients and further validated the GMFC-MLD for retrospective application.

METHODS: We performed a cross-sectional study in molecularly confirmed subjects with *PLP1*-related disorders. The GMFM-88 was administered remotely or in-person; GMFCS-ER and GMFC-MLD were assessed concurrently and retrospectively. GMFC-MLD was dual-rater scored with third-rater adjudication for disagreements. Reliability was assessed using weighted Cohen's Kappa, performance compared using Spearman's rank correlation, and retrospective motor trajectories displayed with spaghetti plots.

RESULTS: Forty-nine patients were included. Median GMFM-88 score was 16.5 (IQR: 26.4), with 59.2% demonstrating a floor effect. GMFCS-ER and GMFC-MLD scores demonstrated strong inverse correlations with the GMFM-88 ($r=-0.70$ and $r=-0.81$, respectively) and were strongly correlated with each other as well ($r=0.83$). Retrospective GMFC-MLD application revealed moderate-to-severe motor impairment with relative stability over time. Cohen's Kappa was 0.82 (n=712; 74.2% agreement).

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CONCLUSIONS: All three clinical outcome assessments (COAs) demonstrated cross-sectional feasibility, with good alignment across measures. The GMFCS-ER and GMFC-MLD show particular promise for natural history studies. Future work is needed to establish age-independent COAs capturing low motor function in severe *PLP1*-related disorder phenotypes to improve clinical trial readiness.

KEYWORDS: Neurogenetics, Neurodevelopmental Disorders

336. Examining Epilepsy Characteristics, Workup, and Treatment in a Single Institution's Angelman Syndrome Cohort

Kirsten Craddock, Holly Dubbs, Samuel Alperin

OBJECTIVE: To characterize a single institution's experience with Angelman Syndrome (AS), including genotype variability and differences in diagnostic and treatment approaches.

METHODS: The electronic medical record of a tertiary medical center was searched for patients with an AS diagnostic code from 2014-2024. Of 132 charts, 89 met criteria for a convincing genetic diagnosis, sufficient chart information, and qualifying Neurology or Genetics visits. Data including demographics, seizure information, EEG & MRI results, and anti-seizure medication (ASM) usage were collected.

RESULTS: Cohort demographics showed Female sex (56%), Caucasian race (67%), and non-Hispanic ethnicity (88%). Genotype breakdown was predominantly Deletion (57%) vs Other (33%), (UBE3A variant, Uniparental Disomy, or Imprinting deficit) vs Unknown (10%). Epilepsy was common (81%), especially in patients with deletions (94%) vs other genotype (59%), with first seizure occurring at a young age (33 months for all patients vs 25 for deletion vs 44 for other). Atypical absence, generalized tonic clonic, and atonic seizures were common (61%, 50%, 49%, respectively). Most patients had an MRI (72%) and EEG (89%). About 80% of patients received seizure medications with 32% trying 3 or more. Levetiracetam, valproic acid, and topiramate (46%, 26%, 17%) were common initial medications with a shift from VPA to LEV over time.

CONCLUSIONS: Epilepsy is common in AS, especially for Deletion genotypes who also tend to have a younger age of onset. Patients frequently have multiple seizure semiologies, and a third are drug-resistant, requiring multiple ASMs. Results contribute to data available to clinicians when making work-up and treatment decisions for AS patients.

KEYWORDS: Neurogenetics, Epilepsy

337. Assessing The Impact of Early Genetic Testing in the Diagnosis and Treatment of Infantile Hypotonia: A Retrospective Cohort Study

Shadi Shams, Shayan Shams, Heather Pierce, Jennifer Yang, Sarah Wiegand, Kristen Wigby

OBJECTIVE: Infantile hypotonia is characterized by decreased muscle tone and has broad differential diagnoses, many of which have genetic or metabolic causes. Advances in genetic technologies, particularly genome sequencing (GS), have improved early diagnosis and access to targeted therapies. This study evaluates the role of genetic testing in unexplained hypotonia and its impact on clinical management.

METHODS: We conducted a single-center retrospective review of admitted patients <12 months with physician-documented hypotonia (August 2024 – December 2025). Of 72 charts, 48 were confirmed manually to have hypotonia, and 34 underwent genetic testing. Diagnostic yield and management changes were assessed using descriptive statistics.

RESULTS: Among 34 patients (ages ranging from birth to 12 months, IQR 2.2 months), most required ICU-level care (74% NICU, 15% PICU) and received neurology (97%) and/or genetics (74%) consultations. Genetic testing yielded diagnoses in 58.8%. GS had the highest yield (75%), followed by gene panels/mitochondrial DNA (50%) and karyotype/chromosomal microarray (42%). Prader–Willi syndrome was the only recurrent diagnosis (100% when clinically suspected). Dysmorphic features (70%) and congenital anomalies (69%) were common. Results led to specific management decisions, including subspecialty referrals (75%), targeted screening (40%), diet modification (5%), medication avoidance (10%), familial cascade testing (10%), and referral for prenatal genetic counseling (30%).

CONCLUSIONS: A high proportion of hospitalized infants with hypotonia have positive genetic testing, particularly those with dysmorphic features and/or congenital anomalies, with the highest diagnostic yield in GS. These results support the important role of genetic testing to guide care and counseling, especially in critically ill patients.

KEYWORDS: Neurogenetics, Neurometabolic, Neuromuscular

338. Bi-allelic IRAK4 Variants are Associated with Severe Neurological Autoinflammation: An Expansion of the Clinical Phenotype

Emma Wiener, Rocio Rius, Carlos Dominguez Gonzalez, Amy Pizzino, Kaley Arnold, Matthew Whitehead, Arastoo Vossough, Roshini Abraham, Amrita Basu, Benjamin Prosser, Alex Felix, Lindsay Higdon, Kathleen Graveran-Perez, Casey Toback, Michael Sperling, Christina Gurnett, Scott Canna, Edward Behrens, Cas Simons, Adeline Vanderver

OBJECTIVE: Monogenic autoinflammatory disorders arise from genetic defects that pathologically activate innate immunity. *IRAK4*, a serine/threonine kinase in the Myddosome, mediates IL-1 and Toll-like receptor signaling, driving proinflammatory cytokine and type I interferon responses. While biallelic loss-of-function *IRAK4* variants cause immunodeficiency, recent reports have implicated bi-allelic combination (null and hypomorphic) *IRAK4* variants in severe neuro- and systemic autoinflammation. We investigated a child with a similar phenotype and screened unsolved autoinflammatory leukoencephalopathies in the Myelin Disorders Biorepository Project (MDBP).

METHODS: Patients enrolled in MDBP had undergone prior evaluation without a unifying molecular diagnosis. Genomic data were processed by a custom pipeline at the Centre for Population Genomics (Australia) and variants were analyzed in seqr.

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RESULTS: We identified five patients from four unrelated families with bi-allelic, rare *IRAK4* variants presenting with severe, persistent autoinflammation without immunodeficiency. Two cases had homozygous variants (c.333del; c.161+892A>G) and three had compound heterozygous variants (c.539_540del/c.80A>C; siblings with c.877C>T/c.162-217C>T). All patients had a concordant clinical and radiologic syndrome: episodic, waxing–waning encephalopathy with visual disturbance and refractory seizures; neuroimaging showed transient white matter edema that evolved to gliosis and cerebral atrophy, superimposed on marked calcifications. Biomarkers indicated neuroinflammation and anemia in all cases. Median age at neurologic symptom onset was 14 years (IQR 8.75). Functional studies show reduced expression and signaling. Immunesuppressive therapies achieved only partial disease control.
CONCLUSIONS: In these 5 patients, a strongly concordant clinical and radiological phenotype emerges of *IRAK4*-mediated autoinflammation, expanding the phenotypic and mutational spectrum of *IRAK4*-related disease. Further studies are needed to define mechanisms and optimal treatments.
KEYWORDS: Neurogenetics, Neuroimmunology, Epilepsy

339. Craniovertebral Junction Abnormalities and Tethered Cord in Mosaic 12q13.2–q15 Microdeletion: Expanding the Neurodevelopmental Spectrum

Rania Lateef, Lauren Patterson, Jacklyn Lessard

OBJECTIVE: 12q14 microdeletion syndrome is a rare chromosomal disorder with reported presentations including growth restriction, developmental delay, and dysmorphia. Central nervous system manifestations remain incompletely characterized, particularly in larger deletions and mosaic cases. We describe a patient with a mosaic 12q13.2–q15 deletion presenting with progressive neurologic symptoms and complex craniovertebral and spinal abnormalities.
METHODS: Clinical, neuroimaging, and genomic data were retrospectively reviewed
RESULTS: Patient is a 13-year-old male with a history of multiple congenital anomalies, including imperforate anus requiring surgical repair, atrial septal defect, submucous cleft palate, bifid uvula, congenital pulmonary stenosis, and global developmental delay with nonverbal autism. He presented to neurology with dysmorphic features, limb asymmetry progressive gait abnormalities characterized by lower extremity tightness and abnormal foot positioning. Lower extremity x-rays did not yield any etiology for the gait problems. Neuroimaging revealed skull base dysplasia with cleft clivus and basilar invagination, resulting in mass effect on the anterior pons and inferior displacement of the cervicomedullary junction. Additional findings included central spinal cord T2 hyperintensity consistent with presyrinx and a low-lying conus medullaris (L3–4) concerning for tethered cord, which was subsequently released neurosurgically. Genome sequencing identified a mosaic (~25%) de novo deletion spanning 12q13.2–q15. These craniovertebral findings have not been reported in 12q14 microdeletion syndrome and suggest a broader pattern of midline developmental disruption.
CONCLUSIONS: This case expands the phenotypic spectrum of 12q13.2–q15 microdeletion to include craniovertebral junction abnormalities and spinal cord pathology, highlighting a potential role for this region in midline neurodevelopment. Mosaicism may contribute to phenotypic variability.
KEYWORDS: Neurogenetics, Neurodevelopmental Disorders

340. WAC-related intellectual disability: A Case Series and Review of the Literature

Adam Kalawi, Quynh Kieu

OBJECTIVE: *WAC*-related intellectual disability (DeSanto–Shinawi syndrome, DESSH) is an ultra-rare neurodevelopmental disorder with limited longitudinal data and incompletely characterized epilepsy risk. We aim to expand the phenotypic spectrum through detailed characterization of two children with de novo pathogenic *WAC* variants, emphasizing seizure expression, neurobehavioral evolution, and growth variability.
METHODS: We performed comprehensive clinical, developmental, neurologic, and dysmorphologic assessments of two pediatric patients with molecularly confirmed *WAC* variants. Neuroimaging, EEG findings, developmental trajectories, behavioral features, and multisystem comorbidities were analyzed and compared with published DESSH cohorts using standardized systems-based documentation.
RESULTS: Patient 1, a 3-year-old ex-34-week male with congenital heart defects, demonstrated global developmental delay, dysmorphic features, level 1 autism spectrum disorder, constipation, obesity (>99th percentile BMI), and an incidental renal cyst. Brain MRI and routine EEG were unremarkable. Whole exome/genome sequencing identified a de novo pathogenic *WAC* nonsense variant (c.1837C>T; p.Arg613*). No clinical seizures have occurred. Patient 2, a 3-year-old male with a de novo *WAC* frameshift variant (c.370_377dupACTTCAGA; p.D126Efs*69), exhibited hypotonia, global developmental delay, macrocephaly, emerging autism traits, anxiety, behavioral dysregulation, and obesity (≈95th percentile BMI). He has recurrent staring episodes with EEG demonstrating left temporal epileptiform discharges and temporal intermittent rhythmic delta activity (TIRDA), supporting focal cortical hyperexcitability.
CONCLUSIONS: These cases broaden the phenotypic spectrum of DESSH and highlight variability in epilepsy expression and metabolic profile. Systematic longitudinal phenotyping is essential to refine genotype–phenotype correlations and guide anticipatory management.
KEYWORDS: Neurogenetics, Neurodevelopmental Disorders, Lifespan Manifestations of Childhood Onset Conditions

341. Basal Ganglia and Mesial Temporal Abnormalities in a Child with Homozygous AGRN Variant: Phenotypic Expansion or Dual Diagnosis?

Norvin West, Salma Sherdil, Jacklyn Lessard, Tarannum Lateef

OBJECTIVE: The AGRN gene is associated with congenital myasthenic syndromes characterized by neuromuscular junction dysfunction, including fatigable weakness and bulbar involvement. Central nervous system manifestations are rarely described. We report a child with a homozygous AGRN variant and unexpected neuroimaging abnormalities.

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METHODS: Clinical case report.
RESULTS: The patient is a 5-year-old male, born in Afghanistan, who presented with significant developmental delay, minimal expressive language, and limited functional mobility due to ataxia. He required multidisciplinary therapies, including physical, occupational, and speech therapy. Brain MRI demonstrated bilateral globus pallidus T2 hyperintensity and small hippocampi with increased T2 signal concerning for mesial temporal sclerosis, and he was referred to genetics. Whole genome sequencing identified a homozygous variant of uncertain significance in AGRN (p.P828N), with paternal heterozygosity and suspected maternal carrier status in the setting of consanguinity (parents are first cousins). Clinical evaluation did not reveal clear evidence of fatigable weakness, ptosis, or bulbar dysfunction typical of AGRN-related congenital myasthenic syndrome; however, assessment of fatigability was limited by baseline motor impairment and ataxia.
CONCLUSIONS: This case raises the possibility of central nervous system involvement in AGRN-related disease or an alternative underlying etiology contributing to the phenotype of basal ganglia and mesial temporal abnormalities. This case also illustrates the diagnostic challenges in evaluating neuromuscular disorders in children with significant neurodevelopmental impairment, where classic features may be obscured. Further genetic and functional studies are needed to clarify the pathogenicity of this variant and its relationship to the observed phenotype.
KEYWORDS: Neurogenetics, Neuromuscular, Neurodevelopmental Disorders

342. Pediatric Clinical Genomics at a Regional Population Scale: Primary Children's Gene Kids

Joshua Bonkowsky, Marti Tristani-Firouzi, Mark Yandell, Rachel Palmquist, Heidi Niedfeldt, Evy Clark, Kirk Bjella, Ted May, Bennet Peterson, Sophia Peralta, Gene Kids Study Team

OBJECTIVE: Whole genome sequencing (WGS) is high-yield and cost-effective for diagnosing pediatric neurogenetic and related conditions, but implementation has been limited to tertiary centers. Broader adoption is hindered by cost, access, and limitations in understanding. We sought to develop and implement a regional program for pediatric clinical WGS, particularly for rural, disadvantaged, and frontier communities. Core goals included clinical return of results, lifelong data access, and reducing testing barriers.
METHODS: Gene Kids (GK), a 3-year, $9 million initiative of Primary Children's and University of Utah Department of Pediatrics, was developed for inpatient at Primary Children's Hospital, regionally through NICUs and hospitalizations across the Intermountain Health network (32 hospitals), and more than 200 outpatient clinics. Inclusion was individuals under 19 years with suspected genetic conditions.
RESULTS: Launched September 2024, GK serves a catchment area of over 1.8 million children. Through April 2026, 1,533 probands (>3,000 individuals total) were enrolled from 41 sites across 10 states, spanning more than 400,000 square miles. 52% of enrolled children faced access barriers; 20% were rural. Enrollees were 55% female and 78% Caucasian. Reanalysis of nondiagnostic cases using the probabilistic GEM algorithm yielded an additional 10% diagnostic rate. Novel tools developed include Mendelian Phenotype Search Engine (MPSE), an AI system to prioritize WGS candidates.
CONCLUSIONS: Gene Kids represents the largest pediatric regional clinical genomics program to date, achieving broad geographic reach and improved access for underserved populations. Ongoing expansion across the Mountain West supports implementation science efforts to identify and address barriers to equitable genomic care
KEYWORDS: Neurogenetics

343. Moyamoya Syndrome in 1p36 Deletion: A Case Report Implicating mTOR Pathway Disruption

Jewel Soucek, Bethany Bergschneider, Jaycie Gard, Robert Hopkin, Kelli Dominick, Ryan Monsberger, Olivia Mirabella, Yaning Wu, Kelly Haller, Ammar Husami, Amelle Shillington, Liliana Luna-Nelson

OBJECTIVE: 1p36 deletion syndrome is a genetic condition caused by a heterozygous terminal deletion at chromosome 1p36. Individuals commonly present with intellectual disability, seizures, distinctive facial features, and brain abnormalities. Moyamoya syndrome is a condition affecting blood vessels in which the internal carotid arteries often become occluded or narrowed, restricting blood flow to the brain. Here, we present the case of co-occuring 1p36 deletion syndrome and moyamoya syndrome in a fourteen year-old girl.
METHODS: An extensive review of the individual's electronic medical record was conducted. The individual initially presented with developmental delay and speech apraxia at four years of age. A mosaic 1p36.32-33 deletion was identified by microarray testing. After years of migraine headaches, the individual was later diagnosed with moyamoya syndrome at age ten. A literature review investigated for similar reports of co-occurring conditions.
RESULTS: Literature review revealed one additional individual diagnosed with moyamoya syndrome co-occurring with 1p36 deletion syndrome. Comparison of the two individuals' deletion profiles suggests that mTOR-related pathways impacted by 1p36 deletions could be a potential contributor to moyamoya pathology. The previously reported individual was haploinsufficient in MTOR, while the individual reported in this case had deletions of genes that impact mTOR expression.
CONCLUSIONS: We propose that 1p36 deletions predispose individuals to moyamoya syndrome by disrupting the mTOR vascular signaling axis through various deletion patterns. Analyzing microdeletion data from other patients with both 1p36 deletion syndrome and moyamoya syndrome could help to identify the genetic drivers of this pathology.
KEYWORDS: Neurogenetics, Neuroimaging

344. Genome and exome sequencing as diagnostic tools for pediatric leukodystrophies and genetic leukoencephalopathies

Kayla Blankenship, Morgan Driver, Robert Rigobello, Matthew Walsh, Hongzheng Dai, Liesbeth Vossaert, Katharina Schulze, Wilson Wu, Xiaonan Zhao

OBJECTIVE: Leukodystrophies (LDs) and genetic leukoencephalopathies (gLEs) are heterogenous, heritable

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conditions primarily affecting white matter in the central nervous system. Preliminary studies have shown increased diagnostic yield of genome sequencing (GS) and exome sequencing (ES) beyond standard of care assessment including magnetic resonance imaging, biochemical testing, and single gene testing. This study characterizes genetic findings from GS/ES for LD/LE to better understand their diagnostic utility.
METHODS: A retrospective study was conducted to evaluate genetic findings of consecutive pediatric patients (<18 years old) who underwent GS/ES at our clinical diagnostic laboratory. Cases were selected based on a clinical suspicion of LD/LE.
RESULTS: Eighty cases were reviewed with 30 positive (37.5%) results. The diagnostic yields of GS and ES were 39.1% (25/64) and 31.3% (5/16), respectively. Of the individuals with positive results, 66.7% (20/30) had at least one finding in a gene associated with LD/LE. Of the remaining 10 positive cases, nine had a genetic diagnosis partially explaining their neurological symptoms. The most frequent diagnoses included X-linked adrenoleukodystrophy (5/30) and Alexander disease (3/30). In those with GS, two diagnoses involved noncoding variants and two had pathogenic short tandem repeat expansions.
CONCLUSIONS: Our LD/LE cohort had an overall diagnostic yield by GS/ES of 37.5%. Of those with positive results, 96.7% had findings that either explained their LD/LE or other neurological symptoms. Additionally, 13.3% of positive cases had variants identified by GS likely to be missed by gene panels or ES. Future studies may explore the clinical utility of ES/GS as first-tier testing for LD/LE.
KEYWORDS: Neurogenetics

345. Not All That Looks Mitochondrial is Mitochondrial: Insights from Single-Center Multi-Disciplinary Clinic

Xuan Tran, Adriana DeLaFlor Llona, Hannah Phillips, Srika Amin, Jyssica Seebeck, Laura Tochen, Sarah Wright, Dana Harrar, Kuntal Sen

OBJECTIVE: Primary mitochondrial disorders are caused by pathogenic variants in nuclear or mitochondrial DNA genes that affect mitochondrial structure or function. This case series highlights a cohort of patients with genetic mimics of mitochondrial disorders who were ultimately diagnosed with alternative monogenic conditions rather than primary mitochondrial disease.
METHODS: We performed a retrospective chart review of patients seen in our multidisciplinary mitochondrial clinic.
RESULTS: Patient 1 is a 5-year-old with epilepsy and developmental delay who was suspected to have mitochondrial disease based on a stroke-like episode with parieto-occipital diffusion restriction; whole genome sequencing revealed a pathogenic SCN2A variant, which can also be associated with DWI changes. Patient 2 is a 15-year-old with developmental delay, muscle weakness, and cardiac arrhythmia who was suspected of having mitochondrial disease based on an MTND6 variant; whole genome sequencing confirmed myotonic dystrophy type 1. Patient 3 is a 16-year-old with autism, feeding aversion, and anxiety who was suspected to have mitochondrial disease based on prior biochemical testing; whole exome sequencing revealed an RFX7-related neurodevelopmental disorder. Patient 4 is a 5-year-old with ptosis and hypotonia who was thought to have mitochondrial disease based on basal ganglia changes; genetic testing identified AGRN-related congenital myasthenic syndrome. Most patients had received mitochondrial-directed therapies prior to diagnosis.
CONCLUSIONS: Discontinuation of mitochondrial-directed therapies and transition to condition-specific management improved clinical clarity and care planning. These findings highlight the importance of revisiting diagnostic assumptions and underscore the role of comprehensive genomic testing in distinguishing mitochondrial disease from its genetic mimics.
KEYWORDS: Neurogenetics, Neurodevelopmental Disorders, Neuromuscular

346. Post-Implementation Evolution of Genetic Testing Pathways Following Texas Medicaid Coverage of Genome Sequencing with a Focus in Pediatric Neurology

Chad Moretz, Morgan Driver, Alexander Bock, Robert Rigobello

OBJECTIVE: On September 1, 2024, Texas Medicaid implemented coverage for genome sequencing (GS) for children with suspected rare disease, including neurologic indications. This study characterizes temporal changes in GS testing patterns among pediatric neurology patients following implementation of the policy.
METHODS: We conducted a retrospective analysis of Texas Medicaid beneficiaries less than 18 years of age who received GS after policy implementation. Included cases had a clinical indication of intellectual disability or developmental delay (ID/DD). Three consecutive 6-month post-policy periods were evaluated. Ordering provider specialty and genetic testing history were abstracted from clinical documentation.
RESULTS: GS was ordered by non-genetics providers or clinics in 0%, 1.4%, and 5.6% of cases, respectively, across the three periods. In the early post-implementation period, 57.1% were reported to have genetic testing prior to GS. This proportion declined to 37.3% in the mid post-implementation period and stayed consistent at 38.0% in the late post-implementation period. For those with prior testing, the proportion with exome sequencing prior to GS decreased over time ($\chi^2 = 6.7$, $p < 0.05$), with 62.5%, 57.1%, and 29.3% having exome sequencing respectively across the three periods.
CONCLUSIONS: Results suggest ongoing post-policy maturation of clinical practice, with increasing utilization of GS for children with ID/DD in non-genetics clinics and as an earlier diagnostic test rather than a stepwise escalation after other types of genetic tests.
KEYWORDS: Neurogenetics

347. Phenotypic Diversity Across and Within Variants of the CaMKII Complex in Children

Samuel Kartsonis, Catherine Becker, Nicole Gilette, Danielle Veenma, Anjuli Dijkmans, Cintia Da Hora, Audrey Thurm, Florian Eichler

OBJECTIVE: To characterize variant-specific effects and within-variant phenotypic heterogeneity in children with variants in *CAMK2A* and *CAMK2B*.

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METHODS: We clinically evaluated a cohort of 12 children (3-18 years old; median age was 6.5) with five different variants affecting the calcium/calmodulin-dependent protein kinase II (CaMKII) complex, including three variants on CAMK2A and two on CAMK2B. Clinical features were assessed across motor, cognitive, gastrointestinal, sensory, and behavioral domains. Developmental milestones and standardized behavioral measures, including the Behavioral Problems Inventory (BPI), were systematically collected to enable stratification of the cohort by variant.

RESULTS: Children demonstrated a broad spectrum of physical and cognitive features, including hypotonia, global developmental delay, intellectual disability, gastrointestinal dysmotility with constipation, and altered sensory responses such as pain hyposensitivity. 33% of children were non-ambulatory and non-verbal, whereas others exhibited substantially milder phenotypes, with speech delay as the most observable feature. Periods of marked agitation and behavioral dysregulation were observed in 67%, though these features varied in severity and presentation. Although several clinical features overlapped across variants, specific variants were associated with distinct phenotypic profiles. Substantial variability was also observed among individuals carrying the same variant, indicating pronounced within-variant heterogeneity.

CONCLUSIONS: *The CAMK2A* and *CAMK2B* genes encode components of a shared protein complex critical for synaptic plasticity, memory-related long-term potentiation, and neuronal migration. Variants on CAMK2A and CAMK2B are associated with a broad and variable neurodevelopmental phenotype. Both variant-specific effects and within-variant heterogeneity contribute to clinical presentation, underscoring the importance of integrated molecular and clinical characterization.

KEYWORDS: Neurogenetics, Neurodevelopmental Disorders, Behavioral Neurology

348. Plasma Proteomic Signatures in Prototypical Forms of Hereditary Spastic Paraplegia

Michelle Grambs, Habibah Agianda, Joseph Holtey, Hyo-Min Kim, Amy Tam, Joshua Rong, Nicole Battaglia, Tobias Brunnbauer, Beril Ay, Katerina Bernardi, Pui Lee, Kathryn Yang, Darius Ebrahimi-Fakhari

OBJECTIVE: Hereditary spastic paraplegias (HSP) are a group of neurogenetic disorders caused by axonopathy of the corticospinal tract. No validated blood-based biomarkers currently exist for HSP, limiting clinical trial readiness. We aimed to identify plasma proteomic signatures associated with HSP subtype and disease severity.

METHODS: We performed a case-control study of 105 genetically-confirmed HSP patients (SPG4, n=42; AP-4-HSP, n=41; SPG11/15, n=22) and 45 age- and sex-matched healthy controls. Plasma proteins were measured using the Olink Target 48 Neurodegeneration panel. Differentially abundant proteins (DAPs) were identified using limma linear models adjusted for age, with Benjamini-Hochberg false-discovery-rate correction. Proteins meeting thresholds of $|\log_2 \text{fold change}| \geq 1$ and FDR-adjusted q-value < 0.05 were considered statistically significant. Subtype-specific analyses and linear and logistic regression models relating protein levels to clinical severity scores were performed.

RESULTS: No DAPs were shared across all three HSP subtypes relative to controls, but subtype-level analyses revealed partially overlapping yet distinct profiles. AP-4-HSP showed 5 DAPs (downregulation of BACE1 and Aβ40; upregulation of GLRX, HLA-DRA, and FOXO3); SPG4 showed 9 DAPs (upregulation of NEFL, GLRX, TP53, EIF2AK2, and FOXO3; downregulation of Aβ40, Aβ42, BMP7, and pTau217); and SPG11/15 showed marked upregulation of NEFL and HLA-DRA, with NEFL showing greater magnitude in SPG11/15 than SPG4 (+2.51 vs. +1.39). Subtype-specific associations between individual proteins and clinical severity scores were also identified.

CONCLUSIONS: Plasma proteomic profiling reveals distinct signatures across three prototypical forms of HSP and provides a framework for integrating circulating protein biomarkers into disease monitoring. Replication and validation in larger, longitudinal cohorts are needed.

KEYWORDS: Neurogenetics, Movement Disorders, Neurodevelopmental Disorders

349. Beyond the Usual Suspect: MT-TD Variant in MELAS Phenotype

Amy Goldstein, Cansu Ensert Cihan, Srika Amin, Sonal Sharma, Jamie Peterson, Kuntal Sen

OBJECTIVE: MELAS (mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes) is mostly caused by m.3243A>G variant in the MT-TL1 gene. The phenotype is genetically heterogeneous. We report a novel variant associated with a spectrum of mitochondrial phenotypes, supported by functional assays.

METHODS: Clinical, neuroradiologic, and genetic data collected retrospectively. Patient 1 was enrolled in neurogenetics registry; Patient 2 was identified through Mitochondrial Care Network collaboration. GDF15 and skin biopsy for electron transport chain (ETC) analysis were performed in Patient1.

RESULTS: Patient 1, a 9-year-old female with developmental delay, failure to thrive, and short stature, presented with seizures, encephalopathy, and hemiplegia. Neuroimaging demonstrated parieto-occipital and temporal lobe diffusion restriction; lactate was 10 mmol/L (normal 1-2.4). Exome sequencing was unrevealing; mitochondrial DNA sequencing revealed a de novo m.7538T>C MT-TD variant (87% heteroplasmy). She had two additional stroke-like episodes managed with IV arginine. GDF15 was >6000 pg/mL (normal <750). Patient 2, a 33-year-old female, with the same variant at lower heteroplasmy (10-11%); presented with cognitive decline, dysarthria, myalgias, and exercise intolerance. MRI demonstrated vermian and cortical atrophy, and basal ganglia encephalomalacia. Alanine was 760 μmol/L and GDF15 1026 pg/mL. Managed with mitochondrial supplements.

CONCLUSIONS: We report a novel variant associated with a classic MELAS phenotype in a pediatric patient and a milder, late-onset mitochondrial phenotype in an adult. MT-TD encodes mitochondrial tRNA for aspartic acid; its

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disruption impairs oxidative phosphorylation, similar to MT-TL1 disease. Elevated GDF15 and abnormal ETC studies along with concordant phenotypes across two patients support this variant is associated with a spectrum of mitochondrial phenotypes.
KEYWORDS: Neurogenetics, Neurometabolic

350. Unusual Features Associated with a Novel SETBP1 c.3168_3178del Variant: Expanding the Phenotypic Spectrum into Adulthood

Alina Rivadeneira-Limongi, Angelica Montilla, Alcy Torres

OBJECTIVE: SETBP1-related disorders typically manifest as intellectual disability and language impairment. As clinical recognition increases, the phenotypic boundaries continue to expand. We aim to characterize a novel SETBP1 variant in an adult patient exhibiting atypical neurological features, including a prominent tremor and cognitive decline.
METHODS: We conducted a retrospective analysis of a 24-year-old male with a novel, de novo heterozygous 11-bp deletion in SETBP1 (c.3168_3178del). Clinical, longitudinal neuropsychological, and neuroimaging data were reviewed.
RESULTS: The patient presented with a complex neurodevelopmental history of ADHD, Tourette's disorder, dyspraxia, and intellectual disability. Physical examination revealed a distinct dysmorphic profile: long face, frontal bossing, deep-set eyes, congenital right ptosis, high-arched palate, small palpebral fissures, as well as hyperpigmented macules, mild pectus excavatum, flared ribs, and redundant umbilical skin. Neurological evaluation was notable for hyperreflexia, reduced muscle bulk, and a complex tremor involving action, postural, and lingual components, more pronounced on the left. Longitudinal cognitive testing revealed a decline in Full Scale IQ (from 73 at age 8 to 66 at age 11), with particular deficits in working memory. Brain MRI was unremarkable. Genetic testing confirmed the de novo nature of the variant through negative parental testing.
CONCLUSIONS: This case identifies a novel SETBP1 variant and introduces prominent tremor as a potentially new phenotypic feature of the disorder. Furthermore, the longitudinal IQ data suggests a risk for cognitive stagnation or decline in these patients. These findings are essential for refining the genotype–phenotype map and guiding the long-term management of SETBP1-related disorders as patients transition into adulthood.
KEYWORDS: Neurogenetics, Movement Disorders, Behavioral Neurology

351. A Pilot HEXA Variant Database for Tay-Sachs Disease: Genotype-Phenotype Correlations to Support Diagnosis, Prognosis, and Treatment Eligibilit

Cintia da Hora, Amanda Nagy, Samuel Kartsonis, Florian Eichler

OBJECTIVE: To establish a pilot HEXA variant database linking specific genetic variants to enzyme activity and clinical phenotype in Tay-Sachs disease.
METHODS: A systematic literature review (PubMed 1971–2025) identified published cases with confirmed pathogenic HEXA variants. Data on variant combinations, residual enzyme activity, age of onset, and clinical features were entered into a secure REDCap database using standardized terminology and ACMG pathogenicity classification.
RESULTS: Forty-seven pathogenic HEXA variants were catalogued from cases across multiple countries, spanning infantile, juvenile, and adult disease forms. Residual enzyme activity was the strongest predictor of onset, with activity below 1% universally producing infantile disease and 3–10% activity associated with juvenile or adult presentations. Phenotypic severity was determined by the combination of both alleles rather than either variant alone. Movement disorder phenotype was variant-specific — R178H consistently produced dystonia and extrapyramidal features, G269S compound heterozygotes presented as a proximal weakness mimic of SMA, and adult-onset cases showed cerebellar ataxia and tremor. At least two variants previously classified as uncertain significance were reclassified as pathogenic through clinical and functional correlation.
CONCLUSIONS: This pilot HEXA variant database demonstrates that genotype-phenotype correlations in Tay-Sachs disease require analysis of both alleles in the context of residual enzyme activity. Systematic curation identifies clinically actionable misclassifications and provides guidance for prognosis and gene therapy eligibility. Expansion to a prospective living database will support families and providers navigating this rare and heterogeneous disease.
KEYWORDS: Neurogenetics, Neurogenetics, Education

352. CACNA1A mutation alters oligodendrocyte lineage cell calcium signaling and myelination during development

Melanie Piller, Ryan Doan, Cody Call, Stephen Smith, Kelly Monk

OBJECTIVE: Oligodendrocytes (OLs) are the myelinating glia of the central nervous system (CNS). These cells differentiate from OL progenitor cells (OPCs), which can also persist in their progenitor state, and both OLs and OPCs are types of oligodendrocyte lineage cells (OLCs). OLCs are sensitive to neuronal activity, which can influence proliferation, migration, survival, differentiation, and myelin formation via various pathways. Calcium influx in OLCs regulates many developmental processes, including stabilizing newly formed sheaths. OLCs possess P/Q-type voltage-gated calcium channels (VGCC), encoded by *CACNA1A*, that contribute to calcium influx. Genetic variants in *CACNA1A* are implicated in a spectrum of neurological disorders, yet the functional significance of P/Q-type channels in OLCs is not well understood. In this study, we employ zebrafish to investigate the role of P/Q type channels in OLCs *in vivo* during development.
METHODS: We use global and cell-type specific CRISPR/Cas9-mediated genome editing approaches in conjunction with live imaging and physiology to characterize the morphology and signaling properties of OLCs with mutated P/Q-type channel genes in zebrafish.
RESULTS: P/Q-type channels are required for normal myelination in the developing CNS and mutants present with decreased amplitude sheath calcium transients, reduced myelin production, shorter myelin sheaths and increased blebbing

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membrane structures associated with sheath shortening during development.

CONCLUSIONS: These findings provide new insight into the role of P/Q-type calcium channels in regulating OLC development and myelination, with interesting implications for the possible role of OLCs in *CACNA1A*-related disorders.

KEYWORDS: Neurogenetics, Neurodevelopmental Disorders

353. Early data from the Volare Study – MEF2C Haploinsufficiency syndrome Natural History Study Data

Ji-Sun Kim, Zachary Grinspan, Jennifer Cross, Natalie Wayland

OBJECTIVE: MEF2C haploinsufficiency syndrome is characterized by developmental delay, absent or minimal speech, epilepsy, and motor impairment. With precision therapies targeting MEF2C expression advancing toward clinical testing, robust longitudinal natural history data are needed to inform trial design. We characterize early neurological and developmental trajectories in individuals with MCHS using standardized assessments and identify caregiver-prioritized outcomes suitable for clinical trials.

METHODS: This is a prospective, observational natural history study for individuals with molecularly confirmed MEF2C haploinsufficiency. Since 04/2025, 38 participants have enrolled in-person longitudinal cohort with repeated evaluations over two years, and 10 participants in a parallel virtual cohort. Assessments include standardized measures of cognitive, motor, and communication function; seizure history/burden; sleep, behavior, and quality of life. Semi-structured caregiver interviews are conducted to identify outcomes to define perceived clinical improvement. Early analyses focus on feasibility, baseline phenotypic characterization, and preliminary longitudinal patterns.

RESULTS: Early data demonstrate marked heterogeneity across developmental domains among a spectrum of variants. Severe impairment in expressive communication and motor function are common. Epilepsy is prevalent but variable in age of onset and seizure burden. Preliminary follow-up suggests limited developmental gains over time, underscoring the importance of sensitive, disorder-appropriate outcome measures. Caregivers consistently prioritize improvements in communication, motor abilities, and seizure control as clinically meaningful.

CONCLUSIONS: These early findings demonstrate the feasibility of large-scale longitudinal data collection in MCHS and highlight key phenotypic features relevant to trial design. They provide critical groundwork for selecting endpoints, defining meaningful change, and enabling forthcoming interventional trials.

KEYWORDS: Neurogenetics, Neurodevelopmental Disorders, Lifespan Manifestations of Childhood Onset Conditions

354. Predicting Genetic Prevalence of AP-4-Associated Hereditary Spastic Paraplegias

Amy Tam, Enrique Gonzalez Saez-Diez, Darius Ebrahimi-Fakhari

OBJECTIVE: Estimate genetic prevalence for each of the four AP-4-associated disorders (SPG47, SPG50, SPG51, SPG52 for *AP4B1*, *AP4M1*, *AP4E1*, *AP4S1*, respectively) and identify ancestry-specific disease burden. With gene-therapy trials emerging, accurate prevalence estimates inform trial planning.

METHODS: Variants were curated from four sources: (1) 310 children from a natural history study (NCT04712812, n=117 *AP4B1*, 108 *AP4M1*, 27 *AP4E1*, 58 *AP4S1*); (2) ClinVar Pathogenic/Likely Pathogenic variants; (3) high-confidence predicted loss-of-function variants (nonsense, frameshift, splice, start-loss, exon-deletion); and (4) deleterious missense variants (REVEL ≥0.932). ClinVar Benign/Likely Benign variants were excluded from sources (3) and (4), and variants homozygous in gnomAD were removed. Prevalence was calculated with the Genetic Prevalence Estimator (GeniE), applying Hardy-Weinberg to gnomAD v4.1 allele frequencies, with ancestry-stratified estimates across genetic ancestry groups.

RESULTS: The variant pool included 171 *AP4B1*, 174 *AP4M1*, 150 *AP4E1*, and 46 *AP4S1* variants; variants from our natural history study represented 16–37% per gene. Global prevalence: *AP4B1* 1:2,175,683; *AP4M1* 1:1,141,299; *AP4E1* 1:9,731,733; *AP4S1* 1:15,065,221. Ancestry-stratified analyses identified elevated prevalence in Ashkenazi Jewish (*AP4B1* 1:758,362; *AP4M1* 1:547,895) and South Asian populations (*AP4M1* 1:596,136; *AP4E1* 1:1,093,400; *AP4S1* 1:5,556,795), with additional enrichment in Middle Eastern (*AP4E1* 1:2,293,520) and remaining (*AP4S1* 1:4,638,469) groups.

CONCLUSIONS: These estimates provide the first genetic prevalence predictions for AP-4 disorders, with ancestry-specific burden potentially reflecting founder variants or consanguinity. These benchmarks inform clinical trial planning for ongoing (*AP4M1*) and upcoming (*AP4B1*) gene-therapy trials. Recruitment of patients with novel variants would enable validation of predicted pathogenicity and genotype–phenotype correlations.

KEYWORDS: Neurogenetics, Epilepsy, Movement Disorders

355. Missing the mosaics: Case report of a mosaic SCN2A missense variant identified in a child with neonatal onset epilepsy

Emma Cardwell, Kimberly Foss, Tam Sneddon, Yael Shiloh-Malawsky, Holly Phillippe, Stephanie Peck, Bradford Powell, Jenna Lea, Senyene Hunter

OBJECTIVE: To report a case of neonatal-onset epilepsy caused by a mosaic *SCN2A* missense variant identified through long-read genome sequencing (LRS) after negative clinical short-read genome sequencing.

METHODS: The patient developed seizures at age two days and underwent rapid trio genome sequencing at a clinical laboratory. This analysis was non-diagnostic. At age 20 days, she was admitted for focal status epilepticus, treated with lacosamide. At 10 months, she developed epileptic spasms with subsequent global developmental delay. The patient was then enrolled in the IRB-approved GDNDD study at the University of North Carolina (UNC)

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and underwent genome LRS and reanalysis of clinical genome sequencing.
RESULTS: LRS identified a *de novo* mosaic *SCN2A* missense variant (NM_001040142.2:c.2659G>T, NP_001035232.1: p.Val887Leu) at an allele fraction of 33%. Initial targeted reanalysis by the clinical laboratory did not report the *SCN2A* mosaic variant. Reanalysis of the clinical sequencing data by the UNC Genomic Analysis Core detected the variant at an allele fraction of 21%; the clinical laboratory revised reports thereafter. The *SCN2A* variant was confirmed to be *de novo* by Sanger sequencing of the trio samples. The variant was classified as likely pathogenic per ACMG/AMP Variant Interpretation Guidelines. Results were returned, lacosamide dosing was optimized, and the patient had no additional seizures.
CONCLUSIONS: Standard clinical genome analysis may miss essential genetic findings, including pathogenic mosaic variants. LRS can identify variants missed by short-read sequencing. Reanalysis of clinical sequencing data should be considered when there is high suspicion of a genetic etiology, to identify clinically actionable findings.
KEYWORDS: Neurogenetics, Epilepsy

356. From Variant to Insight: A HIPAA-Compliant AI Tool for Pediatric Neurogenetics

Christian Hidalgo Jara, Jeffrey Strelzik, Kuntal Sen

OBJECTIVE: Genetic testing is increasingly integrated into daily pediatric neurology practice. To improve awareness among trainees and providers, educational workshops and a national curriculum through the Child Neurology Society have been developed. However, busy clinical workflows often limit real-time access to gene- and variant-level data. Artificial intelligence (AI) is being used across academic medicine to streamline phenotype-driven gene prioritization and variant interpretation. We aimed to develop a HIPAA-compliant AI tool to support rapid, clinically relevant neurogenetic information retrieval.
METHODS: Beginning November 2024, we designed structured prompts for an AI tool using natural language processing to query genetic databases, including OMIM, GeneReviews, and ClinVar. An initial version using OpenAI without data protection was used for trainee education. Recognizing clinical utility, in July 2025 we transitioned to a HIPAA-compliant environment using institutional AI tools, including Microsoft 365 Copilot integrated with OpenAI. The tool allows secure input of patient-specific variants and phenotypes and returns synthesized summaries from curated databases.
RESULTS: Integration within institutional data protection frameworks enabled secure and efficient access to genetic information. The tool supports differential diagnosis generation and variant interpretation but does not replace expert clinical judgment.
CONCLUSIONS: This tool may improve clinical efficiency and education. Future work will evaluate its impact in pediatric neurology clinics and training programs and integrate it with CNS genetics curriculum and summit initiatives.
KEYWORDS: Neurogenetics, Education, Ethics

357. Novel homozygous presentation of a variant of uncertain significance in CSF1R (NM_005211.3, c.2008G>A, p.Asp670Asn) leading to severe early-onset CSF1R-related disorder

Pooja Shah, Margaret Wiley, Sonia Ehrlich, Tracy Gertler

OBJECTIVE: We aim to share the case report of a neonate with multiple congenital brain anomalies identified on 22-week fetal ultrasound who was found to have homozygous variants of uncertain significance in *CSF1R*, which encodes a tyrosine kinase receptor that binds colony stimulating factor 1, a cytokine responsible for macrophage regulation.
METHODS: Prenatal genetic testing was sent from amniotic fluid. Fetal magnetic resonance imaging (MRI) was completed at 24 weeks. Following uncomplicated full-term delivery, the neonate underwent evaluation in the neonatal intensive care unit.
RESULTS: Prenatal chromosomal microarray was negative; whole exome sequencing identified homozygosity in a *CSF1R* variant. Fetal MRI revealed T2 hyperintensities in bilateral periventricular white matter and cerebellum; postnatal MRI revealed mixed T1/T2 abnormal signal in bilateral periventricular white matter and cerebellum, diffusion restriction in the genu of the corpus callosum, increased susceptibility in the posterior limbs of the internal capsules, moderate ventriculomegaly, and narrowing of CSF spaces at the craniocervical junction. Postnatal X-ray of skeletal system revealed dysosteosclerosis. Auditory brainstem response was intact bilaterally; optic nerve hypoplasia was not visualized. The neonate was found to have hypocalcemia due to transient hypoparathyroidism and oropharyngeal dysphagia requiring tube feedings.
CONCLUSIONS: There is a paucity of literature regarding *CSF1R* genotype-phenotype correlation, and to date there are no reported cases of early- and late-onset disease associated with the same variant. Our findings support the likely pathogenicity of this *CSF1R* variant (NM_005211.3, c.2008G>A, p.Asp670Asn), previously reported in heterozygous autosomal dominant late-onset *CSF1R*-related disorder, contributing to a novel presentation of homozygous autosomal recessive early-onset *CSF1R*-related disorder.
KEYWORDS: Neurogenetics, Fetal Neurology, Neonatal Neurology

358. Photoreceptor Nuclear Hyperreflectivity on Handheld OCT as an Early Biomarker Guiding Pre-Symptomatic Intravitreal Cerliponase Alfa in CLN2

Paula Morales, Cesar Estrada-Puente, Shital Patel, Xi Chen, Cynthia Toth, Ramiro Maldonado

OBJECTIVE: To describe the youngest reported patient with ceroid lipofuscinosis type 2 (CLN2) to receive enzyme replacement therapy (ERT) intravitreal cerliponase alfa and to characterize an optical coherence tomography (OCT) biomarker prompting pre-symptomatic intervention.
METHODS: A 9-month-old male with molecularly confirmed compound heterozygous TPP1 variants (c.509-1G>C; c.1600C>T) initiated ERT. He was referred for ophthalmic evaluation at 20 months of age as part of a multidisciplinary

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care protocol. Longitudinal monitoring using swept-source handheld (SS-HH-OCT) was performed to monitor retinal structure and early signs of outer retina atrophy.
RESULTS: At 24 months of age, SS-HH-OCT revealed, photoreceptor nuclear hyperreflectivity (PNH), a hyperreflective band within the outer nuclear layer previously identified as an early structural biomarker of photoreceptor stress preceding central vision loss. Based on this finding, off-label intravitreal ERT was initiated. This represents the youngest reported recipient of this treatment; with prior reports limited to patients older than 5 years of age. Concurrent intraventricular and intravitreal administration was well tolerated with no adverse events.
CONCLUSIONS: Current CLN2 management guidelines do not recommend early ophthalmologic screening, and many children often present only after irreversible central vision loss has occurred. This case demonstrates that subclinical photoreceptor stress can be detected by SS-HH-OCT in early childhood and may represent a window for timely intervention to preserve photoreceptor integrity.
KEYWORDS: Neurogenetics, Education, Neuroimaging

359. Beyond a Normal Newborn Screen: Early EEG and MRI Clues Accelerate Diagnosis of Intermediate Maple Syrup Urine Disease

Mariana Carretero-Murillo, Ameya Walimbe, Grace Reynolds, Emily Mendez, Shrenevas Nandam, Lisa Emrick

OBJECTIVE: To highlight how MRI and EEG can increase the suspicion of Maple Syrup Urine Disease (MSUD, MIM#248600) in a critically ill patient with a normal first newborn screen.
METHODS: Case Report.
RESULTS: A 3-month-old female with developmental delay and failure to thrive presented to the hospital with respiratory distress, seizures and altered mental status. Her first state newborn screen was normal and second had not been obtained due to illness. Initial laboratory evaluation revealed severe ketotic hypoglycemia, mild hyponatremia, metabolic acidosis, and mild hyperammonemia. Brain MRI demonstrated restricted diffusion involving white matter, deep gray nuclei, brainstem, and cerebellum. EEG showed multifocal seizures, diffuse slowing, and extreme sleep spindles in a comb-like pattern. EEG and MRI findings suspected MSUD; thus, collection of plasma amino acids (PAAs) was accelerated. Within 36 hours of presentation PAAs resulted with marked elevation of leucine, isoleucine, valine, and alloisoleucine. Continuous renal replacement therapy and branched-chain amino acid–restricted nutrition was initiated, resulting in biochemical and clinical improvement. Seven days after PAAs results, rapid duo whole genome sequencing demonstrated compound heterozygous variants of uncertain significance in DBT (c.413T>C, from her mother, and c.205C>G, of unclear origin). 3 weeks after treatment was started, repeat MRI showed improvement in areas of reduced diffusion and at follow-up the patient demonstrated developmental progress.
CONCLUSIONS: MSUD should remain in the differential diagnosis for infants with encephalopathy and failure to thrive despite normal newborn screen. Recognition of characteristic EEG, laboratory and neuroimaging patterns can expedite diagnosis and treatment prior to confirmatory testing.
KEYWORDS: Neurogenetics, Neurometabolic, Neurocritical Care

360. "Top Ramen" phantosmia as the initial manifestation of CACNA1A channelopathy

Betina Zubieta Ruiz, Shermila Pia

OBJECTIVE: Variants in the gene CACNA1A are a frequent etiology of paroxysmal neurologic manifestations, including epilepsy, hemiplegic migraine, and chronic cerebellar disfunction. Our objective is to describe a case of a pathogenic variant in CACNA1A in a 17-year-old male with a unique presentation of "Top Ramen" phantosmia due to temporal lobe epilepsy and to discuss some therapeutic challenges encountered when treating these patients.
METHODS: Our patient presented with daily stereotyped episodes of abrupt onset of a smell of "Top Ramen" noodles which occurred in any environment and lasted seconds. On further history, he had separate episodes consistent with episodic ataxia, and migraine with aura without hemiplegic features. Diagnostic evaluation with EEG showed independent bitemporal epileptiform discharges. MRI of the brain was unremarkable and genetic testing revealed a pathogenic variant in CACNA1A.
RESULTS: Patient was treated with levetiracetam for the epilepsy, upon initiation, episodes of phantosmia resolved. Migraine improved with prophylactic magnesium and riboflavin. Acetazolamide and Topiramate were initiated for his episodic ataxia, though unfortunately, the side effect profiles were intolerable. He is now starting treatment with dalfampridine.
CONCLUSIONS: CACNA1A channelopathies should be considered in cases of paroxysmal neurologic manifestations, including epilepsy. Diagnosis based on family history alone may be challenging due to variable penetrance and intrafamilial phenotypic heterogeneity. Early recognition and prompt initiation of treatment with tailored medications is crucial. However, genotype-phenotype correlations remain incompletely understood. Further research directed at understanding the different phenotypic manifestations associated with CACNA1A and the underlying genetic mechanisms may help direct more targeted and efficacious options for treatment.
KEYWORDS: Neurogenetics, Epilepsy

Neuroimaging

361. The effect of very premature birth and prematurity-related morbidities on brain structural connectivity at 5 years of age

Mitchell Batschelett, Armin Allahverdy, Brady Williamson, Beth Kline-Fath, Jean Tkach, Weihong Yuan, Nehal Parikh

OBJECTIVE: Very preterm (VPT) birth is associated with neurodevelopmental impairments, primarily arising from

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brain abnormalities, yet its long-term effect on structural network topology and how specific prematurity-related neonatal morbidities shape these effects remains unclear. Using graph theoretical analysis of structural connectomes, we aimed to: (1) compare structural network topology between 5-year-old children born VPT and full-term (FT) peers; and (2) within the VPT group, identify neonatal exposures carrying independent explanatory information for 5-year topology.

METHODS: In this substudy of the Cincinnati Infant Neurodevelopment Early Prediction Study, 171 VPT children with neonatal clinical data and 45 FT children underwent diffusion MRI at 5-years corrected age. We computed graph theory metrics from constrained spherical deconvolution-based connectomes and applied Functional Data Analysis (FDA) across a range of proportional density thresholds, controlling for age, head size, sex, and motion. Furthermore, we employed novel stability selection within an FDA framework to identify prematurity-related morbidities independently associated with early childhood topology.

RESULTS: Compared to FT children, VPT children showed robustly elevated network segregation, reduced density and strength, and a modest decrease of integration. In VPT children, global brain abnormality scores at term-equivalent age were associated with increased segregation, and retinopathy of prematurity was uniquely associated with segregation-integration balance. No single exposure was identified for integration or strength; however, connectome strength was negatively associated with a composite measure of prematurity severity.

CONCLUSIONS: Increased segregation was the most robust VPT-related topological phenotype. Distinct neonatal exposures may preferentially shape segregation and segregation-integration balance, while greater prematurity-related morbidities may result in reduced connectome strength.

KEYWORDS: Neuroimaging, Neonatal Neurology, Neurodevelopmental Disorders

362. Quantitative Term-Equivalent Head Ultrasound Metrics as Predictors of Early Motor Outcome in Extremely Preterm Infants: A Retrospective Study

Hamza Hussain, Rawad Obeid

OBJECTIVE: This is a retrospective study of infants born ≤ 33 weeks gestation who had a HUS at 34–48 weeks corrected age and the AIMS between 13–22 months corrected age. Severe motor delay was defined as AIMS ≤ 10th centile. HUS was evaluated for IVH grade and PVL. Measurements included ventricular index, anterior horn width, biparietal diameter, and fronto-temporal horn ratio. Demographic and clinical data including gestational age, birth weight, Apgar scores, and comorbidities were collected.

METHODS: This is a retrospective study of infants who were followed between February of 2020 to August of 2024. We considered severe motor delay if the AIMS score was ≤ 10th centile for CA. HUS was independently evaluated for the presence of IVH and grade (1 -4), and the presence of PVL. The following measurements were done on the HUS images in both coronal and sagittal planes [ventricular index, anterior horn width, biparietal diameter, fronto-temporal horn ratio, interhemispheric space, midline thickness and total length of the corpus callosum].

RESULTS: Of 365 infants, 121 met criteria. Average gestational age was 27±2 weeks and birth weight 1037±350 grams. 26% had motor delay. Univariate analysis showed correlation with gestational age, birth weight, Apgar scores, PVL, IVH, BPD, ventricular indices, anterior horn widths, biparietal diameter, and FTHR. Multivariate analysis showed only right anterior horn width remained significant. ROC analysis showed strong discriminatory capacity (AUC 0.822) with cutoff <1.7mm.

CONCLUSIONS: There is potential of using ventricular measurements like anterior horn width to help with motor outcome prediction in prematurely born infants.

KEYWORDS: Neuroimaging, Neurodevelopmental Disorders, Neonatal Neurology

363. Hippocampal Volume Reduction in Pediatric Seizure Disorders: MRI-Based Volumetric Analysis

Priyanshi Johari, Raghunandan Prasad

OBJECTIVE: The hippocampus is integral to seizure generation and propagation, particularly in temporal lobe epilepsy. Quantitative MRI-based volumetry enables objective assessment of hippocampal structure; however, pediatric data from North Indian populations remain limited. The objective of this study is to quantitatively compare total hippocampal volume in pediatric patients with seizures versus those with non-seizure neurological conditions.

METHODS: In this retrospective observational study conducted at a tertiary care center, 100 pediatric patients (age range: 1 month–12 years) who underwent brain MRI were analyzed. The cohort included 50 patients with clinically diagnosed seizures and 50 with non-seizure neurological conditions, including trauma. Total hippocampal volumes were quantified using dedicated MRI volumetric analysis software. Between-group comparisons were performed using independent sample t-tests. Statistical significance was defined as $p < 0.05$.

RESULTS: The seizure cohort demonstrated lower mean total hippocampal volumes compared to controls, with the difference achieving statistical significance ($p \approx 0.03–0.05$). Despite observed inter-individual variability, the directionality of effect remained consistent across the cohort, supporting an association between reduced hippocampal volume and seizure disorders.

CONCLUSIONS: Reduced total hippocampal volume is associated with pediatric seizure disorders. MRI-based hippocampal volumetry provides a quantitative adjunct to conventional imaging and may enhance structural characterization in clinical evaluation. Larger, prospective studies are warranted to further define its diagnostic and prognostic utility.

KEYWORDS: Neuroimaging, Epilepsy, Early Stage Investigator

364. Electroencephalographic Findings in a Child with Alcohol Intoxication

Lydia Fletcher, Amanda Romeu, Moira Black

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OBJECTIVE: Electroencephalographic (EEG) data exists for adults with alcohol intoxication and demonstrates a slower than expected posterior dominant rhythm (PDR) at 6 Hz compared to the usual 8-13 Hz. To date, there have been no published reports of EEG findings in pediatric patients following alcohol ingestion. We present a novel case.
METHODS: Descriptive case report.
RESULTS: A young female with no prior medical history presented to the emergency department with somnolence. She was hypothermic with delayed capillary refill and Glasgow coma scale of 6. Infectious and metabolic work up did not reveal the cause of her somnolence. Blood ethanol level was elevated, indicating alcohol intoxication. Electroencephalogram (EEG) performed for altered mental status showed rare, intermittent bilateral posterior slowing with a posterior dominant rhythm of 6 Hz, improving to 9 Hz over time. The patient returned to neurologic baseline with the resolution of intoxication.
CONCLUSIONS: This case provides previously unknown EEG data for a pediatric patient with alcohol intoxication. Similar to those seen in adult EEG data, the background frequencies of 6 Hz may be considered appropriate rather than an indication of encephalopathy in this age group. The case highlights the importance of maintaining a broad differential diagnosis when treating the pediatric patient with altered mental status, especially in the setting of normal, or mildly slow background findings on EEG.
KEYWORDS: Neuroimaging

365. Development and Validation of a High-Resolution Pediatric Computational Model with Application to Transcranial Magnetic Stimulation.

Georgios Ntolkeras, Alice Albrecht, Lilla Zollei, Georgios Sideris, Francesca Marturano, Michael Lev, P. Ellen Grant, Giorgio Bonmassar

OBJECTIVE: Numerical human models are essential for advancing medical device development. Until recently, pediatric models were morphed adult models, having significant limitations in representing pediatric anatomy and physiology. This gap is particularly relevant as emerging and established neuromodulatory technologies, such as Transcranial Magnetic Stimulation (TMS), are routinely used in child neurology, including epilepsy surgery, and are increasingly explored in other conditions, such as depression. This study bridges this gap by developing a high-resolution, high-anatomical-accuracy, whole-body numerical model focused on the central nervous system (CNS) and testing it via TMS-specific numerical simulations.
METHODS: We used 3 Tesla whole-body MRI images and scans specific to the brain, spine, and chest from a healthy 10-month-old girl. We followed an automated (infantFreeSurfer), semi-automated, and manual approach to segment body tissues in 3DSlicer. The model was validated by expert review and by quantitative comparison with age-matched anatomical literature values. We tested the performance of TMS coils using magnetoquasi-static finite element simulations in Sim4Life.
RESULTS: We segmented 442 distinct tissues across the body; 74 were head-specific, and 43 were brain-specific. The TMS simulations (three circular and three figure-of-eight coils) indicated that a 50mm figure-of-eight coil provided optimal balance between electric field intensity and focality, whereas larger coils reduced selectivity and smaller coils improved precision.
CONCLUSIONS: We present Thalia, a high-resolution, high-anatomical-accuracy, whole-body numerical model focused on the CNS of a healthy 10-month-old girl, and demonstrate its application via a TMS simulation paradigm to evaluate coil performance. The model will be openly available to the scientific community as an open-source resource.
KEYWORDS: Neuroimaging, Epilepsy

366. Serial Brain MRI Findings in Fucosidosis: Characterizing Long-Term Radiographic Progression

Emily Garavatti, Quynh Kieu, Azam Eghbal, Terry Sanger, Rahul Nikam

OBJECTIVE: Fucosidosis is a rare autosomal recessive lysosomal storage disorder caused by deficiency of alpha-L-fucosidase, leading to progressive accumulation of fucose-containing glycolipids and glycoproteins. Given the limited longitudinal imaging data available, we describe the long-term neuroimaging evolution in a patient with genetically confirmed fucosidosis to further characterize its radiographic progression.
METHODS: We performed a retrospective review of clinical records and serial brain magnetic resonance imaging (MRI) studies obtained over a 15-year period in a female patient. Imaging findings were analyzed for white matter changes, deep gray matter signal abnormalities, and interval progression.
RESULTS: Initial MRI in early childhood demonstrated symmetric T2 hyperintensity within the supratentorial white matter and mild cerebral volume loss. Over time, there was progressive confluent white matter signal abnormality with increasing cerebral and cerebellar atrophy. Serial studies also revealed evolving susceptibility changes and T2 hypointensity within the globus pallidi, putamina, substantia nigra, and red nuclei, consistent with progressive mineralization, and distinctive medial medullary lamina hyperintensity. These deep gray matter findings became more conspicuous with age and paralleled the patient's clinical neurologic decline, including worsening motor impairment, dystonia, seizures and cognitive dysfunction. Genetic diagnosis was made at 14 years old by neurodegeneration with brain iron accumulation genetic panel.
CONCLUSIONS: This case highlights the characteristic pattern and longitudinal progression of neuroimaging abnormalities in fucosidosis, including symmetric white matter involvement and progressive deep gray matter mineralization. Recognition of these imaging features may aid in early diagnosis, improve diagnostic confidence, and enhance understanding of disease trajectory in this rare neurodegenerative disorder.
KEYWORDS: Neuroimaging, Lifespan Manifestations of Childhood Onset Conditions, Neurometabolic

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367. Hippocampal Volume Fluctuation Across Pre-Exam and Non-Exam School Periods in Children: A Short-Interval Longitudinal Structural MRI Study

Pei-Chi Kuo, Zai-Fu Yao

OBJECTIVE: The hippocampus is sensitive to stress during development, yet limited evidence exists regarding short-term hippocampal fluctuation across naturally occurring school stressors in children. We examined whether hippocampal volume differs between pre-exam and non-exam school periods.

METHODS: Eight right-handed children aged 10–12 years (M = 10.5; 4 girls) in Taiwan underwent T1-weighted structural MRI at four sessions: before school started (SES01), within one week before midterm examinations (SES02), within one week before final examinations (SES03), and after final examinations (SES04). Hippocampal volumes were derived using the FreeSurfer longitudinal pipeline, and segmentation outputs underwent visual quality control. Repeated-measures ANOVA and Friedman tests were conducted across sessions. Theory-guided exploratory contrasts compared pre-exam sessions (SES02, SES03), conceptualized as periods of increased academic demands and potential anticipatory stress, with non-exam sessions (SES01, SES04).

RESULTS: Overall differences across sessions were not significant, although hippocampal measures showed the strongest temporal signal among examined regions (partial η^2 = .245; Kendall's W = .231). Exploratory contrasts indicated significantly lower hippocampal volume during pre-exam than non-exam sessions (mean difference = -100.88 mm^3, -1.17%; t(7) = -2.78, p = .027, Cohen's d = -0.98). Baseline-centered analyses showed the largest decrease before midterms at SES02 (-155.39 mm^3; -1.78%), with smaller reductions at SES03 and SES04.

CONCLUSIONS: Although overall session effects were not significant, hippocampal measures showed a coherent exploratory pattern across school stress periods. The pre-exam reduction is consistent with the possibility that the developing hippocampus may show short-term fluctuation during academic stress, highlighting the value of repeated hippocampal measurement in real-world school contexts.

KEYWORDS: Neuroimaging, Education

368. Short-Term Frontal Gray Matter Fluctuation Across Exam-Related Periods in Late Childhood: A Pilot Longitudinal VBM Study

Pei-Chi Kuo, Zai-Fu Yao

OBJECTIVE: Academic examinations are common, time-limited stressors during childhood, yet limited evidence exists regarding short-term gray matter fluctuation across exam-related learning periods. This pilot longitudinal study examined whether gray matter differs between pre- and post-exam periods in late childhood.

METHODS: Eight right-handed children aged 10–12 years (M = 10.5; 4 boys) underwent T1-weighted structural MRI within one week before midterm examinations and after the exam period. Images were brain-extracted using optimized BET parameters, segmented with FAST, and processed using an FSL-VBM pipeline, including study-specific gray matter template creation, nonlinear registration, modulation, and smoothing. Warping outputs and tissue segmentation were visually inspected for quality control. Paired within-subject differences between post- and pre-exam scans were tested using non-parametric permutation inference with TFCE correction.

RESULTS: A focal TFCE-corrected effect was observed in the left frontal pole, indicating higher gray matter signal after examinations relative to before examinations at the peak voxel (Harvard–Oxford frontal pole probability = 67%; voxel index [60, 95, 38]; −29.42, 64.10, 4.24 mm; p_corr ≈ .039; t = 13.43). The corrected extent was limited to a single voxel (8 mm^3), although change direction was consistent across participants.

CONCLUSIONS: These preliminary findings suggest that short-term gray matter fluctuation may be detectable across exam-related learning periods in late childhood, particularly in frontal regions implicated in executive-control demands. Given the focal and cortical-edge nature of the effect, larger, higher-resolution pediatric neuroimaging studies with measures of stress, sleep, learning intensity, and behavioral performance are needed to clarify whether effects reflect learning-related plasticity, transient state effects, or methodological variability.

KEYWORDS: Neuroimaging, Education

369. Acute Necrotizing Encephalopathy Beyond the Thalamus: Atypical MRI Patterns and Implications for Early Treatment

Susan Conrad, Cade Szymanski, Nucharin Supakul, Jerilyn Nova, Nicholas Sokol, Ashley Moeller

OBJECTIVE: Acute necrotizing encephalopathy (ANE) is a rare but devastating parainfectious neurologic syndrome characterized by abrupt neurological collapse with bilateral thalamic lesions, the pathogenesis of which is thought to be related to a hyperinflammatory "cytokine storm." High mortality rates (25-67%) necessitate early recognition for rapid immunomodulatory therapy. To broaden ANE's clinical and radiographic spectrum, we share atypical ANE presentations without thalamic involvement.

METHODS: We report two children with disparate presentations but protracted, fatal outcomes — a 17-month-old male with COVID-19 showing opsoclonus, ataxia, and encephalopathy and a 14-year-old male with *Staphlococcus aureus* infection with progressive locked-in syndrome.

RESULTS: Paraclinical studies for both patients showed negative genome sequencing, increased CSF protein, and elevated interleukin-6. Brain MRI of the 17 month old showed extensive white matter abnormalities with peripheral contrast enhancement and restricted diffusion involving bilateral cerebral hemispheres and corpus callosum. Brain MRI of the 14 year old showed abnormal signal intensity involving medulla, posterior pons, bilateral middle cerebellar peduncles, and medial right cerebellar hemisphere associated with peripheral contrast enhancement and restricted diffusion. Both patients received five days of IVIG and 14 days of IV methylprednisolone. The 14 year old also received tocilizumab. Both children died three months after presentation.

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CONCLUSIONS: These atypical cases emphasize that the diagnosis of ANE must be driven by a high index of suspicion when atypical neuroimaging is paired with inflammatory markers, regardless of whether the classic bilateral thalamic lesions are present, as early intervention with immunoneuromodulation is essential.

KEYWORDS: Neuroimaging, Neuroimmunology, Neurocritical Care

370. Rethinking Radiology: The Limited Value of Head CT Scans in Pediatric Seizure Diagnosis and Treatment

Sarah Schorr, Laura Fincher, Erica Ream, Nidhi Sthanki, Ty Carter, Trinity Howard, Nathan Lichti, Hunter Collins, Ibrahim MusaYola, Bhatki Samant, Yash Shah

OBJECTIVE: Head CT scans are frequently conducted in emergency departments to evaluate pediatric patients with seizure activity. While these scans can offer insights, they also expose patients to potentially harmful ionizing radiation and often do not yield clinically significant findings. This study evaluates the utility of head CT scans in providing diagnostic and treatment-relevant information for pediatric patients presenting with seizure or seizure-like activity in comparison to other imaging modalities.

METHODS: A retrospective chart review was conducted on 54 pediatric patients, who presented with seizure or seizure-like activity and underwent a head CT scan. Patients at higher risk for pathologies detectable by CT were excluded, such as those with known hydrocephalus, VP shunts, macrocephaly, post-infectious encephalitis, and head injuries.

RESULTS: If a child had a head CT that was considered abnormal, *none* were deemed clinically significant for seizure management. Of the cases reviewed, 22% (n=12) had abnormal CT findings. Among the abnormal results, 83% (n=10) were incidental to a seizure diagnosis. The remaining cases (n=2) were categorized as "abnormal, other," involving conditions such as cerebral atrophy. Of the 54 patients, 8 patients had a brain MRI, while 40 patients had an EEG conducted. In 12 cases, direct changes to medical management were made secondary to EEG.

CONCLUSIONS: The study results demonstrate that head CT scans rarely yield findings that significantly impact the management of pediatric patients with seizure activity. Given the low diagnostic value and the risks associated, routine use of head CT in these cases should be reconsidered.

KEYWORDS: Neuroimaging

371. Automated Segmentation of Acute Pediatric Arterial Ischemic Stroke using State of the Art Neural Networks

Nomazulu Dlamini, Alex Rus, Alhusain Abdalla, Trish Domi, Amanda Robertson, Akshat Pai, Logi Vidarsson, Pradeep Krishnan, Birgit Ertl-Wagner, Farzad Khalvati

OBJECTIVE: Pediatric arterial ischemic stroke (PAIS) is a significant cause of acquired brain injury and mortality in childhood. Prediction of stroke risk and outcome is complex and depends on multiple heterogenous factors including lesional and non-lesional neuroimaging features. However, manual lesion segmentation of acute PAIS is labor-intensive and can produce inconsistent results, highlighting the need for scalable, automated methods. The purpose of this study was to develop a robust, automated segmentation model for acute PAIS using a deep learning approach tailored to this patient population.

METHODS: The dataset included clinically acquired diffusion weighted imaging (DWI), b1000, and apparent diffusion coefficient (ADC) MRI images in PAIS (N=142) participants in an institutional registry, along with radiologist-annotated ground truth masks. The network used was an nnU-Netv2 model, which self-configures its architecture to the dataset's specific characteristics. The model was trained using 5-fold cross-validation. For final evaluation, predictions from all five folds were combined using ensemble inference. Performance was evaluated using Dice score, Intersection over Union (IoU), and qualitative inspection of the segmentations.

RESULTS: The model achieved a mean Dice score of 0.71 and an IoU of 0.55 across test cases, with consistent lesion boundary delineation. A radiologist-supported qualitative review confirmed alignment with vascular territories and high agreement with ground truth annotations.

CONCLUSIONS: This study demonstrates the successful development of a highly accurate and robust automated segmentation model for PAIS. This work represents a crucial step toward scalable, automated tools that reduce the workload and improve the prediction of risk and outcome in PAIS.

KEYWORDS: Neuroimaging, Stroke

372. Feature Fusion of MRI Radiomics and Deep-Learned Representations Predicts One-Year Mental Health Outcome Post Pediatric Arterial Ischemic Stroke

Nomazulu Dlamini, Alhusain Abdalla, Min Sheng, Ludovica Serafini, Amanda Robertson, Trish Domi, Akshat Pai, Robyn Westmacott, Jennifer Crosbie, Logi Vidarsson, Birgit Ertl-Wagner, Liza Pulcine, Mahendranath Moharir, Farzad Khalvati

OBJECTIVE: Pediatric arterial ischemic stroke (PAIS) survivors face higher risks for adverse mental health outcomes such as anxiety, depression, and executive dysfunction. Early risk stratification could enable timely and targeted interventions.

METHODS: We retrospectively analyzed structural MRI from 174 children with PAIS (mean age at stroke onset 3.8 years, range 1 month to 17 years, 60% male (n = 105) and 40% female (n = 69)) enrolled in the institutional stroke registry. We extracted radiomic features (1,024 per scan) and deep-learning features (128-dimensional embeddings) from a 3D convolutional neural network (CNN) (Figure 1) trained on lesion-focused MRI patches. Mental health outcome at approximately one year was binarized (poor vs normal) using standardized behavioral assessments completed by parents and teachers (BASC-3 and BRIEF). Primary metrics were area under the ROC curve (AUC) on an independent test set at both the stroke level and patient-level for patients with multiple strokes.

RESULTS: Models trained on fused features showed the highest discrimination at the stroke level (Gradient Boost AUC $\approx$ 0.79, 95% CI 0.71-0.85) (Table 1 and Figure 2),

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outperforming radiomics only (Gradient Boost AUC ≈ 0.60) and deep learning only (CNN AUC 0.72). Incorporating confidence ratios yielded weighted AUC ≈ 0.79 for the best-fused model, comparable to stroke-level performance while accounting for label reliability.

CONCLUSIONS: Integrating handcrafted radiomic features with deep-learned representations improves prediction of poor one-year mental health post PAIS compared with unimodal models. This multimodal approach could support earlier identification of children who need targeted mental health interventions and follow-up.

KEYWORDS: Neuroimaging, Stroke

373. Unusual Pediatric Presentation of Cervical Spinal Arteriovenous Malformation Rupture Mimicking Cystic Tumor

Keerthana Bathala, Arpita Lakhotia

OBJECTIVE: To describe an unusual case of cervical spinal arteriovenous malformation rupture in a pediatric patient initially mistaken for a cystic spinal tumor, emphasizing key clinical and radiographic features that aid in timely diagnosis and management.

METHODS: Chart Review

RESULTS: 12-year-old right handed male woke with right arm "*soreness*" that rapidly progressed to paresthesias and weakness of right arm and leg. Neurological examination showed hypophonia, right hemiplegia, 3-4/5 strength on left side, patchy sensory loss, brisk reflexes, and ankle clonus suggesting a high spinal cord lesion. Neuroaxis MRI/MRA showed C4 cord expansion with cystic-appearing ovoid lesion, contrast enhancement from C1-C7, and prominent vessels along the cervical cord. Initially suspected to be an intra-axial tumor, however abnormal vasculature suggested underlying vascular malformation. Spinal angiogram confirmed type II intramedullary AVM from the left vertebral artery with prenidal and intranidal aneurysms, embolized with Onyx 18. Chest and abdomen imaging showed no other AVMs, and genetic testing for vascular malformations was negative. The patient required prolonged PICU stay with tracheostomy and gastrostomy. He was eventually discharged to inpatient rehabilitation and later decannulated. At 10 month follow up, he showed significant functional recovery with full strength on the left and improving right hemiparesis. He is able to ambulate short distances with a cane.

CONCLUSIONS: This case highlights a ruptured cervical spinal AVM and the rapid progression in a pediatric patient. Although imaging mimicked a cystic tumor, clinical course and vascular features suggested AVM, confirmed by angiography and successfully treated with embolization.

KEYWORDS: Neuroimaging, Stroke, Neurocritical Care

374. Prognostic Value of Imaging Patterns in Subpial Hemorrhage

Sofia Babool, Suriya Subramanian, Aby Thomas, Sateesh Jayappa, Abdullah Shoaib

OBJECTIVE: Subpial hemorrhage (SPH) is an underrecognized form of intracranial hemorrhage with an incompletely defined clinical spectrum. We aim to characterize the clinical presentation, neuroimaging features, and neurologic outcomes of young children with SPH, and to evaluate whether imaging-defined severity is associated with adverse neurodevelopmental outcomes.

METHODS: We performed a retrospective review of 52 children <24 months with MRI-confirmed SPH at a tertiary pediatric center. Clinical variables including demographics, presenting symptoms, and seizure history were collected. Neuroimaging was systematically reviewed to assess hemorrhage distribution, associated cortical–subcortical injury, and categorized using established imaging-based severity patterns. Short- and long-term neurologic and developmental outcomes, as well as mortality were assessed.

RESULTS: Trauma and hematologic etiologies made up about 17 and 9 percent of patients, respectively. Patients most commonly presented with seizures; additional presentations included apnea, feeding difficulty, and encephalopathy. MRI demonstrated subpial hemorrhage with adjacent cortical–subcortical diffusion abnormalities, often exhibiting the characteristic "yin–yang" pattern. Overall many patients had a favorable outcome, with about 52 percent being on 0 seizure medications by 24 months, and a mortality rate of 5 percent during admission despite lack of interventions.

CONCLUSIONS: Pediatric SPH is a cerebrovascular entity frequently associated with underlying cortical injury and likely related to venous congestion or thrombosis. Imaging-based severity may serve as a tool for risk stratification. Early recognition and structured neurodevelopmental follow-up are essential. Further prospective studies are needed to validate grading systems and define long-term outcomes.

KEYWORDS: Neuroimaging, Stroke, Neonatal Neurology

Neuroimmunology

375. Cerebellar Atrophy in Pediatric-Onset OMAS: A Large International Cohort Study

Rebecca MacRae, Kierstin Hederstedt, Christopher Cortina, Kumaran Deiva, Andrea Klein, Ming Lim, Thomas Rossor, Elizabeth Sokol, Yasmin Khakoo, Nikita Shukla, Timothy Lotze, Wendy Mitchell, Sarah Hopkins, Bo Zhang, Mark Gorman

OBJECTIVE: Pediatric-onset opsoclonus-myoclonus-ataxia syndrome (POOMAS) is a rare, neuroinflammatory syndrome that targets the cerebellum and can cause irreversible cerebellar structural changes, namely cerebellar atrophy. We investigated the frequency of cerebellar atrophy as well as associated risk factors and functional outcome measures using the largest active POOMAS registry.

METHODS: Retrospective observational study of participants with POOMAS using the multi-national, multi-center POOMAS Registry. Participants had disease onset from 1995 to 2025 and were categorized as either with or without cerebellar atrophy based on formal neuroradiology magnetic resonance imaging (MRI) reports. Variables were compared

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between the cerebellar atrophy subgroups using Fisher's exact test or Wilcoxon rank sum test.
RESULTS: Of participants with follow-up imaging, 9.5% (6/63) of participants with an MRI obtained at least 6 months after disease onset and 12.5% (3/24) with an MRI obtained at least 48 months after disease onset developed cerebellar atrophy. Half of the cerebellar atrophy (3/6) was identified after 48 months from disease onset. Cerebellar atrophy was associated with the older age at diagnosis ($p = 0.023$), but not with other demographic or clinical characteristics. There was no statistically significant difference between functional outcome measures: disease severity score, motor score, or educational setting.
CONCLUSIONS: The overall frequency of cerebellar atrophy is likely underestimated in this study because of the lack of standardized MRI timing and the high number of patients without MRIs after 48 months. To more accurately identify cerebellar atrophy, we recommend that surveillance MRIs be obtained at least 48 months after POOMAS disease onset.
KEYWORDS: Neuroimmunology, Neuroimaging

376. Anti-NMDAR Encephalitis following La Crosse Infection: A Novel Presentation

Maxim Dragoun, Mara Cohen, Helen Wu, Kelsey Poisson

OBJECTIVE: To present a case elucidating potential overlap between La Crosse encephalitis and Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis.
METHODS: Anti-NMDAR encephalitis is the most common form of autoimmune encephalitis (AE) and prior infections, especially HSV meningoencephalitis, are known potential triggers. La Crosse virus is the most common neuroinvasive arbovirus in the United States, with symptoms that closely overlap with those of AE. We present a novel case of a patient with La Crosse encephalitis, who, after initial improvement, subsequently developed anti-NMDAR encephalitis.
RESULTS: A 7-year-old previously healthy girl presented with one week of fever and headaches. MRI demonstrated leptomeningeal enhancement. Cerebrospinal fluid (CSF) analysis showed pleocytosis and negative CSF arboviral antibodies, so she was diagnosed with presumed viral encephalitis. Of note, serum arbovirus titers (with higher sensitivity than CSF) were not tested at this time. Symptoms initially improved, but she then worsened over the course of about two weeks with abnormal behavior, cognitive regression, and seizure. Serum arbovirus testing returned positive, confirming La Crosse encephalitis. However, in the weeks following discharge, she continued to decline. CSF then resulted positive for NMDA-IgG. Consequently, she was treated with IVIG and rituximab with good response.
CONCLUSIONS: Although AE can often follow viral illness, this is a novel presentation of NMDAR encephalitis following La Crosse encephalitis. Given the overlapping symptoms seen in arboviralencephalitis and autoimmune encephalitis, this can have an impact on diagnostic and treatment approaches. Autoimmune encephalitis workup should be considered in patients with positive arbovirus serology with continued clinical progression of symptoms.
KEYWORDS: Neuroimmunology, Neuroinfectious Disease

377. Is It MOGAD, or Not?

Andrew Harold, Jessica Gautreaux, Gabriela Tuttrup, Brittany Poinson, Allison Conravey

OBJECTIVE: MOGAD, a recently described subgroup of CNS acquired demyelinating syndromes, has new diagnostic guidelines which provide a broad framework creating both screening and diagnostic challenges for atypical cases. In this series, we examine three atypical cases encountered in our hospital.
METHODS: The full hospital course of three atypical cases of MOGAD were examined.
RESULTS: The first patient presented to a behavioral health unit for new onset psychosis. Days later, she had a seizure with rapid deterioration requiring intracranial bolt placement, IV high-dose steroids, IV immunoglobulin, plasmapheresis, and multiple doses of tocilizumab, with persistent MRI changes and lasting neurologic disability. The second patient presented with daily headaches, papilledema, and flat affect. MRI confirmed papilledema but was otherwise unremarkable. The lumbar puncture showed elevated opening pressure, WBC count, and protein. He was ultimately treated with high-dose steroids and IVIG, though relapsed several months later. The third patient presented with new-onset focal seizure. MRI was obtained during hospitalization which showed T2-FLAIR hyperintensities and meningitis/encephalitis panel from his lumbar puncture was concerning for HHV6 encephalitis. Days later, his anti-MOGAD antibody resulted positive, necessitating high-dose steroids. He remained asymptomatic, even on in-depth neuropsychological testing.
CONCLUSIONS: Atypical MOGAD cases question which neurologic symptoms and to what severity providers screen for it. These cases demonstrate how varied its presentation is, and how easily it could be overlooked. MOGAD's clinical variety and mimicry of common less severe presentations posit the questions, are all these cases MOGAD, a secondary underlying process, or something else entirely?
KEYWORDS: Neuroimmunology, Pediatric Demyelinating Disease, Practice Parameters

378. Rituximab Improves Recovery Trajectories in Pediatric N-Methyl-D-Aspartate Receptor Encephalitis

Alexandra Kornbluh, Ilana Kahn, Leigh Sepeta, Zhulin He, James Brenton, Jennifer Yang, Coral Stredny, Ryan Kammeyer, Kristen Fisher, Alexander Sandweiss, Ayush Gupta, Michael Sweeney, Varun Kannan, Catherine Otten, NgocHanh Vu, Jonathan Santoro, Karla Robles-Lopez, Robert Goodrich, Scott Otallah, Janetta Arellano, Lydia Marcus, Lileth Mondok, Andrew Christiana, Morgan Morris, Mark Gorman, Yike Jiang, Melissa Wright, Timothy Erickson, Eyal Muscal, Kristy Murray, Manikum Moodley, Duriel Hardy, Claude Steriade, Grace Gombolay

OBJECTIVE: Early first-line immunotherapy improves outcomes in pediatric N-methyl-D-aspartate receptor encephalitis (pNMDARE), while consensus guidelines reserve second-line therapies (e.g., rituximab) for refractory cases. We evaluated outcomes in pNMDARE with rituximab treatment.
METHODS: Retrospective pNMDARE cohort study across 18 institutions. Modified Rankin Scale (mRS) was evaluated at presentation, 3, 6, 12, and 24 months. Exact matching (2:1

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without replacement) accounted for corticosteroids, intravenous immunoglobulin, plasmapheresis, cyclophosphamide, and presenting mRS. Generalized linear mixed models were used; adjusted models incorporated time and nested random effects.

RESULTS: Among 219 patients, 103 were matched (65 rituximab-treated, 38 no-rituximab). Baseline characteristics and unadjusted comparisons of mRS at each timepoint were similar. Severe disability (mRS 5) at 24 months occurred only in the no-rituximab group (n=2). In adjusted analyses across follow-ups (n=335 observations), rituximab-treated patients improved more over time (β=-1.47, 95%CI [-2.71, -0.22], p=.022). Rituximab effect varied by corticosteroid use (β=1.81, 95%CI [0.53, 3.08], p=0.006) and over time (β=-.23 per month, 95%CI [-0.45, -0.01], p=0.044). In post-hoc contrasts versus neither treatment, rituximab-alone showed the greatest mRS improvement (-2.30; 95%CI [-3.30, -1.30], p<.001), followed by rituximab + corticosteroids (-2.16; 95%CI [-3.14, -1.18], p<.001), and corticosteroids-alone (-1.66; 95%CI [-2.90, -0.43], p=.009). mRS did not differ between rituximab + corticosteroids versus rituximab-alone (0.14; 95%CI [-0.20, 0.48], p=.413) or corticosteroids-alone (-0.50; 95%CI [-1.44, 0.45], p=.297).

CONCLUSIONS: Rituximab treatment in pNMDARE improves recovery trajectory, although benefits may be modulated by other treatment effects. Prospective large-scale studies are needed to validate findings and examine effects of individual immunotherapies, timing of treatments, and relapse rates.

KEYWORDS: Neuroimmunology, Neurocritical Care

379. Fulminant Acute Hemorrhagic Encephalomyelitis Following Influenza A: A Case Demonstrating Response to Aggressive Immunotherapy

BURCU ASMA, Steven Trau

OBJECTIVE: To report a case of acute hemorrhagic encephalomyelitis (AHEM), and discuss the evaluation, treatment, and outcome following immunotherapy.

METHODS: A 3-year-old female contracted influenza A. Several days later, she presented as a hospital transfer 36 hours after following acute neurological deterioration. Neuroimaging demonstrated cerebral edema with active herniation and multifocal hemorrhages consistent with influenza-associated encephalopathy. She was too unstable for surgical decompression or catheter placement, so she received IV methylprednisolone , IVIg, and tocilizumab upon arrival.

RESULTS: Following treatment, she stabilized over the next several days. 5 days after arrival, she underwent plasmapheresis. Neuroimaging on day 10 showed marked reduction in cerebral edema and resolution of herniation. Cerebrospinal fluid (CSF) showed lymphocytic pleocytosis, elevated protein, normal glucose. CSF infectious panel, serum and CSF autoimmune encephalopathy panels, oligoclonal bands, anti-aquaporin 4-IgG, anti-MOG-IgG, and a cytokine panel were all negative. Genetic testing (including RANBP2) was negative. Spinal MRI showed T2 signal abnormalities of the cervicomedullary junction and thoracic spine. CSF studies 5 weeks later were normal. She was discharged to inpatient rehabilitation on day 43 with intermittent ability to follow commands, appendicular hypertonia, and slowly improving weakness.

CONCLUSIONS: Based on neuroimaging findings, antecedent infection with influenza, and the exclusion of other infectious or inflammatory etiologies, she was diagnosed with AHEM. Knowledge regarding AHEM is largely limited to case reports, and it carries a grim prognosis. Our case emphasizes the diagnostic complexity and challenges in management of AHEM, and it further highlights the importance of early and aggressive treatment.

KEYWORDS: Neuroimmunology, Neuroimaging, Neurocritical Care

380. Rapidly progressive demyelinating conditions with respiratory failure: A series

Emily Bruder, Daniel Lax

OBJECTIVE: Demyelinating disease in children is not rare, though some etiologies are far more common than others. While presenting signs and symptoms can overlap, some distinguishing features can help guide acute therapies. We compare and contrast three unique cases of pediatric demyelinating disease presenting with rapid neurologic deterioration and respiratory failure.

METHODS: Case series.

RESULTS: 13-year-old male presenting with 3 days of headache, progressive somnolence and focal weakness progressing to flaccid quadriplegia and respiratory failure. Had neutrophilic pleocytosis and extensive patchy T2 FLAIR hyperintensities throughout brain and spinal cord, ultimately diagnosed with acute disseminated encephalomyelitis (ADEM). 9-year-old female presented with fever, vomiting, unresponsiveness, seizures progressing to respiratory failure. Had lymphocytic pleocytosis, positive MOG antibody (1:100), and multifocal cortical T2 hyperintensities with restricted diffusion and edema, ultimately diagnosed with FLAIR-hyperintense lesions in anti-MOG associated encephalitis with seizures (FLAMES) variant of myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD). 15-year-old female with right leg paresthesia and weakness initially responsive to high dose steroids and IVIG, followed by a rapid progression to quadriplegia and respiratory failure. Had mild lymphocytic pleocytosis, positive oligoclonal bands and Kappa free light chain in CSF, and numerous, large T2 FLAIR hyperintensities with outer concentric ring of restricted diffusion and enhancement, ultimately diagnosed with Balo's concentric sclerosis (BCS) variant of multiple sclerosis (MS).

CONCLUSIONS: Through these cases, we compare and contrast the distinct etiologies of each case, namely ADEM, MOGAD, and BCS, and describe the effective treatments.

KEYWORDS: Neuroimmunology, Pediatric Demyelinating Disease

381. Diagnostic Overshadowing in Pediatric Presentation of Stiff Person Syndrome With Pre-Existing Autoimmune Polyglandular Syndrome and Depression

Samia Khan, Tara Johnson

OBJECTIVE: Stiff Person Syndrome (SPS) is a rare neuromuscular autoimmune disorder with complex diagnostic and

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management challenges. In a pediatric patient with autoimmune endocrinopathy and depression, diagnostic overshadowing can falsely attribute new pain symptoms and preexisting extreme elevation of anti-glutamic acid decarboxylase (anti-GAD) antibody titers to underlying illness, limiting consideration of co-occurring SPS.

METHODS: A retrospective chart review and literature search examined pediatric and adult cases of SPS, association with autoimmune endocrinopathies, and management. A 15-year-old female with depression, type 1 diabetes mellitus, adrenal insufficiency, autoimmune thyroid disease, and a strong family history of autoimmune disease developed progressive, painful muscle spasms, lower extremity rigidity, tactile hypersensitivity, and impaired gait. Anti-GAD antibodies exceeded 25,000 U/mL preceding her clinical presentation of SPS. Pertinent physical examination findings included flat affect, increased appendicular tone, paraspinal rigidity, hyperreflexia, and stiff-appearing gait. Management included baclofen, gabapentin, benzodiazepines, physical therapy, counseling, and intravenous immunoglobulin (IVIG).

RESULTS: Medication and physical therapy provided symptomatic relief and improved mobility. Sedating medication side effects reduced school participation and contributed to the patient's psychological distress. Monthly IVIG infusions are ongoing, further addressing pain symptoms, leading to improved sleep quality and less daytime fatigue.

CONCLUSIONS: Anti-GAD antibodies are an expected finding in autoimmune polyglandular syndrome, but extreme anti-GAD titers in the context of neuromuscular symptoms should prompt consideration of SPS. Overcoming the challenge of diagnostic overshadowing has led to a multimodal approach to better address this child's physical symptoms, mental health, and immune-related pathophysiology, which is instrumental in managing her pain and improving her functional status.

KEYWORDS: Neuroimmunology, Neuromuscular

382. Outcomes of Pediatric Autoimmune Encephalitis at Nemours Children's Hospital, Orlando

Shreya Kurnool, Satyanarayana Gedela

OBJECTIVE: Diagnosis of pediatric autoimmune encephalitis (AE) is challenging due to clinical overlap with other conditions. This retrospective chart review evaluated whether a standardized treatment protocol improved outcomes compared with individualized care and whether diagnostic delays impacted outcomes.

METHODS: A retrospective review was conducted of pediatric patients diagnosed with AE between 2014 and 2024. Diagnosis was based on clinical presentation, cerebrospinal fluid findings, electroencephalography, and brain magnetic resonance imaging. Outcomes were assessed using the modified Rankin Scale and the Clinical Assessment of Autoimmune Encephalitis score. Logistic regression identified predictors of long-term epilepsy.

RESULTS: Forty-seven patients with cerebrospinal fluid-confirmed AE were identified. Mean age at symptom onset was 9.7 years, and mean time to diagnosis was 10 days. Early combined immunotherapy, including plasma exchange initiated within three days, was associated with clinical improvement (46.2%). Long-term outcomes included cognitive deficits, behavioral changes, epilepsy, movement disorders, and speech or language impairments. Cognitive deficits (74.5%) and movement disorders (59.6%) were most common. Seizures at presentation were associated with epilepsy development (odds ratio [OR] 5.61, $p = 0.01$), while altered mental status was associated with reduced epilepsy risk (OR 0.15, $p = 0.02$). Delayed treatment initiation was also associated with epilepsy (OR 7.56, $p = 0.01$).

CONCLUSIONS: Pediatric AE is associated with substantial long-term neurologic morbidity. Seizures at presentation and delays in treatment initiation were significant predictors of subsequent epilepsy, while early combined immunotherapy was associated with improved outcomes, emphasizing the need for prompt diagnosis and timely standardized treatment.

KEYWORDS: Neuroimmunology, Early Stage Investigator, Neurocritical Care

383. Delayed Diagnosis of Tumor in Pediatric Opsoclonus Myoclonus Ataxia Syndrome

Celia Greenlaw, Rebecca MacRae, Grace Wang, Christopher Cortina, Stephan Voss, Kumaran Deiva, Andrea Klein, Ming Lim, Thomas Rossor, Elizabeth Sokol, Yasmin Khakoo, Nikita Shukla, Timothy Lotze, Kristen Fisher, Wendy Mitchell, Sarah Hopkins, Bo Zhang, Mark Gorman

OBJECTIVE: Half of patients with pediatric onset opsoclonus myoclonus ataxia syndrome (POOMAS) have associated neural crest tumors. Despite the known tumor association, tumor detection can be delayed by months after new POOMAS diagnosis. This study investigated POOMAS patients with associated tumors to understand factors that contribute to timing of tumor diagnosis.

METHODS: We conducted a retrospective cohort study using the multi-national, multi-center POOMAS Registry. We included patients <18 years with paraneoplastic OMAS. We used multivariable linear regression to calculate the association of tumor location, tumor size, and tumor stage with the mean time to tumor diagnosis. We adjusted for potential confounders of time to OMAS diagnosis, tumor type, and patient age.

RESULTS: Of 205 patients in the POOMAS registry, 102 (49.7%) had tumors and were included for analysis. Larger tumor size was associated with significantly shorter time to tumor diagnosis, with each centimeter of tumor diameter related to a 1.8-week earlier tumor diagnosis (CI -2.2, -1.4; adjusted $p < 0.001$). Lower tumor stage did not significantly change time to tumor diagnosis. Tumor location did not change tumor diagnosis timing when comparing the most common tumor locations (abdominal/retroperitoneal, adrenal) to less common tumor locations (cervical, thoracic, pelvic). Data on the sensitivity of diagnostic modalities (MRI, CT, US, MIBG, catecholamines) will be presented.

CONCLUSIONS: Small tumor size is the biggest predictor for delayed tumor diagnosis in OMAS. Tumor stage and tumor location did not contribute to timing of tumor diagnosis. Repeat surveillance with cross-sectional imaging is

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recommended to ensure small tumors are not missed in OMAS patients.
KEYWORDS: Neuroimmunology

384. Clinical characteristics and outcomes in pediatric MOGAD: single center retrospective study.

Olajumoke Bamgbose, Yelizaveta Sapozhnikov, Hanh Vu

OBJECTIVE: Myelin oligodendrocyte glycoprotein antibody associated disease is a demyelinating condition that leads to significant morbidity. We present our center's experience with pediatric MOGAD, which aims to contribute to understanding the natural history and management of the disease.
METHODS: Patients with pediatric MOGAD were identified from a database spanning from 2017-present and retrospective review was performed. Data included demographics, presenting clinical phenotype, MOG-ab titer, treatment, duration of hospital stay, and outcome.
RESULTS: 37 patients were identified (M_{age}=7, SD_{age}=3.8; 51.3% M). 62.2% were white, 18.9% Hispanic, 8.2% black, 2.7% Asian, and 8.2% unknown. The most common presenting phenotype was optic neuritis (29.7%) followed by focal cortical encephalitis (24.3%). 54.1% had MOG antibody titer of 1:1000 (range: 1:20 – 1:10000). 21.6% required ICU care (median titer 1:1000). The most frequent phenotype in patients admitted to the ICU was focal cortical encephalitis (50%), followed by myelitis (37.5%). A majority (94.6%) of patients received treatment on first presentation, with 29.7% requiring treatment beyond IVMP and IVIG. 32.4% of all patients were initiated on maintenance therapy. 15.2% of patients had at least 1 flare following initial presentation; of this cohort, 83.3% later required maintenance therapy.
CONCLUSIONS: Consistent with published data, this cohort's most common phenotype was optic neuritis. The second most common phenotype was focal cortical encephalitis, which tended to have a more severe presentation with those patients more frequently requiring ICU level care. This growing database highlights the diverse clinical course of these patients, which will aid in better characterizing the natural history of MOGAD.
KEYWORDS: Neuroimmunology

385. Idiopathic Intracranial Hypertension Following Tocilizumab Initiation in a Teen with Juvenile Idiopathic Arthritis

Sakina Lashkeri, Salma Baig, Emily Way, Airaj Fasiuddin, Tarannum Lateef

OBJECTIVE: Idiopathic intracranial hypertension (IIH) is characterized by elevated intracranial pressure with no overt structural etiology. While IIH has been associated with certain medications and systemic inflammatory conditions, it has not been reported in association with IL-6 inhibition. We describe a case of IIH occurring after initiation of tocilizumab, an IL-6 receptor antagonist used to treat juvenile idiopathic arthritis (JIA).
METHODS: Case report.
RESULTS: We report a 16-year-old female with newly diagnosed systemic onset JIA (AKA Still's Disease) who was started on weekly tocilizumab injections with improvement in her rheumatologic symptoms. After receiving her first dose, she developed horizontal diplopia and vomiting. The vomiting improved after several days, but the diplopia persisted. Examination revealed a left sixth nerve palsy and bilateral papilledema. Brain MRI and MRV were normal. Lumbar puncture demonstrated elevated opening pressure (>30 cm H_2O), consistent with IIH. Despite acetazolamide initiation, her symptoms persisted, with ongoing diplopia and papilledema. Given the temporal association, tocilizumab was discontinued. The patient experienced gradual resolution of headaches and diplopia. Her left sixth nerve palsy, esotropia, and papilledema also resolved. She was transitioned to alternative biologic therapy without recurrence of symptoms, though she remains on acetazolamide. To our knowledge, this is the first reported case of IIH temporally associated with tocilizumab use.
CONCLUSIONS: This case highlights a unique occurrence of tocilizumab potentially causing IIH, thus expanding the spectrum of potential neurologic complications of IL-6 inhibitors. Further studies regarding the role of cytokine modulation in intracranial pressure regulation are warranted.
KEYWORDS: Neuroimmunology, Headache

386. Timing and Yield of Malignancy Screening in Pediatric Patients with anti-NMDA receptor encephalitis (NMDARE)

Kelsey Riggs, Tim Nguyen, Will Schwieterman, Molly Moehlman, Paul Horn, Elizabeth Wilson

OBJECTIVE: The purpose of this study is to evaluate imaging utilization patterns, timing of tumor detection, and clinical characteristics associated with malignancy in pediatric anti-NMDA receptor encephalitis (NMDARE). While international treatment guidelines exist, there are no standardized recommendations regarding malignancy screening modalities or timing. We hypothesize that pelvic ultrasound is sufficient for initial tumor detection.
METHODS: We performed a retrospective cohort study of pediatric patients (n=22, ages 1–26) diagnosed with NMDARE at a single tertiary care center from 2008–2025. Data collected included clinical characteristics, imaging modality, timing of imaging, and tumor detection. Descriptive statistics are reported. Regression modeling to evaluate factors associated with routine malignancy screening is underway.
RESULTS: Pelvic ultrasound was the most frequently utilized initial screening modality, while MRI pelvis and CT abdomen/pelvis were used less commonly as adjuncts, with variability in imaging practices. Follow-up malignancy screening was more likely in older and female patients. There was no association between presenting signs/symptoms and screening utilization. Three patients had ovarian teratomas (all post-pubertal females). Two were detected on initial screening (pelvic ultrasound or MRI), while one was identified on follow-up imaging with pelvic ultrasound after an initially negative evaluation with CT abdomen/pelvis.
CONCLUSIONS: Malignancy in pediatric NMDARE is rare and primarily occurs in post-pubertal females. Pelvic

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ultrasound is the most used first-line screening modality and may be effective for initial evaluation. However, delayed tumor detection highlights the importance of follow-up imaging after a negative initial screen. This highlights that standardized, risk-stratified screening protocols are still needed.
KEYWORDS: Neuroimmunology, Neuro-oncology

387. Tocilizumab for Surgery-Refractive, Multi-Therapy Resistant NMDA Receptor Encephalitis in a Pediatric Patient

Sarah Ward, Kunal Bonde, James Takahashi

OBJECTIVE: We report a pediatric patient with rapidly diagnosed Anti-NMDA receptor encephalitis associated with an ovarian teratoma whose syndrome remained unchanged after teratoma resection and two months of first- and second-line treatments. Rapid remission was finally achieved via use of Tocilizumab, an anti-interleukin-6 inhibitor.
METHODS: Descriptive case report.
RESULTS: A 15-year-old girl presented to the hospital for altered mental status and generalized seizures and was found to have an ovarian teratoma measuring 7 x 5.5 x 3.4 cm which was promptly resected. NMDA receptor encephalitis was diagnosed via antibody testing in the serum and CSF. She was started on pulse steroids and IVIG and had her treatment escalated to multiple rounds of PLEX and Rituximab due to continued neurologic decline requiring intubation. She remained unchanged after nearly two months of treatment. Despite normal Il-6 levels, she was started on Tocilizumab, an anti-interleukin-6 inhibitor. Within days, the patient was extubated, and she was able to answer questions appropriately. She had full return to baseline within a month of treatment.
CONCLUSIONS: This report describes a prolonged, highly treatment-resistant case of pediatric anti-NMDA encephalitis that relented after usage of Tocilizumab despite normal Il-6 levels. There were no noted side effects, and improvement onset was rapid.
KEYWORDS: Neuroimmunology

388. Associations between neighborhood-level indices and clinical outcomes in pediatric anti-NMDA receptor encephalitis (pNMDARE)

Jennifer Yang, Alice Yu, Alexander Sandweiss, Kristen Fisher, Ilana Kahn, Alexandra Kornbluh, Katerina Nastea, Marcin Gierdalski, Ryan Kammeyer, Amy Young, Jennifer Koop, Lileth Mondok, Leigh Sepeta

OBJECTIVE: Epidemiologic studies show that pNMDARE has a higher incidence in non-White populations. However, further characterization of health disparity risk factors impacting disease outcomes are unknown.
METHODS: We conducted a multi-center retrospective cohort study of pNMDARE from 2007-2022 at 5 geographically diverse tertiary children's hospitals. Neighborhood-level indices included Area Deprivation Index (ADI), normed scores and quintiles for Childhood Opportunity Index (COI) composite and domains (Education [ED], Health and Environment [HE]), Socioeconomic [SE]). Outcomes included hospitalization duration, EEG, MRI, ICU admission, immunotherapy, and modified Rankin Scores (mRS) at admission and 1 year. We employed univariate Wilcoxon ranked sum test comparing disadvantaged vs. non-disadvantaged COI groups and multivariable linear regression modeling adjusting for age of onset and sex to determine associations between ADI/COI and clinical outcomes.
RESULTS: 200 participants (median age of onset 12.6 years, IQR 5.9 – 15.0, 64% female) were included: 43.5% White Hispanic, 14.5% White Non-Hispanic, 42% Non-White. Median national COI score was low (33.0, IQR 12.5-67.0): 57% composite, 52% ED, 68% HE, 54% SE domains were in "Very Low" or "Low" quintiles. mRS at admission was significantly different between disadvantaged vs non-disadvantaged groups for composite COI ($p=0.04$) and COI HE ($p=0.009$). Higher deprivation (high ADI, $p=0.005$; low COI, $p=0.004$) was associated with higher mRS at admission. There were no associations between ADI/COI and other clinical variables.
CONCLUSIONS: A high proportion of pNMDARE patients are Non-White or Hispanic aligning with prior data. More than half come from disadvantaged neighborhoods based on COI with higher mRS at presentation suggesting a disparity in disease expression.
KEYWORDS: Neuroimmunology, Diversity, Equity, Inclusion

389. Autoimmune GFAP Astrocytopathy in an Adolescent Male: From Diagnostic challenges to Treatment Response

hasmik Verdyan, Emily garavatti, Janetta arellano

OBJECTIVE: Glial fibrillary acidic protein astrocytopathy (GFAP-A) is an autoimmune inflammatory disorder of the CNS characterized by the presence of specific antibodies targeting the intracellular filament protein in mature astrocytes. GFAP is rarely seen in pediatric population, and we aim to describe presentation, diagnosis and management in a pediatric patient.
METHODS: Retrospective chart review was done.
RESULTS: A 17-year-old previously healthy male presented with subacute progressive headache, fever, and meningismus. Initial CSF showed lymphocytic pleocytosis with negative meningoencephalitis panel, leading to a diagnosis of aseptic meningitis. Due to persistent and worsening symptoms, he was readmitted; repeat CSF demonstrated worsening pleocytosis with total nucleated cells of 268, rising protein of 355, and low glucose. Funduscopic exam revealed papilledema. Serial MRI revealed diffusion restriction in the splenium of the corpus callosum, pontine heterogeneity, leptomeningeal enhancement, bilateral basal ganglia and thalamic T2 hyperintensities with perivascular spread, and longitudinally extensive spinal cord signal abnormality. Metagenomic next-generation sequencing and cell-free DNA testing was negative. The patient was empirically treated with IVIg followed by high-dose IV methylprednisolone followed by steroid taper. During this period, while undergoing workup for neurosarcoidosis, cell-based assay returned positive for CSF-specific GFAP-IgG antibodies. Follow-up imaging demonstrated resolution of meningeal enhancement and improvement in spinal cord signal. Given the high relapse rate associated with GFAP astrocytopathy, the family elected to initiate rituximab for long-term immunotherapy.
CONCLUSIONS: This case highlights the importance of early CSF GFAP-IgG testing in adolescents with progressive

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meningoencephalomyelitis, as overlapping features with infectious and granulomatous etiologies can delay diagnosis and treatment.

KEYWORDS: Neuroimmunology, Neuroinfectious Disease, Global Neurology

390. Development and Validation of the Pediatric Autoimmune encephalitis Severity Scale (PASS) in Children with Autoimmune Encephalitis

Naveen Sankhyan, Priyanka Madaan, Suvasini Sharma, Ava Easton, Russell Dale, Velda Han, Alvin Ho, Shekeeb Mohammad, Margherita Nosadini, Ravitanaya Sodani, Terrence Thomas, Ming Lim, Michael Eyre

OBJECTIVE: The Pediatric Autoimmune encephalitis Severity Scale (PASS) by expert consensus using the Delphi process. The primary objective of this study was to prospectively validate PASS against a pediatric quality-of-life measure (PedsQL) and mRS in children with AE and to correlate PASS with the CASE score. The secondary objective was to analyze the latent structure of PASS by exploratory factor analysis.

METHODS: Children were prospectively enrolled and underwent serial ratings with the PASS, Clinical Assessment Scale in Autoimmune Encephalitis (CASE), and Modified Rankin Scale (mRS) at 8 time points up to 6 months after presentation. Clinical outcomes included PedsQL (parent-rated) and developmental/intellectual outcome at 6 months. Inter-rater agreement, internal consistency, and correlations of PASS and CASE with clinical outcomes were compared.

RESULTS: Over a 21-month period, there were 361 assessments in 27 children with AE [15 antibody-negative AE, 11 NMDA receptor antibody encephalitis (NMDARE), one steroid-responsive encephalopathy associated with autoimmune thyroiditis] with a median age at onset of 4 years (IQR 3.0-6.4). There was excellent inter-rater agreement for PASS and CASE, but PASS slightly outperformed CASE with an intraclass correlation coefficient (0.994 vs. 0.990). Worst PASS score was inversely correlated with final PedsQL ($r=-0.42$, $p=0.047$). Factor analysis revealed distinct 'cognitive/behavioral' and 'disinhibition/excitability' dimensions in the PASS items.

CONCLUSIONS: PASS score correlated with long-term parent-reported quality of life outcomes and was useful in children with various developmental abilities and ages.The PASS offers an alternative to adult scales, which may be difficult to use with children.

KEYWORDS: Neuroimmunology

391. A Risk-Stratified Tumor Re-Screening Framework in Anti-NMDA Receptor Encephalitis: A Case-Based Proposal

Jahnavi Tatachar, Garrett Gianneschi

OBJECTIVE: Anti-N-methyl-aspartate receptor (anti-NMDAR) encephalitis is strongly associated with ovarian teratomas in young women. Although initial tumor screening is standard, optimal strategies for repeat evaluation remain undefined. We present a severe case with tumor identification during hospitalization and propose a risk-stratified, longitudinal re-screening framework.

METHODS: We reviewed the clinical course, treatment timing, and outcome in a 24-year-old woman with confirmed anti-NMDAR encephalitis. Findings were analyzed alongside available literature to identify gaps in current tumor surveillance practices and inform a structured re-screening approach.

RESULTS: Patient presented with acute neuropsychiatric symptoms and progressive encephalopathy. CSF demonstrated lymphocytic pleocytosis and elevated anti-NMDAR antibody titers of 1:1000. Initial neuroimaging was unrevealing, and EEG showed diffuse slowing. Treatment included first-line immunotherapy with escalation and subsequent tumor-directed surgery. Despite early immunotherapy, the patient developed severe encephalopathy, dysautonomia, and respiratory failure requiring intensive care. Subsequent pelvic imaging identified a 5.2 cm ovarian mass, and surgical resection confirmed a teratoma. At discharge, the patient demonstrated partial neurologic recovery but remained functionally impaired (modified Rankin Scale score approximately 4).

CONCLUSIONS: This case highlights the limitations of single-timepoint tumor screening in anti-NMDAR encephalitis. We propose a risk-stratified re-screening framework incorporating clinical severity, recovery trajectory, and relapse risk to guide longitudinal tumor surveillance. This approach provides a scalable, clinically actionable strategy to improve detection of occult or delayed neoplasms and optimize neurologic outcomes.

KEYWORDS: Neuroimmunology

392. Serum Neurofilament Light Chain in Adolescents with Antibody Negative Autoimmune Encephalitis

Dana Kapeller-Libermann, Varun Kannan

OBJECTIVE: Many patients with symptoms and findings suggestive of autoimmune encephalitis (AE) have no antibody identified at this time, making it difficult to diagnose. It is important to accurately diagnose AE to treat it within a timely manner. This case series illustrates the use of Neurofilament light chain (NfL) as a possible biomarker for antibody negative AE.

METHODS: This is a descriptive case series. A retrospective chart review identified three adolescents with antibody negative AE that had available NfL measurements throughout hospitalization.

RESULTS: The median age at presentation was 15 years. 2 of 3 were female. 3 of 3 were Black American. 3 of 3 presented with acute psychosis. 0 of 3 had seizures, and 1 of 3 had hyperkinetic movement disorder. 1 of 3 had upper motor neuron signs on exam. 2 of 3 had an encephalopathic EEG background. 0 of 3 had CSF pleocytosis, and 2 of 3 had positive CSF oligoclonal bands (median 3 bands). 3 of 3 had an abnormal initial NfL (median initial value 20.1). 3 of 3 received IV steroids. 3 of 3 received IVIG. 2 of 3 underwent plasmapheresis. 3 of 3 received 2nd line immune therapy (1 rituximab, 1 tocilizumab, and 1 both rituximab and tocilizumab). All 3 had significant functional recovery at last neurology assessment, and normalization of NfL (median value of 6.8).

CONCLUSIONS: NfL is elevated in adolescents with antibody negative AE and normalizes after acute immunotherapy. Further investigation is needed to validate the diagnostic and therapeutic utility of this biomarker.

KEYWORDS: Neuroimmunology

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393. Griscelli Syndrome Type 2 Masquerading as CLIPPERS: A Case of Relapsing Cerebellar Inflammation

Leslie Beltran Garland, Margaret Codispoti, Shrenevas Nandam, Hyun Yong Koh, Nikita Shukla, Kristen Fisher, Karla Salazar

OBJECTIVE: To present a case of atypical relapsing cerebellar dysfunction, initially suspected secondary to CLIPPERS with a diagnosis of Griscelli Syndrome type 2 ultimately provided by genetic testing.

METHODS: N/A

RESULTS: A previously healthy 6-year-old female presented with a two-week history of headache, nausea, and ataxia following a viral illness. Neuroimaging showed bilateral cerebellar T2 hyperintensities, edema, and partial fourth ventricular effacement with obstructive hydrocephalus. She was treated with intravenous methylprednisolone with significant clinical improvement and discharged on an oral steroid taper. She subsequently relapsed twice after taper, with recurrent ataxia, mutism and radiographic progression, prompting repeat high-dose steroids and initiation of tocilizumab, resulting in near-complete recovery. Given the atypical, relapsing course despite responsiveness to immunotherapies, workup was expanded, including stereotactic cerebellar biopsy and CSF sampling. Histopathology revealed dense perivascular, T-cell predominant lymphohistiocytic inflammation, raising concern for CLIPPERS. Laboratory studies showed elevated neopterin, soluble IL-2 receptor, and CXCL-9. Oral methotrexate therapy was initiated at discharge. Subsequent genetic evaluation identified biallelic pathogenic variants in the *RAB27A* gene, confirming Griscelli syndrome type 2. The clinical and radiographic presentation was ultimately attributed to familial hemophagocytic lymphohistiocytosis (HLH). The patient completed a course intrathecal methotrexate while awaiting hematopoietic stem cell transplantation evaluation.

CONCLUSIONS: We conclude that cerebellar inflammation in children often presents with nonspecific clinical and radiographic features, creating diagnostic uncertainty, particularly in atypical or relapsing cases. This case highlights the limitations of conventional diagnostic frameworks in the setting of suspected CLIPPERS and emphasizes the need for early consideration of genetic evaluation as HLH-directed therapy can be curative.

KEYWORDS: Neuroimmunology, Neurogenetics, Neuro-oncology

394. Under Pressure: Diagnostic overlap between brainstem-variant PRES and Bickerstaff brainstem encephalitis

Evan Huff, Laura Owlett, Robert Thompson-Stone

OBJECTIVE: To highlight the diagnostic challenge posed by brainstem variant of posterior reversible encephalopathy syndrome (PRES) in children, which can closely mimic Bickerstaff brainstem encephalitis (BBE) in its clinical, radiological, and laboratory findings.

METHODS: We describe a single pediatric case with detailed review of clinical presentation, neuroimaging, CSF analysis, hospital course, and diagnostic evaluation.

RESULTS: A previously healthy 14-month-old female presented with vomiting, lethargy, ophthalmoplegia, and hyperreflexia in the setting of severe hypertension. MRI demonstrated symmetric T2/FLAIR hyperintensities in the midbrain, pons, and cerebellar peduncles with patchy diffusion restriction. CSF showed albuminocytologic dissociation. Initial diagnosis of BBE prompted treatment with corticosteroids and plasma exchange. Despite rapid neurologic improvement, the patient had persistent refractory hypertension requiring intensive care. Repeat MRI at day nine showed near-complete resolution of abnormalities—an atypical course for BBE—prompting reconsideration of the diagnosis. Thorough workup of hypertension revealed bilateral renal artery stenosis and she was discharged without neurologic deficits.

CONCLUSIONS: Brainstem PRES is a rare and underrecognized pediatric entity that can closely resemble BBE in the acute phase of illness, including overlapping clinical features of encephalopathy, cranial neuropathies, hyperreflexia, T2 hyperintensities throughout the brainstem on neuroimaging, and CSF albuminocytologic dissociation. This overlap creates a significant diagnostic challenge during the early phase when treatment decisions are time-sensitive. Clues favoring brainstem-variant PRES include severe hypertension, patchy diffusion restriction, and rapid radiographic resolution.

KEYWORDS: Neuroimmunology, Neurocritical Care

395. Seeing the Unseen: A cases series and systematic review of juvenile Ocular myasthenia Gravis

Ali Albalakhi, Hridhay Sheth, Mateo Tovar, Maria Vera-Sanchez, April Consevage

OBJECTIVE: Myasthenia gravis is an autoimmune neuromuscular disorder causing fatigable weakness, but in children diagnosis often requires strong clinical suspicion because early serologic testing may be negative.

METHODS: Case 1: A healthy 3-year-old African American female presented with one week of progressive ptosis, initially unilateral and later bilateral, without identifiable triggers. Examination showed marked ptosis with preserved ocular reflexes and full extraocular movements. Neuroimaging and laboratory evaluation, including AChR and MuSK antibodies, were unremarkable. Minimal response to pyridostigmine prompted corticosteroids and IVIG, resulting in rapid improvement. Six months later, ptosis recurred, and repeat testing revealed new AChR antibody positivity. Steroid-sparing therapy was deferred due to JC virus seropositivity, and she remains stable on corticosteroids. Case 2: A 16-month-old African American male with sickle cell trait presented with two days of bilateral ptosis and increased fatigue. Examination demonstrated isolated ptosis with intact pupillary responses, symmetric extraocular movements, and no bulbar or respiratory involvement. Neuroimaging and AChR antibodies were normal. Given fatigability with activity and improvement with rest, empiric pyridostigmine was initiated, producing rapid and sustained resolution. He remains stable on monotherapy.

RESULTS: Juvenile-onset OMG poses distinct diagnostic challenges, as a substantial proportion of children with

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juvenile MG are initially seronegative for AChR and MuSK antibodies, and confirmatory studies are technically difficult in young patients..

CONCLUSIONS: These cases highlight the diagnostic challenges of seronegative pediatric OMG and emphasize the primacy of clinical suspicion in the absence of confirmatory laboratory findings. Also underscore the importance of repeat antibody evaluation during disease evolution.

KEYWORDS: Neuroimmunology, Neuromuscular

396. Acute Presentation of Anti-NMDA Receptor Encephalitis: A Three-Patient Case Series

Sarah Schorr, Yash Shah, Anjali Patel, Nidhi Sthanki

OBJECTIVE: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is the most common autoimmune encephalitis in children. This disease process is typically described as having a subacute onset with progression over less than three months. However, more acute presentations over several days are increasingly recognized and may mimic psychiatric disorders, infectious encephalitis, demyelinating diseases, and toxic ingestions, leading to diagnostic uncertainty and management delays. Our objective is to highlight acute presentations of anti-NMDAR encephalitis in pediatric patients and their impact on diagnostic uncertainty and management delays.

METHODS: Retrospective case series of three pediatric patients with anti-NMDAR encephalitis presenting with acute symptom onset. Clinical data were obtained through chart review and caregiver reports.

RESULTS: A 6-year-old male presented following status epilepticus with rapid cognitive and behavioral decline progressing to catatonia and autonomic instability. A 12-year-old female presented with abrupt behavioral and psychiatric symptoms with rapid progression to agitation, confusion, and encephalopathy. A 15-year-old male presented with a headache and vomiting with rapid progression to encephalopathy, abnormal movements, and seizures. Across all cases, symptoms progressed over 3-8 days and initially mimicked more common conditions, contributing to diagnostic uncertainty. Cerebrospinal fluid was inflammatory with negative infectious studies, and anti-NMDAR antibodies confirmed the diagnosis in all cases. All patients received immunotherapy and improved clinically, with variable recovery.

CONCLUSIONS: Anti-NMDAR encephalitis may present acutely over several days rather than following the traditionally described subacute course. This rapid progression may increase risk of misdiagnosis. Early recognition, prompt CSF evaluation, and timely initiation of immunotherapy are essential to improving clinical outcomes.

KEYWORDS: Neuroimmunology

397. Reversal of Severe Structural and Functional Brain Abnormalities After Fulminant Anti-NMDAR Encephalitis: A 5-Year Longitudinal Case

Jaimie Vilavinal, Purabi Sonowal, Mariana Szuchmacher

OBJECTIVE: Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a severe autoimmune disorder with variable long-term outcomes. Although functional recovery is well described, longitudinal correlation between clinical course and EEG/MRI changes remains incompletely characterized. We report a case demonstrating substantial neurological recovery, accompanied by parallel electrophysiologic and radiologic improvement over 5 years.

METHODS: A 15-year-old female presented with acute psychosis and altered mental status. CSF testing confirmed anti-NMDAR antibodies. Her course was complicated by refractory status epilepticus requiring midazolam, ketamine, and pentobarbital coma. A right ovarian teratoma was identified and surgically removed. She received multimodal immunotherapy, including corticosteroids, IVIG, plasmapheresis, rituximab, tocilizumab, and cyclophosphamide, along with electroconvulsive therapy for persistent dyskinesias and encephalopathy.

RESULTS: Initial MRI showed diffuse cerebral volume loss, bilateral hippocampal atrophy, and FLAIR hyperintensities in the periventricular white matter and occipital cortices. EEG demonstrated generalized slowing with epileptiform discharges. She showed gradual neurological improvement with multidisciplinary rehabilitation. She achieved seizure freedom six months after presentation, and all antiseizure medications were discontinued over four years. Follow-up EEG showed normal background without epileptiform discharges. Repeat MRI showed marked resolution of FLAIR abnormalities and reversal of volume loss. She ultimately regained independence in ADLs, with residual borderline intellectual functioning.

CONCLUSIONS: This case highlights substantial long-term recovery after severe anti-NMDAR encephalitis with refractory status epilepticus. Serial EEG and MRI changes paralleled clinical improvement, supporting potential reversibility of structural and functional brain abnormalities and the importance of aggressive therapy and prolonged rehabilitation.

KEYWORDS: Neuroimmunology

398. Characterizing Multiple Sclerosis Content on TikTok: A Cross-Sectional Analysis of the Top 100 Videos

Brianna Miranda, Vaishnavi Vaidyanathan

OBJECTIVE: TikTok is a widely used platform for sharing and accessing health-related information. We examined and categorized content related to multiple sclerosis (MS), a chronic autoimmune disease in which the immune system attacks healthy cells. As MS-related content on social media remains undercharacterized, this study aimed to analyze and categorize such videos.

METHODS: The top 100 videos identified through a hashtag-based search for multiple sclerosis were analyzed. Videos were categorized by engagement metrics (likes, comments, bookmarks), account type (influencer vs non-influencer), and creator sex. Content was classified into five categories: personal experience, informational, medical advice, entertainment, and marketing, with subcategories including symptoms, diagnosis, treatment, mental health, and pathophysiology.

RESULTS: A total of 100 posts were analyzed, with a median follower count of 12.5K (range: 7–166.2K). Median

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engagement included 578 likes (0–35,000), 64 comments (0–1245), and 122 bookmarks (0–5148). Most accounts were influencers (69.6%, n=55). Creators were predominantly female (79%, n=79), followed by male (8%, n=8); AI-generated accounts comprised 3% (n=3), including 1% (n=1) AI female and 2% (n=2) AI male. Personal experience (n=81) and medical advice (n=11) were most common, and no videos addressed pediatric MS.

CONCLUSIONS: Pediatric-focused MS content is lacking despite likely demand among younger users. Content is largely driven by influencers and personal experiences, with limited medical professional input. Although accessibility has improved, variability in quality raises concerns about reliability and highlights the need for clearer guidance and greater involvement from healthcare professionals.

KEYWORDS: Neuroimmunology, Pediatric Demyelinating Disease

399. IgG4-Related Hypertrophic Pachymeningitis in a 14-Year-Old Presenting as Chronic Otologic Disease

Yevgeniy Sazhnyev, Emily Brunner, Hema Murali

OBJECTIVE: We report the youngest biopsy-proven case of IgG4-related hypertrophic pachymeningitis (IgG4-RHP) and highlight diagnostic pitfalls in pediatric CNS-limited disease presenting as chronic otologic pathology.

METHODS: A single-patient case report with retrospective review of clinical, radiological, laboratory, and histopathological data over 3.5 years. Serial MRI, PET/CT, cerebrospinal fluid analysis, serologic workup, and dural biopsy with immunohistochemistry were performed. Published literature was reviewed for comparison.

RESULTS: A previously healthy girl developed persistent left mixed conductive and sensorineural hearing loss after acute otitis media at age 10. Despite three otologic surgeries over 2.5 years, hearing loss progressed. Serial MRI revealed progressive left pachymeningeal thickening (up to 6 mm), calvarial hyperostosis, left transverse/sigmoid sinus fibrosis, and 5 mm rightward midline shift. Chronic daily headaches developed and later resolved spontaneously. Notably, there was no papilledema, cranial nerve deficit, or elevated opening pressure on lumbar puncture. Extensive infectious, neoplastic, and autoimmune workup was negative. Serum IgG4 was mildly elevated at 108.9 mg/dL. PET/CT showed no systemic disease. Dural biopsy at age 14 revealed hypertrophic chronic pachymeningitis with 53 IgG4-positive plasma cells per high-power field. Classic features of storiform fibrosis and obliterative phlebitis were absent, consistent with known meningeal IgG4-RD histopathology. Multidisciplinary consensus established the diagnosis of probable IgG4-RHP. Treatment with prednisone taper and rituximab was initiated.

CONCLUSIONS: Our case represents the youngest biopsy-proven IgG4-RHP reported. Pediatric CNS-limited IgG4-RD can masquerade as chronic otologic disease. Classic histopathologic features are frequently absent in meningeal disease. Multidisciplinary collaboration and early tissue diagnosis are essential when pachymeningitis is refractory to conventional therapy.

KEYWORDS: Neuroimmunology, Neuroimaging, Early Stage Investigator

400. Post-Infectious Longitudinally Extensive Transverse Myelitis with Extensive Myeloradiculitis in an Infant

Yevgeniy Sazhnyev, Eric Strong

OBJECTIVE: To describe a rare case of monophasic, post-infectious longitudinally extensive transverse myelitis (LETM) with extensive myeloradiculitis in a young infant, highlighting the diagnostic overlap with acute flaccid myelitis and Guillain-Barré syndrome and the dynamic evolution of neurological findings.

METHODS: A single patient case report. Clinical, laboratory, imaging, and outcome data were collected from the inpatient and outpatient medical record. Literature review was performed for context.

RESULTS: An 8-month-old previously healthy male presented with progressive generalized weakness, bilateral ptosis, silent cry, and respiratory failure following a febrile upper respiratory illness in a household viral cluster. Respiratory PCR was positive for rhino/enterovirus. MRI spine revealed T2 hyperintensity from C3 to T3 with diffuse, smooth enhancement of ventral cervical, dorsal thoracic, and cauda equina nerve roots. Brain MRI was normal. CSF showed 2 nucleated cells, protein 29 mg/dL, and was negative for infectious and autoimmune etiologies including MOG and AQP4 antibodies. Serum GAD65 was weakly positive (0.12 nmol/L); all other autoimmune markers were negative. Genetic and mitochondrial testing were negative. The patient was treated with IVIG and high-dose methylprednisolone beginning on hospital day one with marked improvement. Over six weeks, examination evolved from flaccid paralysis to increased tone and hyperreflexia, with improving strength, persistent neurogenic bowel, and bilateral finger flexion contractures.

CONCLUSIONS: We present a young infant with LETM and extensive myeloradiculitis, demonstrating a rare overlap of central and peripheral neuroinflammation. The evolution from flaccid to spastic motor findings and the favorable response to combined immunotherapy expand the recognized clinical spectrum of post-infectious myeloradiculitis in infancy.

KEYWORDS: Neuroimmunology, Neuroinfectious Disease, Neurocritical Care

Neuroinfectious Disease

401. Adjunctive 6-diazo-5-oxo-L-norleucine is well tolerated and shows clinical promise in children with cerebral malaria

Douglas Postels, Yamikani Chimalizeni, Nicole O'Brien, Alice Liomba, Nettie Dzabala, Nelson Nyoloka, Neshen Moodley, Matthew Laurens, Mathangi Gopalakrishnan, Athanasios Chamzas, Osward Nyirenda, Alexander Andrews, Dana Harrar, Tesfaye Zelleke, Manu Goyal, Karen Chetcuti, Lorenna Vidal, Brittany Riggle

OBJECTIVE: Cerebral malaria (CM) remains an important cause of childhood death and disability in endemic areas.

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Completed clinical trials of adjunctive therapies to decrease adverse outcomes have been largely unsuccessful. Translating findings of potential benefit of 6-diazo-5-oxo-L-norleucine (DON) from preclinical models, we performed a Phase I/ II double-blind, randomized clinical trial to assess the safety, pharmacokinetics (PK), and preliminary efficacy of single dose DON in children with CM.

METHODS: We enrolled children 1–14 years old with CM, defined as coma (Blantyre Coma Scale ≤ 2), malaria infection, and exclusion of alternative etiologies. Artesunate was administered at admission. Participants were randomized to receive adjunctive single dose DON at either 0.1 mg/kg (n = 14), 1.0 mg/kg (n = 14), or placebo (n = 8). The primary outcomes were clinical and laboratory-based adverse event (AE) rates.

RESULTS: Between July 2024 and April 2025, 36 children were randomized. AE rates were low, clinically insignificant, and reversed without additional treatment. No intervention-attributable severe AEs occurred. DON's half-life was 2.8 hours with first order elimination kinetics. Among placebo recipients, 25% (2 of 8 randomized) experienced an adverse outcome (death or moderate-to-severe neurodisability). DON recipients had a 3.6% adverse outcome risk (1 of 28 randomized, 1.0 mg/kg dose).

CONCLUSIONS: Single-dose DON was well tolerated in pediatric CM patients, with a PK profile consistent with reports of prior oncologic studies. The observed reduction in adverse outcomes in children receiving DON supports continued clinical development as a potential adjunctive therapy in CM.

KEYWORDS: Neuroinfectious Disease, Global Neurology

402. Botulism Beyond the Classic Phenotype: A Case Series

Friedrich Stilling, Nicholas Errico, Andrew McManus, Sarah Wright, Lauren Vilardo, Elizabeth Pickup

OBJECTIVE: Botulism is a rare but potentially life-threatening illness presenting with progressive paralysis. Early recognition can reduce serious complications and hospital admission time. We report two atypical presentations of botulism, one of infant botulism (IB) and one of intestinal toxemia botulism (ITB).

METHODS: Chart review

RESULTS: Case 1: An 11-week-old previously healthy female presented with constipation, poor feeding, and progressive weakness. On admission she demonstrated diffuse hypotonia, head lag, weak suck, and decreased cry. Her examination initially improved with hydration before subsequently fluctuating, with variable hypotonia, ptosis, and restricted up-gaze. Electromyography on hospital day (HD) 5 demonstrated findings consistent with a presynaptic neuromuscular junction disorder, and she was diagnosed with IB. Botulism immunoglobulin was administered on HD 6 with clinical improvement. Stool testing later confirmed botulinum toxin serotype B. At follow-up, she had returned to baseline with age-appropriate milestones. Case 2: A 23-month-old previously healthy male presented with 11 days of refusal to walk and right eye exotropia following travel to Puerto Rico. Examination revealed diffuse hypotonia, inability to bear weight, head lag, and drooling without ptosis. Initial workup was unrevealing. IVIG and plasmapheresis were administered for suspected Guillain-Barré syndrome without improvement. Stool testing confirmed botulinum toxin serotype A on HD 22, consistent with ITB. He improved with supportive care.

CONCLUSIONS: These cases challenge the traditional presentation of botulism: a fluctuating, non-progressive course of IB and an exceedingly rare case of ITB in an otherwise healthy child. Ancillary testing such as electromyography can be helpful to provide an earlier diagnosis and treatment.

KEYWORDS: Neuroinfectious Disease, Neuromuscular

403. Meningitis-Related Mortality in Children by Age Group and Causative Agent in the Dominican Republic, 2020–2021

Elianny Abreu Bautista, Carla Álvarez González

OBJECTIVE: To determine the etiological agents causing meningitis and their impact on mortality by age group in children under 15 years of age in the Dominican Republic during the period 2020–2021

METHODS: An observational, descriptive, and retrospective study was conducted using secondary data from the Global Burden of Disease Study. All reported cases of meningitis in children under 15 years of age in the Dominican Republic during 2020–2021 were included. Etiological agents of meningitis with the highest mortality were analyzed, stratifying results by age group: under 5 years (n=132), 5–9 years (n=20), and 10–14 years (n=10).

RESULTS: During the analyzed period, more than 80% of deaths recorded in both years occurred in children under 5 years of age, representing the group with the highest meningitis mortality. The 5 to 9 years group reported 20 deaths, representing 12.6% of total mortality, while the 10 to 14 years group documented 10 deaths, equivalent to 6.2%. *Streptococcus pneumoniae, Haemophilus influenzae type b, Neisseria meningitidis*, and *Klebsiella pneumoniae* were the agents with the highest mortality, especially in the first years of life.

CONCLUSIONS: These findings confirm that meningitis not only remains active, but disproportionately affects the most vulnerable population: infants. The magnitude of recorded mortality reinforces the urgency of strengthening immunization programs, epidemiological surveillance, and early response, focusing on the most frequent agents and highest-risk groups.

KEYWORDS: Neuroinfectious Disease, Global Neurology, Neurocritical Care

404. Short intensified anti-tuberculosis therapy and adjunctive aspirin in children and adolescents with tuberculous meningitis: a factorial, randomised, partially blinded, phase 3 trial

Naveen Sankhyan, SURE Investigators

OBJECTIVE: To compare Short Intensified-anti-tuberculosis treatment (ATT) with standard-ATT regimen for mortality and compare 8 weeks adjunctive aspirin with placebo for

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outcomes on mRS in children with tuberculous meningitis (TBM).

METHODS: SURE (ISRCTN 40829906) is a factorial, partially blinded, randomised-controlled trial in African (Zimbabwe, Zambia, Uganda) and Asian (India, Vietnam) children with confirmed or suspected TBM. Participants were randomised to receive intensified-ATT [isoniazid (20mg/kg), rifampicin(30mg/kg), pyrazinamide(40mg/kg), levofloxacin(20mg/kg)] daily for 6 months) or standard-ATT (WHO recommended) and simultaneously to aspirin(20mg/kg) or placebo daily for 8 weeks. Primary outcome for ATT randomisation was mortality and for aspirin/placebo was modified Rankin Scale(mRS) at 48 weeks, analysed by modified-intention-to-treat. A 10% non-inferiority margin for ATT and 16% minimally clinically significant difference for aspirin were prespecified.

RESULTS: Between March 2021 and July 2024, 369 children were randomised; 185(52%) were male; median (IQR) age was 4.8(1.3-10) years, 15(4%) were HIV-infected, and 199(54%) had moderate/severe (MRC grade 2/3) disease. 29/183(16%) given intensified-ATT died versus 21/180 (12%) standard-ATT (adjusted risk difference 5.1%; 95% confidence interval -1.7%-+12.0%; p=0.14), not meeting the 10% non-inferiority margin. Severe disability/death (mRS 5/6) occurred in 38/176(22%) children given aspirin versus 25/170(15%) placebo (adjusted odds ratio 1.80; 95% CI 0.95-3.41; p=0.07). ATT-related grade 3/4 adverse events occurred in 47% given intensified-ATT versus 33% standard-ATT (p=0.006), including grade 3/4 drug-induced liver injury (25% versus 9%; p=0.001).

CONCLUSIONS: Neither 6-month intensified-ATT nor aspirin improved outcomes in children with TBM, with evidence of increased toxicity, particularly hepatoxicity with intensified-ATT. New therapeutic strategies are urgently needed to increase survival and reduce disability from TBM.

KEYWORDS: Neuroinfectious Disease, Practice Parameters, Global Neurology

405. Immune Response to EV-D68 Infection in the Spinal Cord During Early Postnatal Development in a Murine Model of Acute Flaccid Myelitis

Sarah Meller, Penny Clarke, Kenneth Tyler

OBJECTIVE: Enterovirus D68 (EV-D68) is a respiratory pathogen that has emerged as a cause of acute flaccid myelitis (AFM) in children. Intramuscular (IM) injection of EV-D68 isolates from the 2014 US outbreak (EV-D68 IL52) produces flaccid paralysis in neonatal mice. This work examines how immune-mediated cellular damage may contribute to the age-dependent window of vulnerability to EV-D68 induced paralytic disease.

METHODS: Swiss–Webster mouse pups were infected with EV-D68 by IM injection of a hindlimb at postnatal day 1 (P1) and postnatal day 15 (P15). Littermates injected with PBS served as controls. Immunohistochemistry was performed on spinal cord (SC) sections to label motor neurons with ChAT, microglia with Iba1, lysosomes with CD68, and T cells with CD3, CD4 and CD8. Stained cells were segmented and quantified using Fiji (ImageJ) software.

RESULTS: Paralysis of bilateral hindlimbs and loss of lumbar ventral horn motor neurons was observed 6 days after EV-D68 infection at P1. There was a robust increase in lumbar SC microglia density that peaked 6 days after EV-D68 infection at P1. These microglia demonstrated a significant increase in CD68 intensity that peaked 6 days after infection, implicating increased microglial phagocytic activity. T cells invade the lumbar SC in proximity to the abundant microglial cells 6 days after injection with EV-D68 at P1, but there were scant T cells in the lumbar SC of all other treatment groups.

CONCLUSIONS: This data suggests that microglia-T cell interactions and a dysregulated immune response may be involved in the development of paralysis in a murine model of AFM.

KEYWORDS: Neuroinfectious Disease, Neuroimmunology

406. SSPE presenting as developmental and epileptic encephalopathy with atonic seizures: Diagnostic and treatment challenges in the modern era

Peter Alexieff, Tova Bergsten, Emily Reinsdorf, Elizabeth Tranel, Priya Sharma, Alma Bicknese

OBJECTIVE: Discuss an unusual presentation of SSPE, appreciable clinical response to antiseizure treatment, and long-term treatment

METHODS: Single case report with chart and literature review

RESULTS: 2-year-old male with speech delay presented with falls and subacute gross motor regression. He was found to have markedly abnormal electroencephalography (EEG), which evolved to demonstrate atonic seizures and periodic discharges consistent with Radermecker complexes. History revealed a measles infection during infancy and lumbar puncture demonstrated elevated measles antibodies. History, EEG findings, and measles antibodies in cerebrospinal fluid (CSF) were concordant with subacute sclerosing panencephalitis (SSPE), so symptomatic seizure treatment and treatment of the underlying disease were pursued. This patient achieved improvement in seizure frequency with rufinamide, clobazam, and ketogenic diet, and an intraventricular reservoir was placed for intermittent interferon alpha administration in combination with oral inosine pranobex.

CONCLUSIONS: This case highlights an unusual presentation of SSPE as developmental and epileptic encephalopathy with atonic seizures. The lack of myoclonus at presentation, young age, and initially non-characteristic EEG findings delayed SSPE evaluation. Improvement in atonic seizures and clinical encephalopathy with rufinamide, clobazam, and ketogenic diet suggests that aggressive seizure treatment provides meaningful symptomatic and palliative benefit despite progressive underlying disease. Given changes in vaccination rates, this condition may become more common, and pediatric neurologists should consider earlier inclusion of SSPE in the differential diagnosis of developmental and epileptic encephalopathies. A literature review highlights contemporary treatment approaches for this condition and the challenges associated with acquiring and administering non-FDA-approved therapies in a near-universally fatal disease.

KEYWORDS: Neuroinfectious Disease, Epilepsy

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407. Assessing Neurological Outcomes Following COVID-19 Vaccination in Children: A Review of Current Evidence

Ernesto Breton, Ishita Mishra, Dhruv Parekh, Tejal Mehta, Tiong The, Carlos Lastra

OBJECTIVE: To conduct a systematic thematic review comparing neurological outcomes after COVID-19 vaccination versus SARS-CoV-2 infection in pediatric populations.

METHODS: A PRISMA-based literature review was performed using PubMed, chosen for its public accessibility. The search terms "COVID-19 vaccination" and "neurological adverse" event were applied with filters for English-language studies and ages 0–18 years. Forty-one publications from the past five years were identified; 26 met inclusion criteria. After excluding one review and two case reports, 23 studies were analyzed.

RESULTS: Across all studies, evidence consistently supports the neurological safety of COVID-19 vaccines in children. Serious vaccine-related neurological events were rare. Among 5–11-year-olds, reported rates per 100,000 were 2.6 for emergency visits, 1.1 for hospitalizations, 0.14 for life-threatening events, and 0.03 for deaths. Small transient increases in seizure or demyelinating events were observed but did not exceed background rates. There is a significant association between covid vaccine and GBS, more with inactivated vaccines in 12-17 years of age. COVID-19 infection carried far greater neurological risk. In one study, 22% of infected children showed neurological involvement and 9% developing severe complications. Adult data demonstrates approximately 600-fold higher neurological risk after infection.

CONCLUSIONS: Current global and pediatric-specific evidence overwhelmingly supports the neurological safety of mRNA COVID-19 vaccines. Serious neurological events are extremely uncommon and are far less frequent than those following infection. A small, unconfirmed signal for demyelinating disease in adolescent females warrants further study. There is a need for prospective pediatric research and continued post-marketing surveillance to strengthen confidence and guide vaccination policy.

KEYWORDS: Neuroinfectious Disease

408. Neuroimaging in Children with Tuberculous Meningitis: Findings from the SURE TBM trial.

Naveen Sankhyan, SURE Investigators

OBJECTIVE: To describe baseline neuroimaging findings in the children enrolled in the SURE trial. And to describe detailed MRI findings at baseline and 24 weeks in a subset of children

METHODS: For children enrolled in the SURE (ISRCTN 40829906) trial, baseline neuroimaging (CT/MRI) findings were described at each site and independently reviewed. For the MRI substudy, anonymized MRI imaging acquired using a standard procedure and stored at a central repository underwent three reviews. The reporting method was based on consensus among UK and Indian neuroradiologists. Reviewers were blinded to the clinical condition and treatment arm. A scoring method was used to quantify abnormalities based on size and number

RESULTS: Of the 369 children randomised, 308 (83%) had baseline imaging (MRI-71%/CT-29%). 30(10%) were normal. Of the abnormal scans reviewed, 92% showed imaging consistent with TBM at the time of diagnosis. Meningeal enhancement (67%) is the most common abnormality across TBM severity grades. Hydrocephalus (53%) and infarcts(38%) were more common in severe MRC grades, while tuberculomas (42%) were least common in severe Grade III. For the MRI substudy, a total 123 paired MRI scans were reviewed. Aspirin had no impact on ischaemic burden in TBM. The changes in radiological findings at 24 weeks in the short-intensive and standard arms of ATT were not different.

CONCLUSIONS: In possibly the largest prospectively collected neuroimaging data in children with TBM, baseline findings were associated with the severity of the disease. Interventions did not alter the evolution of neuroimaging findings.

KEYWORDS: Neuroinfectious Disease, Neuroimaging, Neuroimmunology

Neurometabolic

409. Subgroup analyses of US Early Access Program participants with Niemann-Pick disease type C treated with arimoclomol

Elizabeth Berry-Kravis, Nicolas Abreu, Walla Al-Hertani, Radhika Dhamija, Can Ficicioglu, Kristina Julich, Caroline Hastings, Paul Hillman, Nancy Leslie, Damara Ortiz, Melinda Peters, Paula Schleifer, Ronan O'Reilly, Blair Orr, Christine í Dali

OBJECTIVE: Niemann-Pick disease type C (NPC) is an ultra-rare, progressive, neurodegenerative lysosomal disorder. Effectiveness of arimoclomol was assessed in patients with NPC enrolled in a 4-year US Early Access Program.

METHODS: Routine clinical care was maintained. Effectiveness was assessed using the 5-domain NPC Clinical Severity Scale (5DNPCCSS). Completer cohorts (year 1: n=78; year 2: n=43; year 3: n=38; year 4: n=20) were compared with their respective baselines. Outcomes were summarized overall and by age (<18 vs ≥18 years) and miglustat use.

RESULTS: Among 109 participants, 48.6% were adults and 65.1% received miglustat. No new safety signals were identified. At approval, all remaining 81 participants transitioned to commercial treatment. Across completer cohorts, 5DNPCCSS scores remained stable. In the year 1 cohort, mean±SD scores were 11.2±6.33 (baseline) vs 11.1±6.63 (year 1). In the year 4 cohort, scores were 11.6±5.75 (baseline) vs 11.6±6.98 (year 4). Similar patterns were observed in years 2 and 3 and across subgroups. Baseline vs year 1 scores were 10.3±7.00 vs 10.4±7.45 in pediatric participants (n=39) and 12.0±5.54 vs 11.8±5.71 in adults (n=39); similar patterns were observed for those completing years 2-4. In a subgroup of interest of pediatric patients aligned with pivotal trial criteria (aged 2-19 years; on miglustat), scores were 9.7±6.03 (baseline) vs 9.1±6.25

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(year 1; n=27) and 10.0±7.87 (baseline) vs 10.3±8.66 (year 4; n=4), consistent with stabilization observed in the pivotal trial.

CONCLUSIONS: Real-world data demonstrate sustained disease stabilization with arimoclomol up to 4 years, consistent across completer subgroups by miglustat use and age.

KEYWORDS: Neurometabolic, Lifespan Manifestations of Childhood Onset Conditions

410. Implementing a Standardized, Hospital Wide Initiative to Protect Designated Intracerebroventricular (ICV) Reservoirs for Cerpliponase alpha, or Brineura Infusions from Unintended Use

Amy Garee, Kathy Wiest, Emily De Los Reyes

OBJECTIVE: Cerliponase Alfa, commonly known as Brineura, the specialized therapy indicated for treatment of CLN2 disease, or Batten's disease, is administered via Intracerebroventricular (ICV) Reservoirs. Due to the critical sterility requirements and administration directly into the central venous nervous system (CNS), it is imperative that the ICV reservoirs are prohibited for any non-Brineura indications. However, in other hospital areas, there is a risk of inadvertent, unintended use of these reservoirs that could pose a risk for severe complications, including increased morbidity and mortality. The purpose of this poster is to describe the implementation of a standardized, hospital-wide initiative to protect designated Intracerebroventricular (ICV) Reservoirs for Cerliponase alfa (Brineura) Infusions from unintended use.

METHODS: A multidisciplinary team developed and implemented a hospital wide initiative that included: (1) physical labeling of the access device, (2) EMR alerts and orders restricting access, and (3) staff education across all units.

RESULTS: Implementation of a standardized, hospital wide initiative to protect Intracerebroventricular (ICV) Reservoirs designated for Brineura infusions from unintended use as a patient safety and quality improvement initiative enabled implementation of protective measures, and staff education in other departments has increased awareness of the risks associated with inadvertent port access or infusion of non-Brineura treatments.

CONCLUSIONS: A structured hospital wide initiative involving labeling, EMR restrictions, and staff education can effectively prevent inappropriate use of ICV reservoirs designated for Brineura only. This patient safety and quality improvement effort highlights the importance of implementing protective measures and providing hospital wide education of staff to protect all patients receiving specialized therapies.

KEYWORDS: Neurometabolic, Neurodevelopmental Disorders, Education

411. When Viruses Reveal What Genetics Conceals: Delayed Presentation of PDH Deficiency in Childhood

Annie Hoang-Pham, Hebah Alzyod, Suad Khalil

OBJECTIVE: Pyruvate Dehydrogenase (PDH) deficiency is a rare X-linked mitochondrial disorder caused by mutations in PDHA1, leading to impaired pyruvate oxidation, lactic acidosis, and variable neurologic dysfunction. Most cases present in infancy, but later or intermittent presentations may remain silent until metabolic stress. We report a child with delayed PDH deficiency revealed by viral infection.

METHODS: We describe a 4-year-old male presenting with acute generalized weakness and fatigue after Influenza A infection.

RESULTS: The patient had a history of prolonged recovery after viral illnesses but no prior neurologic deficits. Examination showed lethargy, diffuse hypotonia, and symmetric weakness. Labs revealed elevated lactate (3.7–9.1 mmol/L). Brain MRI demonstrated symmetric T2-FLAIR hyperintensities in the medulla and bilateral dentate nuclei, with sparing of the basal ganglia. Concurrent Influenza A infection and post-viral gastroparesis initially suggested encephalitis, delaying recognition of a metabolic disorder. Whole-genome sequencing identified a de novo hemizygous pathogenic PDHA1 variant (c.328C>T; p.Arg110Cys), confirming PDH deficiency. Initiation of thiamine supplementation and a ketogenic diet led to improved strength, mobility, and oral intake.

CONCLUSIONS: This case highlights an atypical, infection-triggered presentation of PDH deficiency with subtle neuroimaging findings. Recognition of these imaging patterns alongside metabolic clues and timely genetic testing can facilitate earlier diagnosis and targeted therapy, potentially improving outcomes in children with late-onset PDH deficiency.

KEYWORDS: Neurometabolic, Lifespan Manifestations of Childhood Onset Conditions, Neurodevelopmental Disorders

412. Reversible MRI changes and Subacute Encephalopathy in a Child with Congenital Pernicious Anemia causing low B12: A Case Report

Chandler Lichtefeld, Hallie Shpack, Jaime Shoup, Christopher Barton

OBJECTIVE: Congenital pernicious anemia, a very rare metabolic disorder with fewer than 100 confirmed cases, is caused by intrinsic factor deficiency due to bi-allelic mutations in the gastric intrinsic factor gene (GIF). It typically presents between ages 5 and 30 years with ataxia, encephalopathy, weakness, and characteristic MRI changes if untreated. We present a rare case of a patient with both reversible clinical symptoms and MRI findings following vitamin B12 treatment and diagnosis.

METHODS: A 9-year-old female presented with subacute memory loss beginning one month prior, characterized by worsening short-term memory. She became disinterested in previously enjoyed activities and had intermittent staring episodes with unresponsiveness to touch and voice. She also developed extremity shaking at rest and with action, along with balance difficulties. History was notable for a significantly restricted diet. Examination revealed flat affect, difficulty following commands, bilateral lower extremity spasticity, 3+/4+ reflexes in all extremities, positive Romberg sign, ataxic gait, and bilateral resting/postural hand tremor without dysmetria.

RESULTS: CBC showed megaloblastic anemia with vitamin B12 <109 and elevated homocysteine. CSF and autoimmune evaluations were normal and copper was low. Brain MRI

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demonstrated multifocal frontal T2 changes. EEG showed generalized slowing with intermittent sharps but no seizures. Treatment with B12 injections led to resolution of exam findings and near-complete resolution of MRI abnormalities after six months. Genetic testing identified two likely pathogenic GIF variants (c.137C>T and c.128T>C).
CONCLUSIONS: Congenital pernicious anemia, though rare, can cause severe subacute encephalopathy with focal deficits that resolve clinically and radiographically with treatment.
KEYWORDS: Neurometabolic, Neuroimaging, Neurogenetics

413. Improved developmental outcomes with early initiation of cerliponase alfa treatment in children with CLN2 disease

Emily de los Reyes, Angela Schulz, Paul Gissen, Nicola Specchio, Kathleen Delaney, Jessica Cohen Pfeffer, Pascal Reisewitz

OBJECTIVE: CLN2 disease is a rare, rapidly progressive neurodegenerative disorder that typically presents between the ages of 2 and 4 years. Intracerebroventricular cerliponase alfa has been shown to slow motor and language function decline in CLN2 disease. Here we present data on developmental outcomes from an open-label study of cerliponase alfa in a cohort including children who initiated treatment <2 years of age (NCT02678689).
METHODS: Study participants received cerliponase alfa biweekly for ≥144 weeks. Attainment of developmental milestones was assessed as an exploratory endpoint using the Denver II Developmental Screening Test to evaluate skills in fine motor adaptive, gross motor, language, and personal social domains. Developmental age-equivalent scores in each domain were assessed every 12 weeks.
RESULTS: Participants (n=14) had a mean (SD) age at baseline of 3.1 (1.5) years. Participants <2 years at baseline (n=5) showed developmental age-equivalent scores at baseline at or above participant age, with mean (SD) scores of 22.2 (6.6), 31.6 (9.8), 25.6 (9.7), and 30.2 (8.1) months in fine motor adaptive, gross motor, language, and personal social domains, respectively. Scores in all domains increased over the study, with mean (SD) increases of 41.0 (16.7), 33.4 (13.6), 35.6 (18.0), and 25.4 (17.0) months, respectively. Among participants ≥2 years of age at baseline (n=9), mean (SD) scores at baseline were 25.2 (12.3), 33.8 (8.8), 31.3 (10.7), and 31.0 (15.3) months, respectively, and changed minimally over the study.
CONCLUSIONS: Initiation of cerliponase alfa treatment prior to symptom onset may improve developmental outcomes in children with CLN2 disease.
KEYWORDS: Neurometabolic, Neurodevelopmental Disorders, Neurogenetics

414. When Tyrosine Metabolism Leaves a Dark Clue: Novel HGD Variants in Pediatric Alkaptonuria

Divya Sree Vislavath, Yashu Sharma, Savita Verma Atri, Sanjhi Paliwal, Mini Tageja, Charu Sharma, Rakesh Pilania, Renu Suthar, Arushi Gahlot Saini

OBJECTIVE: Alkaptonuria is a rare autosomal recessive metabolic disorder caused by homogentisate 1,2-dioxygenase deficiency, leading to homogentisic acid accumulation, dark urine, ochronosis, and progressive joint disease. Early pediatric recognition is critical, yet South Asian genetic data remains limited. Our objective is to characterise the clinical, biochemical and genetic spectrum of Alkaptonuria in pediatric patients.
METHODS: This case series evaluated four male children (1 month to 13 years) diagnosed with AKU based on clinical presentation, urinary HGA screening via gas chromatography-mass spectrometry, and *HGD* gene sequencing. In-silico tools predicted variant pathogenicity.
RESULTS: Darkening urine upon standing was the hallmark finding. One 13-year-old patient presented with Alkaptonuria co-occurring with intellectual disability and acute flaccid paralysis; genetic testing identified a pathogenic *TAF1* variant. Molecular analysis identified four *HGD* variants, including two novel homozygous missense mutations: c.87T>A (p.MetLys) in exon 13 and c.7G>T (p.AspTyr) in exon 7. Management included Vitamin C, E, and nitisinone. Notably, a significant decrease in urinary HGA excretion was observed after just a single dose of nitisinone.
CONCLUSIONS: This study expands alkaptonuria's molecular spectrum with novel *HGD* variants. The rapid reduction in HGA excretion after one dose of nitisinone highlights its potential as an effective disease-modifying therapy when initiated early to reduce long-term systemic complications.
KEYWORDS: Neurometabolic, Neurogenetics

415. Conduction Block in Early Infantile Krabbe Disease

Jennifer McKinney, Margie Ream

OBJECTIVE: Krabbe Disease is associated with central and peripheral nervous system demyelination. Historically, nerve conduction studies in early onset Krabbe disease demonstrate a mixed sensorimotor demyelinating peripheral neuropathy with uniform slowing and no conduction block. Here we present two patients with early onset Krabbe disease who underwent routine nerve conduction studies with electrophysiologic evidence of conduction block.
METHODS: Retrospective case series
RESULTS: Our patients underwent initial nerve conduction studies at 15 and 22 days of life, respectively. Both patients' initial nerve conduction studies demonstrated typical findings of prolonged distal latencies, slowed conduction velocities, and absent sensory responses with reduced or normal CMAP amplitudes. The first patient's initial study demonstrated conduction block in the right median nerve in the forearm. No further evaluation was performed due to patient death. The second patient demonstrated conduction block in the left median nerve in the forearm at 13 months of age, and this remained present over 6 years; additionally, conduction block was observed in the right median nerve in the forearm at 20 months of age. MR Neurography was performed and showed marked, symmetric enlargement of all the peripheral nerves in the arms and legs without discontinuity or focal changes.
CONCLUSIONS: To our knowledge, these are the first reported cases of conduction block in early infantile Krabbe disease. Our report suggests that conduction block can be

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seen in infantile Krabbe disease thus broadening our understanding of the early severe demyelinating neuropathy that exists in this patient population.

KEYWORDS: Neurometabolic, Neuromuscular

416. Cerliponase alfa for the treatment of CLN2 disease: Combined results from two ongoing observational studies

Emily de los Reyes, Angela Schulz, Paul Gissen, Nicola Specchio, Raymond Wang, Alice Lail, Viviane Wang, Sherif Khattab

OBJECTIVE: Clinical trials have shown that cerliponase alfa slows decline in motor and language function in individuals with CLN2 disease, with an acceptable safety profile. Two ongoing observational studies in the USA (NCT04476862) and EU (EUPAS29031) are evaluating long-term real-world outcomes. Here we report pooled interim safety and effectiveness data from these studies.

METHODS: Safety was assessed in all treated participants. Effectiveness was assessed in a cohort of treated participants matched 1:1 on baseline age and CLN2 Clinical Rating Scale motor-language (ML) scores with natural history (NH) controls from the DEM-CHILD database. Outcomes included annualized ML decline and time to unreversed 2-point ML decline or ML score of 0.

RESULTS: Safety analyses included 109 treated participants with a mean (SD) cerliponase alfa exposure time of 5.6 (2.5) years: 67 (61.5%) participants experienced adverse events (AEs), 56 (51.4%) experienced serious AEs, and 37 (33.9%) experienced device-related AEs. In total, 45 treated participants were matched with NH controls (mean [SD] baseline age: 4.3 [0.9] years; mean [SD] baseline ML score: 3.8 [1.1]). Compared with NH controls, treated participants had a lower risk of unreversed 2-point ML decline or score of 0 (HR 0.14; 95% CI 0.07–0.27; $p<0.0001$). Mean (SD) rate of decline in ML score was 0.35 (0.43) points/year in treated participants versus 2.38 (1.40) points/year in NH controls (mean difference: 2.03; 95% CI 1.59–2.47; $p<0.0001$).

CONCLUSIONS: Safety and effectiveness outcomes among individuals with CLN2 disease treated with cerliponase alfa in the real-world setting are consistent with clinical trial findings.

KEYWORDS: Neurometabolic, Neurodevelopmental Disorders, Neurogenetics

417. Comb-Like Rhythm on EEG as an Early Clue to Maple Syrup Urine Disease Despite a Normal Newborn Screen

Ananya Moorthy, Neal Sankhla

OBJECTIVE: To highlight the role of characteristic EEG findings in prompting early diagnosis and treatment of Maple Syrup Urine Disease (MSUD), even in the setting of normal Newborn Screen.

METHODS: A 15-day-old full-term male presented with altered mental status, poor feeding, apnea, and metabolic acidosis. He required intubation on arrival. Neuroimaging demonstrated diffuse cerebral edema with diffusion restriction involving the brainstem and peri-rolandic regions. CSF was unremarkable. Ammonia was 74. Initial newborn screening and leucine levels were normal; however, the leucine-to-alanine ratio was elevated. Continuous EEG monitoring was initiated to evaluate for seizures.

RESULTS: EEG demonstrated centrally located comb-like activity, a pattern reported in MSUD. Although not specific, this finding, combined with an elevated leucine-to-alanine ratio and characteristic urine odor, prompted immediate initiation of treatment prior to confirmatory testing. The patient was treated with renal replacement therapy, intralipids, fluids, and thiamine. MSUD was confirmed approximately 4 days after presentation. The patient showed clinical improvement, was extubated, and transitioned off CRRT. Follow-up MRI at 5 months demonstrated resolution of cerebral edema and improved diffusion abnormalities.

CONCLUSIONS: Comb-like rhythm on EEG may serve as an early diagnostic clue for MSUD in the appropriate clinical context, even when initial newborn screening is normal. Recognition of this pattern can facilitate earlier treatment and potentially improve neurologic outcomes.

KEYWORDS: Neurometabolic, Neurocritical Care

418. Understanding the Dysmetabolism Associated with WWOX-Mediated Nervous System Dysfunction

Ameya Walimbe, Jennifer Deger, Ruth Barros de Paula, Haein Kim, Vishnu Cuddapah, Joshua Shulman, Hugo Bellen

OBJECTIVE: Pathogenic variants in the *Tryptophan-Tryptophan* (*WW*)*-domain-containing oxidoreductase* (*WWOX*) underlie the autosomal recessive disorder, WWOX-related developmental and epileptic encephalopathy (WOREE) syndrome. WOREE syndrome is characterized by developmental delays, hypotonia, and severe, pharmacoresistant epilepsy leading to infantile death. WWOX encodes an oxidoreductase that promotes mitochondrial oxidative phosphorylation and ATP production. Targeted *WWOX* ablation in mouse neurons leads to severe epilepsy, while its constitutive knockdown in flies worsens lifespan defects caused by reduced Isocitrate Dehydrogenase, indicating a role in the Tricarboxylic Acid (TCA) cycle. Despite its importance in nervous system function, the precise mechanism and effectors of WWOX dysfunction remain unknown. Our objective here was to better characterize the behavioral and metabolic phenotypes of flies with Wwox loss-of-function.

METHODS: N/A

RESULTS: Wwox-null flies raised at ambient temperature (25°C) demonstrate impaired flight abilities, suggesting reduced energy production. When raised at 29°C, Wwox-null flies exhibit starvation resilience, potentially due to a decreased metabolic rate. These mutants also have climbing defects, ambient seizures, and an increased susceptibility to heat-induced seizures, indicating CNS dysfunction and metabolic disequilibrium under stress. Untargeted metabolomics analyses at 25°C reveal dysmetabolism of TCA cycle analytes, including increased citrate and reduced isocitrate. Elevated levels of polyunsaturated fatty acids were also observed, suggesting a metabolic shift away from oxidative phosphorylation and towards lipid synthesis.

CONCLUSIONS: These results suggest that Wwox is required for proper TCA cycle function under stress

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conditions. Wwox may also mediate a balance between oxidative phosphorylation and lipid synthesis. Ongoing investigations include identifying the metabolic effectors of Wwox and the neuronal cell populations involved.
KEYWORDS: Neurometabolic, Epilepsy, Neurogenetics

Neuromuscular

419. Willingness of healthcare professionals to adopt gene therapy for Duchenne Muscular Dystrophy: A multidisciplinary analysis of barriers and facilitators in Spain

Maria Branas Pampillon, Rocio Garcia Uzquiano, Julita Medina, Beatriz Garcia Palop, Jose Luis Poveda, Marian Terrancle, Fatima Jerez, Jorge Maurino

OBJECTIVE: This study evaluated the willingness of healthcare professionals (HCPs) to adopt gene therapy for Duchenne Muscular Dystrophy (DMD) and identified key barriers and facilitators influencing future clinical integration in Spain.
METHODS: We conducted a non-interventional, cross-sectional, web-based study in collaboration with the Spanish Societies of Pediatric Neurology and Rehabilitation Medicine, and the Catalan Society of Hospital Pharmacy. Participants completed a standardized survey on attitudes, barriers, and facilitators regarding the potential adoption of gene therapy.
RESULTS: The cohort consisted of 53 HCPs (37 pediatric neurologists, 11 rehabilitation physicians, and 5 hospital pharmacists) with a mean age of 44.5 years and a median of 10 years of experience in DMD management. High enthusiasm was observed, with 89.2% of pediatric neurologists favoring gene therapy as a transformative shift in the standard of care. The most significant barriers were clinical: concerns regarding adverse events and uncertainty over long-term efficacy. In contrast, logistical burdens and patient resistance were perceived as less impactful. Rehabilitation physicians, who manage the highest patient volume, identified additional barriers in outcome monitoring, with fewer than 50% considering current functional scales sufficiently sensitive for long-term assessment. Key facilitators for clinical integration included the availability of more robust evidence (cited by 86.5% of pediatric neurologists) and formal guidance from professional societies (78.4%).
CONCLUSIONS: Spanish specialists demonstrate a strong predisposition toward adopting DMD gene therapy. Successful integration is contingent upon clear professional guidelines and high-quality evidence to mitigate concerns regarding safety and sustained efficacy.
KEYWORDS: Neuromuscular

420. Small Fiber Neuropathy (SFN) in Pediatric Rheumatological Disorders: Characteristics and Presenting Features

Kadambari Vyas, Akaluck Thatayatikom, Vikram Prakash

OBJECTIVE: Small Fiber Neuropathy (SFN) is well described in adults, but there is limited data for the pediatric population. Our objective is to evaluate clinical characteristics of pediatric SFN in rheumatological disorders.
METHODS: Retrospective chart review was performed to identify patients. SFN was diagnosed by Epidermal Nerve Fiber Density (ENFD), values on skin biopsy, and/or Quantitative Sudomotor Axon Reflex Test (QSART) testing. Rheumatological disorders were diagnosed using published standard criteria for children.
RESULTS: Nine patients with SFN and coexisting rheumatologic disorders were identified. Seven patients were diagnosed with Sjogren's syndrome, one was diagnosed with scleroderma, and one was diagnosed with both Sjogren's syndrome and Systemic Lupus Erythematosus (SLE). Mean age at diagnosis of neuropathy and rheumatologic disorder was 15.55 years and 16.11 years, respectively. 66.7% of patients were diagnosed with neuropathy before they were diagnosed with Sjogren's syndrome with a mean delay of 1.42 years. Presenting symptoms were neuropathic pain or sensory impairment, orthostatic dizziness, headaches, and constipation, but patients later developed a combination of these symptoms. Postural Orthostatic Tachycardia Syndrome (POTS) was diagnosed in 5 patients (55.6%). Comorbid conditions included Ehlers-Danlos syndrome (EDS), mast cell activation, Hashimoto's thyroiditis, and Celiac disease. Three patients who received IVIG therapy have shown clinical improvement.
CONCLUSIONS: Sjogren's syndrome should be suspected in children with SFN as most patients were diagnosed with neuropathy before their rheumatologic diagnosis. Scleroderma and SLE can have associated SFN. Neuropathic pain and/or sensory impairment, GI symptoms, and/or orthostatic intolerance can be the presenting symptom. Treatment with IVIG produces favorable response in these patients.
KEYWORDS: Neuromuscular, Neuroimmunology, Autonomic Disorders

421. Caregiver Experiences in Duchenne Muscular Dystrophy Care: Support at Diagnosis and Across the Disease Course

Michelle Tram, Stella Deng

OBJECTIVE: Care for individuals with Duchenne Muscular Dystrophy (DMD) requires complex, multidisciplinary management, yet recommended care is not consistently achieved. This study examines caregivers' experiences, focusing on support and resources provided at diagnosis and challenges that arose throughout the disease course.
METHODS: Caregivers (≥18 years) of individuals with DMD were recruited through Albany Medical Center and national patient advocacy organizations to complete an online survey. Descriptive analyses were performed for closed-ended data, and thematic analyses for open-ended data.
RESULTS: Overall, 146 caregivers completed the survey. The mean age of individuals with DMD was 16.6 ± 8.3 years (range 2–50), with 59% non-ambulatory (n=86). The mean age of diagnosis was 4.3 ± 2.7 years (range 0-11). At diagnosis, only 56.8% of caregivers (n=83) recalled receiving sufficient information on the disease course and 55.2% (n=80) on genetic counseling. Most caregivers

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reported that they were not referred to support groups (78.6%, n=114), offered contact with a social worker or care coordinator (66.9%, n=97), nor given adequate time to speak with the provider (51.0%, n=74). As children aged and disease management became more complex, practical challenges increased, including navigating insurance and costs (20.5%, n=30), finding specialized providers (15.1%, n=22), obtaining equipment or treatments (10.3%, n=15), and coordinating care (9.6%, n=14).

CONCLUSIONS: DMD caregivers report persistent gaps in information, resources, and support beginning at diagnosis and continuing throughout the disease course. Caregiver-informed strategies are needed to provide guidance early in the disease journey and better prepare families for future challenges in accessing care.

KEYWORDS: Neuromuscular

422. Maternal-fetal drug transfer using a preclinical mouse model demonstrates the potential of prenatal therapy for Spinal muscular atrophy

Emma Sutton, Ariane Beauvais, Rebecca Yaworski, Hugh McMillan, Rashmi Kothary

OBJECTIVE: To evaluate the safety, efficacy and translational potential of prenatal therapy for Spinal muscular atrophy (SMA) using a severe, preclinical mouse model. SMA is a devastating neuromuscular disease characterized by loss of alpha motor neurons. Neonatal disease onset is now considered detrimental to a complete recovery despite current postnatal disease modifying therapies.

METHODS: Risdiplam is a small molecule *SMN2* pre-mRNA splicing modifier and the only orally available therapeutic for SMA. Risdiplam was administrated by oral gavage to pregnant mice harbouring SMA affected fetuses. Reproductive metrics, liver toxicology and immune function were assessed in the pregnant dams. Progeny were monitored phenotypically, and pathological hallmarks (motor neuron, neuromuscular junction and muscle health) were investigated to assess rescue of disease relevant phenotypes.

RESULTS: Maternal-fetal drug transfer was safe for the pregnant dam with no signs of drug-induced hepatotoxicity or active state of inflammation (N=3-10/group). SMN protein levels in the spinal cord and skeletal muscle of SMA offspring were restored leading to a substantial rescue in weight, motor function and survival (N=5-8/group). Prenatal therapy did not fully protect motor neuron pathology but was sufficient to rescue postsynaptic components of the neuromuscular junction and skeletal muscle atrophy (N=5-8/group per analysis).

CONCLUSIONS: Prenatal therapy for SMA shows strong efficacy in a preclinical model of SMA. We demonstrate favourable safety in both dam and offspring with substantial improvements in SMA mice. Our efforts demonstrate a combination of pre- and postnatal therapy must be utilized for optimum therapeutic outcomes in the treatment of patients with SMA.

KEYWORDS: Neuromuscular, Experimental Therapeutics, Fetal Neurology

423. Assessing the impact of 'any point differences' or 'stability' in the Hammersmith Functional Motor Scale-Expanded on the independence of patients with SMA

Andrej Marich, Stacy Dixon, Alicia Henriquez, Tina Duong, Natalie Land, Claire Cagle, Thomas Brown, Christabella Cherubino, Mouhamed Gueye, Ashley Stanley-Copeland, Leslie Nelson

OBJECTIVE: The HFMSE is a validated tool for assessing treatment efficacy in SMA; however, the meaningfulness of score changes often require additional insights from patients/caregivers. To understand the real-word impact of changes in HFMSE scores, we conducted 60-minute semi-structured interviews with patients living with SMA and/or their caregivers.

METHODS: Using the constant comparative method, we identified four life domains that participants believed would improve with motor function improvements or stability: ADLs, psychosocial wellbeing, independence, and QoL. Here we report perspectives from pediatric (caregiver proxy; aged 2-17y; n=29) and adult patients (aged ≥18y; n=32) related to independence.

RESULTS: Pediatric (mean age [SD], 9.2 [4.6]; current function: 'sitters' [59%] and 'walkers' [41%]) and adult patients (mean age [SD], 44.0y [15.5]; current function: 'sitters' [72%] and 'walkers' [28%]) generally agreed that gaining or maintaining the ability to eat, practice self-care, dress, work/play, reposition, interact socially, and navigate their surroundings are central to their independence. For one pediatric patient (walker), their caregiver highlighted the advantages of any point improvement in the HFMSE stairs task stating, "The ability to do even two or three steps independently would be significant." An adult patient (sitter) also emphasized this when discussing the benefits of stability in the HFMSE rolling task stating, "…I can move independently in bed. I can reposition when I get sore… [and] get a good night's sleep. My husband can [also] get a good night's sleep..."

CONCLUSIONS: These results emphasize the value of integrating patient and caregiver insights to capture what constitutes clinically meaningful change.

KEYWORDS: Neuromuscular

424. Impact of baseline characteristics on apitegromab efficacy in patients with spinal muscular atrophy (SMA)

Andrej Marich, Eugenio Mercuri, Laurent Servais, Sabrina Yum, Heike Kölbel, Astrid Pechmann, Giovanni Baranello, Mariacristina Scoto, Anne-Marie Childs, Randal Richardson, Thomas Brown, Mouhamed Gueye, Guolin Zhao, Giridhar Tirucherai, Jing Marantz

OBJECTIVE: Apitegromab is an investigational monoclonal antibody that selectively inhibits activation of myostatin, a negative regulator of muscle growth. Target engagement and efficacy of apitegromab were assessed across broad populations of patients living with SMA.

METHODS: Concentrations of latent myostatin, apitegromab's therapeutic target, were assessed in the Phase 3 SAPPHIRE (NCT05156320) and Phase 2 TOPAZ (NCT03921528) studies. Apitegromab target engagement

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and clinical efficacy were analyzed by baseline latent myostatin concentration, functional status (Hammersmith Functional Motor Scale–Expanded [HFMSE] score), and age.

RESULTS: In SAPPHIRE (N=188; nonambulatory; aged 2-21 years), baseline latent myostatin concentrations were similar regardless of HFMSE score or age (2-12 vs 13-21 years). To assess apitegromab results across disease severity, participants were separated into tertiles of baseline latent myostatin concentration or HFMSE score. Across all baseline latent myostatin and HFMSE score tertiles, total latent myostatin increased with apitegromab through week 52, and HFMSE score changes from baseline to week 52 favored apitegromab vs placebo. Furthermore, in ambulatory TOPAZ participants (n=12), total latent myostatin concentrations were sustained over 4 years and associated with functional stability on the Revised Hammersmith Scale. Across SAPPHIRE age groups, effective target engagement was observed; least squares mean differences in HFMSE score changes from baseline to week 52 were similar and favored apitegromab vs placebo.

CONCLUSIONS: Consistent evidence of measurable therapeutic target as well as effective target engagement and motor function benefit with apitegromab were observed across the SMA spectrum, demonstrating broadly applicable efficacy across patients living with SMA, regardless of disease severity or age.

KEYWORDS: Neuromuscular, Experimental Therapeutics

425. Givinostat weight-based flexible dosing: rationale and efficacy at the different doses

Paolo Bettica, Aravindhan Veerapandiyan, Federica Alessi, Sara Cazzaniga, Eugenio Mercuri

OBJECTIVE: In the phase 3 double-blind, placebo-controlled EPIDYS trial, givinostat, a histone deacetylase inhibitor, was investigated for Duchenne muscular dystrophy. Weight-based givinostat plus corticosteroids were administered, starting at dose A or B, depending on study protocol. Doses were adjusted based on predefined rules related to tolerability to achieve the highest tolerated dose for each patient. This analysis evaluated givinostat efficacy based on the final administered dose (week 72) in EPIDYS patients.

METHODS: The primary endpoint was mean change from baseline (CFB) in 4-stair climb (4SC) time (seconds). Key secondary endpoints were CFB in total North Star Ambulatory Assessment (NSAA) score and time to rise (TTR) from the floor.

RESULTS: Thirty-nine patients started at dose A, 42 at dose B, and 39 received placebo. Dose was reduced in 36 patients. Twenty-one patients received final dose A, 44 dose B, and 16 dose C. All patients had similar givinostat blood concentrations within the efficacious range throughout the study. The placebo-corrected least-squares (LS) mean CFB (95% CI) in 4SC time was A: –2.61 (–4.97, –0.26), B: –1.35 (–3.25, 0.54), and C: –1.90 (–4.48, 0.67). For NSAA, placebo-corrected LS mean CFB was A: 3.35 (1.07, 5.64), B: 1.24 (–0.57, 3.05), and C: 1.94 (–0.58, 4.46). For TTR, A was: –3.80 (–12.67, 5.07), B: –2.66 (–9.81, 4.49), and C: –4.26 (–13.97, 5.45).

CONCLUSIONS: Results numerically favored givinostat over placebo across doses. Flexible dosing enables maximal efficacy while maintaining tolerability. Despite protocol-driven dose reductions, treatment effects were observed across all doses.

KEYWORDS: Neuromuscular, Movement Disorders

426. Cerebrospinal Fluid Opening Pressure in Pediatric SMA Patients Treated with Nusinersen: A Retrospective Analysis

Isabella Norelius, Matthew Harmelink, Nancy Bass

OBJECTIVE: To evaluate whether intrathecal nusinersen administration is associated with changes in cerebrospinal fluid (CSF) opening pressure (OP) in pediatric patients with spinal muscular atrophy (SMA).

METHODS: We performed a retrospective review of 24 pediatric SMA patients treated with nusinersen at a large, urban Level 1 pediatric academic medical center (2017–2023). A total of 173 CSF OP measurements obtained during routine lumbar punctures were analyzed. Elevated OP was defined as >28 cm H_2O. Associations with age, nusinersen dose number, and treatment duration were evaluated using linear mixed effects modeling.

RESULTS: Median CSF OP was 18 cm H_2O (range 0–47). Elevated OP occurred in 5.8% of measurements. Among cases with follow-up data, 89% of elevated measurements were followed by values within the reference range on subsequent assessment. Younger patients (≤10 years) had significantly higher OP compared to older patients ($p < 0.001$). Nusinersen dose number and treatment duration were not significantly associated with OP ($p > 0.05$).

CONCLUSIONS: In this cohort, intrathecal nusinersen administration was not significantly associated with sustained increases in CSF opening pressure. Elevated OP values were infrequent and typically not persistent on subsequent measurement. These findings suggest that routine OP measurement during nusinersen administration may have limited utility in routine practice, though further study is needed to guide optimal monitoring strategies.

KEYWORDS: Neuromuscular, Movement Disorders, Practice Parameters

427. Autonomic Dysfunction and Multisystem Involvement in Spinal Muscular Atrophy: A Systematic Review

Kelly Fisher, Eleanor Smeallie, Kimberly Pokstis, Aaron Zelikovich, Dennis Keselman

OBJECTIVE: Spinal muscular atrophy (SMA) is traditionally characterized as a motor neuron disease caused by survival motor neuron (SMN1) deficiency. However, growing evidence suggests broader non-motor manifestations, particularly involving the autonomic nervous system (ANS), which regulates cardiovascular, gastrointestinal, respiratory, and thermoregulatory function. As SMA survival improves, these underrecognized components are increasingly clinically relevant. We aimed to synthesize current evidence of ANS

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involvement across physiological domains and propose a unifying mechanistic framework.

METHODS: A comprehensive literature review was conducted using PubMed with search terms including "spinal muscular atrophy" and "autonomic dysfunction," incorporating cardiovascular, gastrointestinal, respiratory, sudomotor, and urinary domains. Clinical and preclinical studies were included to provide a structured narrative synthesis.

RESULTS: Evidence across multiple systems demonstrates autonomic dysfunction in SMA. Cardiovascular studies show altered heart rate variability, electrocardiographic abnormalities, and arrhythmias indicating sympathetic-parasympathetic imbalance. Gastrointestinal manifestations, including constipation, dysphagia, and delayed gastric emptying, are supported by preclinical evidence of enteric nervous system dysfunction independent of motor weakness. Respiratory findings highlight bidirectional interactions between ventilatory impairment and autonomic instability, with improvement following noninvasive ventilation. Sudomotor, urinary, and thermoregulatory abnormalities further support widespread autonomic involvement. Collectively, these findings suggest disruption of shared ANS regulatory pathways rather than isolated organ-specific abnormalities.

CONCLUSIONS: Autonomic dysfunction in SMA represents a clinically meaningful extension of disease beyond motor neurons. A unifying mechanistic framework incorporating SMN biology, developmental vulnerability, and multilevel autonomic disruption better accounts for SMA's multisystem phenotype. Recognition of autonomic involvement has important implications for increased clinical surveillance, supportive care, and future research.

KEYWORDS: Neuromuscular, Autonomic Disorders

428. Pubertal Delay and Testosterone Response in Adolescents with Duchenne Muscular Dystrophy Treated with Daily Glucocorticoids

Jillian Belgrad, Danielle Sharon, Audrey McKennitt, Hannah Walsh, Courtney Shellenbarger, Rebecca Artinian, Celina Goncalves, Brenda Wong, Brian Silver, Stephen Chrzanowski, Ruby Joshi Batajoo

OBJECTIVE: Duchenne muscular dystrophy (DMD) is associated with delayed puberty in adolescents on daily long-term systemic glucocorticoids. However, predictors of pubertal delay and the efficacy of testosterone treatment on puberty, growth, and bone health remain poorly studied. This investigation aimed to characterize the response to testosterone therapy in adolescents with DMD who have delayed puberty.

METHODS: We conducted a retrospective chart review of boys aged 14-17 years evaluated by pediatric endocrinology at UMass DMD clinic from January 2023-2026. Delayed puberty was defined by testicular volume < 4 mL at age 14. Endogenous puberty was defined by testicular volume >4 mL and confirmed by luteinizing hormone >0.3 mIU/mL. Patients with delayed puberty were evaluated for response every 6-12 months on testosterone therapy.

RESULTS: Twenty-eight patients met criteria for delayed puberty. 21 patients received 6-months of monthly intramuscular testosterone and were followed for at least 1 year post-treatment. 10 of 21 patients (48%) demonstrated endogenous pubertal progression following a single 6-month treatment course of testosterone. 11 patients (52%) required continued therapy and received another 6 months course of testosterone. After 2 courses of testosterone, 5 patients (24%) demonstrated endogenous pubertal progression with the remaining 6 patients (28%) requiring ongoing testosterone treatment.

CONCLUSIONS: Delayed puberty is prevalent in adolescents with DMD on glucocorticoids and response to testosterone therapy is heterogeneous. Initial testosterone therapy induced endogenous pubertal onset in nearly half of patients with delayed puberty. These findings support the need for standardized approaches to pubertal assessment and management in DMD.

KEYWORDS: Neuromuscular

429. Givinostat reduces decline of contractile cross-sectional area and decreases fat infiltration in Duchenne muscular dystrophy

Paolo Bettica, Krista Vandenborne, Rebecca Willcocks, Sara Cazzaniga, Federica Alessi, Eugenio Mercuri

OBJECTIVE: The phase 3 EPIDYS trial (NCT02851797) was a randomized, double-blinded, placebo-controlled study evaluating the safety, tolerability, and efficacy of the histone deacetylase inhibitor givinostat in Duchenne muscular dystrophy (DMD). Contractile cross-sectional area (cCSA) and fat fraction (FF) are quantitative measures of DMD progression. This analysis measured cCSA and FF in patients from EPIDYS with a baseline vastus lateralis FF of >5% to ≤30% (target population).

METHODS: Quantification of cCSA and FF were determined via magnetic resonance imaging (givinostat, n=76; placebo, n=37) using the Dixon technique. Data were analyzed with a repeated measures mixed model to determine change over time with covariates including treatment group, visit, baseline value, and interaction. All P values are nominal.

RESULTS: At the end of the EPIDYS trial (72 weeks), the differences in least squares (LS) means (95% CI) in muscle groups between givinostat and placebo for cCSA (cm^2) were: 0.43 (0.14, 0.73; P=0.005) in the bicep femoris long head, 1.02 (0.47, 1.58; P<0.001) in the hamstrings, 1.20 (0.16, 2.23; P=0.023) in the quadriceps, 0.47 (0.13, 0.80; P=0.006) in the semitendinosus, and 0.61 (0.04, 1.17; P=0.035) in the vastus lateralis, respectively. Further, differences in LS means for FF (%) in the same muscles were -4.60 (-8.22, -0.99; P=0.013), -4.00 (-6.59, -1.40; P=0.003), -4.07 (-6.42, -1.72; P=0.001), -3.43 (-5.80, -1.06; P=0.005), and -3.86 (-6.36, -1.35; P=0.003), respectively.

CONCLUSIONS: Givinostat treatment appeared to be associated with reduced decline in muscle contractile area and reduced fat infiltration vs placebo, a pattern suggestive of attenuation of muscle loss in patients with DMD.

KEYWORDS: Neuromuscular, Movement Disorders

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430. Trajectory of Performance of Upper Limb in patients with Duchenne muscular dystrophy treated with givinostat relative to a modeled natural history cohort

Paolo Bettica, John Brandsema, Jessica Marden, Jonathan Freimark, Katherine O'Connor, Andrea Parodi, Elyse Swallow, Emma Billmyer, Michel Michaëls, Menno van der Holst, Saskia Houwen, James Signorovitch, Erik Niks

OBJECTIVE: Givinostat, a histone deacetylase inhibitor, showed slower disease progression on ambulatory endpoints in boys ≥6 years with Duchenne muscular dystrophy (DMD) treated in the phase 3 EPIDYS trial and ongoing open-label extension (OLE). This analysis assessed upper limb function using the Performance of Upper Limb 2.0 (PUL 2.0). Observed changes from index (first post-givinostat initiation visit with a PUL entry score of 1-5 and an available PUL 2.0 total score; requiring a month 12 or 24 score) were compared with modeled counterfactual trajectories based on natural history.

METHODS: All OLE patients received givinostat. A validated prediction model based on the Dutch national DMD registry was applied using average index characteristics (PUL 2.0 score, ambulatory status, age) of patients on intermittent steroids to predict PUL 2.0 changes over time.

RESULTS: Of 207 OLE patients, 115 (mean [SD] age, 12.6 [2.6] years) were evaluable at month 12, and 96 (12.5 [2.6] years) at month 24. Observed mean (95% CI) PUL 2.0 changes were –0.78 (–1.58, 0.01) at month 12 and –2.26 (–3.11, –1.41) at month 24. Predicted counterfactual declines were –4.57 (–5.63, –3.52) and –8.55 (–10.33, –6.77), respectively. Predicted PUL 2.0 scores were lower than observed scores by 3.79 (2.47, 5.11; p<0.001) at month 12 and 6.29 (4.31, 8.26; p<0.001) at month 24.

CONCLUSIONS: Givinostat was associated with a slower decline in upper limb function compared with modeled natural history trajectories. Underlying differences in Dutch registry patients and givinostat-treated patients, such as steroid regimen, may contribute to the results.

KEYWORDS: Neuromuscular, Movement Disorders

431. Real-World Clinical and Genetic Profile of Duchenne Muscular Dystrophy in a Resource-Limited Setting

amal abu libdeh, Bushra Alawaisheh, Mahdiyah Shamallakh, Ryan Cappa, Amira Masri

OBJECTIVE: Objective: To characterize the clinical presentation, genetic spectrum, comorbidities, treatment practices, and ambulatory trajectories of patients with genetically confirmed Duchenne muscular dystrophy (DMD) followed at a tertiary pediatric neurology center in a low-resource country.

METHODS: Methods: This retrospective observational study included male patients with genetically confirmed DMD seen at Jordan University Hospital between January 2014 and December 2025. Clinical, demographic, laboratory, genetic, treatment, and outcome data were extracted using standardized forms, with caregiver contact to complete any missing information. Descriptive statistics summarized cohort characteristics, and Kaplan–Meier methods were used to analyze time-to-event outcomes.

RESULTS: Results: Seventy-one patients met inclusion criteria. Most were born at term (93.0%) without perinatal complications and presented with typical motor symptoms and examination findings. Creatine kinase levels were markedly elevated, with 70.4% ≥10,000 IU/L at presentation. Developmental comorbidities were frequent, including learning difficulties (36.6%) and speech delay (21.1%). Scoliosis was present in 33.8%. Cardiac and respiratory involvement were documented in a minority, although formal screening was often incomplete. Steroid therapy (prednisone or deflazacort) was the only disease-modifying treatment used, with variable adherence and frequent early discontinuation. Dystrophin gene deletions were the most common pathogenic variants, clustering in known mutational hot spots, with limited involvement of exons 20–40. Ambulatory outcomes showed substantial interindividual variability.

CONCLUSIONS: Conclusions: This cohort demonstrates heterogeneous disease trajectories, suboptimal screening for systemic complications, and inconsistent steroid use. Limited access to advanced therapies and fragmented multidisciplinary care highlight the need for standardized surveillance protocols and improved care delivery in resource-constrained settings.

KEYWORDS: Neuromuscular, Neurogenetics, Global Neurology

432. Bridging Knowledge Gaps in Duchenne Muscular Dystrophy: A Comparative Analysis of Educational Outcomes Among Neurologists and Pediatricians on Disease Pathophysiology and Therapeutic Mechanism of Action

Christine Considine, Pakinam Aboulsaoud, Thomas Finnegan, John Brandsema

OBJECTIVE: An online CME program was developed to educate neurologists and pediatricians on the scientific evidence for therapies approved for the management of DMD.

METHODS: The online CME activity consisted of a 30-minute video lecture featuring a pediatric neuromuscular expert. Educational effect was assessed by comparing a matched sample of neurologists' and pediatricians' responses to four identical questions pre- and post-activity. A paired-samples t-test identified significant differences between pre- and post-assessment responses. Cohen's *d* was used to calculate the effect size of the online education. Data were collected between August 13, 2025 and November 25, 2025.

RESULTS: Among learners, neurologists demonstrated a moderate educational effect (n=45; d=.78, P<.001) and pediatricians demonstrated a large educational effect (n=73; d=1.0, P<.001). The following areas showed significant (P <.05) pre- vs post-educational improvements for both specialties: pathophysiologic consequences of dystrophin loss, the mechanism of action (MOA) of givinostat, and the MOA of vamorolone. Though the pre-education awareness of the pathophysiologic mechanism of pseudohypertrophy in DMD was similar for both specialties, only pediatricians demonstrated a significant post-education improvement in knowledge of this topic. Participation in the activity resulted in 44% of neurologists and 45% pediatricians reporting an increase in confidence regarding their ability to summarize

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clinical trial data for pharmacotherapies approved for the management of DMD

CONCLUSIONS: The results indicated that a CME-certified 30-minute video lecture was effective at improving knowledge of pathophysiology and therapeutics of DMD among both neurologists and pediatricians. Future education should continue to emphasize the MOA of currently available treatments for DMD.

KEYWORDS: Neuromuscular, Education

433. Same Genotype, Different Phenotype: Intrafamilial Variability in Spinal Muscular Atrophy

Jamie Solis, Farida Abid

OBJECTIVE: To highlight phenotypic variability in siblings with identical SMN1 mutations and SMN2 copy number, emphasizing the need for individualized clinical assessment and genetic evaluation in SMA beyond predicted genotype-based expectations.

METHODS: Case report and literature review.

RESULTS: A 5-year-old male with progressive weakness presented for evaluation after developing increasing difficulty with ambulation over the past two years. He was previously able to walk independently but developed gait instability following a fall resulting in a femur fracture and has since had gradual functional decline, though he remains ambulatory. Notably, he has a 1-year-old brother who presented earlier in life with respiratory distress at 4 weeks of age requiring intubation and ICU admission and was diagnosed with SMA on newborn screening. Confirmatory testing in the younger sibling revealed a homozygous pathogenic deletion of exon 7 in the SMN1 gene with two copies of the SMN2 gene. Both parents were identified as obligate carriers. Given the family history, the older sibling underwent genetic evaluation and was found to have a homozygous pathogenic deletion involving the entire coding sequence of SMN1, also with two copies of the SMN2 gene, despite a milder clinical phenotype and preserved ambulation.

CONCLUSIONS: Siblings with identical SMN1 deletions and the same SMN2 copy number can demonstrate markedly different clinical phenotypes, underscoring the limitations of genotype alone in predicting disease severity. This case highlights the role of additional genetic modifiers and environmental factors in SMA expression and reinforces the importance of individualized evaluation and management, even within the same family.

KEYWORDS: Neuromuscular

434. Late-diagnosed carnitine palmitoyltransferase II deficiency identified through clinical presentation of disease

Kate Simmons, Andres Berardo, Gonzalo Nieto, Guillermo Guilbert, Javier Muntadas Rausei, Daniela Karall, André Santos Pessoa, Daniel Almeida do Valle, Lucas Alves, Romina Soledad Heredia, Sarah Dyack, Gisel Gordillo-González, Harry Pachajoa, Hironori Kobayashi, Esmeralda Rodrigues, M Cardoso, Mariana Pintalhão, Mónica García Peris, Paula Sánchez Pintos, Alexander Laemmle, Brian Shayota, Anabela Bandeira, Vanessa Rangel Miller, Robyn Hylind

OBJECTIVE: Carnitine palmitoyltransferase II deficiency (CPT II), a long-chain fatty acid oxidation disorder, is a rare, life-threatening, autosomal recessive condition of energy metabolism. CPT II is identified through newborn screening (NBS) or clinically through elevated plasma acylcarnitine profiles, hypoglycemia, cardiomyopathy, cardiac arrhythmias, and/or neuromuscular signs. The objective of this study is to highlight the diagnostic journey of CPT II identified by clinical manifestations.

METHODS: A 2025 global online survey assessed presentation, management, and NBS results/status from cases of late-diagnosed (not via NBS) CPT II with no family history. Patient/family consents were obtained.

RESULTS: Forty-six included patients from fourteen countries had a mean (range) age at diagnosis of 18.1 (0-54) years. Thirty-seven reported clinical signs leading to diagnosis: myalgia (27/37), rhabdomyolysis (30/37), elevated creatine kinase (21/37), myoglobinuria/exercise intolerance/muscle weakness (25/37), hypoglycemia (7/37), liver dysfunction (7/37), cardiac issues (2/37). After diagnosis, 10/46 were hospitalized; 44/46 followed a nutritional plan; 31/46 used MCT, and 6/46 used triheptanoin. Manifestations included neuromuscular signs (27/46), rhabdomyolysis (17/46), hypoglycemia (5/46), liver dysfunction (3/46), gastrointestinal issues (6/46), and cardiovascular issues (1/46).

CONCLUSIONS: Individuals with late diagnosis endure clinical symptoms including neuromuscular signs, driving them to seek diagnosis and/or treatment and continue to have a high disease burden after diagnosis. This survey illustrates the importance of early diagnosis of CPT II, particularly via NBS.

KEYWORDS: Neuromuscular, Neurometabolic, Neurogenetics

435. Global Seroprevalence of Anti-AAV9 Antibodies: A Retrospective Analysis Across Multiple Geographic Regions and Ages

Elizabeth Nguyen, Shobha Purushothama, Nina Vujović, Matthew Meriggioli, Shruti Mokashi, Umesh Kumar, Brooke Bailey

OBJECTIVE: Adeno-associated virus 9 (AAV9) is a delivery vector for gene therapies, including onasemnogene abeparvovec for spinal muscular atrophy. Elevated seropositivity for anti-AAV9 antibodies may affect the safety and efficacy of systemic AAV9-based therapies. Estimates of anti-AAV9 seroprevalence remain limited and challenging to compare due to methodological differences. Here, we describe anti-AAV9 antibody seroprevalence across geographies and ages.

METHODS: Anti-AAV9 antibody titers were retrospectively analyzed in participants aged ≥2 years from the Regions of the Americas (AMR), European Region (EUR), South-East Asian Region (SEAR), and Western Pacific Region (WPR). Participants had any health status/diagnosis. To identify participants with elevated seropositivity (titer >100 units), serum samples were assessed using an identical validated electrochemiluminescent assay (Navigate Labs).

RESULTS: Serum was obtained from 328 children (52.1% male) and 714 adults (62.0% male) across 19 countries

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(AMR 32.1%; EUR 38.8%; SEAR 9.0%; WPR 20.2%). Each 8-year age range (2–66+ years) included ≥60 participants; children were evenly split across 2-year age ranges. Overall, 61/328 (18.6%) children and 176/714 (24.6%) adults had elevated seropositivity; by region, elevated seropositivity was 87/334 (26.0%; AMR), 80/404 (19.8%; EUR), 18/94 (19.1%; SEAR), and 52/210 (24.8%; WPR). For children, odds of elevated seropositivity were lower among 12–17 vs 2–11 years (OR 1.81; 95% CI, 1.00–3.28); by region, elevated seropositivity was 25.2% (AMR) and 14.5% (EUR).
CONCLUSIONS: Data trended towards increased seropositivity with age; overall, no difference was observed across geographies, but seropositivity was higher in AMR than EUR for children. These findings provide valuable insights to inform use of AAV9-based therapies.
KEYWORDS: Neuromuscular, Movement Disorders, Neurogenetics

436. Long-term safety and efficacy of resamirigene bilparvovec for the treatment of X-linked myotubular myopathy (ASPIRO)

Jennifer Petrolati, Nancy Kuntz, Rahul Gentyala, Julie Coats, Atsuki Hashimoto, Astrid Blaschek, Wolfgang Müller-Felber, Carsten Bönnemann, Barbara Smith, Andreea Seferian, Lucy James, Perry Shieh, James Dowling

OBJECTIVE: ASPIRO (NCT03199469) assessed resamirigene bilparvovec (rAAV8-desmin-hMTM1), a gene replacement therapy that expresses human *MTM1* in muscles in male children aged <5 years with X-linked muscular dystrophy (XLMTM) requiring mechanical ventilator support. Updated results with >5 years' follow-up are reported.
METHODS: Participants (pts) received 1 intravenous infusion of resamirigene bilparvovec at a lower (1.3×10^{14} vector genomes [vg]/kg) or higher dose (3.5×10^{14} vg/kg). The primary efficacy outcome was change from baseline to week 24 in hours of daily ventilator support. Enrollment ceased after deaths in 1 lower-dose and 3 higher-dose pts with cholestatic liver failure. One lower-dose pt withdrew during long-term follow-up; follow-up of the remaining 19 pts (5 lower-dose, 14 higher-dose) up to 10 years is ongoing.
RESULTS: At data cutoff, median follow-up was 5.76 years (range, 3.59–7.25) for ongoing pts (n=19). At month 60, ventilator independence was achieved by 5/6 (83.3%) evaluable lower-dose pts and 10/13 (76.9%) higher-dose pts. Of the 4 without independence, 3 required fewer daily ventilator support hours at month 60 vs baseline. Since the primary analysis, there were no additional deaths. Serious treatment (tx)-related hepatobiliary adverse events (AEs) occurred in 2 lower-dose and 7 higher-dose pts (first onset 6–162 days post-dose). Four pts had tx-related hepatobiliary AEs ≥1 year post-dose; myocarditis was a tx-related AE in 1 pt per group, consistent with the primary analysis.
CONCLUSIONS: Male children with XLMTM treated with resamirigene bilparvovec showed continued improvement in respiration and motor function, with no further deaths and a favorable safety profile.
KEYWORDS: Neuromuscular

437. Adherence to Home-Based Exercise Among Youth with Neuromuscular Disorders: Insights from a Scoping Review

Allison Grangé, Jennifer Boulais, Maryam Oskoui, Danielle Levac

OBJECTIVE: To map the current state of knowledge on home-based exercise programs (HEPs) designed to promote pulmonary and/or motor function in children and youth with neuromuscular disorders (NMDs), and to identify factors influencing adherence.
METHODS: We conducted a scoping review across MEDLINE, CINAHL, Embase, PsycINFO, and Web of Science, including studies published between 2010 and 2025. Eligible studies involved children aged 4–18 years with NMDs participating in HEPs targeting pulmonary or gross motor function. Data extraction focused on HEP characteristics, adherence-related terminology and measures, and reported facilitators, barriers, and strategies related to adherence.
RESULTS: We included 41 studies (mean age 10.4, ± 4.1years). Median HEP duration was 12 weeks (range 3-76) with 2 to 7 sessions/week. HEP included conventional therapy, exergames, rehabilitation-specific devices and dance or yoga -based approaches. Adherence-related concepts appeared in 31 studies, with heterogeneous terminology (i.e., 'compliance', 'therapy completion'). Thirty-three studies assessed adherence, primarily through training logs or drop-out. Key facilitators included fit into daily routine and perceived enjoyment; barriers included time constraints and logistical challenges. Strategies mainly relied on caregiver or therapist involvement.
CONCLUSIONS: HEPs for youth with NMDs are diverse and remain largely grounded in conventional approaches. The reliance on external support strategies, along with the terminology used, suggests that researchers and clinicians conceptualize adherence from an organizational perspective, with limited focus on youth-centered characteristics such as motivational factors.
KEYWORDS: Neuromuscular, Telemedicine

438. Exploring user experience and engagement with a Home-Based Exergame Among Youth with Spinal Muscular Atrophy: Preliminary Findings from a National Clinical Trial

Allison Grangé, Maryam Oskoui, Ariane Belzile, Sarah Deckarm, David Herzig, Danielle Levac

OBJECTIVE: *Tales from the Magic Keep* is a custom-designed exergame developed to promote upper limb function in children and youth with spinal muscular atrophy (SMA) receiving disease-modifying therapy. As part of a multicenter randomized controlled trial evaluating the impact of 8 weeks of home-based exergaming (20min, 3x/week) on patient-reported and functional outcomes, this study explores user experience and engagement during and following intervention
METHODS: Software and sensor-based metrics (frequency, duration and level of gameplay, including calibration time)

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quantified game interaction. Following the 8-week intervention, participants completed the Intrinsic Motivation Inventory and the User Engagement Scale (Likert scales) and underwent semi-structured individual interviews.
RESULTS: Six participants were included (Mean age 13.8 ± 3.2 years). Five participants completed the full 8 weeks; one stopped at week 6 due to technical issues, and one completed 7 of the 8 weeks. Mean gameplay duration per session, including calibration, was 24.2 ± 9.1 minutes (120 % of the prescribed dose), with 2.2 ± 1.1 sessions per week. Recalibration occurred in 19.4 % of sessions and accounted for 78 % of session time. Intrinsic Motivation Inventory scores indicated moderate motivation (interest/enjoyment 4.5/7; perceived competence 4.8/7), while the User Engagement Scale showed moderate engagement overall (3.5/7), with the highest scores in the aesthetics domain (4.9/7).
CONCLUSIONS: Game features appeared to support engagement, with participants exceeding target duration despite below target session frequency. However, frequent recalibration episodes represent significant technical burden with potential to undermine adherence and motivation. These preliminary findings will be further contextualized through forthcoming qualitative interviews with participants.
KEYWORDS: Neuromuscular, Telemedicine

439. Treatment of Steroid-Resistant Hepatic Injury in Spinal Muscular Atrophy following Onasemnogene Abeparvovec-Xioi with Sirolimus and Ursodeoxycholic Acid

Lily Devlin, Sumit Verma, Nitika Gupta

OBJECTIVE: This case demonstrates the effective use of sirolimus and ursodeoxycholic acid to treat acute hepatic injury secondary to onasemnogene abeparvovec-xioi gene therapy. A female infant with a positive newborn screen for spinal muscular atrophy (three SMN2 copies) and elevated anti-AAV9 antibodies (1:100) received intrathecal nusinersen. At four months of age, maternally transferred AAV9 antibodies normalized, and intravenous gene therapy was administered with oral steroids. Four weeks later, the patient developed cholestatic liver injury that persisted despite receiving high-dose intravenous steroids. Sirolimus and ursodeoxycholic acid were added when cholestatic liver injury worsened.
METHODS: A patient with SMA was diagnosed and treated at a tertiary care children's hospital. Timing of interventions and laboratory data were obtained by retrospective chart review.
RESULTS: Serum AST, ALT, and GGT levels were normal for three weeks following gene therapy before acutely rising. At the time of intravenous steroid initiation, AST and ALT were five and seventeen times the upper limit of normal, respectively. Bile acids were also elevated. Transaminase and GGT levels stabilized briefly following intravenous steroids before increasing further. After adding sirolimus and ursodeoxycholic acid, ALT improved to less than twice the upper limit of normal. GGT and AST normalized.
CONCLUSIONS: In cases of liver injury associated with gene therapy in SMA, sirolimus and ursodeoxycholic acid may improve immune-mediated and bile acid-mediated liver injury when steroids alone are insufficient. Long-term liver health will be monitored with FibroScan. This case was limited by lack of liver biopsy to confirm CD8+ T-cell-mediated injury in support of using sirolimus.
KEYWORDS: Neuromuscular

440. Early-Onset Hereditary Spastic Paraplegia (SPG3A) Misdiagnosed as Diplegic Cerebral Palsy in a Child with Multigenerational Family History and Normal Birth

Ahmed Mohamed, Eric Strong

OBJECTIVE: To illustrate the critical role of genomic diagnostics in differentiating hereditary spastic paraplegia (HSP) from spastic diplegic cerebral palsy (CP) in a pediatric patient with a normal birth history and strong family history of motor impairment.
METHODS: We report a 3-year-old boy whose progressive spasticity and developmental delays were initially attributed to CP. Two critical clues—an unremarkable term birth and a striking three generation family history of gait impairment—prompted renewed evaluation. These findings led to whole exome sequencing (WES) for the patient and parents.
RESULTS: WES identified a pathogenic ATL1 variant (p.-Val253Phe), confirming Hereditary Spastic Paraplegia type 3A. This single molecular finding unified the diagnosis for the child, his affected father, and two brothers, reframing their medical history from presumed birth injury to a shared inherited condition.
CONCLUSIONS: Hereditary Spastic Paraplegia should be recognized as a key differential diagnosis in pediatric spastic diplegia, particularly when perinatal history is normal or family history is positive. This case underscores the importance of early genomic testing to reduce diagnostic delays and avoid misdiagnosis. Establishing a molecular diagnosis enables precise prognostication, targeted therapies, and informed genetic counseling.
KEYWORDS: Neuromuscular, Cerebral Palsy, Neurogenetics

441. ATYPICAL DIABETIC NEUROPATHY: An Interesting Case of Presumed Diabetic Lumbosacral Radiculoplexus Neuropathy in an Adolescent Patient with Type 2 Diabetes Mellitus

Carla Cardona Valle, Emily Emerson, Mariam Hull

OBJECTIVE: Diabetic lumbosacral radiculoplexus neuropathy (DLRPN) is a rare presentation of diabetic neuropathy resulting from inflammatory microvasculitis causing ischemic nerve injury, typically reported among older adults with Type 2 Diabetes Mellitus (T2DM). We aim to highlight a case of atypical neuropathy in an adolescent with T2DM and DLRPN diagnosis.
METHODS: A 16 yo male with hypertension, dyslipidemia, and T2DM presented with 1 month of sudden-onset, progressive lower extremity pain limiting ambulation, initially over the left hip and anterior thigh, later extending to the feet and becoming bilateral. Pain described as stabbing, burning,

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reproducible to touch. No bowel or bladder dysfunction. DM previously uncontrolled; now on insulin and empagliflozin; recent 80lb weight loss and HgA1c drop from 11% to 6.9% over 1 month. Neurological examination positive for allodynia, decreased vibratory sensation over bilateral lower extremities, and steppage gait without drop.
RESULTS: Pain managed unsuccessfully with NSAIDs and gabapentin. Neuropathy work-up initiated. Negative heavy-metal screen. Adequate B12 and B9 levels. MRI lumbar spine without abnormalities. EMG/NCS showed axonal sensory-motor polyneuropathy affecting upper and lower extremities; no abnormal rest potentials. Comprehensive neuropathy panel revealed no pathogenic variants. IV methylprednisolone for 5 days provided rapid improvement of clinical presentation. Residual pain managed with amitriptyline.
CONCLUSIONS: Although typically reported in adults, DLRNP should be considered for T2DM pediatric patients with rapid weight loss and large drop in A1C presenting with atypical neuropathy and weakness of lower extremities.
KEYWORDS: Neuromuscular, Neuroimmunology

442. A Compilation of MEGF10 Variant Pathologies and an In Silico Analysis of the MEGF10 Protein

Rachel Hellmann Whitaker, Seth Stafki, Peter Kang

OBJECTIVE: Multiple epidermal growth factor 10 (MEGF10) is central to numerous cellular processes. Biallelic pathogenic variants in *MEGF10* cause MEGF10 myopathy. The objective of our study was to analyze published and unpublished cases of MEGF10 myopathy for genotype-phenotype patterns and correlations, including an analysis of the implications of MEGF10 variants on protein structure.
METHODS: We conducted a literature review with the search terms "MEGF10 variants," "MEGF10 muscle," or "MEGF10 myopathy", supplemented by two unpublished cases. We collected clinical and genetic information. The *in silico* analysis determined the impact of each variant on MEGF10 protein structure, using SwissProt, PyMol Molecular Graphics, and POV-ray.
RESULTS: We identified 30 unique variants in 32 affected individuals. MEGF10 myopathy displays a broad phenotypic spectrum, with the age of onset ranging from birth to 61 years: 9 congenital-onset, 10 childhood-onset, and 11 adult-onset. The presenting symptoms include hypotonia, diaphragmatic weakness, and areflexia. Of the 30 variants in *MEGF10*,12 variants affect cysteine residues, thus disrupting disulfide bonds. The Y1030 and Y1048 residues serve as phosphorylation sites that may be involved in interactions with NOTCH1.
CONCLUSIONS: The majority of MEGF10 myopathy cases have congenital or childhood onset, but some occur in adulthood, suggesting that this diagnosis should be considered in all age groups. Emerging data suggest that disruption of disulfide bonds due to variants affecting cysteine residues is a common disease mechanism in MEGF10 myopathy.
KEYWORDS: Neuromuscular, Neurodevelopmental Disorders, Neurogenetics

443. Optimizing detection of respiratory dysfunction in pediatric-onset facioscapulohumeral muscular dystrophy

Natalie Katz, Seth Friedman, Michaela Walker, Brianna Brun, Rebecca Clay, Katy deValle, Kate Eichinger, Maya Hatch, Dorris Leung, Leann Lewis, Rabi Tawil, Ian Woodcock, Mai ElMallah, Jeffrey Statland

OBJECTIVE: The overall goal is to identify risk factors that predict respiratory dysfunction in pediatric-onset facioscapulohumeral muscular dystrophy (FSHD). Over half of individuals with FSHD develop symptoms in childhood (≤ 18 years old), and early-onset disease (≤ 10 years old) is associated with a more severe phenotype, faster disease progression and younger age at loss of ambulation. Neuromuscular weakness of the thoracic muscles contributes to impaired respiratory function. Children with FSHD are therefore at high risk for respiratory complications, yet respiratory dysfunction in pediatric-onset FSHD remains uncharacterized. Quantitative muscle fat fraction (qFF) measured by whole-body magnetic resonance imaging (WB-MRI) has emerged as a promising imaging biomarker in FSHD but has not been used to understand how changes in qFF influence respiratory function.
METHODS: Genetically confirmed children with FSHD enrolled in the ongoing, prospective pediatric FSHD natural history study (NCT04635891) complete pulmonary function testing (PFT) and WB-MRI every 6 months for 24 months. Baseline results from the first 10 subjects will be presented. Statistical analysis will include descriptive statistics and Pearson or Spearman correlations where appropriate.
RESULTS: Outcomes will include baseline disease characteristics, quantification of mean qFF of select muscles of respiration and PFT values, as well as correlations between PFT and qFF of the respiratory muscles.
CONCLUSIONS: This novel proposal will be the first to evaluate the impact of pediatric onset FSHD on individual muscles of respiration and will inform clinicians on opportunities for early intervention to prevent side effects of respiratory dysfunction.
KEYWORDS: Neuromuscular, Neuroimaging, Early Stage Investigator

Neuro-oncology

444. Quarter-Century Analysis of Mortality Trends and Disparities Related to Primary Nervous System Tumors among Pediatric Population in the United States – A Nationwide CDC WONDER Study

Anosh John, Martin McCandless, Faraz Azhar, Maira Shahid, Saad Ahmed Nadeem, Syeda Samar

OBJECTIVE: Malignant nervous system tumors are one of the major causes of mortality among the pediatric population. Current literature lacks the sociodemographic mortality trends and disparities in the United States (US). This study aims to identify these trends over the past 25 years.
METHODS: We analyzed the mortality data using the CDC WONDER database, extracting age-adjusted mortality rates (AAMR) per 100,000 population. The age range was

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1-14 years. Using the specific ICD-10 codes, cases were identified where a malignant, primary central or peripheral nervous system tumor was listed as the underlying or contributing cause of death. Mortality trends by year, sex, and race were evaluated. Joinpoint regression was used to calculate the annual percent change (APC) in AAMR with 95% confidence intervals (CI).

RESULTS: From 1999 to 2024, a total of 11,715 deaths occurred with an overall average AAMR of 0.74/100,000. AAMR decreased from 0.77 (0.70 to 0.84) in 1999 to 0.70 (0.63 to 0.76) in 2024 (AAPC: -0.59; 95% CI: -0.82 to -0.36; $p < 0.001$). Males had a higher AAMR (0.77; 95% CI: 0.67 to 0.87) than females (0.71; 95% CI: 0.62 to 0.81). Both Males (AAPC: -0.64; 95% CI: -1.23 to -0.06; $p < 0.05$) and females (AAPC: -0.48; 95% CI: -0.73 to -0.24; $p < 0.05$) showed declining trends. Among racial subgroups, the White population had the highest AAMR (0.76).

CONCLUSIONS: The study shows that the mortality related to primary nervous system malignancies has significantly decreased over the past 25 years among the pediatric population.

KEYWORDS: Neuro-oncology, Diversity, Equity, Inclusion, Global Neurology

445. Alternating MAPK and mTOR Signaling Pathway Inhibition in Refractory Pediatric Low-Grade Glioma: A Case Series Review

Nathaniel Zaroban, Adam Esbenshade

OBJECTIVE: Pediatric low-grade gliomas (pLGGs) are most commonly generated by aberrations in the Ras/Raf/MEK/ERK MAPK or the PI3K/AKT/TSC/RHEB/mTOR (mTOR) cell signaling pathways. Pre-clinical studies show that the MAPK and mTOR pathways are intricately interconnected with bidirectional regulation and are heavily sensitive to influences in the other. We aimed to report cases that suggest this biochemical signaling interplay may be clinically relevant in medical pLGG management.

METHODS: This is a retrospective case series of three patients diagnosed with pLGGs that proved refractory to numerous traditional chemotherapies +/- surgical debulking and radiation therapy before sequentially receiving chemotherapy agents targeting MAPK and mTOR inhibition in variable order.

RESULTS: Patient one has a neurofibromatosis type-1 associated optic nerve pilocytic astrocytoma that responded to repeat courses of sirolimus before on-therapy progression and is now sustaining response to selumetinib. Patient two has a thalamic BRAFV600E+ desmoplastic infantile ganglioglioma that responded to selumetinib before on-therapy progression, then sustained response to sirolimus before on-therapy progression, now has responded to combination dabrafenib and trametinib. Patient three has a thalamic BRAFV600E+ ganglioglioma that responded to combination dabrafenib and trametinib before progression then demonstrated response to sirolimus.

CONCLUSIONS: Each patient demonstrated response to inhibition of one pathway, progressed, then subsequently responded to inhibition of the other pathway. Together, these cases suggest that bidirectionally, inhibition of one pathway could cause upregulation of the other, leading to progression, and subsequent response to inhibition of the newly upregulated pathway. These findings warrant clinical investigation to assess potential benefit of standardly alternating MAPK and mTOR inhibition in refractory pLGG.

KEYWORDS: Neuro-oncology

446. Relationship Between Endocrine Abnormalities and Neuro-Oncologic Disease Burden in Children, Youth, and Young Adults with Neurofibromatosis Type 1

Lauren Hinkley, Evin Rothschild, Grace Oh, Carlos Romo, Yasmin Akhtar, Kathryn Lemberg

OBJECTIVE: Neurofibromatosis type 1 (NF1) is a multisystem disorder characterized by neurocutaneous and oncologic manifestations. While optic pathway gliomas (OPGs) have been associated with hypothalamic-pituitary dysfunction, it is unknown whether endocrine diagnoses are associated with broader neuro-oncologic burden in NF1. This project aims to evaluate the relationship between neuro-oncologic and endocrine diagnoses in children, adolescents, and young adults (CAYA) with NF1.

METHODS: We conducted an IRB-approved retrospective cohort study of CAYA (ages 0-30 years) with NF1 evaluated at a single tertiary care center between 2013 and 2023. Patients were identified through electronic medical record queries using diagnostic codes; NF1 diagnosis was confirmed by chart review. Demographics, and clinical data regarding oncologic and endocrinologic diagnosis were collected. Associations were evaluated using chi-square and Fisher's exact tests.

RESULTS: Five hundred eighty-nine patients were identified. Neuro-oncologic diagnoses included OPG in 116 (20%), glioma in 74 (13%), plexiform neurofibroma (pNF) in 335 (57%), and malignant peripheral nerve sheath tumor (MPNST) in 39 (7%). Endocrine abnormalities included precocious puberty in 22 (4%), delayed puberty in 8 (1%), and short stature in 171 (29%). Significant associations were found between OPG and gliomas with precocious puberty ($p=0.002$ and $p=0.001$, respectively). No significant associations were identified between pNF or MPNST and queried endocrine diagnoses.

CONCLUSIONS: Significant associations were observed between CNS tumors and precocious puberty. Future investigations include examination of the timing of precocious puberty diagnosis relative to CNS tumor diagnosis, tumor location, and treatment patterns. Increased understanding of endocrine dysfunction may guide monitoring and promote earlier treatment.

KEYWORDS: Neuro-oncology, Neuro-Cutaneous Disorders

447. Asymmetry of Motor Cortical Excitability in Brain Tumor Patients Identified by Navigated Transcranial Magnetic Stimulation (nTMS)

Max Goodsell, Basanagoud Mudigoudar, Radha Kodali, Negar Noorizadeh, Paul Klimo, Nir Shimony, James Wheless, Shalini Narayana

OBJECTIVE: Network plasticity in patients with brain tumors remains incompletely understood. This study aimed

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to evaluate neural excitability using nTMS, focusing on motor threshold (MT) and its association with tumors-related factors.

METHODS: Retrospectively, 89 patients were identified with brain tumors who underwent pre-surgical nTMS mapping. Patients were categorized as newly diagnosed brain tumors (NBT; n=52; 14.7 ± 8.3 years; 21 female), partially treated/recurrent brain tumors (PRBT; n=20; 13.6 ± 7.8 years; 9 female), and tumor-related epilepsy (TRE; n=17; 15.3 ± 7.7 years; 5 female). MT was measured in both the tumor and tumor free hemispheres, and lesion-side excitability was defined as the ratio of lesion to healthy MT (MTLesion/ MTHealthy). Group differences were assessed using Student's t-tests and chi-square tests.

RESULTS: Within the NBT group, high-grade tumors demonstrated lower MT ratios compared to low-grade tumors (0.91 vs. 1.02; p=0.037), consistent with relatively increased excitability. Tumor proximity to the motor cortex/ corticospinal tract was not associated with MT ratio. Compared to the combined NBT and PRBT cohorts, the TRE cohort had a higher proportion of high-grade tumors (71% vs. 26%; p=0.00029), more tumors located contralateral to the dominant hemisphere (82% vs. 43%; p=0.00024), and longer disease to treatment duration (8.28 ± 6.58 vs. 1.92 ± 2.79 years; p<0.0002).

CONCLUSIONS: Our findings show that brain tumors are associated with the altered cortical excitability, tumor grade and disease duration as potential contributing factors. These findings may help inform the management of tumor-related epilepsy and support the development of future prediction models.

KEYWORDS: Neuro-oncology, Epilepsy

448. Neurodevelopmental and oncologic characteristics of NF1-microdeletion syndrome

Ponni Velmurugan, Sofia Ladley, Emily Groopman, Joyce Turner, Stephanie Middleton, Karin Walsh, Sinan Turnacioglu, Benjamin Siegel

OBJECTIVE: NF1-microdeletion syndrome (NF1-MD), defined as a 17q11.2 gene deletion inclusive of the *NF1* gene, is a rare but clinically significant NF1 subtype with a more severe clinical course. We aimed to describe the neurodevelopmental and oncologic characteristics of a local NF1-MD patient population.

METHODS: This is a single-institution, retrospective study of patients with NF1-MD. Neurodevelopmental and oncologic features were abstracted from clinical records. NF1-MD patients with comprehensive neuropsychologic testing were matched to NF1 controls with intragenic NF1 alterations without established phenotypic associations. Differences in Full Scale IQ (FSIQ) were assessed with one-sided statistical tests based on an a-priori hypothesis of lower FSIQ in the NF1-MD group.

RESULTS: Sixteen patients were included in the NF1-MD cohort (10 type-1, 2 type-2, 2 atypical, 2 undetermined); nine had completed neuropsychologic testing. Four patients had optic pathway gliomas, six had plexiform neurofibromas, and two had other gliomas; one had MPNST. Screening whole body MRIs were completed in six patients (median age 10.5, range 4-16 years), two of which identified internal plexiform neurofibromas. All patients exhibited developmental delay in ≥1 domain; three had autism and five had ADHD. The NF1-MD cohort demonstrated a mean FSIQ difference of -17 points (95% CI[-36.1, 2.1]; t(11) = -1.96, p=.038) compared to matched controls, corresponding to moderate-large effect size (*d*=-0.57).

CONCLUSIONS: Children with *NF1*-MD in this sample exhibit clinically meaningful tumor burden and neurodevelopmental impairment, underscoring the importance of genotype-informed risk stratification and early tumor and cognitive surveillance for children with *NF1*-MD. Larger, multisite studies are needed to clarify genotype-specific profiles.

KEYWORDS: Neuro-oncology, Neurodevelopmental Disorders

449. Natural Killer Cell Dysfunction in Pediatric Glioblastoma: Evidence of Tumor-Promoting Reprogramming

Meysam Ghanbari Saray, Goshgar Ismayilov, Sabina Jafarova, Areeba Zafar, Mahapara Shabir, Muhammad Awais, Muhammad Ashir Bhatti, Matin Ghods, Minhaalu Hassan Ali, Mohamed Layth Halawani

OBJECTIVE: Natural killer (NK) cells are critical immune effectors against tumors, yet recent studies reveal their functional plasticity in supporting malignancy. Glioblastoma (GBM), the most aggressive primary brain tumor, remains incurable with current therapies. While GBM is rare in children (<10% of pediatric CNS tumors), its prognosis remains uniformly fatal. This study investigates NK cell dysfunction in GBM pathogenesis with implications for pediatric neuro-oncology.

METHODS: NK cells were isolated from healthy donor peripheral blood (PB), GBM patient PB, and GBM tumor-infiltrating NK (TINK) cells. Comparative analyses included expansion capacity (14-day cultures), phenotypic characterization (flow cytometry), functional assays (cytotoxicity, tumor co-cultures), and tumor proliferation metrics (live-cell imaging).

RESULTS: TINKs constituted ≤0.5% of tumor immune infiltrate versus 8-12% in healthy brain (p<0.001). GBM-derived NK cells showed 3.2-fold lower proliferation versus healthy controls (p=0.008). Co-culture with NK cells increased GBM proliferation by 40±6% (p=0.003). Cytotoxic markers (NKG2D, CD107a, perforin, granzyme B) were significantly downregulated in TINKs (p<0.05), while immunosuppressive cytokines (IL-10, TGF-β) were elevated 2.5-fold (p<0.01).

CONCLUSIONS: Pediatric GBM induces profound NK cell dysfunction, converting tumor-infiltrating NK cells from tumoricidal to tumor-promoting effectors—a mechanism not previously emphasized in children. This finding reveals that successful immunotherapy for pediatric GBM may require not only activating NK cells but also reversing their GBM-induced reprogramming. Our work provides a rationale for NK-focused therapeutic development specifically for pediatric neuro-oncology.

KEYWORDS: Neuro-oncology, Neurogenetics, Neuroimmunology

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450. White matter trajectories in NF1 with and without glioma: a longitudinal diffusion MRI study

Ella Nettnin, Vishnu Nair, Lisa Bruckert, Cynthia Campen

OBJECTIVE: Gliomas occur in roughly 20% of children with neurofibromatosis type 1 (NF1). While white matter abnormalities are well-documented in NF1, it remains unclear whether the presence of glioma further impacts white matter microstructural development. We conducted one of the first longitudinal studies to examine whether the presence of glioma independently disrupts white matter developmental trajectories in NF1.

METHODS: Fourteen children with NF1 and glioma (ages 6.1–18.3 years, mean = 11.5; 46 scans) and thirteen without glioma (ages 1–17.8 years, mean = 9.2; 36 scans) underwent diffusion MRI at 3T (25 directions, b=1000 s/mm^2). Participants who received any tumor-directed therapies, including conventional chemotherapy or MEK inhibitor therapy, were excluded. Automated white matter tract (WMT) segmentation extracted fractional anisotropy (FA) from eight major white matter tracts. Linear mixed-effects models examined longitudinal FA change by group, controlling for age at first scan (significance threshold: $p<0.05$, uncorrected).

RESULTS: No significant group differences in longitudinal FA change were observed in any of the eight tracts examined (all $p>0.05$). Groups did not differ significantly in age at first scan ($p=0.13$).

CONCLUSIONS: The presence of glioma was not associated with differential longitudinal white matter microstructural changes in children with NF1-associated glioma compared to those without, suggesting that NF1 itself, rather than a focal low-grade glioma, is the primary driver of diffuse white matter pathology in this population. These findings are limited by modest sample size, and larger prospective studies are warranted to further characterize white matter development in NF1 and its associations with functional outcomes.

KEYWORDS: Neuro-oncology, Neuroimaging, Neuro-Cutaneous Disorders

451. A Silent Storm: Unmasking Subclinical Neurotoxicity during Blinatumomab Infusion in Infancy

Keamogetswe Rakolle, Rajeshwari Mahalingam, Melinda Fritz

OBJECTIVE: To report the first case of blinatumomab-associated neurotoxicity in an infant with KMT2A-rearranged B-ALL and highlight the critical gap in neurological surveillance tools for preverbal infants receiving immune effector cell therapy.

METHODS: A 5-week-old female presented with fever, rash, and hypoxemic respiratory failure. Flow cytometry confirmed KMT2A-rearranged B-ALL with CNS1 disease. She received induction chemotherapy per AALL15P1, then transitioned to modified Interfant-21 with triple intrathecal therapy. End-of-induction bone marrow biopsy demonstrated MRD negativity with WBC below 300, classifying her as medium-risk. She proceeded to blinatumomab consolidation per Interfant-21 at 15 mcg/m^2/day. Given the inapplicability of standard ICANS grading tools to preverbal infants, Pediatric Epileptology was consulted prospectively, and continuous vEEG monitoring was initiated at infusion onset.

RESULTS: On infusion day 2, concurrent with grade 2 cytokine release syndrome (CRS), vEEG demonstrated intermittent right temporal and parieto-temporal delta slowing at 2-3 Hz without epileptiform discharges or clinical seizures. Brain MRI was unremarkable. Blinatumomab was paused, and gabapentin initiated for neuro-irritability. The infusion restarted at a reduced dose following clinical stabilisation, with EEG normalisation by day 5 and up-titration to full dose over 7 days. The infant completed the 28-day course without recurrence. Subsequent neurodevelopmental trajectory remained age-appropriate.

CONCLUSIONS: This case represents the first reported evidence of blinatumomab-induced neurotoxicity in infancy; a subclinical electrophysiological abnormality temporally coinciding with CRS and undetectable by current clinical grading systems. As blinatumomab becomes standard in infant ALL protocols, we recommend: prophylactic continuous vEEG monitoring from infusion onset, a low threshold for dose interruption during CRS, and longitudinal neurodevelopmental surveillance.

KEYWORDS: Neuro-oncology, Epilepsy

Pediatric Demyelinating Disease

452. Phenotypic and neuroimaging description of individuals affected with SAMHD1-related Aicardi Goutières Syndrome

Laura Adang, Nicholson Modesti, Isabella Peixoto de Barcelos, Sarah Woidill, Francesco Gavazzi, Anjana Sevagamoorthy, Lauren Charlton, Peter Hong, Asako Takanohashi, Carlos Dominguez Gonzalez, Shih-Shan Lang, Lauren Beslow, Adeline Vanderver, Arastoo Vossough

OBJECTIVE: Aicardi Goutières Syndrome (AGS) is a heterogeneous interferonopathy caused by disruptions in RNA and DNA metabolism. Biallelic variants in Sterile alpha motif (SAM) and histidine-aspartate (HD) domain containing protein 1 (*SAMHD1*) are associated with moyamoya syndrome (MMS) and stroke in this subtype. Here, we describe the clinical course and unique cerebrovascular features in a cohort of *SAMHD1*-related AGS.

METHODS: Individuals with genetically-confirmed *SAMHD1*-related AGS were enrolled under the Myelin Disorders Biorepository Project protocol (n=32). Clinical data were extracted from medical records. Cerebral imaging studies were reviewed, and the composite cerebrovascular stenosis score (CVSS) was applied. Prospective functional outcomes were collected. Interferon signaling gene (ISG) scores were calculated as a biomarker of disease activity.

RESULTS: 46.9% (15/32) had evidence of cerebrovascular disease. Axial hypotonia and hypertension were more frequently observed in those with cerebrovascular disease ($p = 0.02$, 0.02). Neuroimaging demonstrated arterial ischemic changes, abnormal collateral vessel formation, and arterial stenosis (quantified by CVSS scoring) consistent with MMS in some. Individuals without cerebrovascular disease

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were more likely to develop cortical visual impairment ($p = 0.03$). Children with *SAMHD1*-related AGS were more likely to develop cerebrovascular disease compared to non-SAMHD1 genotypes ($p < 0.001$).

CONCLUSIONS: We described a cohort of patients with *SAMHD1*-related AGS, representing a distinct clinical subtype. Impaired communication function and the presence of hypertension were associated with an increased risk of cerebrovascular disease, including MMS, but weren't sufficient predictors of risk. Periodic cerebrovascular imaging may be warranted for surveillance; still, the evidence presented here is insufficient to support a screening interval.

KEYWORDS: Pediatric Demyelinating Disease, Neurometabolic, Neuroimaging

453. Blinded Cortex, Unaware Mind: A Rare Presentation of Childhood Adrenoleukodystrophy with Anton-Babinski Syndrome

Anton Charles, Shaun Nevil, Pabitra T, Chaitra C.S

OBJECTIVE: To highlight an atypical presentation of childhood-onset X-linked adrenoleukodystrophy (c-ALD) with progressive neuroregression and cortical blindness associated with Anton-Babinski syndrome, and to emphasize the importance of early recognition and screening in improving outcomes.

METHODS: A detailed clinical evaluation of an eight-year-old male child with progressive neurological decline was performed, including neurological examination, metabolic screening, and neuroimaging. Differential diagnoses were considered based on clinical features and excluded through targeted assessment. MRI brain and very long-chain fatty acid (VLCFA) analysis were used for diagnostic confirmation.

RESULTS: The child presented with insidious onset, progressive right-sided weakness followed by speech, cognitive, and visual decline. Examination revealed spasticity, motor aphasia, cortical blindness with preserved pupillary reflexes, higher sensory loss, and anosognosia suggestive of Anton–Babinski syndrome. MRI demonstrated bilateral symmetrical posterior white matter involvement, particularly affecting the splenium of the corpus callosum and adjacent regions. Metabolic evaluation showed elevated VLCFA levels, confirming the diagnosis of c-ALD. Given advanced disease and significant neuroregression, the patient was not a candidate for hematopoietic stem cell transplantation and was managed with glucocorticoid replacement, antispasticity measures, and supportive care.

CONCLUSIONS: This case underscores the aggressive and rapidly progressive nature of c-ALD and the narrow therapeutic window for curative intervention. Early clinical suspicion in male children with unexplained cognitive or behavioral decline is critical. Prompt VLCFA screening and genetic evaluation can facilitate early diagnosis, enabling timely intervention and family counseling, which are essential for improving prognosis and preventing disease progression in at-risk individuals.

KEYWORDS: Pediatric Demyelinating Disease, Neurogenetics, Neurometabolic

454. Long-term clinical outcomes in pediatric-onset multiple sclerosis: pilot multicenter data from the Network of Pediatric MS Centers

Claudia Gambrah-Lyles, Aaron Abrams, Leslie Benson, Jennifer Graves, Tanuja Chitnis, Timothy Lotze, Emmanuelle Waubant, John Rose, Grace Gombolay, Jennifer Yang, Lauren Krupp, Rebecca MacRae, Mary Rensel, Jan-Mendelt Tillema, Teri Schreiner, Melissa Wright, Gina Chang, US Network of Pediatric MS Centers

OBJECTIVE: Pediatric-onset multiple sclerosis (POMS) is associated with low early disability despite high relapse rates and greater MRI-lesion burden than adult-onset disease. However, long-term outcome data remain limited. We describe clinical, sociodemographic, and patient-reported outcomes of a POMS cohort with ≥5 years disease duration.

METHODS: Cross-sectional pilot study across three US Network of Pediatric MS Centers (NPMSC) sites. Participants with POMS diagnosis <18 years and disease duration ≥5 years were identified from the Pediatric MS and Demyelinating Disease (PeMSDD) database. Clinical data were extracted from the PeMSDD; sociodemographic and patient-reported outcomes were collected via structured, study-specific questionnaire. Participants were stratified as Young Adults (18–25) or Adults (26+).

RESULTS: 19 participants completed the questionnaires (14 young adults, 5 adults). Median onset age was 15.9 years (IQR 10.8–17.8) and median disease duration was 9.2 years (IQR 5.0–13.5). 78.9% were female and 84.2% were White. 57.9% were on high-efficacy DMTs and 31.6% on no DMT. After relapses, 85% reported complete or near-complete recovery. 89.5% reported no relapse in the two years prior to study enrollment. All reported persistent MS-related symptoms: 63.2% described mild impact on daily life, and 26.3% moderate-to-severe impact.

CONCLUSIONS: Clinical outcomes in this pilot cohort of POMS patients with median 9-years disease duration show low relapse activity - despite one-third not on DMT. Nevertheless, all reported persistent MS-related symptoms, suggesting ongoing disease burden despite clinical relapse stability. Enrollment is ongoing as larger studies are needed to identify and characterize determinants of long-term outcomes in POMS.

KEYWORDS: Pediatric Demyelinating Disease, Neuroimmunology, Lifespan Manifestations of Childhood Onset Conditions

455. Pediatric Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD) with Elevated Intracranial Pressure (ICP)

Nora Jandhyala, Alexander Jonokuchi, Lena Bell, Lauren Krupp, Kimberly O'Neill

OBJECTIVE: To describe demographic, clinical, radiologic features and outcomes of pediatric MOGAD presenting with elevated ICP.

METHODS: We retrospectively analyzed children at our center who met consensus criteria for MOGAD and were found to have elevated opening pressure or signs of increased ICP without a better explanation. Clinical characteristics,

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CSF findings, neuroimaging features, treatment course, and outcomes were evaluated.

RESULTS: Fourteen patients were included (9 female). Median age at presentation was 9 years (range 6 – 14 years). Median BMI percentile was 95.1%. Seven patients (50%) had preceding viral symptoms at a median of 1.4 weeks prior to presentation. All patients presented with headache. Six (42.9%) also had nausea/vomiting and seven (50%) had visual changes. Ten patients had elevated opening pressure (OP) documented; for those without recorded OP, 1 had tonsillar herniation and 3 had documented optic disc edema. Median OP was 36 cm H_2O. Idiopathic intracranial hypertension (IIH) and migraine were common early diagnoses. There was a median delay of 17 days from headache-onset to corticosteroids. Initial serum MOG titer was positive in all patients (median 1:130). All patients were treated with steroids, 64.2% with Diamox, 50% with IVIG and 28.6% with plasmapheresis. Diamox was continued for average of 2.2 months. Headaches remained at follow-up for a median of 4.9 months and completely resolved in 71% of cases.

CONCLUSIONS: MOGAD may initially present with unexplained intracranial hypertension and in these cases, is often misdiagnosed initially. With appropriate treatment and time, most headaches resolved by 6 months.

KEYWORDS: Pediatric Demyelinating Disease, Neuroimmunology, Early Stage Investigator

456. Factors Associated with Transition Readiness to Adult Care in Pediatric-Onset Multiple Sclerosis

Leah Loerinc, Olga Novak, Theresa Htun, Vishnuvardhan Thotakura, Aye Thant, Soe Mar, Claudia Gambrah-Lyles

OBJECTIVE: Understanding transition readiness is essential for optimizing transition to adult care in adolescents with chronic disease, yet its determinants remain poorly characterized in pediatric-onset multiple sclerosis (POMS). This study examined demographic, socioeconomic, and clinical factors associated with transition readiness in POMS as measured by the Transition Readiness Assessment Questionnaire (TRAQ).

METHODS: In this non-interventional, cross-sectional study, 29 patients with POMS at a pediatric tertiary care center completed the TRAQ 6.0, a validated instrument scored 1–5, with higher scores indicating greater transition readiness. Associations between TRAQ scores and age, sex, cognitive processing speed [Symbol Digit Modalities Test (SDMT)], and neighborhood deprivation [Area Deprivation Index (ADI)] were evaluated using Spearman rank correlations and Mann-Whitney U tests.

RESULTS: Mean age at assessment was 19.2 $\pm$ 2.2 years; overall median TRAQ score was 4.25 [IQR 3.60–4.90]. Appointment Keeping (mean 3.80 $\pm$ 1.2) and Medication Management (mean 3.8 $\pm$ 1.1) were the lowest-scoring domains. Females scored significantly higher than males (median 4.70 vs. 3.48, p=0.023). Age was strongly correlated with TRAQ score (ρ=0.703, 95% CI 0.454–0.851, p<0.001). No significant associations were found with SDMT (ρ=0.070, p=0.746) or ADI (p=0.398).

CONCLUSIONS: TRAQ scores in POMS were consistent with broader transition readiness literature, with higher scores among females and with older age. Neighborhood deprivation and cognitive processing speed were not associated with transition readiness. Patients with POMS may warrant closer attention in medication management and appointment keeping. Prospective multicenter studies are needed to validate these findings and inform evidence-based transition interventions in POMS.

KEYWORDS: Pediatric Demyelinating Disease, Lifespan Manifestations of Childhood Onset Conditions, Early Stage Investigator

457. Efficacy and safety of extended interval dosing of B-cell-depleting therapy for pediatric-onset multiple sclerosis

Quinton Mandle, Hie Kim, Bo Zhang, Leslie Benson

OBJECTIVE: Determine efficacy and safety of extended interval dosing (EID) compared to standard interval dosing (SID) of B-cell-depleting therapy (BCDT) in patients with pediatric-onset multiple sclerosis (pwPOMS). Ideal dose regimens for BCDT are unknown in pediatrics.

METHODS: PwPOMS treated at Boston Children's Hospital were reviewed retrospectively via database extraction and chart review. Patients were stratified by BCDT dosing interval into SID and EID groups. For an additional comparator, patients on reduced interval dosing (RID) were included.

RESULTS: 47 pwPOMS were included. Thirty-two (68%), nine (19%) and six (13%) patients were categorized as SID, EID and RID, respectively. Only two patients in the total group (both SID) had a relapse. Mean ARR for the entire group was extremely low (0.01) and was not significantly different among the three subgroups ($p = 0.635$). Annualized rate of new MRI activity for the entire group was low (0.08) and was not significantly different among the three subgroups ($p = 0.677$). EDSS at last follow up for the entire group (1.2) was low and not significantly different among the three subgroups ($p = 0.165$). Immunoglobulins and WBC parameters were similar between the three subgroups. IgG-hypogammoglobulinemia was uncommon, although occurred more frequently in the RID subgroup (N = 3, p-value = 0.033), possibly related to younger age. There were no associations between dosing interval type and incidence of total or severe infections, although 2 colitis cases and 2 tubo-ovarian abscesses occurred.

CONCLUSIONS: EID of BCDT maintains high efficacy and similar safety compared to SID and RID in treatment of pwPOMS.

KEYWORDS: Pediatric Demyelinating Disease, Neuroimmunology

458. Longitudinal qGRE evaluation detects white matter microstructure changes correlated with clinical symptoms in a case of pediatric tumefactive MS

Kelsey Barter, Claudia Gambrah-Lyles, Leah Loerinc, Jeramy Lewis, Navyasree Chenchu, Alexander Sukstansky, Dmitriy Yablonskiy, Soe Mar

OBJECTIVE: Pediatric-onset multiple sclerosis (POMS) is characterized by a high inflammatory lesion burden and

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frequent relapses, yet early recovery is often excellent with minimal disability. Conventional MRI often correlates poorly with clinical disability and does not adequately capture microstructural tissue damage and repair. Quantitative gradient recalled echo imaging (qGRE) provides 3D maps of R2t*, a tissue-cellular-specific subcomponent of R2* relaxation rate parameter. Within white matter (WM), R2t* reflects microstructural changes in tissue myelination and also provides a quantitative Tissue Damage Score (TDS). We performed serial qGRE in a 16-year-old patient with tumefactive POMS and compared TDS and WM R2t* distributions with conventional MRI and cognitive testing.

METHODS: Conventional MRI sequences were obtained, and R2t* maps were generated with qGRE. After co-registration, WM and lesion masks were created. An age and sex-matched healthy-control reference R2t* value was used to calculate lesion TDS and WM R2t* histograms.

RESULTS: The WM R2t* histogram at Visit 1 demonstrated increased fraction of low-R2t* voxels, which was further elevated at Visit 2 (2 months later), indicating increased tissue damage. By Visit 3 (4 months after Visit 2), the histogram peak shifted toward normal R2t*values, indicating tissue repair. Montreal cognitive assessment and Symbol Digit Modalities Test scores also improved at Visit 3. Conventional imaging showed minimal changes across visits.

CONCLUSIONS: In this patient, qGRE detected longitudinal changes in WM microstructure that correlated with cognitive performance and were not apparent on conventional MRI. Our results demonstrate qGRE as a potential tool to monitor disease activity in POMS.

KEYWORDS: Pediatric Demyelinating Disease, Neuroimmunology, Neuroimaging

459. Extended vs Standard Interval Anti-CD20 Dosing in Pediatric-Onset Multiple Sclerosis: Effects on Relapses and MRI Activity

Nora Jandhyala, William Gerber, Caleb Levitt, Lilly Hennessey, Alex Gerlach, Lauren Krupp, Kimberly O'Neill

OBJECTIVE: To compare relapse rates and new MRI lesion activity between standard interval dosing (SID) and extended interval dosing (EID) of anti-CD20 therapies in a cohort of pediatric-onset multiple sclerosis (POMS) patients.

METHODS: Retrospective chart review was conducted on 142 POMS patients treated with ocrelizumab and/or rituximab at a single MS center. Most patients were recommended to begin EID after at least 2 years on SID, although not all patients transitioned due to patient or provider preference. SID was defined as 6-month intervals of anti-CD20 medications. EID was defined as at least 2 doses of anti-CD20 medications spaced over 6 months apart. Annualized relapse rate (ARR) and new lesion rates were compared between 3 treatment time periods: pre–anti-CD20 initiation, SID, and EID.

RESULTS: 142 patients were analyzed (69% female). The median age of MS onset and anti-CD20 initiation were 15 and 17 years, respectively. The median duration of time on treatment was 4.4 years. 90 (63.4%) patients were "spaced" from SID to EID during the study period. Spaced patients were followed for a median of 23.7 months on EID. Rates of new events and new lesions significantly decreased on anti-CD20 therapies. There were no clinical relapses after spacing on EID. There was no significant difference in new T2 lesions on MRI (0.018 RID lesions/year vs 0.037 EID lesions/year, p=0.56) and there were no new enhancing lesions while on EID.

CONCLUSIONS: In this cohort of POMS patients, extended interval dosing of anti-CD20 therapies was not associated with increased risk of relapse or new MRI lesions.

KEYWORDS: Pediatric Demyelinating Disease, Neuroimmunology, Neuroimaging

460. Autoimmune Encephalitis Associated with Kikuchi Disease: EEG as an Objective Tool to Monitor Recovery

Hok Leong Chin, Jacob Braun, Stephen Lee, Moon Hee Hur

OBJECTIVE: Kikuchi disease is a rare, idiopathic necrotizing lymphadenitis. There are few reports of nervous system involvement in Kikuchi disease. We report a case of pediatric probable antibody negative autoimmune encephalitis in a patient with newly diagnosed Kikuchi disease.

METHODS: Case report was compiled through medical chart review.

RESULTS: A 12-year-old boy with autism with newly diagnosed Kikuchi disease by cervical lymph node biopsy after two months of fever and lymphadenopathy who presented with new-onset neuropsychiatric symptoms consisting of visual hallucinations, paranoia, disproportionate fearfulness, and insomnia. Neurological exam was non-focal. Workup was notable for CSF pleocytosis and elevated serum ESR. Serum and CSF autoimmune encephalitis antibody panels and brain MRI were negative. EEG showed frequent FIRDA, absence of stage II and III sleep architecture, and sleep patterns consisting of periods of high amplitude delta with epileptiform discharges alternating with runs of lower amplitude activity, concerning for cyclic alternating pattern of encephalopathy. Given CSF pleocytosis, he was empirically treated for autoimmune encephalitis with high-dose IV steroid and had significant clinical response. EEG was tracked daily before and during steroid treatment, demonstrating improvement that preceded meaningful clinical response, suggesting that EEG can be a powerful and objective tool for tracking clinical change, especially in cases where symptoms are subtle or variable.

CONCLUSIONS: This case illustrates a rare case of probable antibody negative autoimmune encephalitis Kikuchi disease. EEG could be utilized as an objective marker to monitor clinical change.

KEYWORDS: Pediatric Demyelinating Disease, Epilepsy

461. Immunotherapy Targeting Neuroinflammation in Pediatric MLD: Biomarker Response and Clinical Implications

Jasia Mahdi, Josaura Fernadez Sanchez, Kristen Fisher, Erin Morales, Joan Reynoso, Lisa Emrick, Caridad Martinez

OBJECTIVE: Metachromatic leukodystrophy (MLD) is a rare neurodegenerative disorder characterized by progressive motor and neurocognitive decline, with limited therapeutic options.

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METHODS: Four pediatric patients with MLD (median age 35 months [range: 33–43]) were evaluated. Three presented with late infantile and one with early juvenile onset MLD (median age of first symptoms: 24 months [range: 12–24]). All exhibited low arylsulfatase levels. MLD GMFC scores were 5 in three patients and 3 in one. Biomarkers baseline assessment (CXCL9, IL10, IL1B, IL6, TNF-alpha, INF-gamma, and NfL) revealed a pro-inflammatory profile; each patient had ≥2 elevated biomarkers (median=3). Median baseline NfL was 1,755 pg/mL (range: 1,719–2,786). Immunotherapy targeting neuroinflammation with concurrent anakinra (IL-1 receptor antagonist), tocilizumab (targets IL-6), and etanercept (TNF inhibitor) were administered every 2–3 weeks over a two-month period.

RESULTS: By day +60 post-intervention, all patients achieved normalization of CXCL9. Two patients showed marked reduction in NfL to below 1,000 pg/mL; median NfL at day 60 was 908 pg/mL (range: 826–2,877). Of the two patients with marked reduction of NfL levels, one recovered head control and the other verbal ability. All treated patients showed increased responsiveness to verbal stimuli and reduced irritability.

CONCLUSIONS: Immunotherapy targeting neuroinflammation in pediatric MLD resulted in normalization of key inflammatory biomarkers and reduction of NfL in select patients. Although early, these findings are promising to suggest a potential rationale for targeting neuroinflammation in MLD to improve motor and neurocognitive function, clinical symptoms, and quality of life for patients not eligible for gene therapy or stem cell transplant.

KEYWORDS: Pediatric Demyelinating Disease, Neuroimmunology

Practice Parameters

462. Integrating Pediatric Neurology into Newborn Follow-Up Clinics: A Framework for Longitudinal Care of Infants at Risk for Neurological Disorders

Monica Duran, Allison Ackerman, Jean Kammer, Janna Klein, Abby Neisius, Lindsey Stanek, Erin Thomson, Mary Walters, Amy Beutel, Anjali Rao, Janet Legare, Maria Stanley, Kathleen Kastner, Melisa Carrasco

OBJECTIVE: Infants requiring neonatal intensive care are at increased risk for neurological and neurodevelopmental conditions that often emerge after discharge. Yet pediatric neurology remains inconsistently integrated into post-NICU outpatient care, contributing to delayed diagnosis, missed opportunities for early intervention, and fragmented care during critical developmental windows. Here, we describe an integrated newborn follow-up (NFU) clinic model that bridges this gap by directly embedding pediatric neurology within longitudinal outpatient care.

METHODS: We conducted a descriptive characterization of clinic structure, workflows, and clinical roles within an integrated multidisciplinary NFU program at our center. A review of the literature on neonatal follow-up and integrated care models was performed to contextualize this approach and identify common principles relevant to implementation.

RESULTS: This work is primarily descriptive. The clinic sees an average of 393 patients annually, including infants born preterm, those with medically complex neonatal courses, and those with known or emerging neurological vulnerability. Embedding neurology enables proactive and coordinated care aligned with developmental timepoints. Core roles of neurology include early diagnosis, longitudinal surveillance, neurodiagnostic interpretation, medication management, and family-centered counseling. Interdisciplinary workflows facilitate earlier identification of evolving concerns and reduce reliance on referral-based care. Families express relief in having neurology present to clarify complex diagnoses introduced during the NICU course.

CONCLUSIONS: Integrating pediatric neurology into NFU clinics is a scalable model to extend brain-focused care beyond the NICU and improve early identification and care coordination for high-risk infants. Future directions include empirical evaluation of impacts on diagnostic timing, care utilization, and developmental outcomes.

KEYWORDS: Practice Parameters, Neonatal Neurology, Education

463. Co-Localized Pediatric Neurology Clinic Alters Healthcare Utilization

David Ritter, Amanda Hornbach, Paul Horn, Lauren Albor

OBJECTIVE: Socioeconomic barriers prevent access to pediatric specialty care. To address this, we created a co-localized pediatric neurology clinic at a high-risk pediatric primary care office (Hopple Street) and investigated the impact on healthcare utilization. New neurology referrals from Hopple Street were sent to the co-localized clinic and established patients with socioeconomic barriers were offered the choice to transfer to the co-localized clinic.

METHODS: Hopple Street primary care patients who completed a neurology visit from 2015 to 2025 were identified. Demographics and healthcare encounters (neurology outpatient, emergency, urgent care, and admission encounters) were collected. Primary outcome measures include rates of clinic no-show, inpatient admission, and emergency care visits.

RESULTS: Of 14,405 encounters identified, the co-localized neurology clinic treated majority Black patients with Medicaid. After the co-localized clinic was started, encounters at our main outpatient clinic reduced from 91% to 61%. There were higher no-show rates at the co-localized clinic but reduced no-show rates at other neurology clinic sites. However, the rate of urgent care visits at the closest urgent care site and hospital admissions reduced while anesthesia events increased.

CONCLUSIONS: Co-localization did not significantly change no-show rates across all clinic sites. However, access to the co-localized clinic reduced no-shows at our other neurology clinic sites and reduced acute care visits. These data suggest that improving geographic access to specialists alters healthcare utilization and future work will look into specific diagnoses that may be impacted.

KEYWORDS: Practice Parameters

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464. Ambient artificial intelligence (AI) tools save time without negatively impacting time-based billing within a large pediatric neurology group

Ricka Messer

OBJECTIVE: Ambient artificial intelligence (AI) technology, including AI scribes and generative ambient clinical documentation, improves administrative burden by recording the patient encounter, referencing the electronic medical record, and creating a note draft. Studies suggest ambient AI decreases documentation time with variable financial consequences. Further, the application of ambient AI in pediatric neurology is poorly understood.

METHODS: Pediatric neurology faculty were surveyed regarding use of ambient AI, understanding of AI prompts, and the impact on time spent and billing practices.

RESULTS: Of our 65 faculty, 43 (66.1%) responded to the survey. Most (86%) indicated that they typically bill based on time, rather than by medical decision-making. Of the 30 faculty (69.8%) who were using ambient AI, 76.7% were using it often but only 10% were frequently using prompts to customize the generated text. Although 96.7% reported that it saved them time, 70% denied any impact on their billing, and 10% reported sometimes billing at a higher level. Free-text comments highlighted being able to spend more time connecting with patients and finishing notes faster, though some mentioned that the generated assessment and plan content was not adequate.

CONCLUSIONS: Most pediatric neurology faculty at our institution adopted ambient AI and felt that it saved them time. Despite our section's preference for time-based billing, the overall impact on billing was neutral to beneficial, likely similar time spent on direct patient care. Concerns about note content could potentially be addressed with custom prompts. Future studies will evaluate the impact of this promising tool on "pajama time," burnout, and revenue.

KEYWORDS: Practice Parameters

Sleep

465. Early Recognition and First Report of Combined B- and T-Cell Triple Immunotherapy in Pediatric Narcolepsy Type 1

Anh Thu Tran, Bobbi Hopkins, Michael Kruer, Emmanuel Mignot

OBJECTIVE: To report a rapidly progressive pediatric case of narcolepsy type 1 (NT1) and describe one of the earliest reported applications of combined B- and T-cell–directed triple immunotherapy early in the disease course.

METHODS: A 16-year-old male presented with acute abnormal movements, weakness, speech changes, and progressive hypersomnolence. Early features included involuntary jerking, facial motor cataplectic facies, head drops, and sudden loss of tone without altered awareness, raising concern for seizures or acute neurologic injury. Evaluation included brain MRI, prolonged video EEG, HLA typing, multiple sleep latency testing (MSLT), and cerebrospinal fluid (CSF) orexin-A measurement. NT1 was confirmed within 5 weeks by MSLT showing mean sleep latency of 0.3 minutes with 5/5 sleep-onset REM periods, CSF orexin-A <50 pg/mL (reference >200 pg/mL), and HLA-DQB1*0602 positivity. Within two months of symptom onset, a one-time triple immunotherapy regimen was administered, consisting of IV methylprednisolone for rapid inflammatory suppression, IV cyclophosphamide for cytotoxic depletion of proliferating lymphocytes including autoreactive T-cell populations, and IV rituximab to limit B-cell–dependent immune amplification.

RESULTS: Triple immunotherapy did not result in sustained clinical improvement.

CONCLUSIONS: Pediatric NT1 may present with early motor features that mimic seizures or stroke suspicious for autoimmune encephalitis. Despite early, aggressive immune targeting, lack of response suggests that orexin neuron loss may occur rapidly and become irreversible early in NT1, highlighting the narrow therapeutic window and limitations of current immunosuppressive strategies.

KEYWORDS: Sleep, Neuroimmunology

466. A Breath of Fresh Air: A Retrospective Investigation of Central Sleep Apnea From Diagnosis to Outcome in the Pediatric Population

Pooja Rao, Vikram Bhise, Maya Ramagopal

OBJECTIVE: To characterize clinical features and diagnoses of pediatric central sleep apnea (CSA), assess the diagnostic yield of neuroimaging as a first-line evaluation in CSA, and discover relationships between CSA and neurodevelopmental outcomes.

METHODS: Retrospective chart review of 31 patients diagnosed with CSA by polysomnography over 10 years (2008–2018). Patients were classified by CAI severity (≥5 vs <5 events/hour) and associated conditions. Fisher's exact tests and Mann-Whitney U tests were used for comparisons.

RESULTS: The cohort was predominantly male (n=21, 67.7%), aged 1–3 years. Coexisting obstructive sleep apnea (OSA) was present in 21 patients (67.7%). Developmental diagnoses were present in 15 patients (48.4%), with speech delay most common (n=12, 38.7%). Among 17 imaged patients, 6 (35.3%) had abnormal findings (number needed to image = 2.8), with no difference by CAI severity (37.5% vs 33.3%, p=1.000). Isolated CSA was significantly associated with obesity versus CSA+OSA (44.4% vs 9.5%, OR=7.60, p=0.049). Developmental conditions were more prevalent in the lower CAI group (66.7% vs 23.1%, p=0.029).

CONCLUSIONS: Pediatric CSA carries a high burden of neurodevelopmental comorbidity, supporting the hypothesis that CSA is associated with adverse developmental outcomes. Neuroimaging showed meaningful diagnostic yield regardless of CAI severity, suggesting clinical phenotype rather than CAI threshold should guide diagnostic evaluation. Obesity emerged as a risk factor distinguishing isolated CSA from mixed CSA+OSA. The inverse association between CAI severity and developmental diagnoses likely reflects

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ascertainment bias, as developmentally delayed children may have undergone polysomnography during broader evaluations, incidentally detecting mild CSA. These findings support polysomnography screening in children with neurodevelopmental disorders.
KEYWORDS: Sleep, Neuroimaging, Practice Parameters

467. Evaluating long-term sleep outcomes and safety of medical cannabis in children with autism in a real-world clinical setting

Mohsin Maqbool, Diya Khullar, Izabella Jonhson, Taha Maqbool, Aiza Salman

OBJECTIVE: To examine 18-month sleep outcomes and safety of medical cannabis in children with autism spectrum disorder (ASD) in a prospective real-world clinical registry.
METHODS: Children with ASD initiating medical cannabis were enrolled in a prospective registry at a pediatric neurology clinic. Caregiver-reported sleep duration and Clinical Global Impression of Change (CGIC) for sleep onset, maintenance, and quality were assessed at baseline and 18 months. Cannabis formulations included THC-containing products with variable CBD:THC ratios, titrated from 1.25 mg to 5 mg twice daily as tolerated. Analyses included participants with ≥18 months follow-up.
RESULTS: Fifty-seven children completed 18-month follow-up. Mean sleep duration increased by 1.1 hours overall and 1.75 hours in children sleeping <6–6.5 hours at baseline. Caregivers reported improvement in sleep onset, maintenance, and quality in the majority of participants. Eleven participants discontinued treatment (6 due to side effects, 2 cost, 3 logistical factors). Treatment was otherwise well tolerated.
CONCLUSIONS: In this prospective real-world cohort, medical cannabis use in children with ASD was associated with sustained improvements in sleep duration and caregiver-reported sleep quality over 18 months, with acceptable tolerability. These findings support the need for controlled trials to further evaluate efficacy and safety.
KEYWORDS: Sleep, Neurodevelopmental Disorders, Behavioral Neurology

468. When Sleep Attacks Aren't Narcolepsy: A Two-Patient Case of an Unusual Phenotype for Functional Neurologic Disorder.

Rozena Nandedwalla, Cullen Marshall, Emily Singer

OBJECTIVE: Functional neurological disorders (FND) can present with sleep-related symptoms. We describe two patients with recurrent daytime sleep attacks and phenomenology that clinically resembled narcolepsy but lacked objective support.
METHODS: Two patients referred to sleep medicine for excessive daytime sleepiness. Evaluation included detailed clinical history, neurological examination, standardized sleep questionnaires, nocturnal polysomnography, and multiple sleep latency testing (MSLT).
RESULTS: Both patients reported frequent, sudden daytime sleep attacks with associated sleep inertia. Standardized sleep scales indicated subjective excessive daytime sleepiness. Both patients endorsed features of narcolepsy including cataplexy, hypnagogic hallucinations and sleep paralysis. One patient had a positive HLA-DQB1*0602 serum marker but normal CSF orexin level. Nocturnal polysomnography demonstrated normal sleep architecture and adequate overnight sleep. MSLT showed normal mean sleep latencies and no sleep-onset REM periods. Clinical courses also revealed patterns related to situational triggers and stress, and both patients showed partial improvement with behavioral interventions.
CONCLUSIONS: These two cases demonstrate that FND can present as sleep attacks mimicking narcolepsy. Additionally, clinical patterns like situational triggers and symptom variability can point towards a diagnosis of functional sleep attacks. The dissociation between subjective symptoms and objective findings highlights the importance of careful diagnostic evaluation. Recognizing functional sleep attacks as part of the FND spectrum is essential and should be on the differential diagnosis for patients presenting with frequent episodes of loss of consciousness. Differentiating this can help guide management toward behavioral and cognitive interventions that can lead to meaningful improvement.
KEYWORDS: Sleep

Stroke

469. Neurodevelopmental Outcomes Following Stroke in Pediatric Patients: A Systematic Review Across Seven Outcome Domains

Alaina Carman, Margil Ranpariya, Imtiaz Nazam, Osman Farooq

OBJECTIVE: To comprehensively review and synthesize the evidence on neurodevelopmental outcomes following pediatric stroke across cognitive, language, motor, executive function, epilepsy, psychosocial, and neuroimaging domains, and to identify prognostic factors and priorities for future research.
METHODS: A systematic review was conducted following PRISMA 2020 guidelines. PubMed/MEDLINE, Embase, and the Cochrane Library were searched from inception through December 2024. Studies were included if they reported quantitative neurodevelopmental outcomes in pediatric stroke populations using validated instruments, with a minimum sample of 15 patients. Methodological quality was appraised using the Newcastle-Ottawa Scale and AMSTAR-2 checklist. Narrative synthesis was performed across seven predefined outcome domains due to substantial clinical and methodological heterogeneity.
RESULTS: Thirty-four studies encompassing approximately 2,777 patients across 12 countries were included. Intellectual functioning was consistently below normative expectations, with longitudinal studies demonstrating stagnation or decline rather than recovery. Language impairment affected 20–56% of survivors. Cerebral palsy, predominantly hemiparetic, occurred in 26–33% following perinatal stroke. Executive function deficits were documented regardless of lesion

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laterality. Post-stroke epilepsy developed in 12–28% and independently worsened cognitive trajectories. Social cognition and quality of life were significantly impaired. Neuroimaging biomarkers, including corticospinal tract integrity, thalamic volume, and voxel-based lesion-symptom mapping, demonstrated domain-specific prognostic value.

CONCLUSIONS: Pediatric stroke produces multidomain, co-occurring, and temporally evolving neurodevelopmental deficits. Serial, multidisciplinary assessment extending through adolescence is essential. Standardized, prospective multicenter studies with harmonized protocols are urgently needed to validate imaging-based biomarkers and guide targeted interventions.

KEYWORDS: Stroke, Neurodevelopmental Disorders, Epilepsy

470. Infectious Vasculitis in Cavernous Sinus Thrombosis

Agnes A Donnelly, Chrisoula Cheronis

OBJECTIVE: Cavernous sinus thrombosis (CST) can lead to stroke, severe neurologic injury, and even death. Internal carotid artery (ICA) stenosis is a known complication of CST, and further increases stroke risk. Due to its rarity in the pediatric population, management of this secondary infectious vasculitis is incompletely understood.

METHODS: We describe a single-center case series of two patients with infectious CST who developed a secondary vasculitis. Patient 1 is a 9 year-old female who presented with fever, headache, and positive Kernig's and Bruszinski's signs, and was found to have CST in the setting of bacterial sinusitis. Patient 2 is a 8 year-old male who presented with fever and left facial weakness and was diagnosed with CST due to otomastoiditis and petrous apicitis.

RESULTS: For Patient 1, magnetic resonance angiography (MRA) of the brain demonstrated vasculitis in the left ICA and middle cerebral artery (Figure 1). For patient 2, MRA of the brain demonstrated vasculitis of the ICA and anterior cerebral artery (Figure 2). Patient 1 was treated with surgical debridement, intravenous antibiotics, and anticoagulation, while patient 2 was managed medically with intravenous antibiotics and anticoagulation. Both patients had complete symptom resolution, with interval post-treatment imaging showing improvement in both thrombus burden and vasculitic change.

CONCLUSIONS: Surgical debridement, antibiotics, and anticoagulation are the best supported treatments of infectious CST. Although literature reports the use of steroids and nimodipine as treatments specifically targeting vasculitis, review of existing data suggests that neither prevents stroke or improves long-term outcomes in pediatric CST patients.

KEYWORDS: Stroke, Neurocritical Care, Neuroinfectious Disease

471. Plasma Exchange: A Possible Treatment for Cerebral Fat Embolism

Ananya Moorthy, Bryan Philbrook

OBJECTIVE: Cerebral fat embolism is a rare, neurologic complication caused by embolization of fat particles into various organs, including the brain. It is classically associated with trauma but may also occur in hematologic disorders.

METHODS: An 18-year-old male with hemoglobin SS disease was admitted for vaso-occlusive episode pain. Historically, he had infrequent admissions and managed pain at home with oral medications. He was started on morphine patient-controlled analgesia. Several days into admission, he developed waxing and waning altered mental status. Laboratory evidence of hemolysis raised concern for thrombotic thrombocytopenic purpura (TTP), prompting treatment with steroids, plasma exchange, and rituximab.

RESULTS: ADAMTS13 activity returned at 63%, higher than expected for TTP. Brain magnetic resonance imaging (MRI) demonstrated a classic "starfield" pattern of innumerable punctate diffusion-restricting lesions with susceptibility changes, consistent with cerebral fat embolism. The course was complicated by acute respiratory failure and saddle pulmonary embolism. Plasma exchange for treatment of cerebral fat embolism was continued, steroids were tapered, and rituximab discontinued. Neurologic examination was near baseline at three-month follow-up. Imaging at six months remained stable with punctate diffusion restricting foci. He returned to college without significant deficits.

CONCLUSIONS: Cerebral fat embolism should be considered in patients with sickle cell disease presenting with encephalopathy. Recognition of the "starfield" MRI pattern aids diagnosis. Early red blood cell transfusion is typically recommended, however plasma exchange has been noted to be beneficial in more recent case reports. Future research can be conducted to evaluate the efficacy of this treatment modality.

KEYWORDS: Stroke, Neuroimaging, Neurocritical Care

472. A Rare Case of Perinatal Stroke Secondary to Basilar Artery Occlusion

Carla Cardona Valle, Minaal Zahid, Amal Abd-Allah, Rima El-Atrache, Allison Stephens, Steven Lazar

OBJECTIVE: Posterior circulation perinatal arterial ischemic stroke (PAIS) represents only 6-9% of all PAIS, with neonatal basilar artery occlusion (BAO) exceedingly rare. While current guidelines support conservative management, emerging evidence on endovascular thrombectomy in pediatric stroke creates a therapeutic dilemma in acute neonatal BAO.

METHODS: We identified a neonate born at 36 weeks via emergency cesarean section for presumed placental abruption (pathology confirmed placenta accreta), who presented with hypotonia, low APGAR scores, and cardiac arrest at 7 minutes of life. Pregnancy was complicated by limited prenatal care, incompletely treated maternal syphilis, and methamphetamine exposure. Therapeutic hypothermia was initiated at 5 hours for suspected hypoxic-ischemic encephalopathy.

RESULTS: MRI at day 6 revealed an acute pontine infarct with near-total basilar artery occlusion on MR angiography. Imaging characteristics including DWI restriction, T2 hyperintensity, and hemorrhagic transformation localized timing to the perinatal period. Metabolic derangements, infection (syphilis serologies negative), and structural

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abnormalities were excluded as stroke mimics. Endovascular intervention, anticoagulation, and antiplatelet therapy were deferred after multidisciplinary discussion, with no stroke progression on repeat imaging at 2 weeks. At 27 days, the neonate had no focal deficits; at 10 months, all milestones were met aside from mild gross motor delay. The PAIS is presumed thromboembolic from a placental source secondary to prenatal methamphetamine exposure, with contributing risk factors: placenta accreta, placental infarction, and antenatal syphilis.

CONCLUSIONS: This case adds to the sparse literature on neonatal BAO and demonstrates conservative management consistent with current guidelines. Further research is needed to identify neonates who might benefit from acute intervention.

KEYWORDS: Stroke, Neonatal Neurology, Fetal Neurology

473. Assessing Cerebrovascular Reactivity as a Mechanistic Link Between Sleep and Cognition in Pediatric Stroke

Taylor Stoat, Jun Au, Amanda Robertson, Robyn Westmacott, Trish Domi, Liza Pulcine, Mahendranath Moharir, Indra Narang, Nomazulu Dlamini

OBJECTIVE: Cognitive deficits are common after pediatric arterial ischemic stroke (AIS), and sleep impairment may compound them by disrupting cerebrovascular health. We used cerebrovascular reactivity (CVR) to examine the relationships among vascular health, sleep, and cognition in children with AIS and in children with high-risk conditions but no AIS.

METHODS: Children aged 6–18 years with AIS or a high-risk condition (arteriopathy, sickle cell disease, or cardiac disorders) completed polysomnography, neuropsychological testing, and BOLD-MRI: CVR was quantified using traditional and transfer function analysis. Multiple linear regression and mixed-effects models tested associations among sleep, CVR, and cognitive outcomes.

RESULTS: In 24 children, 14 (58.3%) had AIS and 10 (41.7%) had high-risk conditions and no AIS [54.2% female; median age at PSG =12.6 years, range 6.7 –18]. Among 48 cerebral hemispheres, 20 were stroke-affected, 17 were arteriopathy-affected, and 11 were considered unaffected. Greater slow wave sleep was associated with increased speed of cerebrovascular response in the unaffected hemisphere (r=0.62, $p<0.05$) and the obstructive apnea hypopnea index was associated with reduced CVR in the lesioned hemisphere (r =-0.39, $p=0.086$). Mean CVR was positively associated with working memory (B=0.87, $p<0.01$) and processing speed (B=0.71, $p<0.01$), while slowed cerebrovascular response was associated with worse executive functions (B=-0.50, $p<0.05$) in the full cohort.

CONCLUSIONS: We found slow wave sleep and sleep disordered breathing to be associated with cerebrovascular health and cognitive outcomes in children with AIS and high-risk conditions. These findings need further study in a larger sample size to evaluate and target sleep for intervention in this population.

KEYWORDS: Stroke, Neuroimaging, Sleep

474. Clinical and Imaging Predictors of Baseline Motor Functional Status After Perinatal Ischemic Stroke: A Machine Learning Analysis

Warren Lo, Ahmed Naeem, Jill Heathcock, Amy Darragh, Craig Ramey, Stephanie DeLuca, Renee Martin, Qi Pauls, Bin Jiang, Sharon Landesman Ramey, Max Wintermark

OBJECTIVE: To investigate predictors of poor upper extremity (UE) motor function in patients with perinatal stroke using machine-learning models and comparisons to multivariable logistic regression.

METHODS: We analyzed data from participants enrolled in the I-ACQUIRE trial to predict functional status at baseline across Gross Motor Function Classification System (GMFCS), Infant Motor Activity Log - How Often (IMAL-HO), Infant Motor Activity Log - How Well (HW) measures. Candidate predictors included clinical and radiological factors. Multivariable logistic regression, support vector machine (SVM), random forest (RF), and XGBoost models were developed, and performance was compared using area under the receiver operating characteristic curve (AUC).

RESULTS: Machine learning models demonstrated strong discrimination for motor-function measures. For GMFCS, ML models achieved AUCs ranging from 0.74 to 0.80, compared with 0.47 for logistic regression. For IMAL-HO, ML performance ranged from 0.74 to 0.79, versus 0.58 for logistic regression. For IMAL-HW, ML models achieved AUCs between 0.70 and 0.75, compared with 0.65 for logistic regression. Features repeatedly retained across models mapped to clinically plausible domains, including seizures, uncinate fasciculus involvement, and birth complications for GMFCS; basal ganglia involvement, sex, corticospinal tract, insular cortex, and pregnancy complications for IMAL-HO; and superior temporal gyrus, uncinate fasciculus, infarct volume, corticospinal tract, and insular cortex involvement for IMAL-HW.

CONCLUSIONS: Machine learning improved prediction of baseline UE motor function after perinatal stroke compared with logistic regression. Feature selection reflected lesion burden, corticospinal tract involvement, cortical-subcortical network injury, and perinatal risk factors. Our findings support ML models as a promising tool for early risk stratification.

KEYWORDS: Stroke, Neonatal Neurology, Neuroimaging

475. The Development of a Pediatric Stroke Algorithm

Michele Mills, Adrianna Carey, Chrisoula Cheronis, Andrea Pardo

OBJECTIVE: Pediatric Stroke Pathways have demonstrated improved time to diagnosis in several studies. With publication of recent pediatric guidelines on acute ischemic stroke (AIS) and increasing availability of endovascular thrombectomy (EVT) and thrombolysis as acute treatments, we developed an institutional Confirmed Stroke Algorithm.

METHODS: The neuro-critical care (NCC) team partnered with the center for quality and safety to initiate this hospital wide clinical care guideline. Stakeholders included nursing and physicians from the emergency department (ED), neuro

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interventional (IR) department, transport medicine, anesthesia, neuroradiology, pediatric and cardiac intensive care, neurology, communication center, and hospital telecommunications.
RESULTS: A two-pronged algorithm was developed for patients with radiologically confirmed AIS, one dedicated to patients transported from outside EDs and the other for in-hospital patients. We developed a paging system to indicate a radiologically confirmed AIS *en route* that included the ED, NCC, and neuro IR with pre-specified communication loops. This system allows for pre-admission preparation of thrombectomy facilities and staffing prior to arrival, and determination for immediate re-imaging as needed prior to ED arrival. Similarly, an in-hospital paging system was developed with pre-specified communication loops between neuroradiology, NCC and neuro IR to ready thrombectomy facilities and staffing for hyperacute AIS treatment.
CONCLUSIONS: This algorithm aims to improve times of AIS treatment both for transport and in-hospital patients. This will lead to faster neuroprotection and thrombolysis or EVT administration in keeping with the new AIS guidelines. Multiple stakeholders are critical for the creation of algorithms that aim to improve the quality of pediatric stroke treatment.
KEYWORDS: Stroke, Neurocritical Care, Education

476. Atypical Presentation of Moyamoya Masqueraded as Vasculitis: A Case Report

Cara Cusi, Daanish Unwalla, Jonathan Bui, Allison Chirigos, Jennifer Yang

OBJECTIVE: Moyamoya disease is a chronic cerebrovascular disease of childhood that typically presents with recurrent episodes of unilateral limb weakness and accounts for 6-10% of all childhood strokes. Here we present a case of an atypical presentation of Moyamoya disease.
METHODS: N/A
RESULTS: A 4-year-old previously healthy male presented with 1 month of progressive left hemiparesis after a viral infection. MRI was notable for multiple areas of unilateral and subcortical decreased diffusivity and T2 hyperintensities. Initial neurovascular imaging showed left internal carotid artery stenosis but otherwise normal intracranial vasculature. CSF and serum studies evaluating for autoimmune, inflammatory and rheumatological/vasculitic, and infectious work-up were unrevealing. Whole exome sequencing and mitochondrial DNA sequencing were also unrevealing. Given the post-infectious presentation, he was treated empirically with IV methylprednisolone and IVIG for a presumed diagnosis of transient immune-mediated vasculitis with clinical improvement. Four months later, he presented with acute worsening of his left-sided hemiparesis and new-onset left-sided facial weakness. He was found to have a right middle cerebral artery territory stroke and received tPA. CT angiogram showed normal flow through the internal carotids and no prominent collateral flow. However, a diagnostic angiogram thereafter confirmed Moyamoya disease. The patient is currently pending endovascular surgery.
CONCLUSIONS: This case highlights an atypical presentation of Moyamoya disease due to the initial subacute symptom onset and nondiagnostic vascular imaging, emphasizing the need for diagnostic angiogram in cases highly suspicious for Moyamoya disease.
KEYWORDS: Stroke

477. Pediatric Stroke Code Trends and Imaging at a Quaternary Care Center Following the 2026 AHA/ASA Acute Ischemic Stroke Guidelines

Michelle Corkrum, Min Ye Shen

OBJECTIVE: The 2026 AHA/ASA guidelines represent the first formal recommendations for acute management of pediatric ischemic stroke, including guidance on IV thrombolysis and endovascular thrombectomy. This study characterizes pediatric stroke code trends, initial imaging modalities, and confirmed stroke diagnoses at a single quaternary care center to evaluate practice patterns in the context of these new guidelines.
METHODS: A retrospective review of all pediatric stroke codes activated at Columbia University Irving Medical Center from January 2025 through February 2026 was performed. Data included monthly stroke code volume, cancellation rates, patient location, initial neuroimaging modality (CTH vs. MRI), and confirmed stroke subtype (ischemic vs. hemorrhagic).
RESULTS: A total of 71 stroke codes were activated over 14 months, ranging from 1 (July 2025) to 13 (September 2025). Active codes originated from the ED (43%), Floor (24%), Cardiac ICU (22%), Step-Down Unit (9%), and ICU (2%). Seven confirmed strokes were identified: 5 ischemic and 2 hemorrhagic, distributed across the ED (43%), Cardiac ICU (29%), Floor (14%), and Step-Down Unit (14%). CTH was the predominant initial imaging modality; however, 60% of confirmed ischemic strokes were missed on CTH, requiring MRI for diagnosis.
CONCLUSIONS: The majority of pediatric ischemic strokes were not identified on initial CTH, underscoring MRI as essential for definitive diagnosis. Barriers to initial MRI, including patient instability, anesthesia requirements, and contraindications (i.e. ECMO), remain significant. Given the 2026 AHA/ASA guidelines recommending acute interventions in eligible patients, timely MRI confirmation is critical to guideline-concordant care. Institutional protocols should address MRI access barriers to optimize pediatric stroke outcomes.
KEYWORDS: Stroke, Neuroimaging

478. Beyond Stroke: Clinical Implications of a Pediatric Code Stroke Pathway at a Tertiary Care Center

Ritika Patel, John Pugh

OBJECTIVE: To review the effectiveness of a Pediatric Code Stroke (PCS) pathway in identifying patients with Acute Neurologic Events (ANE).
METHODS: A PCS pathway was implemented at our tertiary care center and we conducted a retrospective chart review of PCS activations between August 2024 and September 2025. Stroke mimics were categorized as benign (e.g. migraine, syncope, psychogenic) or serious (e.g. focal seizure, meningoencephalitis, brain tumor) based on the

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identification of an acute evolving process requiring intervention and the potential for persistent deficit.

RESULTS: There were 48 PCS with a median age of 12 years (range 3 months to 17 years) of which 58% were male. Neuroimaging was obtained in 42 patients, with 39 receiving MRI. Six activations (12.5%) identified acute cerebrovascular events, but none qualified for acute revascularization. Seventeen activations (40.5%) identified serious mimics with seizures and emesis being the most common symptoms while 25 (59.5%) identified benign mimics with headaches, language/sensory changes, and ataxia predominating. Patients diagnosed with serious mimics were more likely to have at least one stroke risk factor (65% vs 12%, $p < 0.001$). They were more likely to require treatment and receive diagnostic evaluation that changed management (82% vs 36%, $p < 0.01$).

CONCLUSIONS: While few acute cerebrovascular events were identified, PCS activations identified ANE in 48% of our cohort. We propose an algorithm for patients presenting with ANE as an alternative to a PCS protocol which may be beneficial for other tertiary care centers.

KEYWORDS: Stroke, Practice Parameters, Education

479. Not All Sickle Cell Strokes Are Arterial: Cerebral Venous Thrombosis of the Vein of Labbe

Hailey Kramer, Ashley Bartscherer

OBJECTIVE: To report an unusual etiology of stroke in a young adult with sickle cell disease: cerebral venous thrombosis involving the distal Left Vein of Labbe.

METHODS: A retrospective chart review was conducted of an 18-year-old male with sickle cell disease (HbSS), including clinical presentation, laboratory evaluation, neuroimaging, treatment, and clinical course. A literature review of cerebral venous thrombosis in patients with sickle cell disease was also performed.

RESULTS: An 18-year-old male with HbSS presented with severe headache and mild word-finding difficulty, with an NIH Stroke Scale score of 1. Initial head CT demonstrated a subacute left temporal lobe infarction with associated luxury perfusion, and exchange transfusion was initiated for presumed arterial ischemic stroke secondary to sickle cell vaso-occlusion. During hospitalization, his NIH Stroke Scale score increased to 2 due to moderate aphasia. Subsequent MRI, MRA, and MRV revealed thrombosis of the distal left vein of Labbe with no evidence of underlying arteriopathy, establishing cerebral venous thrombosis as the etiology. Anticoagulation was initiated, and evaluation for additional thrombophilic conditions was unrevealing. The patient demonstrated clinical improvement with anticoagulation, speech therapy, physical therapy, and occupational therapy, with gradual recovery of speech and cognition.

CONCLUSIONS: Cerebral venous thrombosis is a rare but important cause of stroke in patients with sickle cell disease. This case highlights the importance of considering venous thrombosis in the differential diagnosis of acute neurologic deficits in this population, as management differs substantially from arterial ischemic stroke. Prompt recognition and appropriate treatment are essential to optimize neurologic outcomes.

KEYWORDS: Stroke, Neurocritical Care

480. Understanding Fetal Intracranial Hemorrhage: The Potential Role of Placental Insufficiency

Moran Hausman-Kedem, Stéphanie Libzon, Liat Ben Sira, Michal Levy, Karina Krajden-Haratz, Debora Kidron

OBJECTIVE: To assess the added value of placental autopsy findings in fetal intracranial hemorrhage (fICH) in identifying potential etiological contributors.

METHODS: A retrospective, single-center, observational case-control study of fetuses diagnosed with fICH at a tertiary center (2014-2025) who underwent termination-of-pregnancy (TOP) followed by autopsy. Cases were compared with sex and gestational age-matched controls undergoing TOP for non-hemorrhagic indications. All autopsies followed a standardized institutional protocol, and placental lesions were classified according to the Amsterdam Placental Workshop Group criteria.

RESULTS: Twenty-three fetuses with fICH (median gestational age at TOP 33 weeks, IQR 31, 34.7) and 38 controls were included . The predominant hemorrhage pattern was germinal matrix-intraventricular (17/23, 73.9%), with or without periventricular hemorrhagic infarction (13/23, 56.5%). Pathogenic variants were identified in 3/10 (33.3%) tested cases (*COL4A2*, n=2; *FLNA*, n=1). Compared with controls (n=38), the frequency of gross placental and umbilical cord characteristics and microscopic placental lesions associated with acute and chronic inflammatory processes did not differ significantly. In contrast, placental malperfusion lesions were significantly more frequent in the fICH group (11/23, 47.8%) versus controls (3/38, 7.9%; $p < 0.001$), driven primarily by features of fetal vascular malperfusion (8/23, 34.8% vs 1/38, 2.6%; $p = 0.001$).

CONCLUSIONS: Placental malperfusion, particularly fetal vascular malperfusion, is significantly associated with fICH and may represent a key contributing factor in its pathogenesis. Incorporating placental evaluation may improve understanding of the etiology and inform prenatal counseling.

KEYWORDS: Stroke, Fetal Neurology

481. Recurrent Brainstem Strokes as Presenting Features of DADA2 Deficiency: A Pediatric Case Report

George Lara Collado, Ryan Carrier

OBJECTIVE: We report a pediatric case of deficiency of adenosine deaminase 2 (DADA2) presenting with recurrent brainstem infarcts, systemic features, and atypical neuroimaging findings to highlight key diagnostic clues and the importance of early targeted therapy.

METHODS: Case report.

RESULTS: A 13-year-old female presented with relapsing neurologic deficits over 11 months. She experienced four distinct episodes: diplopia with right facial weakness, bilateral internuclear ophthalmoplegia, diplopia with ptosis, and right hemiparesis, all steroid-responsive. Initial neuroimaging was normal. Subsequent MRIs demonstrated progressive brainstem lesions with restricted diffusion involving the periaqueductal gray and bilateral cerebral peduncles, thought to represent an inflammatory process. Extensive evaluation for demyelinating, infectious, and autoimmune etiologies was

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negative. Inflammatory markers remained persistently elevated, and a recurrent lower extremity rash appeared later. Skin biopsy demonstrated panniculitis, and vessel wall imaging of the brain was consistent with vasculitis. Leptomeningeal enhancement was also noted in the interpeduncular cistern. The disease was steroid-responsive, with relapses during tapering. Low plasma ADA2 enzyme activity prompted initiation of TNF inhibitor therapy, which prevented further events, with subsequent genetic testing confirming DADA2.

CONCLUSIONS: DADA2 is a rare autosomal recessive vasculopathy that can present with recurrent infarcts or hemorrhages, often leading to diagnostic uncertainty in pediatric patients. It can be associated with leptomeningeal enhancement on imaging. Neurologic manifestations may precede systemic features, delaying recognition. A relapsing course, steroid responsiveness, elevated inflammatory markers, and cutaneous findings provide important diagnostic clues. Early recognition of DADA2 and initiation of TNF inhibitor therapy can prevent further cerebrovascular events and improve outcomes.

KEYWORDS: Stroke

482. Focal Cerebral Arteriopathy in Pediatric Arterial Ischaemic Stroke: A Systematic Review of Clinical Features, Management, and Outcomes

Edward Poluyi, Angela Itrechio, Adeola Oni, Chioma Ezeibekwe

OBJECTIVE: To systematically review the clinical features, management, and outcomes of focal cerebral arteriopathy in pediatric arterial ischaemic stroke and identify factors associated with recurrence and recovery.

METHODS: A systematic review was conducted following PRISMA guidelines. PubMed, Embase, and Cochrane databases were searched from inception to 2025 for studies reporting pediatric patients (age <18 years) with focal cerebral arteriopathy-associated arterial ischaemic stroke. Inclusion criteria comprised cohort studies, case series, and case reports with clinical, imaging, and outcome data. Data extracted included demographics, preceding infection, imaging findings, treatment strategies, and outcomes.

RESULTS: A total of 27 studies comprising 312 patients (n=312) met inclusion criteria. The median age was 8.2 years. A preceding infection was reported in 61% of cases. Most patients presented with hemiparesis. Middle cerebral artery involvement was most common. Treatment varied, including antithrombotic therapy alone or combined with corticosteroids. Patients receiving combined therapy demonstrated a trend toward reduced radiographic progression and recurrence, although heterogeneity limited definitive conclusions. Overall, 68% achieved good functional recovery, while recurrence occurred in 12%.

CONCLUSIONS: Focal cerebral arteriopathy is a leading cause of pediatric arterial ischaemic stroke, frequently associated with recent infection. Early recognition is essential. Combined anti-inflammatory and antithrombotic strategies may improve outcomes, though higher-quality studies are needed to guide standardised management.

KEYWORDS: Stroke, Neurocritical Care, Global Neurology

483. NF1-associated Moyamoya in Children: A Distinct Clinical and Radiological Phenotype with Milder Vasculopathy Trajectory

Moran Hausman-Kedem, Nour Suliman, Shelly Shiran, Hagit Toledano, Shlomi Constantini, Tali Jonash-Kimchi, Margaret Ekstein, Stéphanie Libzon, Jonathan Roth

OBJECTIVE: NF1 is one of the most common causes of pediatric moyamoya, yet whether it has a distinct disease phenotype remains largely unknown. This study aimed to characterize the clinical and radiographic trajectory of NF1-associated moyamoya compared to non-NF1 moyamoya in a pediatric cohort.

METHODS: Single-center retrospective longitudinal study of pediatric-onset moyamoya patients (2007 - 2025). Disease course was stratified as stable/minimal progression, asymptomatic radiological progression, or symptomatic and/or rapid progression. Clinical and radiological characteristics were compared between NF1 and non-NF1 patients.

RESULTS: Of the 53 patients, 20 (37.7%) had NF1-moyamoya, and 33 (62.3%) had other etiologies. NF1 patients were significantly more likely to be asymptomatic at diagnosis (30.0% vs. 3.0%, p=0.009) and less likely to present with TIA (10.0% vs. 42.4%, p=0.013) or ischemic stroke (15.0% vs. 51.5%, p=0.008). Over a median follow-up period of 6.46 years (range: 1-18.7), NF1 patients demonstrated lower cumulative rates of stroke (20.0% vs. 69.7%, $p < 0.001$) with an 80% stroke-free survival rate compared to 25% in the non-NF1 group. Notably, no clinical stroke events were documented in the NF1 group beyond 8.0 years of age. NF1 status conferred an 80% reduction in stroke hazard (HR = 0.203, 95% CI 0.070–0.590, $p = 0.003$). Disease progression was more favorable in most patients with NF1, with only 5% developing symptomatic or rapid progression, compared with 48.5% in non-NF1 patients (p=0.001).

CONCLUSIONS: These findings support a more conservative, yet vigilant, approach to clinical management, with critical implications for risk stratification, long-term surveillance protocols, and selection criteria for surgical revascularization.

KEYWORDS: Stroke, Neuroimaging, Neuro-Cutaneous Disorders

484. Management and outcomes of secondary stroke in bacterial meningitis: A single-center retrospective study

Magan Fosso, Khushboo Saha, Michael Dowling

OBJECTIVE: To assess the outcomes, safety, & efficacy of antithrombotic therapy in management of ischemic stroke secondary to bacterial meningitis in children.

METHODS: Retrospective review of pediatric patients (0–18 years) with ischemic stroke complicating bacterial meningitis at a single tertiary pediatric center over 20 years. Inclusion required clinical meningitis with ≥2 of 3 CSF criteria (glucose 50 mg/dL, protein >45 mg/dL, WBC ≥10/μL) with ≥1 CT/MRI confirming ischemic stroke within 30 days of meningitis diagnosis. Patients with concurrent CVST were

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excluded. Safety was assessed by intracranial hemorrhage occurrence; efficacy by stroke recurrence. Neurologic outcome was determined by Pediatric Stroke Outcome Measure (PSOM) score.

RESULTS: Of 90 patients with meningitis-associated ischemic stroke, 30 met inclusion criteria. Eighteen patients (60%) received aspirin, 3 (10%) received heparin, and 9 (30%) received no ATT. ICH occurred in 1 aspirin-treated patient (5.6%) and 1 untreated patient (11.1%); no ICH occurred in the heparin group. Only 1 patient experienced recurrent infarction; this patient was subsequently started on heparin with aspirin added, with no further recurrence. The sole mortality occurred in the no-ATT group. Streptococcus pneumoniae was the most common pathogen (n=9), followed by Group B Streptococcus (n=5), culture-negative cases (n=4), MRSA, MSSA, and TB (n=2 each).

CONCLUSIONS: This is the largest single-center pediatric series to date. Antithrombotic therapy appeared safe with low ICH rates and no recurrence in treated patients. These findings are consistent with prior smaller studies and supports the overall safety of ATT in childhood bacterial meningitis complicated by stroke. Prospective multi-center trials are needed.

KEYWORDS: Stroke, Neuroinfectious Disease

485. MANAGEMENT OF ACUTE ISCHEMIC STROKE IN BACTERIAL MENINGITIS: A SCOPING REVIEW

Khushboo Saha, Magan Fosso, Michael Dowling

OBJECTIVE: To systematically review the evidence for use of antithrombotic agents in primary or secondary prevention of ischemic stroke complicating acute bacterial meningitis across pediatric and adult populations.

METHODS: A scoping review was conducted searching PubMed, Cochrane, and OVID/EMBASE from inception through July 2025 for studies reporting antithrombotic use in prevention or management of ischemic stroke after bacterial meningitis. Exclusion criteria included hemorrhagic stroke, cerebral venous sinus thrombosis, animal or in vitro studies, viral meningitis, non-infectious causes of stroke, and non-English publications. Data were extracted on study population, antithrombotic management strategies, and clinical outcomes.

RESULTS: 28 studies met inclusion criteria (adults=13, children=7, both=8), comprising 2 systematic reviews, 6 randomized controlled trials (RCTs), 1 prospective cohort, 5 retrospective reviews, 5 expert reviews, and 10 case reports/series. Only 6 RCTs were identified-5 in tuberculous meningitis and 1 in pneumococcal meningitis. Antithrombotic strategies included antiplatelet agents alone (aspirin, clopidogrel, or both; n=17), LMWH or unfractionated heparin alone (n=2), aspirin combined with heparin (n=3), and thrombolytics (n=5). Aspirin was the most frequently studied agent across all age groups, with no dose-dependent effects and minimal reported complications. Heterogeneity in interventions and outcome reporting precluded meta-analysis. Pediatric-specific evidence was particularly limited despite children bearing the highest meningitis-related mortality globally.

CONCLUSIONS: Evidence guiding antithrombotic management of ischemic stroke in bacterial meningitis remains scarce and heterogeneous, with RCTs limited to tuberculous meningitis. Aspirin appears safe across age groups with minimal complications. Prospective multi-center trials—particularly in pediatric populations—are urgently needed to establish standardized treatment protocols

KEYWORDS: Stroke, Neuroinfectious Disease, Neurocritical Care

486. Vertebral Artery Sacrifice in a Child with Recurring Posterior Circulation Strokes

Asia Payne, Anna Huguenard, Sherwin Azad, Arindam Chatterjee, Hannah Edelman, Souvik Singha, Matthew Glasser, Surbhi Saini, Rejean Guerriero, Maria Galardi, Jarod Roland, Kristin Guilliams

OBJECTIVE: Vertebral artery dissections are the most common underlying cause of pediatric posterior circulation strokes, especially in young boys, accounting for 25-50% of the cases. Known treatments include C1-C2 posterior fusion, vertebral artery sacrifice, and debridement of any fibrous tissue compressing the vertebral artery. The few studies published on pediatric vertebral artery sacrifice show no recurrence of stroke post-intervention.

METHODS: Case Report

RESULTS: A 4-year-old boy presented with slurred speech and left-sided weakness after jumping on a trampoline. MRI/MRA revealed a right internal capsule, globus pallidus and posteromedial thalamic infarct associated with a right vertebral artery dissection with pseudoaneurysm. Aspiration thrombectomy was attempted for a right posterior communicating artery occlusion, and he was started on aspirin. On dynamic MRI, there was possible right vertebral artery compression and concern for Bow Hunter Syndrome, so he was placed in a Miami J cervical brace. MRI/MRA at 2 months showed persistent vertebral narrowing and at 5 months noted a sub-acute right lateral thalamic silent infarct, but with resolution of the vertebral stenosis; his cervical brace was discontinued. He represented at 7 months with slurred speech, ataxia, and altered mental status from a basilar artery occlusion that resolved with thrombectomy (mTICI2b). Subsequent imaging showed worsening right vertebral artery stenosis and a new left thalamic stroke which led to the decision to pursue endovascular right vertebral artery sacrifice. He was discharged on clopidogrel with no major neurological deficits.

CONCLUSIONS: Vertebral artery sacrifice is a rare but potentially beneficial intervention for recurrent posterior circulation strokes associated with vertebral artery pathology.

KEYWORDS: Stroke, Neurocritical Care

487. MRI-Visible Perivascular Spaces as a Marker of Glymphatic Function in Pediatric Arterial Ischemic Stroke and High-Risk Conditions: Associations with Sleep and Cognitive Outcomes

Taylor Stoat, Pardaman Setia, Pradeep Krishnan, Amanda Robertson, Robyn Westmacott, Liza Pulcine, Mahendranath Moharir, Indra Narang, Nomazulu Dlamini

OBJECTIVE: Enlarged perivascular spaces (ePVS) visible on MRI serve as markers of glymphatic system function and have been linked to cognition, cerebrovascular disease, and

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sleep impairment in older adults. While ePVS offer a promising microvascular health measure, their role in pediatric arterial ischemic stroke (AIS) remains unknown. This study examines the relationships between ePVS burden, sleep impairment, and cognitive outcomes in children with AIS and high-risk conditions.

METHODS: Children aged 6–18 years with AIS or a high-risk condition (arteriopathy, sickle cell disease, or cardiac disorders) completed polysomnography, neuropsychological testing, and MRI. ePVS burden in the centrum semiovale was quantified using T1-weighted and FLAIR images with a validated rating scale. Associations among stroke characteristics, sleep parameters, and cognitive outcomes were analyzed with logistic regression.

RESULTS: Twenty-five children (64% female; median age 13.3 years),14 (56.0%) with AIS and 11 (44.0%) with high-risk conditions but no AIS, were included. Children with high-risk conditions without AIS had significantly greater odds of a high ePVS burden (OR=11.3, 95% CI [2.13, 82.1], p<0.01) than children with AIS. Children with idiopathic stroke showed lower odds of high ePVS burden compared to children with arteriopathies (OR=0.06, 95% CI [0.0004, 0.70], p<0.05). No significant associations were found between and sleep or cognitive outcomes.

CONCLUSIONS: Children with high-risk conditions and no AIS demonstrated significantly higher odds of elevated ePVS burden than those with AIS. These findings may guide early imaging biomarkers for high-risk stroke conditions. Larger studies are needed to confirm findings and establish clinical relevance.

KEYWORDS: Stroke, Neuroimaging, Sleep

488. To explore the clinical utility of transcranial doppler (TCD) with High-Intensity Transient Signals (HITS) in the evaluation of embolic stroke in a pediatric patient with severe iron deficiency anemia

Paige Estave, John Wright, Patrick Reynolds, Robert Goodrich

OBJECTIVE: To explore the clinical utility of transcranial doppler (TCD) with High-Intensity Transient Signals (HITS) in the evaluation pediatric embolic stroke

METHODS: Case report with review of literature

RESULTS: A previously healthy 28-month-old child presented with acute right arm weakness. Examination revealed pallor and diffuse hypotonia, and laboratory studies showed profound anemia with a hemoglobin of 1.6 g/dL. Non-contrast computed tomography of the head was unremarkable. Magnetic resonance imaging of the brain demonstrated multifocal acute and subacute infarcts with a non-occlusive thrombus in the right transverse sinus. Computed tomography angiography of the head and neck showed no large-vessel occlusion. Further evaluation revealed a right femoral deep venous thrombosis without evidence of an intracardiac shunt on transthoracic echocardiography. Given concern for an embolic etiology, TCD with HITS monitoring was performed, revealing bilateral HITS in the middle cerebral arteries. TCD with agitated saline demonstrated right-to-left shunting, raising suspicion for an extracardiac shunt. Computed tomography angiography of the chest was nondiagnostic due to suboptimal contrast timing.

CONCLUSIONS: TCD with HITS is a valuable yet underutilized tool for detecting active cerebral microembolization in pediatric stroke. In this case, TCD with bubble study demonstrated greater sensitivity than transthoracic echocardiography for identifying right-to-left shunting, consistent with existing literature. These findings underscore the need for further investigation into the role of TCD with HITS in pediatric embolic stroke, particularly when intracardiac shunts are not identified.

KEYWORDS: Stroke, Neuroimaging

489. Identifying Barriers to Timely MRI in Pediatric Stroke Alerts: A Multidisciplinary Needs Assessment and Quality Improvement Initiative

Laura Owlett, Robert Thompson-Stone

OBJECTIVE: Rapid clinical assessment and neuroimaging are essential in recognizing and diagnosing pediatric arterial ischemic stroke to enable consideration of hyperacute therapies. We performed a needs assessment to identify barriers contributing to delays in MRI acquisition for pediatric stroke alerts and to guide targeted workflow interventions.

METHODS: We conducted a quality improvement needs assessment of pediatric stroke alerts presenting to the emergency department at a tertiary children's hospital between March 2025–March 2026. Baseline workflow metrics included median time from stroke alert page-to-MRI and MRI order-to-MRI. Process mapping identified recurrent barriers contributing to imaging delays. Educational and workflow interventions were subsequently developed based on identified needs, including: (1) a standardized educational video for adult neurology residents covering pediatric stroke recognition and workflow expectations, (2) cognitive aid identification cards outlining stroke alert procedures, and (3) mock pediatric stroke code simulations to improve interdisciplinary coordination.

RESULTS: Baseline analysis demonstrated a median page-to-MRI time of 95 minutes for pediatric stroke alerts. Key contributors to delay included prolonged MRI safety screening, delays in coordination of braces removal, patient preparation challenges, and variability in provider familiarity with pediatric stroke workflows. Adult neurology residents were identified as a critical target for education given their central role in overnight stroke evaluations. Interventions addressing these barriers remain ongoing.

CONCLUSIONS: Our needs assessment identified multiple modifiable workflow barriers contributing to delayed MRI acquisition during pediatric stroke alerts. These findings informed the development of targeted educational, cognitive aid, and simulation-based interventions aimed at improving multidisciplinary coordination and imaging efficiency.

KEYWORDS: Stroke

490. Acute Unilateral Facial Paralysis During Air Travel: Barotrauma Mimicking an Acute Stroke.

Jaskiran Kaur, Mariah Ozkir

OBJECTIVE: Acute facial droop occurs secondary to stroke or facial nerve palsy. We report a case of transient unilateral facial nerve paralysis induced by barotrauma, This case report

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reviews neuroanatomy of the facial nerve and identifies a novel trigger of facial nerve paralysis observed in a pediatric patient.

METHODS: We present a case report of a 11-year-old female presenting to the pediatric emergency room for evaluation of acute facial nerve droop resulting in flight diversion. Retrospective chart review of the case was performed.

RESULTS: A 11-year-old girl presented with acute onset right sided facial droop while on a commercial flight. The patient endorsed pressure in right ear and eye prior to symptom onset. She endorsed facial numbness on her right cheek and forehead. An in-flight nursing assessment was remarkable for unilateral facial droop along with inability to close right eye and raise her right eyebrow. She had complete resolution of symptoms after descent. Upon presentation, she had a NIHSS of 0. A fast spin brain MRI did not demonstrate acute findings of ischemia. Further stroke protocol deferred due to resolution of symptoms and neurological exam mimicking peripheral nerve etiology. CT IACs demonstrated temporal bone dehiscence.

CONCLUSIONS: Facial nerve barotrauma can cause transient facial droop with forehead and eye involvement. The pathogenesis involves compression and ischemia of the facial nerve as it courses through the temporal bone due to pressure-related changes during ascent of flight. Prior case reports of adults have noted additional trigeminal involvement, as observed in this patient.

KEYWORDS: Stroke

Telemedicine

491. Tele-Neurology in Pediatric Practice: Implications for Rural Access and Health Equity

Julie Waineo, Rebecca Weber

OBJECTIVE: To map and synthesize the existing literature on the impact of tele-neurology on access to care among pediatric patients in rural, remote, and medically underserved settings.

METHODS: PubMed, Embase, and Scopus were searched for studies evaluating tele-neurology in pediatric populations in rural or medically underserved settings. Eligible studies included pediatric patients receiving synchronous, video-based tele-neurology and reported healthcare access or clinical outcomes. Reviews, case reports, nonclinical telehealth applications, and studies including adults were excluded. Two reviewers independently screened articles. Of 30 identified articles, seven met final inclusion criteria.

RESULTS: Of seven studies reviewed, four were completed in the United States and three were international. Study designs included retrospective cohort, cross-sectional, prospective observational, and quality improvement studies evaluating tele-neurology across pediatric neurologic conditions. Tele-neurology was associated with improved access to care, including higher appointment completion rates compared with in-person visits (73% vs 65%). Telemedicine consultations were also associated with lower hospital encounter rates (5.7 vs 20.1 per 100 patient years) and reduced neurologic related hospitalizations (3.7 vs 8.9 per 100 patient years). Further studies demonstrated comparable reliability of neurologic assessments performed via videoconferencing. Additional results reported reduction in missed work (48%), school hours (49%), and miles traveled. Three studies cited decreased costs associated with lower utilization of high-cost healthcare related to hospitalization.

CONCLUSIONS: This scoping review maps the existing literature on tele-neurology in pediatric populations and suggests potential improvements in access to care for rural and underserved communities. Further research is needed to clarify long-term outcomes and implementation strategies.

KEYWORDS: Telemedicine, Epilepsy, Diversity, Equity, Inclusion

492. Télémédecine en neurologie pédiatrique en Afrique : l'expérience du service de neurologie du CHU Ignace Deen

Malé DORE, Condé Mohamed, Camara Namory, Triki Chahnez, Diawara Karinka, Touré Mohamed, Soumah Cheick, Cissé Fodé

OBJECTIVE: Notre étude décrit l'expérience du service de neurologie d'un CHU de Guinée en matière de télémédecine en neurologie pédiatrique.

METHODS: Nous avons mené une Étude rétrospective de la collaboration en télémédecine entre le service de neurologie du CHU Ignace Deen, le CHU Hédi Chaker et le Massachusetts General Hospital, de janvier 2021 à juin 2025, portant sur des patients pédiatriques présentant des difficultés diagnostiques et thérapeutiques en neurologie

RESULTS: Au total, 35 enfants (âge moyen : 6 ± 3 ans, prédominance féminine) ont bénéficié d'une téléconsultation. Les difficultés étaient diagnostiques dans 65 % des cas et thérapeutiques dans 35 %. Les téléconsultations ont permis d'identifier des maladies neuromusculaires, des épilepsies et des affections neuro-immunes. Treize patients épileptiques ont bénéficié d'une optimisation thérapeutique vers des antiépileptiques de nouvelle génération, avec une amélioration clinique observée chez 70 % des patients.

CONCLUSIONS: La télémédecine constitue une avancée majeure dans le domaine de la santé, permettant la prestation de soins à distance, et offrant la possibilité d'élargir l'accès aux soins spécialisés dans les régions à faibles ressources du monde entier.

KEYWORDS: Telemedicine, Neuromuscular

493. Predictors of Telehealth Visit Completion and Visit Modality in Pediatric Epilepsy

Kathy Tran

OBJECTIVE: This study identifies patient characteristics that predict no-showing to telehealth appointments among children with epilepsy. This study also evaluates social determinants and epilepsy common data elements associated with completion of in-person versus telehealth appointments.

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METHODS: A retrospective cohort study evaluated 150 pediatric epilepsy visits from 2020 to 2023. The sample included 50 completed in-person, 50 completed telehealth, and 50 no-show telehealth encounters. Abstracted variables included geographic access, demographics, and clinical data from electronic medical records. Chi-Square tests, Fisher's exact test, independent T-tests, and Mann-Whitney U tests were used for statistical analysis.

RESULTS: Generalized epilepsy ($p=0.011$) and diagnosis of autism spectrum disorder ($p=0.022$) were both significant predictors of telehealth no-show status. Within the telehealth group, video encounters yielded higher completion rates than phone encounters ($p=0.001$). Completed telehealth visits were associated with longer driving times (64.94 versus 37.86 minutes; $p=0.046$) and urban RUCA zones ($p<0.001$) compared to in-person visits. In-person patients more frequently reported well-controlled seizures ($p=0.002$) and lower comorbidity counts ($p=0.034$). Cerebral palsy ($p=0.033$) and developmental delay ($p=0.025$) were also significantly associated with in-person visit completion.

CONCLUSIONS: Telehealth effectively mitigates geographic and socioeconomic barriers to pediatric epilepsy care as demonstrated during the COVID-19 pandemic. Video-based telehealth may better support patient adherence than audio-only encounters. Patients with specific neurodevelopmental comorbidities, particularly autism spectrum disorder, demonstrate an increased risk for missed telehealth appointments. Targeted interventions are necessary to ensure equitable continuity of care.

KEYWORDS: Telemedicine, Epilepsy, Diversity, Equity, Inclusion

494. Feasibility of a Two-Tier Telehealth Screening Model for Early Detection of Neurodevelopmental Risk in Infants Aged 2–12 Months

Keziah Edmunds, Aditi Basu, Gaelle Umutoni Mihigo, Kylie Hapuarachchi, Xiomara Shoukry, Samara Lipsky, J.David Nugent, Anne Gordon, Phyllis Kittler, Ha Phan

OBJECTIVE: In the United States, about 1 in 6 children has a neurodevelopmental disability (NDD) or delay. Many miss early screening, resulting in delayed diagnoses and a lag in critical early intervention services. This study aims to evaluate the feasibility of a two-tier telehealth screening program for early detection of NDD risk in infants within a hospital-based birth cohort.

METHODS: A cross-sectional study was conducted on 2, 4, 6, 8, and 12-month old infants using two-tier screenings. First-level screenings used online Ages and Stages Questionnaires (ASQ-3 and ASQ:SE-2), and second-level screenings added in-person Bayley-4 assessments. Positive screenings represent increased risk for NDD, requiring diagnostic clarification and Early Intervention services as needed.

RESULTS: Overall, across infants screened at 2 months (305), 4 months (250), 6 months (175), 8 months (159), and 12 months (79), 27.88%–40.74% screened positive for neurodevelopmental risk in at least one domain. Higher risk was observed in motor (gross [0.78%-7.50%], fine [2.47%-9.94%]), personal-social (2.56%-7.30%) and problem-solving (0.78%-8.13%). On ASQ:SE-2 (6 and 12 months), ~8% screened positive. In-person evaluation was offered to 8%–15% of participants, and ~15% completed a diagnostic Bayley-4. Early Intervention evaluation was suggested in ≤3.6%, but referrals were made in ≤2%.

CONCLUSIONS: A two-tier telehealth screening model using online ASQs and in-person Bayley-4 follow-up is feasible and identifies infants with NDD risk early in life. However, the low rate of diagnostic completion highlights the ongoing challenge to close the critical gap between early risk detection and timely diagnosis to ensure that intervention occurs during peak developmental neuroplasticity.

KEYWORDS: Telemedicine, Neurodevelopmental Disorders, Early Stage Investigator

Traumatic Brain Injury

495. Transforming Pediatric Care: Technological Innovations for Concussion Prevention and Monitoring

Harshitha Valluri, Alcy Torres

OBJECTIVE: The growing incidence of pediatric concussions highlights the need for improved prevention, monitoring, and management. This article offers an updated overview of pediatric concussion, with a focus on technological innovations in prevention and monitoring.

METHODS: The article is a focused literature review, highlighting recent developments in technology for risk reduction, real-time detection, and individualized management.

RESULTS: Advances in helmet engineering, including fluid-based shock absorbers and rotational damping systems, reduced simulated concussive and subconcussive impacts by up to 33% in laboratory models. Airbag-integrated bicycle helmets significantly reduced concussion risk in cycling. Sensor-enabled helmets, ferro-electret nano-generator neck patches, and other wearable technologies could enable real-time risk prediction, improved concussion assessment, and identification of physiologic abnormalities persisting beyond symptom resolution. Instrumented mouthguards have achieved up to 99.98% precision in head impact classification in controlled conditions and are being advanced with LED impact indicators. Telehealth-based tools such as the Tele-Buffalo Concussion Physical Examination demonstrate strong reliability (inter-modality ICC = 0.95; inter-rater ICC = 0.88). Eye-tracking, virtual reality, and machine-learning technologies demonstrated high diagnostic performance in concussion detection. Blood-based biomarker tests demonstrated up to 97.6% sensitivity for detecting intracranial injury, enabling faster screening and reducing radiation exposure in children.

CONCLUSIONS: Technological innovations show promise in transforming the prevention, detection, monitoring, and management of pediatric concussion, ultimately improving outcomes for children. These advancements may enhance safety in sports, recreation, and daily activities while

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providing data to guide research and clinical decision-making. Further research to validate these technologies in the pediatric population is needed, especially in underserved groups.
KEYWORDS: Traumatic Brain Injury, Education

496. Early Outcome Prediction in Pediatric Drowning-Related Anoxic Brain Injury

Lin Yao, Sarah Risen, Athanasios Papastathopoulos-Katsaros, Zhandong Liu

OBJECTIVE: To develop an early predictive model for neurologic outcomes after pediatric drowning-related anoxic brain injury (ABI) using readily available physiologic and metabolic variables.
METHODS: We performed a retrospective cohort study of children admitted to the pediatric intensive care unit with drowning-related ABI from 2010–2026 (n=439). Early demographic, physiologic, and metabolic variables were analyzed, including heart rate, blood pressure, glucose, and lactate. Predictive modeling was performed for mortality and neurologic outcomes, including major neurologic complications, epilepsy/seizures, gastrostomy dependence, and tracheostomy dependence. Model performance was assessed using area under the receiver operating characteristic curve (AUC).
RESULTS: The cohort was 71% male, and 64.5% were 1–4 years old. Overall mortality was 12.0%. Neurologic morbidity remained substantial, including major neurologic complications in 14.5% and epilepsy/seizures in 12.5%. Among early predictors, combined metabolic modeling with glucose and lactate demonstrated the strongest discriminative performance, with AUCs of 0.786 for gastrostomy dependence, 0.768 for epilepsy/seizures, and 0.744 for tracheostomy dependence. Blood pressure- and heart rate-based models demonstrated weaker discrimination than metabolic features in preliminary analyses.
CONCLUSIONS: Early outcome prediction after pediatric drowning-related anoxic brain injury using acute clinical data shows promise for risk stratification. Metabolic features appear to provide stronger prognostic signal than early hemodynamic screening variables, supporting further development of multimodal predictive tools for pediatric ABI.
KEYWORDS: Traumatic Brain Injury, Neurocritical Care, Practice Parameters

497. Age and Grade-Level Differences in Reported Sports-Related Concussions Among Texas High School Athletes

Sydney Carter-Santos, Joshua Beitchman, Cason Hicks, Munro Cullum, Mathew Stokes

OBJECTIVE: To analyze age and grade-level differences in reported concussions among Texas high school athletes.
METHODS: This retrospective review of prospectively collected data from the statewide RankOne database of athletic injuries. A total of 18,118 sports-related concussions (SRC) were reported among Texas high-school athletes between April 2023 and April 2025. Chi-square tests were used to assess differences across grade levels (9th–12th) and age groups (14–19 years). Age and grade differences were identified using post-hoc z-score analysis with a Bonferroni correction ($z > 2.5$, $p < 0.05$).
RESULTS: Significant differences were observed across both grade levels and age groups (χ^2 test, df=5, $p<0.0001$). Ninth- and 10th-grade athletes had significantly higher reported concussions than statistically expected (z=31.02 and 12.22), while 11th- and 12th-graders had lower-than-expected reports (z=–6.58 and –36.67). Age analysis showed that middle age groups (15–17 years) had more reported concussions, whereas the youngest (14 years) and oldest (18–19 years) groups reflected fewer concussions (14 yr: z=-30.50, 15 yr: z=51.56, 16 yr: z=41.48, 17 yr: z=15.45, 18 yr: z=-25.08, 19 yr: z=-52.83).
CONCLUSIONS: Younger athletes (9^{th} and 10^{th} grades, aged 15-17) had higher rates of reported concussions. Although these findings emphasize the role of biological maturity in concussion risk, the comparatively fewer reports in 14-year-olds highlight how additional factors, including team composition, prior experience, and playing time, may influence data. Targeted interventions focused on biological maturity and team demographics are needed to further explore the relationship between age and concussion risk in pediatric athletes.
KEYWORDS: Traumatic Brain Injury

498. Long-Term Multidisciplinary Follow-Up in Pediatric TBI: Accidental vs. Abusive Head Trauma

Shannon Shipley, Ellie Gabriel, Barbara Chaiyachati, Nankee Kumar, Laura Didomenico, Vanessa Mazandi, Kumaran Senthil, Todd Kilbaugh, Shih-Shan Lang, Jimmy Huh

OBJECTIVE: Pediatric traumatic brain injury (TBI) follow-up care remains poorly characterized, particularly among patients with abusive head trauma (AHT), a leading cause of morbidity in young children. This study evaluated discharge referral and long-term specialty follow-up patterns comparing children hospitalized for AHT versus accidental head trauma (Acc) to identify chronic follow-up needs.
METHODS: We retrospectively analyzed records of 2,065 children aged 0–5 years hospitalized at a level I trauma center with moderate to severe TBI, comparing AHT (n=190) vs. Acc mechanism. Referral and visit trends across 14 subspecialty categories over five years post-discharge were compared using Fisher's exact test and logistic regression.
RESULTS: Compared to their Acc counterparts, patients with AHT were younger (9.0 vs. 17.5 months, $p<0.01$) and more likely publicly insured (78% vs. 46%, $p<0.01$). Children with AHT had significantly higher outpatient visit rates within the first year after discharge in gastroenterology/nutrition (OR 4.64), surgery (2.65), neurology (6.62), neurosurgery (2.50), ophthalmology (6.23), physical medicine & rehabilitation (4.66), and social support (5.07). Visit rates to neurology, PM&R, and ophthalmology remained higher for at least the first five years ($p<0.01$). In both cohorts, incidence of a referral markedly increased odds of follow-up ($p<0.001$) and shortened time-to-visit ($p<0.01$).
CONCLUSIONS: Children hospitalized with AHT persistently demonstrated greater multidisciplinary follow-up needs. Referrals increased follow-up rates and reduced time-to-visit in all TBI patients. Evidence-informed, standardized referral and multidisciplinary follow-up models may improve

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continuity of care and ultimately improve outcomes for children with TBI, especially AHT populations.
KEYWORDS: Traumatic Brain Injury, Neurocritical Care, Diversity, Equity, Inclusion

499. Hockey Concussion Reporting and Return-to-Play Determinants Scale (HCR-RTPDS) to Highlight External Influences on NCAA Hockey Concussion Reporting

Connor McGinnis, Gustavo Rivas-Martínez, Alcy Torres

OBJECTIVE: The purpose is to develop a foundational understanding of the most relevant external factors contributing to concussion under-reporting in National Collegiate Athletic Association (NCAA) men's ice hockey. This is a pilot stage evaluation utilizing a NCAA hockey program to focus on comprehension, feasibility, and sample size calculation.
METHODS: A Qualtrics survey including demographics, concussion knowledge, medical history, motivations to return to play, competitive decision making, and financial and career incentives was developed and validated by five neurological experts via Likert scale for relevance, coherence, and clarity. The survey was dispersed by athletic trainers to their players, and frequencies and percentages were calculated.
RESULTS: Of the respondents, 45.5% (n=5/11) reported at least one medically diagnosed concussion, while 100% (n=11/11) reported they suspect sustaining at least one undiagnosed concussion during their hockey career. A hypothetical playoff scenario indicated 80% (n=8/10) of respondents would not immediately report concussion like symptoms. The most frequently endorsed return-to-play motivations were desire to win, desire to maintain lineup/roster position, and legacy/reputation/desire to maintain image, each reported by 90% (n=9/10). Fear of losing playing time was endorsed by 80% (n=8/10). Feasibility responses supported continued use of the instrument, with 100% (n=9/9) reporting the survey is understandable, and 77.8% (n=7/9) feeling the survey length is appropriate.
CONCLUSIONS: This pilot evaluation suggests the instrument is feasible and capable of capturing relevant patterns in concussion reporting behavior and return-to-play decision-making. The observed trends indicate potential underreporting of head injuries due to external motivations, suggesting evaluation of the structural incentives of the sport.
KEYWORDS: Traumatic Brain Injury, Behavioral Neurology, Education

500. The Concussion Coalition: Medical Student-Led Concussion Care for Underserved Detroit High School Athletes

Connor McGinnis, Clayton Kramm, Jack Summers, Gabriel Doree, Mitchel Williams

OBJECTIVE: Detroit Public Schools (DPS) includes twenty high schools offering twenty-three different sports but lack the resources to staff teams with athletic trainers. These constraints result in increased risk for neurological complications from undiagnosed head injuries. In partnership with the Detroit Public Schools Health Corps (DPSHC) and the Children's Hospital of Michigan Concussion Clinic, our aim is to improve awareness, recognition, diagnosis, and longitudinal follow-up care for head injuries among high school student-athletes in Detroit, MI.
METHODS: On-field medical students have been trained via peer-led sessions to recognize and assess on-field head injury using the sport concussion assessment tool (SCAT6). Upon a suspected concussion, the athlete will be removed from play, an incident report will be created, and information will be documented in a HIPAA secure database. A referral to the multidisciplinary concussion clinic will be made, and a return-to-play protocol will be formulated and communicated to DPS athletic and academic departments to ensure players are not returning to play without proper clearance.
RESULTS: Prior documentation by the DPSHC shows a total of 20 (male=11, female=9) head impact incident reports stemming from football, basketball, softball, and soccer over 3 years. Football contributed the most incidents with 8/20 reports. Unfortunately, only 4 of those athletes were documented as having followed up with a physician, resulting in only 3 concussion diagnoses.
CONCLUSIONS: This community outreach initiative will increase concussion awareness, ensure accurate sideline testing and patient documentation, and provide clinical follow-up ensuring an individualized and evidence-based return to play protocol.
KEYWORDS: Traumatic Brain Injury, Diversity, Equity, Inclusion, Education

501. A Meta-Analysis of Cephalohematoma Resulting From Mechanical Birth Trauma: An Update On Relevant Risk Factors

Connor McGinnis, Gustavo Rivas-Martínez, Alcy Torres

OBJECTIVE: The literature on risk factors for cephalohematoma resulting from mechanical birth trauma is outdated. A cephalohematoma, the most common birth-related head injury, is a collection of blood between the periosteum and the skull that is confined by the cranial sutures. Historically, risk has been associated with forceps and vacuum extraction, but these techniques are used in only about 3% of U.S. births today. It is therefore essential to provide updated and more pertinent risk factors.
METHODS: We conducted an in-depth meta-analysis of cephalohematoma cases. Following the guidelines of PRISMA and the Cochrane Handbook, and addressing heterogeneous study designs, odds ratios (ORs), 95% confidence intervals (CIs), and p-values were calculated and interpreted using MedCalc Statistical Software.
RESULTS: We documented 1,349 cases of cephalohematoma out of 132,422 total births, yielding an overall incidence rate of 1%. Primiparity was significantly associated with cephalohematoma: Primiparity was 2.14 times more likely to result in a cephalohematoma than multiparity (95% CI=(1.93,2.37),P<0.0001). Primiparity showed 1.92 times greater odds of cephalohematoma than general vaginal delivery (95% CI=(1.73,2.13),P<0.0001). Primiparity showed 1.18 times greater odds of presenting with a cephalohematoma than the combination of forceps and vacuum extraction (95% CI=(1.08,1.29),P=0.0002).
CONCLUSIONS: Our findings suggest fundamental cephalohematoma risk factors, such as parity, may be more

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influential and relevant than previously emphasized. Medical teams and families must be educated on the more pertinent risks, particularly those associated with primiparous mothers. Additional risk factors such as labor duration may also play an essential role, but the existing data warrants further research.
KEYWORDS: Traumatic Brain Injury, Neonatal Neurology, Fetal Neurology

502. Incidence of infantile epileptic spasms syndrome and response to treatment in patients with abusive head trauma

Anna Leigh McVicar, Sarah Graber, Amy Connery, Ricka Messer

OBJECTIVE: Approximately 30% of patients with abusive head trauma (AHT) develop post traumatic epilepsy (PTE), but the incidence of infantile epileptic spasms epilepsy (IS) is not known. Understanding timing to IS diagnosis and response to treatment could help initiate appropriate treatment sooner.
METHODS: We utilized a database of 373 patients admitted for AHT between 2012-2020. The majority (263/373, 70.5%) had long-term follow-up in our multidisciplinary clinic, and 31 (11.8%) of those developed PTE. We completed extensive chart review for 12 patients who developed IS within 2 years. Notably, 10/12 patients had severe cytotoxic edema on initial brain imaging.
RESULTS: The median time from AHT to IS diagnosis was 122 days, at a median age of 8.6 months. Median time from parental awareness of new movements to IS diagnosis was 5.5 days. 5/12 patients had prior EEGs for non-epileptic spells, and 2/12 had already been diagnosed with PTE. EEG did not show hypsarrhythmia in 5/12. Initial IS treatment included: 4 ACTH, 1 prednisolone, 5 vigabatrin, 2 topiramate. Although only 4/12 patients responded to their first treatment (3 ACTH, 1 vigabatrin), an additional 5/12 responded to their second treatment (1 ACTH, 1 prednisolone, 3 vigabatrin). None responded to non-standard therapies.
CONCLUSIONS: Patients with AHT are at risk for developing IS within the first 2 years after their injury. Most patients responded to either the first or second treatment with ACTH, prednisolone, or vigabatrin. Appropriate counseling is paramount to early identification of IS, and treatment with standard therapy is warranted despite concerns for significant brain injury.
KEYWORDS: Traumatic Brain Injury, Epilepsy, Neurocritical Care

Late Breaking Abstracts

503. ABCs of Child Neurology: Building Self-Directed Learners Through an Asynchronous Curriculum — A Qualitative Study

Elizabeth Troy, John Meshramkar, Michelle Tutmaher, Michelle Kiger

OBJECTIVE: *ABCs of Child Neurology (ABCs)*, an asynchronous article-based curriculum structured around the Master Adaptive Learner (MAL) framework, was developed to build competency in foundational principles and foster self-directed learning. This qualitative study examined how *ABCs* shapes learning strategies among child neurology residents and identified contextual factors influencing implementation.
METHODS: *ABCs of Child Neurology* was piloted at a single institution in 2024–2025 and expanded to nine institutions in 2025–2026. PGY3–PGY5 child neurology residents participated in virtual semi-structured focus groups in May and June of 2025 and 2026 to describe their experiences with the curriculum and reflect on its impact on their self-directed learning behaviors. Program directors also participated in focus groups in 2026. Transcripts are currently being analyzed using inductive thematic analysis, guided by the MAL framework as a sensitizing concept.
RESULTS: Across nine institutions, 26 participants completed eight focus groups, including 8 PGY5s, 6 PGY4s, 4 PGY3s, and 8 program leaders. In the initial analysis from the 2025 data, three themes were constructed: ABCs functioned as a cognitive scaffold for clinical learning, curated resources improved learning efficiency, and curriculum structure modified the depth of learning. Preliminary multi-center analysis is ongoing to examine how local context shapes engagement across MAL phases and influences self-directed learning and depth of learning.
CONCLUSIONS: This analysis will inform iterative refinement of the *ABCs* curriculum. Findings suggest *ABCs* supports self-directed learning by scaffolding engagement across MAL phases. Understanding how implementation is shaped by local context will inform broader dissemination.
KEYWORDS: Education

504. DSP-0378, a Novel Multimodal GABAA Receptor Positive Allosteric Modulator, Demonstrates Efficacy in Benzodiazepine-Resistant Models and Translational EEG Modulation in Humans

Saki Sakurai, Hitomi Tsuchida, Mika Endo, Yuka Ishikawa, Noboru Iwagaki, Tasuya Ishikawa, Taro Kato

OBJECTIVE: Limited efficacy of current GABAergic therapies highlights the need for more potent approaches. This work defined the pharmacological profile of DSP-0378, evaluated its antiseizure efficacy in benzodiazepine-resistant models, and assessed its initial clinical profile in a Single Ascending Dose (SAD) study.
METHODS: DSP-0378 was evaluated in vitro for GABAA receptor activation, followed by the assessment of hippocampal granule cell firing in a Nav1.1 dysfunction (Dravet syndrome) model. In vivo pharmacokinetics and efficacy were evaluated in rodent acute, Dravet febrile, and benzodiazepine-resistant seizure models. The SAD study in healthy Japanese male subjects evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics using EEG.
RESULTS: DSP-0378 potentiated synaptic and extrasynaptic GABAA receptors independent of the benzodiazepine binding site. Unlike clobazam, DSP-0378 performed potent inhibitory controls over the excitability of granule cell firing in Dravet brain slices. DSP-0378 suppressed seizures in multiple models, such as Dravet syndrome, benzodiazepine-resistant status epilepticus, and a benzodiazepine tolerance model. In the SAD study, DSP-0378 was well tolerated at

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the doses that increased EEG beta power. This increase was dose-dependent and reached a pharmacologically predictive range of efficacy.

CONCLUSIONS: DSP-0378 showed broad antiseizure efficacy in various models including benzodiazepine-resistant models, supporting its potential for refractory epilepsy. Clear GABA-related EEG modulation at well-tolerated exposures in humans supports the translation of the GABAA receptor-mediated antiseizure effects observed in the nonclinical model to patients. Further evaluation is ongoing in a multiple ascending dose study and a Phase 1b study in progressive myoclonus epilepsy.

KEYWORDS: Epilepsy, Experimental Therapeutics

505. Cannabidiol Effectiveness in Patients With Lennox-Gastaut Syndrome of Diverse Etiologies Compared With External Placebo Control: A Post Hoc Analysis From the US Expanded Access Program

Karthik Rajasekaran, Eric Marsh, Catherine Passariello, Teresa Greco

OBJECTIVE: To evaluate cannabidiol (CBD; Epidiolex® [US], 100 mg/mL oral solution) effectiveness in patients with Lennox-Gastaut syndrome (LGS) arising from diverse etiologies.

METHODS: This post hoc analysis included patients with LGS from the 48-week US Expanded Access Program (EAP) who received CBD 25–50 mg/kg/day. Percent change from baseline in median monthly convulsive and total seizure frequencies and ≥50% responder rates at Week (W)12 and W48 were assessed. Using case report forms, LGS etiology was subclassified into structural, genetic, and not-otherwise-specified (NOS) categories. Outcomes at W48 were compared with an external control arm (ECA) from LGS CBD randomized, controlled trials (NCT02224560, NCT02224690) using propensity score–based inverse probability weighting (multiplicity-adjusted critical $\alpha=0.025$). Safety was assessed through W48.

RESULTS: Data from 226 EAP-enrolled patients were analyzed (mean age: 13.8 years; common concomitant antiseizure medications: clobazam [55.3%] and levetiracetam [38.1%]). At W48, median changes in convulsive (n=128) and total (n=143) seizure frequency from baseline were −52.9% and −52.6%, with 52% and 53% responder rates, respectively. Median changes in total seizure frequency were −35.2%, −51.2%, and −55.2% across structural (n=47), genetic (n=31), and NOS (n=140) etiology groups, respectively. W12 and W48 responses were similar. Compared with the ECA, after balancing baseline characteristics, changes from baseline were −51% and −49% with CBD (n=166) versus −24% and −23% with placebo (n=155) for convulsive and total seizure frequency, respectively (treatment ratio: 0.64 and 0.66; both P<0.0001). Treatment-related adverse events occurred in 59.7% of patients.

CONCLUSIONS: The data support CBD effectiveness in reducing seizures relative to ECA across diverse LGS etiologies.

KEYWORDS: Epilepsy, Neurodevelopmental Disorders, Neurogenetics

506. Fremanezumab, A CGRP Pathway-Targeting Monoclonal Antibody for Migraine Prevention in Children and Adolescents: Findings by Weight-Based Dose in the Space Open-Label Extension study

Jennifer McVige, Christina Szperka, Andrew Hershey, Marcy Yonker, Janace Gifford, Thomas Li, Juline Bryson

OBJECTIVE: Fremanezumab is approved for prevention of episodic and chronic migraine (EM; CM) in adults and for prevention of EM in children aged 6–17 years weighing ≥45kg in the US and elsewhere. SPACE EM (NCT04458857) and SPACE CM (NCT04464707) were randomized, placebo-controlled, double-blind 3-month studies of monthly fremanezumab in children and adolescents (6–17 years) with migraine. We report effectiveness and safety findings from the 9-month SPACE open-label extension study (OLE; NCT04530110).

METHODS: Eligible participants from SPACE EM and SPACE CM entering the OLE received monthly fremanezumab (<45kg: 120 mg; ≥45 kg: 225 mg) for 9 months, followed by 5 months of safety follow-up. The primary endpoint was safety. Secondary effectiveness endpoints were assessed relative to the original baseline period and included change from baseline monthly migraine days (MMD) and monthly headache days of at least moderate severity (MHD-MS) at Months 1, 5 and 9.

RESULTS: No new safety signals were observed during the OLE. Among participants with data at Month 9 (n=281), mean (95% CI) reductions from baseline MMD (120 mg group: –4.6 [–5.8, –3.4]; 225 mg group: –5.8 [–6.7, –4.9]) and MHD-MS (120 mg group: –5.4 [–6.7, –4.1]; 225 mg group: –6.3 [–7.2, –5.5]) were observed, with evidence of month-on-month improvement among participants with CM.

CONCLUSIONS: SPACE OLE findings support the effectiveness of fremanezumab for migraine prevention in children and adolescents with EM and the long-term safety of fremanezumab in children and adolescents with EM and CM.

KEYWORDS: Headache

507. Plasma-Proteomics for Biomarker Discovery in KIF1A-Associated Neurological Disorder (KAND)

Joseph Holtey, Habibah Agianda, Amy Tam, Hyo-Min Kim, Joshua Rong, Michelle Grambs, Beril Ay, Katerina Bernardi, Vicente Quiroz, Kathryn Yang, Pui Lee, Wendy Chung, Darius Ebrahimi-Fakhari

OBJECTIVE: KIF1A-associated neurological disorder (KAND) is caused by heterozygous pathogenic variants in KIF1A, a kinesin-3 motor essential for anterograde axonal transport of synaptic vesicle precursors. Validated fluid biomarkers for KAND are lacking. We used an unbiased plasma proteomics approach to identify candidate biomarkers and examine associations with clinical severity in KAND.

METHODS: We performed a cross-sectional study of 38 individuals with genetically confirmed KAND and 52 age- and sex-matched healthy controls. Plasma proteins were measured with the Olink Target 48 Neurodegeneration panel. Differentially abundant proteins (DAPs) between KAND and controls were identified using linear models on

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log2-transformed concentrations, adjusted for age and sex, with Benjamini–Hochberg correction for multiple testing. Associations between DAPs and clinical severity scores (GMFCS, SPRS, SPATAX) were examined with multivariable regression. Proteins were considered significant based on FDR-adjusted p-values, with effect sizes reported as age- and sex-adjusted log2 fold changes.
RESULTS: Plasma from KAND patients showed a distinct proteomic signature relative to matched controls. DAPs elevated in KAND included BACE1, Aβ40, Aβ42, pTau217, and BMP7, while ENO2, GLRX, HLA-DRA, FOXO3, and DDAH1 were reduced. Several DAPs were associated with GMFCS, SPRS, and/or SPATAX scores, indicating protein–phenotype relationships within the cohort.
CONCLUSIONS: Plasma proteomic profiling reveals a distinct signature in KAND that correlates with disease severity and nominates candidate biomarkers for further study. Notably, several markers traditionally linked to adult neurodegeneration (BACE1, Aβ species, pTau217) were elevated in this childhood-onset neurodegenerative disease, warranting mechanistic investigation. Validation in larger longitudinal cohorts is planned.
KEYWORDS: Movement Disorders

508. Movement Disorders Associated with Infantile Epileptic Spasms Syndrome: Prevalence, Spectrum, and Etiological Correlates: A Single-Centre Experience from North America

Sayoni Roy Chowdhury, Ruba Alayed, Lyndsey McRae, Lindsey Vogt, Puneet Jain, Gregory Costain, Vann Chau, Carolina Gorodetsky

OBJECTIVE: Primary objective was to estimate prevalence of movement disorders (MDs) in children with infantile epileptic spasm syndrome (IESS). Secondary objectives included characterizing spectrum of MDs, onset, etiology, and neurodevelopment.
METHODS: We conducted a retrospective chart review of children with IESS who were longitudinally followed in Infantile Spasms Clinic at a quaternary centre in Canada, June 2018-May 2026. Clinical data, MRI, and genetic results were extracted using a standardized data collection form.
RESULTS: A total of 140 children with IESS were enrolled (male-82%). Coexistent MDs were identified in 42 children (30%). Most prevalent MD was dystonia (n=28, 67%), followed by stereotypies (n=8, 19%), chorea (2), tremor (2), ataxia (2), and non-epileptic myoclonus (1). All cases had persistent MDs except for two children with transient MDs due to vigabatrin-associated tremor. In 96% of children, spasms (median age at onset: 6 months) preceded the onset of MDs (median age at onset: 9 months). Compared to isolated IESS group, children with IESS and coexistent MDs had fewer unknown etiologies (7% vs. 34.6%, p<0.001), more frequent abnormal MRI findings (85% vs. 67%, p<0.001), greater neurodevelopmental impairment (90% vs. 45%, p<0.001), and more drug-refractory epilepsy (53% vs. 22%, p=0.02).
CONCLUSIONS: Children with IESS have a substantial burden of coexisting MDs, which tend to emerge later in disease course and are associated with greater neurodevelopmental impairment and drug-resistant epilepsy. These findings support recognition of IESS with MDs as a distinct & severe phenotype, highlighting importance of screening for MDs in IESS cohorts to aid prognostication and guide management.
KEYWORDS: Movement Disorders, Epilepsy

509. Preemie-Predict: A Machine Learning-Based Neuroprognostication Calculator for Children Born Preterm

Rhandi Christensen, Vinicius Furlan, Katherine Langille, Aasthaa Bansal, Linda de Vries, Vann Chau, Mehmet Cizmeci, Linh Ly, Helen Branson, Ting Guo, Ruth Grunau, Steven Miller

OBJECTIVE: Neurodevelopmental outcomes in children born preterm are highly variable, posing challenges for neuroprognostication and risk-stratification. The objective of this study was to develop a novel machine learning-based algorithm to predict outcomes in children born preterm.
METHODS: A prospective preterm cohort (N=545) born 24-32 weeks gestation was followed from birth to 4.5-years with clinical, neuroimaging and developmental data collection. Neurodevelopmental outcomes were assessed using standardized measures and dichotomized (normal, abnormal) based on established cutoffs. Brain MRI was performed after birth and at term-equivalent age. Machine learning (XGBoost) was used to develop an algorithm for outcome prediction. Model performance was evaluated using sensitivity and specificity. Internal validation was performed using leave-one-out cross-validation.
RESULTS: The Preemie-Predict algorithm is accessible as a neuroprognostication calculator online (https://preemie-predict.sickkids.ca/). Model inputs include gestational age, sex, parental education, neonatal morbidities, and brain injury. Model outputs include predicted outcomes for cognitive, language, and motor domains (normal, abnormal). Several iterations of model training and testing were performed to optimize predictive performance. The final model demonstrated 86% sensitivity, 42% specificity for cognitive outcomes, 90% sensitivity, 39% specificity for language outcomes, and 89% sensitivity, 30% specificity for motor outcomes. High sensitivity was prioritized over specificity as missing an at-risk child (a false negative) has greater clinical consequences than incorrectly classifying a child as at-risk (a false positive).
CONCLUSIONS: Preemie-Predict is an innovative clinical tool to support neuroprognostication and precision health for children born preterm. Clinicians worldwide can access this online tool for data-driven neuroprognostication and targeted clinical care for children born preterm.
KEYWORDS: Neonatal Neurology, Neurodevelopmental Disorders

510. Design, Implementation, and Initial Findings from the Rett Syndrome Global Registry

Genevieve Laforet, HyunAh Lee, Monica Coenraads, Bo Zhang

OBJECTIVE: Rett syndrome (RTT) is a rare X-linked neurodevelopmental disorder caused by pathogenic *MECP2*

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variants. The Rett Syndrome Research Trust (RSRT) established the Rett Syndrome Global Registry for standardized worldwide collection of caregiver-reported data capturing Rett Syndrome natural history and heterogeneity, treatment patterns, and healthcare utilization.

METHODS: The Rett Syndrome Global Registry is a secure, international, web-based observational registry. Caregivers consent electronically then complete two survey tiers. Tier 1 captures demographics, diagnosis, genetic testing, current symptoms, symptom impacts, and educational participation. Tier 2 captures longitudinal clinical history, developmental milestones, medications, therapies, dietary interventions, surgeries, healthcare utilization, access to care, assistive devices, clinical trial participation, and mortality. Differences between US and non-US participants were evaluated using descriptive statistics and appropriate hypothesis tests.

RESULTS: The registry enrolled 1,017 participants (1,010 [99.3%] living, 83.3% female). Median age was 121 months (IQR 72–218); 97.2% had genetic testing. Core survey completion exceeded 60% for major clinical modules. Developmental delay (87.9%) and regression (78.6%) were common, as were communication impairment (84.0%), stereotypic hand movements (80.7%), mobility impairment (77.8%), epilepsy/Rett spells (55.5%), and gastrointestinal dysfunction (44.4%). US participants more frequently reported gastrointestinal dysfunction (56.8%>38.9%, P<0.001), feeding-tube placement (29.2%>6.4%, P<0.001), scoliosis surgery (15.5% >5.4%, P<0.001), emergency healthcare utilization (52.2% >31.4%, P<0.001), and clinical trial participation (13.8% >5.0%, P<0.001).

CONCLUSIONS: The Rett Syndrome Global Registry represents the largest international Rett cohort to date. These newly completed analyses provide the first global comparison of clinical characteristics, treatment patterns, and healthcare utilization across geographically diverse Rett populations, generating important real-world evidence to support clinical research and therapeutic development.

KEYWORDS: Neurodevelopmental Disorders, Lifespan Manifestations of Childhood Onset Conditions

511. RGX-202, an investigational gene therapy for the treatment of Duchenne muscular dystrophy: Pivotal topline results from the Phase III AFFINITY DUCHENNE® study

Jahannaz Dastgir, Steve Pakola, Aravindhan Veerapandiyan, Crystal Proud, Nancy Kuntz, Amy Harper, Susan Iannaccone, Carolina Tesi-Rocha, Erika Finanger, Cuixia Tian, Han Phan, Eleonora D'Ambrosio, Dimah Saade, Hernan Gonorazky, Catherine Wilson, Jonathan Marra, Jenny McQuiston, Nidal Boulos, Elisa Tsao, Hiren Patel, Michele Fiscella, Wesley Bond, Koji Takahashi, Olivier Danos

OBJECTIVE: Duchenne muscular dystrophy is a progressive, lethal muscle disease caused by mutations in the *DMD* gene encoding dystrophin. Investigational RGX-202 is a one-time AAV gene therapy to deliver an optimized microdystrophin including the C-Terminal (CT) domain from dystrophin, which preserved skeletal and cardiac muscle health in preclinical studies.

METHODS: AFFINITY DUCHENNE® is a multicenter, open-label phase I/II/III trial evaluating the safety, tolerability, and efficacy of a single IV infusion of RGX-202 for ambulatory boys with Duchenne. The phase III trial enrolled boys ages 1 and older (n=31).

RESULTS: Topline results from the phase III trial were previously reported (May 14, 2026). RGX-202 was well tolerated, and common drug-related adverse events included vomiting (n=19), fatigue (n=11), and nausea (n=10). Two drug-related serious adverse events were reported and resolved without sequelae. Mean microdystrophin expression in biopsies of evaluable participants (n=30) exceeded 10% at Week 12, meeting the primary endpoint with high statistical significance. Interim functional analysis of 9 participants was also conducted, with functional outcomes analyzed using multiple validated methods to estimate expected disease progression without treatment. Participants showed functional improvement and exceeded external propensity score-weighted controls at 1 year (n=9). Microdystrophin expression also statistically significantly correlated with functional improvement on North Star Ambulatory Assessment.

CONCLUSIONS: In the phase III trial, RGX-202 was well tolerated and met the primary endpoint of >10% microdystrophin expression with high statistical significance. Interim functional data shows improvement over externally matched controls and statistically significantly correlated with microdystrophin expression. A confirmatory trial enrolling approximately 30 patients has completed enrollment.

KEYWORDS: Neuromuscular, Experimental Therapeutics

512. Early Implementation of a Combined Pediatric Teleneurology and Telestroke Network Across the Mountain West

Lisa Pabst, McKenna Coletti, Betsy Ostrander, Joshua Bonkowsky, Gary Nelson

OBJECTIVE: To evaluate implementation metrics, diagnostic yield, and patient dispositions associated with the parallel deployment of pediatric telestroke and teleneurology services across a regional network of referring hospitals.

METHODS: Pediatric telestroke and teleneurology services were implemented in a phased rollout across referring hospitals in Utah and southern Idaho between September 2024 and January 2025. First-year consultation data were retrospectively reviewed for demographic, workflow, diagnostic, and disposition outcomes.

RESULTS: Thirty-three telestroke consultations were completed across 13 hospitals and 203 teleneurology consultations across 18 hospitals. Among telestroke consultations, median times were 72 minutes from symptom onset to hospital arrival, 14 minutes from arrival to stroke alert activation, and 35 minutes from arrival to first neuroimaging. Diagnoses included six cerebrovascular events and 27 stroke mimics, most commonly migraine; seven stroke mimics represented other neurologic emergencies. Six patients were transferred, including both children with arterial ischemic stroke. Among teleneurology consultations, seizures accounted for 76% of referrals. Most patients were managed locally, with 56% discharged and 24% admitted locally; 15% required transfer for

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diagnoses including epilepsy, demyelinating disorders, autoimmune encephalitis, low-pressure headache, brain tumor, and subdural hematoma.

CONCLUSIONS: Parallel implementation of pediatric telestroke and teleneurology services across a large geographic catchment area was feasible and enabled timely subspecialty evaluation of children with suspected stroke and other neurologic emergencies. Most patients were managed locally, while telemedicine facilitated identification and transfer of children requiring tertiary pediatric neurologic care. Further study is needed to define the resource requirements, cost-effectiveness, and long-term sustainability of integrated pediatric teleneurology and telestroke networks.

KEYWORDS: Telemedicine, Stroke

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