FORTY-FIFTH NATIONAL MEETING OF THE CHILD NEUROLOGY SOCIETY

PLANNING COMMITTEE

Child Neurology Society Executive Board

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Nina F. Schor, Past President
Bruce Cohen, Secretary-Treasurer
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Kara Lewis, Councillor
Phillip Pearl, Councillor
Renée Shellhaas, Councillor

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Rochester, NY
Akron, OH
Nashville, TN
Phoenix, AZ
Boston, MA
Ann Arbor, MI

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Nigel Bamford
Brenda Banwell
Keith Coffman
Alexander Cohen
Anne Comi
Ed Gilmore
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Neel Kamal
Yasmin Khakoo
Sookyung Koh

Rochester, MN
Hartford, CT
New Haven, CT
Philadelphia, PA
Kansas City, MO
Boston, MA
Cleveland, OH
Baltimore, MD
Charlottesville, VA
Baltimore, MD
Philadelphia, PA
London, UK
New York, NY
Atlanta, GA

Rebecca Lehman
Daniel Licht
Warren Lo
Laura Ment
Jonathan Mink
John Mytinger
Steven Pavlakis
Toni Pearson
Gerald Raymond
Terri Schreiner
Lily Tran
Peter Tsai
Yvonne Wu

Charleston, SC
Philadelphia, PA
Columbus, OH
New Haven, CT
Rochester, NY
Columbus, OH
Brooklyn, NY
St. Louis, MO
Minneapolis, MN
Aurora, CO
Orange, CA
Dallas, TX
San Francisco, CA

National Office
Roger Larson, Executive Director
Sue Hussman, Associate Director
Kathy Pavel, Office Administrator
Emily McConnell, Professional Development Manager

Presented at Vancouver Convention Centre
Vancouver, BC, Canada
October 26-29, 2016

ACCREDITATION

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint providership of the Minnesota Medical Association and the Child Neurology Society. The Minnesota Medical Association (MMA) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Minnesota Medical Association designates this live activity for a maximum of 32.75 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

To receive CME credits, physicians must complete the on-line CME survey accessed via the CNS website (www.childneurologysociety.org) on or before November 20, 2016

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PAST OFFICERS

President
Kenneth Swaiman 1972-73
Gerald Fenichel 1973-74
Manuel Gomez 1974-75
James Schwartz 1975-76
Richard Allen 1976-77
Bruce Berg 1977-78
N. Paul Rosman 1978-79
Arthur Prensky 1979-80
Paul Dyken 1980-81
Mary Anne Guggenheim 1981-82
Raymond Chun 1982-83
Robert Eiben 1983-85
David Stumpf 1985-87
Marvin Fishman 1987-89
Darryl C. De Vivo 1989-91
Peter H. Berman 1991-93
Joseph J. Volpe 1993-95
Michael E. Cohen 1995-97
Alan K. Percy 1997-99
Michael J. Painter 2001-2003
James Bale 2003-2005
John Menkes 1972-74
James Schwartz 1972-74
Karim Nelson 1973-74
Raymond Chun 1973-75
Bruce Berg 1974-76
Paul Dyken 1974-76
Arthur Prensky 1975-77
N. Paul Rosman 1975-77
Jack Madsen 1976-78
Peggy Copple (Ferry) 1976-78
Joseph French 1977-79
Francis Wright 1977-79
Mary Anne Guggenheim 1978-80
Gerald Golden 1978-80
Gerald Erenberg 1979-81
John Freeman 1979-81
Marvin Weil 1980-82
Marvin Fishman 1980-82
Peter Huttenlocher 1981-83
Michael Bresnan 1981-83
David Stumpf 1982-84
Gwendolyn Hogan 1982-84
Joseph Volpe 1983-85
Barry Russman 1983-85
Russell Snyder 1984-86
Ian Butler 1984-86
W. Edwin Dodson 1985-87
Michael Painter 1985-87
Robert Zeller 1986-88
Doris Trauner 1986-88
Darryl De Vivo 1987-88
Gary Goldstein 1987-89
Robert Vannucci 1988-89
Stephen Ashwal 1988-90
Jack Pellock 1988-90
Joseph Pasternak 1989-91
Patricia Duffner 1989-91
O. Carter Snead 1990-92
Edwin Meyer 1990-92
Israel Abroms 1991-93
William Logan 1991-93
Mary Johnson 1992-94
Alan Percy 1992-94
Phyllis Sher 1993-95
Gregory Holmes 1993-95
W. Donald Shields 1994-96
John Bodensteiner 1994-96
Patricia Crumrine 1995-97
James Bale 1995-97
Alan Hill 1996-98
Ann Tilton 1996-98
Edward Kovnar 1997-99
Richard Nordgren 1997-99
Michael Goldstein 1998-2000
E. Steve Roach 1998-2000
Faye Silverstein 1999-2001
Michael Johnston 1999-2001
Carmela Tardo 2000-02
Pauline Filipek 2000-02
Michael Noetzel 2001-03
Carl Cushey 2001-03
Julie Parke 2002-04
Roy Elterman 2002-04
Marc Patterson 2003-05
Douglas Nordli 2003-05
Donna Ferriero 2004-06
Leon Dure 2004-06
Kenneth Mack 2005-07
Laura Ment 2005-07
Leslie Morrison 2006-08
Anne Anderson 2006-08
Steven Leber 2007-09
Jonathan Mink 2007-09
Robert Rust 2008-10
Wendy Mitchell 2008-10
Warren Lo 2009-11
Sakkuval Naidu 2009-11
Gary Clark 2010-12
Sidney Gospod 2010-12
Barry Kosofsky 2011-13
Suresh Kotagal 2011-13
Vinodh Narayan 2012-14
Jayne Ness 2012-14
Bruce Cohen 2013-15
Roger Packer 2013-15
Kevin Ess 2014-16
Kara Lewis 2014-16
Phillip Pearl 2015-
Renée Shellhaas 2015-

Secretary-Treasurer
Richard Allen 1972-75
Raymond Chun 1975-78
Robert Eiben 1978-81
Lawrence Lockman 1981-84
Marvin Fishman 1984-86
Ira Lott 1986-89
Peggy Copple (Ferry) 1989-93
Stephen Ashwal 1993-97
Patricia Crumrine 1997-2002
Ann Tilton 2003-2004
Nina F. Schor 2004-2010
Harvey Singer 2010-2015
Bruce Cohen 2015-

Councillor
Isabelle Rapin 1972-73
Manuel Gomez 1972-73
NATIONAL MEETINGS

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## PHILIP R. DODGE
### YOUNG INVESTIGATOR AWARD

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<td>Adre J. du Plessis</td>
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<td>Bradley Schlaggar</td>
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<td>Mustafa Sahin</td>
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<td>Mirjana Maletic-Savatic</td>
<td>Stony Brook</td>
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<td>Seattle</td>
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<td>Jeffrey Neul</td>
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<td>Stephen Maricich</td>
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<td>James Dowling</td>
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<td>Yoon Jae-Cho</td>
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<td>Peter Tsai</td>
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<td>2014</td>
<td>Christopher Smyser</td>
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<td>2015</td>
<td>Jimmy Holder, Jr.</td>
<td>Houston</td>
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<td>2016</td>
<td>Diana Bharucha-Goebel</td>
<td>Bethesda</td>
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</table>
ROGER & MARY BRUMBACK LIFETIME ACHIEVEMENT AWARD

2004  
Jean Holowach Thurston  
St. Louis, MO

2005  
Robert Eiben  
Cleveland, OH

Arnold Gold  
New York, NY

2006  
Raymond Chun  
Madison, WI

Barry Russman  
Portland, OR

2007  
William Kennedy  
Watertown, ME

Gordon Watters  
Montreal, Quebec

2008  
Cesare Lombroso  
Boston, MA

2009  
Niels Lowe  
Tenafly, NJ

Mary Anne Guggenheim  
Helena, MT

2010  
G Dean Timmons  
Akron, OH

Russell Snyder  
Albuquerque, NM

2011  
Warren Grover  
Philadelphia, PA

2012  
Bhuwan Garg  
Indianapolis, IN

M. Richard Koenigsberger  
Demarest, NJ

2013  
Arthur Rose  
Brooklyn, NY

A. David Rothner  
Cleveland, OH

2014  
G. Robert DeLong  
Durham, NC

Richard Nordgren  
Hanover, NH

2015  
Pat Crumrine  
Pittsburgh, PA

Suresh Kotagal  
Rochester, MN

2016  
Kalpathy Krishnamoorthy  
Boston, MA

Doris Trauner  
La Jolla, CA

ARNOLD P. GOLD FOUNDATION  
HUMANISM IN MEDICINE AWARD  
AT THE CHILD NEUROLOGY SOCIETY

2010  
Ruth Nass  
New York, NY

2011  
Shaul Harel  
Tel Aviv, Israel

2012  
Marvin Fishman  
Houston, TX

2013  
Douglas Postels  
East Lansing, MI

2014  
Kenton Holden  
Mt. Pleasant, SC

2015  
Robert Zeller  
Houston, TX

2016  
Oscar Papazian  
Miami, FL
<table>
<thead>
<tr>
<th>Year</th>
<th>Name</th>
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<td>Meral Ozmen</td>
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<td>Tunis, Tunisia</td>
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<td>Sergio A. Antoniuk</td>
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<td>Kuala Lumpur, Malaysia</td>
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<td>Shan Wei Song</td>
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<td>Aleksandra Djukic</td>
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## OUTSTANDING JUNIOR MEMBER AWARD

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<td>Gyula Acsadi</td>
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<td>Sucheta Joshi</td>
<td>Stanford University Medical Center</td>
</tr>
<tr>
<td></td>
<td>Lauren Plawner</td>
<td>Stanford University Medical Center</td>
</tr>
<tr>
<td>2001</td>
<td>Maria Acosta</td>
<td>Children’s National Medical Center</td>
</tr>
<tr>
<td></td>
<td>Randa Jarrar</td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td></td>
<td>Steven Miller</td>
<td>UC San Francisco</td>
</tr>
<tr>
<td></td>
<td>Jayne Ness</td>
<td>Children’s Hospital of Alabama</td>
</tr>
<tr>
<td>2002</td>
<td>Taeun Chang</td>
<td>Children’s National Medical Center</td>
</tr>
<tr>
<td></td>
<td>Mirjana Maletic-Savatic</td>
<td>SUNY Stony Brook</td>
</tr>
<tr>
<td></td>
<td>Lauren Plawner</td>
<td>Stanford University Medical Center</td>
</tr>
<tr>
<td></td>
<td>Michael Seyffert</td>
<td>University of Washington Med Ctr</td>
</tr>
<tr>
<td>2003</td>
<td>Taeun Chang</td>
<td>Children’s National Medical Center</td>
</tr>
<tr>
<td></td>
<td>Yoshimi Sogawa</td>
<td>Schneider Children’s Hospital</td>
</tr>
<tr>
<td></td>
<td>Ignacio Valencia</td>
<td>St. Christopher’s Hospital</td>
</tr>
<tr>
<td></td>
<td>Adeline Vanderver</td>
<td>Children’s National Medical Center</td>
</tr>
<tr>
<td>2004</td>
<td>Ignacio Valencia</td>
<td>St. Christopher’s Hospital</td>
</tr>
<tr>
<td></td>
<td>Brannon Morris</td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td></td>
<td>Haim Bassan</td>
<td>Boston Children’s Hospital</td>
</tr>
</tbody>
</table>
William Benko  
Children’s National Medical Center

2005  
William Benko  
Children’s National Medical Center

Alexander Bassuk  
Children’s Memorial Hospital, Chicago

Josh Bonkowsky  
University of Utah Medical Center

Robert Safier  
Children’s Hospital of Pittsburgh

Renee Shellhaas  
Children’s Hospital of Philadelphia

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

2007  
Keith Abe  
Stanford University Medical Center

Tarannum Lateef  
Children’s National Medical Center

Joseph Scafidi  
Children’s National Medical Center

Marie-Pierre Thibeault-Eybalin  
McGill University

2008  
Gregory Aaen  
Loma Linda University

Robert Avery  
Children’s Hospital of Philadelphia

Joseph Scafidi  
Children’s National Medical Center

Karen Powers  
Virginia Commonwealth University

2009  
Bennett Gertz  
Children’s National Medical Center

Ryan Lee  
Kennedy Krieger Institute

John Mytinger  
University of Virginia

Brandon Zielinski  
University of California San Francisco

2010  
Dawn Gano  
University of British Columbia

Radhika Dhamija  
Mayo Clinic

Patricia Musolino  
Massachusetts General Hospital

Thitiwan Simasathien  
University of Alabama-Birmingham

2011  
Partha Ghosh  
Cleveland Clinic Foundation

Andrea Pardo  
Cincinnati Children’s Hospital Medical Center

Thitiwan Simasathien  
University of Alabama-Birmingham

Syndi Seinfeld  
Virginia Commonwealh University

2012  
Partha Ghosh  
Cleveland Clinic Foundation

J.J. Gold  
University of California San Diego

Gayatri Mainali  
Cleveland Clinic Foundation

Christopher B. Oakley  
Johns Hopkins Medical Institute
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

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

2015
Robert Blake
Cincinnati Children’s Hospital Medical Center

Dana Marafie
Texas Children’s Hospital

Davut Pehlivan
Texas Children’s Hospital

Siddharth Srivastava
Kennedy Krieger Institute

2016
Sonika Agarwal
Baylor College of Medicine

Darius Ebrahimi-Fakhari
Boston Children’s Hospital

Juliane Gust
Seattle Children’s Hospital

Manisha Malik
Emory University

M. RICHARD KOENIGSBERGER SCHOLARSHIP
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

2013
Louis Dang
Children’s Hospital of Michigan

2014
Joshua Bear
University of California San Francisco

2015
Vincent Carson
Pittsburgh Children’s Hospital

2016
Ann McCarthey
Children’s Hospital Philadelphia

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### AAP SECTION ON NEUROLOGY TRAINEE TRAVEL AWARD

**2015**  
Jennifer Jaskiewicz  
Walter Reed National Military Medical Center

**2016**  
Sharoon Qaiser  
University of Kentucky

### BHUWAN GARG HIGH SCHOOL STUDENT NEUROSCIENCE PRIZE

<table>
<thead>
<tr>
<th>Year</th>
<th>Name</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>Karla Malloy</td>
<td>Richmond, VA</td>
</tr>
<tr>
<td>1999</td>
<td>Nihar Gupta</td>
<td>New York, NY</td>
</tr>
<tr>
<td>2000</td>
<td>Rishikesh Dalal</td>
<td>Lenexa, KS</td>
</tr>
<tr>
<td>2001</td>
<td>Melanie Napier</td>
<td>Laurelton, NY</td>
</tr>
<tr>
<td>2002</td>
<td>Corinna Zygourakis</td>
<td>Houston, TX</td>
</tr>
<tr>
<td>2003</td>
<td>Henry Marr</td>
<td>Alhambra, CA</td>
</tr>
<tr>
<td>2004</td>
<td>Debashish Zircar</td>
<td>Bronx, NY</td>
</tr>
<tr>
<td>2005</td>
<td>Max Christie</td>
<td>Briarcliff Manor, NY</td>
</tr>
<tr>
<td>2006</td>
<td>Shoshana Tell</td>
<td>Coral Springs, FL</td>
</tr>
<tr>
<td>2007</td>
<td>David Shiovitz</td>
<td>Briarcliff Manor, NY</td>
</tr>
<tr>
<td>2008</td>
<td>Lauren Lisann</td>
<td>Dix Hills, NY</td>
</tr>
<tr>
<td>2009</td>
<td>Inar Zhang</td>
<td>Mercer island, WA</td>
</tr>
<tr>
<td>2010</td>
<td>Pragya Kakani</td>
<td>Jericho, NY</td>
</tr>
<tr>
<td>2011</td>
<td>Spencer Chan</td>
<td>Forest Hills, NY</td>
</tr>
<tr>
<td>2012</td>
<td>Vincent Shieh</td>
<td>Bronx, NY</td>
</tr>
<tr>
<td>2013</td>
<td>Anna Thomas</td>
<td>San Jose, CA</td>
</tr>
<tr>
<td>2014</td>
<td>Laura Mariah Herman</td>
<td>Ft. Lauderdale, FL</td>
</tr>
<tr>
<td>2015</td>
<td>Amrita Mohanty</td>
<td>Woodbury, MN</td>
</tr>
<tr>
<td>2016</td>
<td>Ryan Infante</td>
<td>Armonk, NY</td>
</tr>
</tbody>
</table>
INTERNATIONAL VISITING PROFESSOR

2003
Kenton Holden
Mt. Pleasant, SC

Anita Belman
Stony Brook, NY

2004
Robert Rust
Charlottesville, VA

2006
Vinodh Narayanan
Phoenix, AZ

Peter Camfield
Halifax, NS

2008
Douglas Postels
East Lansing, MI

2010
John Bodensteiner
Phoenix, AZ

BLUE BIRD CIRCLE
TRAINING PROGRAM DIRECTOR AWARD

2013
Harvey Singer
Baltimore, MD

2014
Steve Leber
Ann Arbor, MI

2015
Robert Rust
Charlottesville, VA

2016
David K. Urion
Boston, MA
ASSOCIATION OF CHILD NEUROLOGY NURSES
CLAIRe CHEE AWARD FOR EXCELLENCE

2000
Jan Mims
Minneapolis, MN

2001
Claire Chee
Philadelphia, PA

2002
Rhonda Roell Werner
New Berlin, WI

2003
Elizabeth F. Hobdell
Chester Brook, PA

2004
Jane Meyer
Cottage Grove, WI

2005
Debbie Terry
Westerville, OH

2006
Amy Vierhile
Rochester, NY

2007
Elizabeth Tate
Springfield, IL

2008
Irene M. Elliott
Toronto, ON

2009
Christine O’Dell
Bronx, NY

2010
Julie Sprague-McRae
Fremont, CA

2011
Yolanda Harris
Birmingham, AL

2012
Jane Lane
Birmingham, AL

2013
Cheryl Fischer
New York, NY

2014
Jo Ellen Lee
Columbus, OH

2015
Nancy Elling
Washington, DC

2016
Kathryn O’Hara
Richmond, VA

ASSOCIATION OF CHILD NEUROLOGY NURSES
NURSE PRACTITIONER EXCELLENCE AWARD

2015
Regina Laine
Boston, MA

2016
Sue Yudovin
Los Angeles, CA
THE CHILD NEUROLOGY SOCIETY GRATEFULLY ACKNOWLEDGES THE FINANCIAL SUPPORT OF

- Akron Children’s Hospital
- Arnold P. Gold Foundation
- Biogen
- Blue Bird Circle
- Child Neurology Foundation
- Eisai, Inc.
- GW Pharmaceuticals
- Ipsen Pharmaceuticals
- Jett Foundation
- Mallinckrodt, Inc.
- Sarepta Therapeutics
- Seattle Children’s Hospital
45th Annual Meeting of the Child Neurology Society
Scientific Program

Vancouver, BC, Canada

October 26 – October 29, 2016

Kenneth Mack, MD, PhD, President, CNS
Marc Patterson, MD, Chair, CNS Scientific Selection and Program Planning Committee

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint providershio of the Minnesota Medical Association and the Child Neurology Society. The Minnesota Medical Association (MMA) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Minnesota Medical Association designates this live activity for a maximum of 32.75 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

PROGRAM

Wednesday, October 26

7:30 AM-5:00 PM

SYMPOSIUM I: Neurofibromatosis
Organizer: Bernard L. Maria, MD, MBA, Goryeb Children's Hospital, Morristown, NJ

Supported by the National Institutes of Health (NIH grant 5R13NS040925-21), the Child Neurology Society, and the Children's Tumor Foundation

7:30 AM-7:45 AM
Opening Comments/Introduction
Bernard L. Maria, MD, MBA

7:45 AM-9:20 AM
SESSION I: CLINICAL ASPECTS & GENETIC DIAGNOSIS
Co-Director and Moderator: Bruce Korf, MD, PhD; University of Alabama Birmingham, Birmingham, AL

9:05 AM-9:20 AM Question and Answer Session

9:20 AM-9:35 AM Coffee Break

9:35 AM-12:00 PM
SESSION II: NF FEATURES & PATHOGENESIS
Co-Director and Moderator: David Gutmann, MD, PhD; Washington University, St. Louis, MO

9:35 AM-10:05 AM Optic Gliomas
David Gutmann, MD, PhD

10:05 AM-10:35 AM Behavior and Learning
Maria Acosta, MD; Children's National Medical Center, Washington, DC

10:35 AM-11:05 AM Plexiform Neurofibromas and Malignant Peripheral Nerve Sheath Tumors
Wade Clapp, MD; Indiana University, Bloomington, IN

11:05 AM-11:35 AM Bone Defects
Florent Elefteriou, PhD; Vanderbilt University, Nashville, TN

11:35 AM-12:00 PM Question and Answer Session

12:00 PM-1:00 PM Lunch and Children's Tumor Foundation Presentation
**SESSION III: THERAPEUTIC TARGETS AND TRANSLATIONAL OPPORTUNITIES**  
Co-Director and Moderator: Brigitte Widemann, MD; NCI, Bethesda, MD

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>12:50 PM</td>
<td><strong>NF Preclinical Consortium</strong></td>
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<tr>
<td>1:25 PM</td>
<td>Wade Clapp, MD</td>
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<tr>
<td>1:25 PM</td>
<td><strong>NF Clinical Trials Consortium</strong></td>
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<td>2:00 PM</td>
<td>Roger Packer, MD; Children's National Medical Center, Washington, DC</td>
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<tr>
<td>2:00 PM</td>
<td><strong>NCI Clinical Trials for NF1 Related Tumors/REiNS International Collaboration</strong></td>
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<tr>
<td>2:40 PM</td>
<td>Brigitte Widemann, MD</td>
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<tr>
<td>2:40 PM</td>
<td>Question and Answer Session</td>
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<tr>
<td>2:55 PM</td>
<td>Break</td>
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<tr>
<td>3:10 PM</td>
<td>EXECUTIVE SUMMARY OF THE DAY</td>
</tr>
<tr>
<td>3:55 PM</td>
<td>Co-Directors and Moderators:</td>
</tr>
<tr>
<td></td>
<td>• Bruce Korf, MD, PhD</td>
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<td>• David Gutmann, MD, PhD</td>
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<td>• Brigitte Widemann, MD</td>
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<td>3:55 PM</td>
<td><strong>SESSION IV: FUTURE DIRECTIONS PANEL DISCUSSION</strong></td>
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<td>4:55 PM</td>
<td>Moderator: Bernard L. Maria, MD, MBA</td>
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<td>PANELISTS:</td>
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<tr>
<td></td>
<td>• David Viskochil, MD, PhD</td>
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<td></td>
<td>• Roger Packer, MD</td>
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<td>• Wade Clapp, MD</td>
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<td>• David Gutmann, MD, PhD</td>
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<td>• Bruce Korf, MD, PhD</td>
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<td>• Brigitte Widemann, MD</td>
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<td>4:55 PM</td>
<td>Closing Comments and Thanks</td>
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<td>5:00 PM</td>
<td>Bernard L. Maria, MD, MBA</td>
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**Additional Wednesday Meetings/Sessions**

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<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>9:00 AM</td>
<td>Program Coordinators</td>
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<tr>
<td>8:00 AM</td>
<td>Association of Child Neurology Nurses</td>
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<tr>
<td>4:15 PM</td>
<td>Professors of Child Neurology</td>
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<tr>
<td>2:00 PM</td>
<td>WELCOME RECEPTION</td>
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<tr>
<td>5:00 PM</td>
<td>Vancouver Convention Centre, Sponsored by Seattle Children's Hospital</td>
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<tr>
<td>6:00 PM</td>
<td>SIG MEETINGS</td>
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<tr>
<td>8:00 PM</td>
<td>Including Movement Disorders</td>
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<td>8:00 PM</td>
<td>10:00 PM</td>
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Brain Dysmaturation: New Opportunities for Improving Outcomes
Stephen Back, MD, PhD; Oregon Health & Science University, Portland, OR

Breakfast Seminar 2: Pediatric Multiple Sclerosis: Updates in Diagnosis and Treatment
Organizer: Jayne Ness, MD, PhD; University of Alabama Birmingham, Birmingham, AL
Pediatric MS Diagnosis: Application of Revised Criteria
Amy Waldman, MD, MSCE; The Children's Hospital of Philadelphia, Philadelphia, PA
Pediatric MS Treatment: What Do You Start With, When Do You Switch?
Timothy Lotze, MD; Baylor College of Medicine, Houston, TX

Breakfast Seminar 3: Lawful Physician Aid-In-Dying: Ethical, Legal, and Pediatric Perspectives from Oregon to Belgium
Organizer: William Graf, MD; Connecticut Children's Medical Center, Hartford, CT
The History of Physician-Assisted Dying: Recent Changes and International Perspectives
William Graf, MD; Connecticut Children’s Medical Center, Hartford, CT
Ethical Conflicts in Physician-Assisted Dying in Legal Jurisdictions
Leon Epstein, MD; Lurie Children's Hospital, Chicago, IL
Moral Relationships Between Physicians and Pediatric Patients: Trust and Vulnerability
Geoffrey Miller, MD; Yale University School of Medicine, New Haven, CT

AWARD PRESENTATIONS

8:45 AM - 9:15 AM

Association of Child Neurology Nurses
Claire Chee Award for Excellence
- Kathryn O’Hara, Virginia Commonwealth University, Richmond, VA

Association of Child Neurology Nurses
Nurse Practitioner Excellence Award
- Sue Yudovin, RN, MN, CPNP; David Geffen UCLA School of Medicine, Los Angeles, CA

CNS Roger & Mary Brumback Lifetime Achievement Awards
- Kalpathy Krishnamoorthy, MD; Massachusetts General Hospital, Boston, MA

9:15 AM - 12:00 PM

SYMPOSIUM II: PRESIDENTIAL SYMPOSIUM: EVIDENCE BASED TREATMENT OF CHILDHOOD MIGRAINE
Organizer: Kenneth Mack, MD, PhD; Mayo Clinic, Rochester, MN
The CHAMPS Study of Childhood Migraine
Andrew Hershey, MD, PhD, FAHS; University of Cincinnati, Cincinnati, OH
The Current Evidence Base for Pediatric Migraine Preventive Treatment and the Role for Cognitive Behavioral Therapy
Scott Powers, PhD, ABPP; University of Cincinnati, Cincinnati, OH
A Global Perspective to Headache Management
Ishaq Abu-Arafeh, MD; Fort Valley Royal Hospital, Larbert, Scotland, United Kingdom
Botox, Trigger Point Injections, Stimulation and Other Approaches to Headache Management
Kenneth Mack, MD, PhD

12:00 PM - 12:30 PM

CNS Business Meeting

12:30 PM - 2:00 PM

Committee Meetings
Lunch & Exhibit & Poster Viewing

2:00 PM - 4:15 PM

SYMPOSIUM III: ZIKA VIRUS UPDATE FOR CHILD NEUROLOGISTS
Organizer: Edwin Trevathan, MD, MPH; Vanderbilt University School of Medicine, Nashville, TN
Zika Virus and Microcephaly – Development of a Worldwide Public Health Emergency
Edwin Trevathan, MD, MPH
The Public Health and Medical Response to Zika Virus
Cynthia Moore, MD, PhD; National Center on Birth Defects and Developmental Disabilities, Atlanta, GA
The Impact of Zika Virus on the Developing Brain
William Dobyns, MD; University of Washington School of Medicine, Seattle, WA

Development of a Zika Virus Vaccine
Julie Ledgerwood, DO; National Institute of Allergy and Infectious Diseases, Bethesda, MD

4:30 PM - 6:00 PM
CHILD NEURO NEWS BREAK: POSTER REVIEW
WINE & CHEESE RECEPTION
Exhibit Viewing

SIG Meetings

4:45 PM - 6:15 PM
Headache SIG (1 CME Credit)
Organizer: Alma Bicknese, MD; Lurie Children's Hospital, Chicago, IL

Trends in Headache Management for Children and Young Adults
Alma Bicknese, MD

Practical Approach to Botox and Blocks in Adolescent Migraine
Marcy Yonker, MD; Barrow Neurological Institute at Phoenix Children's Hospital, Phoenix, AZ.

Additional Thursday Meetings/Sessions

9:00 AM - 5:00 PM
Program Coordinators

12:00 PM - 2:30 PM
Association of Child Neurology Nurses

Friday, October 28

7:00 AM - 8:15 AM
CONTINENTAL BREAKFAST AND POSTER SESSION
EXHIBIT VIEWING

8:30 AM - 10:15 AM
PLATFORM SESSIONS 1 & 2

Platform Session 1:
8:30 AM - 8:45 AM
PL 1-1 Gust et al
Brain Inflammation in Neurologic Complications of Chimeric Antigen Receptor (CAR)-T Cell Therapy for Pediatric Leukemia

8:45 AM - 9:00 AM
PL 1-2 Bonkowsky et al
Novel Therapeutic Discovery for Leukodystrophies Using Zebrafish

9:00 AM - 9:15 AM
PL 1-3 Singer et al
GABA and Glutamate in Children with Tourette Syndrome; A 1H-MRS Study at 7T

9:15 AM - 9:30 AM
PL 1-4 Scheinost et al
Amygdala Connectivity is Reduced in Preterm Neonates with Prenatal Stress Exposure

9:30 AM - 9:45 AM
PL 1-5 Bonkowsky et al
A Novel Developmental Requirement for NMDA Receptors in Axon Guidance is Disrupted by Hypoxic Injury

9:45 AM - 10:00 AM
PL 1-6 Sturm et al
The SMN2 Splicing Modifier RG7916 Induces a Dose-Dependent Increase of Full Length SMN2 mRNA

10:00 AM - 10:15 AM
PL 1-7 Carson et al
Pathologic Mechanisms Underlying Hypomyelination Following Loss of Tsc2 From Oligodendrocytes

Platform Session 2:
8:30 AM - 8:45 AM
PL 2-1 Singer et al
Development, Psychometric Validation, and Feasibility of the Gitwe Developmental Delay Screening Tool (GDDST), a Low-Tech, Culturally Contextualized Tool to Assess Developmental Milestones of Children Under-5 in Rural Rwanda

8:45 AM - 9:00 AM
PL 2-2 Gilbert et al

9:00 AM - 9:15 AM
PL 2-3 Shellhaas et al
Profile of Neonatal Epilepsies: Characteristics of a Prospective US Cohort

9:15 AM - 9:30 AM
PL 2-4 Lateef et al
Headaches and Sleep Problems Among Adolescents in the United States: Findings from the National Comorbidity Survey - Adolescent Supplement (NCS-A) Study

9:30 AM - 9:45 AM
PL 2-5 Wu et al
Neonatal Erythropoietin and Therapeutic Hypothermia for HIE - A Phase II Trial

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9:45 AM-10:00 AM  PL 2-6 Suner et al
Novel Automated Method to Quantify Vision in Children with Brain Injury Who Cannot Follow Commands

10:00 AM-10:15 AM  PL 2-7 Kruer et al
Heterozygous de novo Mutations in EEF1A2 Lead to an Epileptic-dyskinetic Encephalopathy

AWARD PRESENTATIONS

10:30 AM-10:40 AM  AAP Award
• Sharoon Qaiser, MD; University of Kentucky, Lexington, KY

Outstanding Junior Member Awards
• Sonika Agarwal, MD; Baylor College of Medicine, Houston, TX
• Juliane Gust, MD, PhD; Seattle Children’s Hospital, Seattle, WA
• Darius Ebrahimi-Fakhari, MD; Boston Children's Hospital, Boston, MA
• Manisha Malik, MD; Emory University, Atlanta, GA

M. Richard Koenigsberger Scholarship Award
• Ann McCarthy, MD; Children's Hospital Philadelphia, Philadelphia, PA

Bhuwan Garg High School Student Neuroscience Award
• Ryan Infante, Armonk, NY

10:40 AM-10:45 AM  CNS/PCN Blue Bird Circle Training Program Director Award
• David K. Urion, MD; Boston Children’s Hospital, Boston, MA

10:45 AM-10:55 AM  Arnold P. Gold Humanism in Medicine Award
• Oscar Papazian, MD, Miami, FL

10:55 AM-11:00 AM  Child Neurology Foundation Scientific Award Announcements

11:00 AM-11:30 AM  Philip R. Dodge Young Investigator Award Lecture: First In-human Intrathecal AAV9-Mediated Gene Transfer in Giant Axonal Neuropathy
• Diana Bharucha-Goebel, MD; National Institutes of Health, Bethesda, MD

11:30 AM-12:15 PM  Bernard Sachs Lecture: Timing in Morphogenesis and Genetic Gradients during Normal Development and Malformations of the Nervous System
• Harvey Sarnat, MS, MD, FRCPC; Alberta Children's Hospital, Calgary, AB, Canada

12:30 PM-2:30 PM  Lunch & non-CME SIG Meetings

12:30 PM-2:00 PM  Sleep SIG (1 CME Credit)
Organizer: Sejal Jain, MD; Cincinnati Children's Hospital, Cincinnati, OH

Assessment and Management of Sleepiness in Childhood Neurological Disorders
Timothy Hoban, MD; CS Mott Children's Hospital, Ann Arbor, MI

Sleep in Children with Autism
Jennifer Accardo, MD, PhD; Kennedy Krieger Institute, Baltimore, MD

Sleep Disorders in Children with Neuromuscular Disorders
Han Phan, MD; Children's Healthcare of Atlanta, Atlanta, GA

2:30 PM-4:45 PM  SYMPOSIUM IV: THE FUTURE OF CHILD NEUROLOGY: CHALLENGES AND OPPORTUNITIES
Organizer: Mark Mintz, MD; The Center for Neurological and Neurodevelopmental Health, Voorhees, NJ

Co-Organizer: James Bale, Jr., MD; University of Utah, Salt Lake City, UT

Results of the AAP/CNS Workforce Survey: Fears, Tears, Burnout, Yet Hope
Peter Kang, MD, FAAP, FAAN; University of Florida College of Medicine, Gainesville, FL

What is an Academic Child Neurologist?: The Future of Graduate Medical Education and Training
Donald Gilbert, MD, MS, FAAN, FAAP; Cincinnati Children’s Hospital Medical Center, Cincinnati, OH

Meaningful and Meaningless Use: Innovative Healthcare Technologies
Sucheta Joshi, MD, MS, FAAP; University of Michigan, Ann Arbor, MI

Changing and Alternative Models of Health Care Delivery and Payment: Opportunities for Child Neurologists
Mark Mintz, MD

Panelists:
• James Bale, Jr., MD
• Lynn Colegrove, MBA; American Academy of Neurology, Chicago, IL
• Donald Gilbert, MD, MS, FAAN, FAAP
• Sucheta Joshi, MD, MS, FAAP
• Peter Kang, MD, FAAP, FAAN
• Mark Mintz, MD

5:00 PM-6:00 PM  JUNIOR MEMBER SEMINARS
Junior Member Seminar 1: Medical Students: Finding a Residency
Junior Member Seminar 2: Residents: Finding a Fellowship
Junior Member Seminar 3: Residents & Fellows: Getting your First Job

5:00 PM - 6:30 PM  
Neurogenetics & Neurodevelopmental SIG (1 CME Credit)  
Organizer: Miya Asato, MD; Children’s Hospital of Pittsburgh, Pittsburgh, PA  
Pyridoxine Responsive Epileptic Encephalopathies  
Sylvia Stockler, MD, PhD; BC Children’s Hospital, Vancouver, BC, Canada  
Treatable Neurometabolic Diseases in the 21st Century  
Clara van Karnebeek, MD, PhD; Children’s Hospital Vancouver, Vancouver, BC, Canada

7:00 PM - 10:00 PM  
GALA RECEPTION

Additional Friday Meetings/Sessions

10:00 AM - 2:30PM  
Association of Child Neurology Nurses

Saturday, October 29

7:00 AM - 8:15 AM  
CONTINENTAL BREAKFAST & SEMINARS  
Breakfast Seminar 4: The Genomics Revolution and Child Neurology: Diagnosis, Care and Emerging Therapies  
Organizer: Adeline Vanderver, MD; Children’s National Medical Center, Washington, DC  
Understanding Next Generation Sequencing Tools and Diagnosis  
Ryan Taft, PhD; Illumina, San Diego, CA  
Gene Discovery to Disease Mechanisms: How a Diagnosis Can Lead to a Therapy  
Adeline Vanderver, MD  
Gene Therapy Approaches in Neurodegenerative Conditions  
Beverly Davidson, PhD; The Children’s Hospital of Philadelphia, Philadelphia, PA

Breakfast Seminar 5: Active Management of Concussions  
Organizer: Sharief Taraman, MD, FAAP, DABPN, DABPM; University of California-Irvine School of Medicine, Irvine, CA  
Overview of the Pathophysiology of Concussions  
Meeryo Choe, MD; David Geffen School of Medicine at UCLA, Los Angeles, CA

8:45 AM – 9:30 AM  
The Key Elements of an Initial Concussion Evaluation  
Sharief Taraman, MD, FAAP, DABPN, DABPM

Return to Cognitive Activity, Mental Health Aspects of Concussion, and the Role of Computerized Neuropsychological Therapy  
Jonathan Romain, PhD; University of California-Irvine School of Medicine, Irvine, CA

Rehabilitation and Return to Physical Activity  
Isabelle Gagnon, PhD; McGill University, Montreal, Quebec, Canada

Breakfast Seminar 6: Emerging Therapies for Genetic Leuko and Poliodystrophies  
Organizer: Florian Eichler, MD; Massachusetts General Hospital, Boston, MA  
Co-Organizer: Marc Patterson, MD; Mayo Clinic, Rochester, MN

Co-Organizer: Alessandra Biffi, MD; Children’s Hospital Boston, Boston, MA

Lentiviral Gene Therapy for Metachromatic Leukodystrophy  
Alessandra Biffi, MD

Strategies for Gene Correction in Adrenoleukodystrophy  
Florian Eichler, MD

Novel Therapeutics for Niemann Pick Type C  
Marc Patterson, MD

8:45 AM – 9:30 AM  
Hower Award Lecture: A Series of Experiences  
• Harvey Singer, MD; Johns Hopkins, Baltimore, MD

9:30 am – 12:00 pm  
SYMPOSIUM V: THE NEW CHAPTER OF NEONATAL-ONSET EPILEPSIES  
Organizer: Sarah Mulkey, MD, PhD; Children’s National Medical Center, Washington, DC  
Co-Organizer: Maria Roberta Cilio, MD, PhD; University of San Francisco, San Francisco, CA

Metabolic Epilepsies  
Phillip Pearl, MD; Boston Children’s Hospital, Boston, MA  
The Neonatal Phenotype of Genetic Epilepsies  
Maria Roberta Cilio, MD, PhD

Genotype-Phenotype Correlation: Does it Matter?  
Sarah Mulkey, MD, PhD

KCNQ2: What You Need to Know in 2016  
Edward Cooper, MD, PhD; Baylor College of Medicine, Houston, TX
1:00 pm – 4:00 pm
SYMPOSIUM VI: CHILD NEUROLOGY FOUNDATION SYMPOSIUM:
CANNABIS IN EPILEPSY: CLINICAL SCIENCE, PARENT & ADVOCACY PERSPECTIVES
Sponsored by an unrestricted educational grant from the Child Neurology Foundation
Organizer: Child Neurology Foundation
Understanding Current Use and Attitudes Towards Cannabis within the Child Neurology Community: Results from Membership and Caregiver Surveys
William Trescher, MD, President Child Neurology Foundation; Penn State Children's Hospital, Hershey, PA
State of Science: Cannabis
Elizabeth Thiele, MD, PhD; Massachusetts General Hospital, Boston, MA
Parent Perspectives: Cannabis Use in Pharmaceutical Form vs. Non-pharmaceutical Form
Catherine Jacobson, Patient Advocate and Parent, Director, Clinical Research Tilray, Mill Valley, CA
Lolly Bentch, Parent Advocate, Harrisburg, PA
Cannabis Use in Child Neurology
Anup Patel, MD; Nationwide Children's Hospital, Columbus, OH
Advocacy Voices: Dravet Syndrome Foundation, Lennox-Gastaut Syndrome Foundation, Tuberous Sclerosis Alliance, and Child Neurology Foundation
Amy Brin Miller, MSN, MA, PCNS-BC, Executive Director, Child Neurology Foundation, Minneapolis, MN

1:00 pm – 5:00 pm
Biomedical Writing Workshop
Organizer: E. Steve Roach, MD; Nationwide Children's Hospital, Columbus, OH
Co-Organizer: Marc Patterson, MD
Manuscripts 101: Introduction to Biomedical Publishing
Short-cuts to Better Papers
Responding to Reviews & Revising Your Manuscript
Keeping Things Moving: Combating Writer's Block
The Plot Thickens: Creating a Story in Scientific Papers
Rules of the Road: Permissions, Consents & Other Potholes
Informal Meet the Editors
• Jonathan Mink, MD, PhD; University of Rochester Medical Center, Rochester, NY
• Scott Pomeroy, MD, PhD; Boston Children's Hospital, Boston, MA
• Marc Patterson, MD
• E. Steve Roach, MD
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<thead>
<tr>
<th>Time</th>
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<tbody>
<tr>
<td>6:00 pm –</td>
<td>ACNN Welcome Reception (Nurses Only)</td>
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<td>9:00 pm</td>
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<tr>
<td>8:00 am –</td>
<td>Welcome</td>
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<td>8:15 am –</td>
<td>Janet Bruckner Keynote Address: <em>Moral Distress: Not Just for Critical Care Nurses</em></td>
<td>Nancy Thornton, RN, MSN, CNN (C); Alberta Children's Hospital, Calgary, AL, Canada</td>
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<td>9:00 am –</td>
<td>Clinical Evaluation of Hypotonia</td>
<td>Regina Laine, MSN, PNP-BC, CNRN; Boston Children's Hospital, Boston, MA</td>
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<td>10:00 am –</td>
<td>Break</td>
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<td>10:15 am –</td>
<td>Non-Epileptic Events</td>
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<td>10:45 am –</td>
<td>School Nurse Perceptions of Psychogenic Non-Epileptic Events in Schools</td>
<td>Debbie Terry, MS, APRN; Nationwide Children's Hospital, Columbus, OH</td>
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<td>11:15 am –</td>
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<td>11:15 am –</td>
<td>Epilepsy Checklists: Engaging Parents and Teens to Tick all of the Boxes</td>
<td>Jennifer Boyd, RN, MHSc, CNN (C); The Hospital for Sick Children, Toronto, ON, Canada</td>
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<td>11:45 am</td>
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<tr>
<td>12:00 pm –</td>
<td>Lunch – Regional Networking</td>
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<td>1:00 pm –</td>
<td>Anti-NMDA Encephalitis: 2016 Update on Research and Treatment</td>
<td>Mariam Kolodgie, BSN, MSN, CPNP; Children's National Health System, Washington, DC</td>
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<td>2:00 pm –</td>
<td>When your Brain Turns on You: Exploring Anti-NMDA Receptor Encephalitis in the Pediatric Population</td>
<td>Katanya Fuerst, MSc, BScN, RN; The Hospital for Sick Children, Toronto, ON, Canada</td>
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<td>2:30 pm –</td>
<td>5k Fun Run/Walk</td>
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### Friday, October 28

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<tr>
<th>10:00 am – 11:00 am</th>
<th>Recognizing and Managing Paroxysmal Autonomic Instability After Acute Neurologic Injury</th>
<th>Michele Grimason Mills, RN MSN FNP-BC PNP-AC; Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL</th>
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<tr>
<td>11:00 am – 12:00 pm</td>
<td>Opsoclonus Myoclonus Ataxia Syndrome (OMS)</td>
<td>Michelle Souris, CPNP, CNRN; Boston Children's Hospital, Boston, MA</td>
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<tr>
<td>12:00 pm – 1:00 pm</td>
<td>Lunch &amp; SIGS</td>
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<tr>
<td>1:00 pm – 1:30 pm</td>
<td>Advances in Care for Duchenne Muscular Dystrophy</td>
<td>Regina Laine, MSN, PNP-BC, CNRN</td>
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<td>1:30 pm – 2:00 pm</td>
<td>Telemedicine: A Vision for Child Neurology Care</td>
<td>Amy Vierhile, RN, MS, PNP; University of Rochester Medical Center, Rochester, NY</td>
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<td>2:00 pm – 2:30 pm</td>
<td>How to Host a Regional Child Neurology Nursing Educational Program – The Nationwide Children's Hospital Experience</td>
<td>Jo Ellen Lee, MSN, APRN; Nationwide Children's Hospital, Columbus, OH</td>
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<td>October 26, 2016</td>
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<td><strong>9:00 a.m.</strong></td>
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<td><strong>Welcome and Opening Remarks</strong></td>
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<td>Julie Campbell, C-TAGME</td>
<td>Terri Feist, C-TAGME</td>
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<td>President, Program Coordinators of Child Neurology</td>
<td>Cincinnati Children's Hospital Cincinnati, OH</td>
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<td><strong>9:15 a.m.</strong></td>
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<td><strong>Common Curriculum: Integrating Trainees and Becoming Involved as a Faculty Member While Serving as a Program Coordinator</strong></td>
<td><strong>OSCEs, Oral Boards and Other Methods to Evaluate Milestones</strong></td>
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<td>Rachel Laws</td>
<td>Julie LaBare</td>
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<td>Children's Mercy Hospital Kansas City, MO</td>
<td>Mayo Clinic Rochester Rochester, MN</td>
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<td><strong>Integrating Business Best Practices with the Coordinator Role</strong></td>
<td><strong>The Program Coordinator's Guide to Surviving your FULL ACGME Site Visit</strong></td>
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<td>Adam Finney</td>
<td>Sarah Slyosfski</td>
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<td>University of Colorado Boulder, CO</td>
<td>University of Florida Gainesville, FL</td>
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<td><strong>10:45 a.m. Break</strong></td>
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<tr>
<td><strong>Keynote Address</strong></td>
<td><strong>Dealing with Difficult Residents: One Institution's Standardized Approach</strong></td>
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<td>Karen Keough, M.D.</td>
<td>Julie Campbell, C-TAGME</td>
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<td>Program Director, Pediatric Neurology Residency Program</td>
<td>Nationwide Children's Hospital Columbus, OH</td>
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<td>University of Texas at Austin Dell Medical School</td>
<td><strong>11:45 a.m. Panel Discussion Opening Remarks</strong></td>
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<td><strong>12:00 p.m. Networking Lunch</strong></td>
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<td><strong>12:45 p.m. MedHub User Demonstration</strong></td>
<td><strong>1:30 p.m. Panel Discussion</strong></td>
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<td>Julie LaBare</td>
<td><strong>Some of Our Greatest Challenges in Program Management: What Are They and How Can We Collectively Work to Overcome Them?</strong></td>
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<td>Mayo Clinic Rochester Rochester, MN</td>
<td>Moderators: Julie Campbell, Terri Feist, Julie LaBare, Adam Finney</td>
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<td><strong>1:30 p.m. Break</strong></td>
<td><strong>2:30 p.m. Using ERAS for the Ultimate Interview Experience</strong></td>
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<td><strong>2:00 p.m. Professors of Child Neurology Meeting</strong></td>
<td>Megan Poeschl</td>
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<td><strong>5:00 p.m. Adjourn following PCN</strong></td>
<td>The Cleveland Clinic</td>
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<td><strong>3:15 p.m. Webinars! What Are They; Are They Useful?</strong></td>
<td>Cleveland, OH</td>
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<td>Adam Finney</td>
<td><strong>4:00 p.m. Conclusion</strong></td>
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<td>University of Colorado Boulder, CO</td>
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PL1-1. Brain Inflammation in Neurologic Complications of Chimeric Antigen Receptor (CAR)-T Cell Therapy for Pediatric Leukemia
Gust J (Seattle, WA), Finney O, Gardner R

Objective: CAR-T cell therapy is a novel cancer treatment that modifies the patient’s own T cells with a chimeric antigen receptor designed to target the malignant cells. Upon infusion of the CAR-T cells, patients experience a severe inflammatory response that is frequently accompanied by neurologic complications. We sought to determine which patients are at increased risk of complications, and whether their CNS inflammatory profile is distinct from unaffected patients.

Methods: In this study, 36 pediatric patients with refractory acute lymphoblastic leukemia were treated with CAR-T cells directed against CD19. We collected daily clinical data for 28 days following infusion of the CAR-T cells. CSF and serum were analyzed on day 21 after treatment for persistence of the CAR-T cells, and inflammatory markers.

Results: 18/36 patients (50%) had neurologic complications such as delirium, headache, seizures, and altered consciousness. Preexisting neurologic disorders significantly increased the risk of complications. 60% of affected patients had acute MRI abnormalities, often similar to atypical posterior reversible encephalopathy syndrome (PRES). CAR-T cell persistence in the CSF was significantly more common in affected patients, and their CSF interleukin-6 levels were higher.

Conclusions: The novel pattern of neurologic dysfunction, imaging findings, and cytokine elevations as a complication of CAR-T cell therapy overlaps with other inflammatory syndromes that can affect the CNS. Understanding the biology of the complications in CAR-T cell therapy may help our understanding of these disorders, and be a step toward targeted therapies.

Keywords: Brain Tumors/Oncology, Infections/Neuroimmunology, Translational/experimental therapeutics

PL1-2. Novel Therapeutic Discovery for Leukodystrophies using Zebrafish
Bonkowsky J (Salt Lake City, UT), Strachan L, Keefe M, Stevenson T

Objective: For most leukodystrophies there are no curative treatments despite their significant morbidity and mortality. Although some mouse models have been generated, their use for drug discovery has been hampered by impracticality of screening, slow and uneven progression of disease, and by high costs. Our objectives were to generate small vertebrate (zebrafish) models for adrenoleukodystrophy (ALD) and for vanishing white matter disease (VWMD); to demonstrate recapitulation of key disease pathology; and to use these models to identify novel therapeutics.

Methods: We used TALEN and CRISPR mutagenesis to generate zebrafish mutants for ALD (ABCD1 gene) and for VWMD (eif2B5 gene). We used transgenic lines including fluorescent reporters, immunohistochemistry, measures of myelin and of very long chain fatty acids (VLCFAs), and a screenable 96-well format system tracking behavior and movement, to characterize the mutants.

Results: abcd1 mutants have elevated VLCFAs levels; abnormal CNS development; by day of life 5 abcd1 mutants demonstrate impaired motor function; and overall survival to adulthood of mutants is decreased. Expression of human ABCD1 in oligodendrocytes rescued apoptosis in the abcd1 mutant. The eif2B5 mutants have impaired somatic growth; normal overall survival; but with increased apoptosis in the fore-and-mid-brain. 96-well screening of mutants with compound libraries demonstrates several promising drugs that inhibit myelin loss and maintain normal motor behavior.

Conclusion: In summary, we have established zebrafish models of ALD and VWMD that recapitulate key features of human disease pathology; uncovered novel elements of underlying disease pathogenesis; and demonstrated utility of these models for therapeutics discovery.

Keywords: Demyelinating Disorders, Translational/experimental therapeutics

PL1-3. GABA and Glutamate in Children with Tourette Syndrome: A 1H-MRS Study at 7T
Singer H (Baltimore, MD), Mahone E, Putts N, Tischen L, Edden R

Objective: The underlying neurobiological basis of Tourette syndrome (TS) is unknown, but evidence strongly supports involvement of cortical-striatal-thalamo-cortical (CSTC) pathways. Two major neurotransmitters within these circuits are glutamate and GABA. Glutamate is the primary excitatory neurotransmitter of neurons within cortical, thalamic and subthalamic nuclei. GABA is the primary inhibitory neurotransmitter of striatal projection neurons, the globus pallidus, and interneurons within the cortex and striatum. 7T MR spectroscopy permits separation of glutamate and glutamine, not available with 3T scanning.

Methods: GABA and glutamate were measured in five frontostriatal regions, using 1H MR spectroscopy (MRS) at 7T. 32 children with TS and 37 typically developing controls, ages 5-12 years, completed MRS at 7T. Single voxel STEAM acquisitions from the dorsolateral prefrontal cortex (DLPFC), ventromedial prefrontal cortex (VMPFC), pre-motor cortex (PMC), motor cortex (M1), and striatum were obtained and metabolites were quantified with respect to both Cr and water using the LCModel.

Results: Compared to typically developing controls, children with TS showed significantly increased GABA in the striatum and increased glutamate within the striatum and PMC. No changes were present in the DLPFC, VMPFC, or M1 (GABA only) regions. Within the TS group,
increased PMC glutamate was significantly associated with increased symptoms of ADHD and faster performance on motor examination.

**Conclusions:** Historically the dopaminergic system has long been considered to have a dominant role in TS; however, accumulating evidence strongly suggests involvement of other neurotransmitter systems. Data is presented supporting alterations of both GABA and glutamate within CSTC pathways of children with TS.

**Keywords:** Movement Disorders

**PL1-4. Amygdala Connectivity is Reduced in Preterm Neonates with Prenatal Stress Exposure**


**Objective:** Preterm neonates (PTs) are at high risk for neurobehavioral disorders. Emerging data suggest that exposure to prenatal stress results in both aberrant neurodevelopment and alterations in neural connectivity in typically developing infants, but the impact of prenatal stress exposure (PNSE) on the functional organization of developing brain in the prematurely-born has yet to be explored. To test the hypothesis that PNSE alters cortical organization in extremely PTs, we interrogated left amygdala functional connectivity, a network sub-serving social cognition, in PTs with and without PNSE.

**Methods:** We enrolled 25 term controls, 28 PTs without PNSE, and 10 PTs with PNSE. PNSE included maternal diagnoses of depression and/or anxiety. None had neonatal brain injury and there were no differences in birth weight, sex, and gestational age at birth or MRI between PNSE and no PNSE neonates. All underwent resting state fMRI at term equivalent age; standard connectivity methods were employed.

**Results:** We enrolled 25 term controls, 28 PTs without PNSE, and 10 PTs with PNSE. PNSE included maternal diagnoses of depression and/or anxiety. None had neonatal brain injury and there were no differences in birth weight, sex, and gestational age at birth or MRI between PNSE and no PNSE neonates. All underwent resting state fMRI at term equivalent age; standard connectivity methods were employed.

**Conclusion:** Functional connectivity from the left amygdala to other subcortical regions is decreased in PTs compared to term controls. In addition, these data, for the first time, suggest that PNSE further decreases these connections.

**Keywords:** Neuroimaging, Neonatal Neurology

**PL1-5. A Novel Developmental Requirement for NMDA Receptors in Axon Guidance is Disrupted by Hypoxic Injury**

Bokovsky J (Salt Lake City, UT), Gao J

**Objective:** Hypoxic injury in the developing human brain is a major cause of chronic neurodevelopmental impairments in part through loss of connectivity although the mechanisms are poorly understood. Our goal was to characterize the mechanisms by which hypoxia causes disruptions of normal axon connections in the brain. Previous work has shown that developmental hypoxia causes specific errors in axon guidance.

**Methods:** We used the small vertebrate model zebrafish (Danio rerio) with transgenic reporters in a published model of developmental hypoxic injury (Stevenson et al., 2012). We used immunohistochemical visualization following hypoxia, and pharmacological manipulation, to study the role of the N-methyl-D-aspartate (NMDAR). NMDARs are glutamate-gated heteromeric ion channels that play key roles in excitatory synaptic transmission in the adult brain and in synapse stabilization and have recently been identified to play developmental roles.

**Results:** We found that hypoxic injury down-regulates NMDAR expression in the developing brain. Interestingly, commissural axon pathfinding is disrupted by pharmacological inhibition of NMDARs. We demonstrate that the NMDAR NR1 subunit is expressed in commissural axons, and that vglut1, the biosynthesis enzyme for glutamate, is expressed in neurons adjacent to the commissural axons. We further show that an NMDAR agonist can rescue hypoxic-induced commissural neuron pathfinding defects.

**Conclusions:** In summary, we report an unexpected developmental role for NMDARs in axon pathfinding, and show that disruption of normal NMDAR function by hypoxia contributes to connectivity disruption.

**Keywords:** Neonatal Neurology

**PL1-6. The SMN2 Splicing Modifier RG7916 Induces a Dose-Dependent Increase of Full Length SMN2 mRNA**


**Objective:** RG7916 is an oral splicing modifier of SMN2 exon 7 in development for the treatment of spinal muscular atrophy (SMA). This First-In-Human study assessed the safety and tolerability, pharmacokinetics and pharmacodynamics of single doses of RG7916 in healthy men including the effects of food and a strong CYP3A inhibitor (itraconazole) on the pharmacokinetics of RG7916.

**Methods:** Single ascending oral doses ranging from 0.6 mg to 18 mg of RG7916 or placebo were administered under fasted or fed conditions. The effect of multiple doses of itraconazole on the pharmacokinetics of RG7916 was assessed in a two-period cross-over design.

**Results:** RG7916 was safe and well tolerated at all dose levels. No clinically significant changes were observed in adverse events, vital signs, ECG, laboratory parameters or ophthalmological assessments. Plasma concentrations of RG7916 increased in a dose-proportional manner. Food had no relevant effect on the pharmacokinetics of RG7916. A dose-dependent effect of RG7916 on the SMN2 FL/SMNΔ7 mRNA ratio was observed. Itraconazole had a minor effect on the PK of a single oral dose of RG7916 resulting in a slight increase of the AUC.

**Conclusions:** Single doses of RG7916 were safe and well tolerated. Proof of mechanism was demonstrated by the intended shift in SMN2 alternative splicing towards full length SMN2 mRNA. There is a low likelihood of
significant drug-drug interaction with selective inhibitors and inducers of CYP3A enzymes. Results from this study fully support further clinical development of RG7916 for the treatment of SMA.

Keywords: Translational/experimental therapeutics

PL1-7. Pathologic Mechanisms Underlying Hypomyelination Following Loss of Tsc2 from Oligodendrocytes
Carson R (Nashville, TN), Grier M, Parker B, Verdier K, Eis K

Objective: A positive link between PI3-K/mTORC1 signaling and myelination has been established, though recent data has demonstrated a paradoxical hypomyelination following loss of Tsc1 or Tsc2 from oligodendrocytes. Data from mice lacking Tsc2 in oligodendrocyte precursor cells (OPCs) suggests OPC loss contributes to the hypomyelination. The objective of this study is to determine mechanisms and pathways leading to hypomyelination following loss of Tsc2.

Methods: To inactivate the Tsc2 gene in oligodendrocytes, we generated a conditional knock-out (CKO) mouse using Cre-recombinase driven by the Olig2 promoter, which demonstrates marked hypomyelination. From these animals, primary mixed glial cultures were derived and underwent a shaking protocol to enrich cultures of OPCs and astrocytes, followed by differentiation into mature oligodendrocytes.

Results: To assess the requirement for Tsc2 in oligodendrocyte development, maturation of OPCs deficient for Tsc2 was characterized. A 90% reduction in mature oligodendrocytes was seen after 6-9 days in culture. CKO astrocytes and oligodendrocytes were larger and demonstrated altered morphology as compared to control cells, consistent with loss of Tsc1 or Tsc2. Additional studies underway will characterize cell autonomous signaling changes which may alter cell proliferation, apoptosis, or maturation.

Conclusions: Homozygous loss of Tsc2 in oligodendrocytes results in hypomyelination likely due to loss of oligodendrocyte precursors. Understanding the mechanisms for the cell loss and whether similar mechanisms are at play in heterozygous OPCs may provide novel molecular targets for improving myelin integrity in human disease.

Keywords: Translational/experimental therapeutics, Cognitive/Behavioral Disorders, Epilepsy

Platform Session 2
Friday, October 28
(8:30 am - 10:15 am)

PL2-1. Development, Psychometric Validation, and Feasibility of the Gitwe Developmental Delay Screening Tool (GDDST), a culturally-contextualized, low-tech, questionnaire that Community Health Workers (CHWs) can administer to assess milestone achievement in children under 5 in Rwanda.

Objective: We developed the Gitwe Developmental Delay Screening Tool (GDDST), a culturally-contextualized, low-tech, questionnaire that Community Health Workers (CHWs) can administer to assess milestone achievement in children under 5 in Rwanda.

Methods: Focus groups - Rwandan physicians (12), pediatric nurses (8), CHWs (9) and parents of children under-5 (16) - explored cultural themes of “normal” development in the five domains of development – social, language, cognitive, gross and fine motor. The GDDST was authored thereafter. Psychometrics were analyzed (n=384) and face and content validity solicited. Sixteen CHWs were trained. A pilot study assessed our method (n=172).

Results: Socialization in groups, recognition of family, articulation of foods, and playing games requiring gross and fine motor development were identified as indicators of “normal” development. Kappa scores across all domains were 0.95, 0.80, and 0.78 for intra-rater delayed, inter-rater no delay, and inter-rater delayed reliability and by domain: gross motor (0.97), fine motor (0.97), social (0.72), language (0.74), and cognitive (0.79). In the pilot (n=163) CHWs categorized 9% of children as suspected “delayed” or “normal” before administering the GDDST with matching (delayed, normal, 2.95 vs. 3.15 years, p<0.005). For children 2-5 years, those suspected as delayed performed significantly less well in all domains (n delayed = 26, n normal = 146, T-Test Statistics all = <.0005).

Conclusions: Providing the first estimates of developmental delay prevalence in Rwanda, the GDDST can be used in routine health evaluations of the 2,000,000 children under-5 living in rural communities in Rwanda.

Keywords: Cognitive/Behavioral Disorders, Translational/experimental therapeutics

Gilbert D (Cincinnati, OH), Kang P, Horn P, Mintz M, Joshi S, Ruch-Ross, H, Bale J

Objective: To assess attitudes regarding residency training and recruitment in child neurology.

Methods: A joint taskforce of the American Academy of Pediatrics (AAP) and the Child Neurology Society conducted an electronic survey of child neurology residents (n=305), practicing child neurologists (n=1290), and neurodevelopmental disabilities specialists (n=30) in 2015. Statistical analysis was conducted using SAS v9.3 (SAS Institute, Inc., Cary, NC).

Results: Response rates were 32% for residents (n=97; 36% male; 65% white) and 40% for practitioners (n=523; 63% male; 80% white; 30% lifetime certification). Seventy-three percent favored a certification option with fewer adult and more child neurology training months (Figure 1) (strongest predictors: fewer years since medical school p = 0.003; non-American Academy of Neurology
Should fewer months of adult neurology be established as a training option for board eligibility in pediatric neurology?

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<thead>
<tr>
<th>Percent Respondents</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

FIGURE 1: Abstract PL2-2.

What clinical areas should receive more emphasis in child neurology training in the future?

<table>
<thead>
<tr>
<th>Clinical Area</th>
<th>Residents</th>
<th>Child Neurologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetics</td>
<td>60%</td>
<td>50%</td>
</tr>
<tr>
<td>Neurodevelopment incl</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>Traumatic Brain Injury</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>Fetal/Neonatal</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>Neuroimmunology</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>Neuropsych incl ADHD</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>Metabolic Diseases</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Seizure</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Movement incl Tourette</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Headache</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Neuro-oncology</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* p<0.01 for Fetal, Neuromuscular, Neuro-immunology

FIGURE 2: Abstract PL2-2.

 membership p = 0.04; more half day clinics p = 0.005), and 58% favored one year of pediatric training/total training of 4 years (strongest predictor: non-AAP membership p = 0.03). Respondents supported increased training emphasis for multiple areas, particularly genetics and neurodevelopmental disabilities (Figure 2). Recruitment difficulty was commonly attributed to insufficient early exposure to child neurology. Although a majority reported that their medical school required a neurology clerkship, less than 40% offered education in child neurology. Eighty percent would definitely or probably choose child neurology again.

Conclusions: In this survey of child neurologists in training and practice, most respondents favored options for certification with reduced training in adult neurology or general pediatrics and increased emphasis on subspecialty areas. Recommendations for changing child neurology certification requirements should account for the possibility of responder bias.

Keywords: History/Teaching of Child Neurology

PL2-4. Headaches and Sleep Problems Among Adolescents in the United States: Findings from the National Comorbidity Survey - Adolescent Supplement (NCS-A) Study

Lateef T (Washington, DC), He J, Merikangas K

Objective: While there is substantial literature on the relationship between disordered sleep and headache among adolescents utilizing clinical samples, population based studies on this subject are scarce and none have examined this association across the headache spectrum. This study examines the association of specific sleep complaints with recurrent headache, migraine without and with aura, in the US adolescent population.

Methods: The National Comorbidity Survey-Adolescent Supplement (NCS-A) is a face-to-face survey of 10,123 adolescents aged 13-18 years which assesses DSM IV disorder symptoms, sleep patterns, headache, health related information as well as demographic characteristics. The International Headache Society criteria were used to define migraine with and without aura over past 12 months. The DSM-5 insomnia symptom criterion was used to define sleep disorders.
Results: There was a significant association between headache and disordered sleep after fully adjusting for demographics, health related variables and DSM-IV disorders. Insomnia was reported by more adolescents with non-migraine headache (OR=2.06 [95% CI 1.41-3.01]), migraine without aura (3.02 [1.97-4.62]) and migraine with aura (6.12 [1.19-17.00]) when compared to those without headache. At least 3 insomnia symptoms including difficulty initiating sleep, difficulty staying asleep, early morning awakening and daytime fatigue occurred among adolescents with non-migraine headache (1.62 [1.08-2.42]), migraine without aura (2.47 [1.71-3.57]), and migraine with aura (3.37 [1.85-6.51]) compared to those without headache. Chronic insomnia was more prevalent in youth with any headache (1.78 [1.01-3.14]) compared with no headache.

Conclusions: Adolescent migraineurs are at significantly higher risk of also suffering from sleep problems. Optimal treatment of headache must include investigation for sleep disorders and vice versa.

Keywords: Headache/Migraine

PL2-5. Neonatal Erythropoietin and Therapeutic Hypothermia for HIE - A Phase II Trial


Objective: To determine if multiple doses of erythropoietin (Epo) administered with hypothermia improve neuroradiographic and short-term outcomes of newborns with moderate/severe hypoxic-ischemic encephalopathy (HIE).

Methods: In a phase II double-blinded placebo-controlled trial, we randomized newborns to receive Epo 1000 U/kg IV (n=24) or placebo (n=26) at 1, 2, 3, 5 and 7 days of age. All infants had moderate/severe encephalopathy; perinatal depression (10 minute Apgar < 5, pH < 7.00 or base deficit ≥ 15, or resuscitation at 10 minutes); and received hypothermia. Neurodevelopment at 12 months was assessed by Alberta Infant Motor Scale (AIMS) and Warner Initial Developmental Evaluation (WIDEA). Analysis was by intention-to-treat. Two independent observers rated MRI brain injury severity using an established scoring system.

Results: Mean age at 1st study drug was 16.5 hours (SD 5.9). Neonatal deaths did not significantly differ between Epo and placebo groups (8% vs. 19%, P=0.42). Brain MRI at mean 5.1 (SD 2.3) days showed lower global brain injury score in Epo-treated infants (median 2 vs. 11, P=0.01). Moderate/severe brain injury (4% vs. 44%, P=0.002), subcortical (30% vs. 68%, P=0.02) and cerebellar injury (0 vs. 20%, P=0.05) were less frequent in the Epo than placebo group. At mean age 12.7 months (SD 0.9), motor performance scores in Epo (n=21) vs. placebo-treated (n=20) infants were as follows: AIMS (53.2 vs. 42.8, P=0.03) and WIDEA (28.6 vs. 23.8, P=0.05).

Conclusions: High doses of Epo given with hypothermia for HIE may result in less MRI brain injury and improved one-year motor function.

Keywords: Neonatal neurology, Translational/experimental therapeutics, Neuroimaging

PL2-6. Novel Automated Method to Quantify Vision in Children with Brain Injury Who Cannot Follow Commands

Saner M (White Plains, NY), Prusky G, Hill J, Carmel J

Objective: Cerebral visual impairment (CVI) is a leading cause of disability in children. Diagnosing CVI is difficult, however, since patients often have cognitive impairments that preclude the use of standard visual assessment procedures. We addressed this problem by designing a computer-based system that measures vision in children based on the reflexive tracking of spatially-defined visual stimuli.

Methods: Visual stimuli are moved horizontally across a large computer screen while an eye tracker measures the gaze position of a subject facing the screen. An algorithm determines in real time whether the eyes are smoothly following stimulus movement. When the algorithm detects smooth tracking, it confirms that the subject can see, the behaviour is rewarded with musical feedback. To determine visual thresholds, such as acuity and contrast sensitivity, the system automatically adjusts the stimulus characteristics until the limit of ability is identified.

Results: We tested children with brain injury that varied in cognitive function. In the majority of children, the system was able to detect eye movements and determine thresholds of visual ability. Measures in healthy children and children with brain injury who can follow commands, showed that tracking thresholds correlated well with classical measures of vision.

Conclusions: Our system enables the detection and quantification of CVI from patients who lack the verbal or cognitive skills to participate in standard visual assessment procedures. The measurement of visual thresholds in children with brain injury should enable future studies to determine incidence, natural history and treatment of CVI.

Keywords: Cognitive/Behavioral Disorders, Translational/experimental therapeutics, Neuromuscular disorders

PL2-7. Heterozygous de novo Mutations in EEF1A2 Lead to an Epileptic-Dyskinetic Encephalopathy


Objective: The epileptic-dyskinetic encephalopathies represent a recently recognized class of neurological disorders that combine features of an epileptic encephalopathy with severe chorea and/or dystonia. Known causes of epileptic-dyskinetic encephalopathies include mutations in ARX, STXBP1, FOXG1, SCN2A, SCN8A and FRRS1L. Heterozygous de novo mutations in the eukaryotic translation factor EEF1A2 have been previously reported in isolated patients with epilepsy, but their pathologic relevance has remained uncertain. We sought to characterize clinical and genetic features of 14 patients with an epileptic encephalopathy and/or...
dyskinesia and a de novo mutation in EEF1A2 and to validate putative mutations.

**Methods:** We applied a combination of clinical phenotyping, whole exome sequencing, bioinformatic analysis, and in vitro and in vivo validation studies.

**Results:** Patients exhibited focal or generalized epilepsy, chorea and/or dystonia, and developmental encephalopathy. The majority of patients were nonverbal. Neuroimaging features included global cortical volume loss and hypomyelination. Protein modeling predicted that most mutations fell within the GTP binding pocket (switch I/II regions) and would be inactivating. In vivo studies in zebrafish indicated that ref1a2 is highly expressed in the brainstem and cerebellum. Heterologous expression studies in yeast were used to evaluate the effect of de novo sequence variants on protein function.

**Conclusions:** Using these complementary approaches, we validated a role for putative mutations in this disease. Our results indicate that de novo mutations in EEF1A2 represent an important new cause of epileptic-dyskinetic encephalopathy and implicate deficient protein synthesis in this class of disorders.

**Keywords:** Movement Disorders, Genetics, Epilepsy

**POSTER PRESENTATIONS**

**Headache/Migraine**

1. **Concussion in High School Athletes: A Study on Substance Abuse Risk**
   *Cachia B (Loma Linda, CA), Freier Randall K, Gleason P, Lenihan J, Randall M, Clever J, Ashwal S*

   **Objective:** Consequences of sport-related concussions necessitate concussion prevention among young athletes. This study focused on identifying a relationship between illegal substance use and concussion history.

   **Methods:** With IRB and high school approval, researchers attained parental consent and student assent. Athletes completed the Athlete Risk and Resiliency Survey based on the Center for Disease Control’s Youth Risk Behavior Survey. Questions regarding concussion history and sports were included.

   **Results:** 131 male athletes ages 14-18 (M=15) participated. They were evenly split between football (51.6%) and soccer (48.4%). Overall, 29% reported concussion history: (49% football & 6% soccer). 33% of the athletes reported illegal use of substances (no differences by sport). Among participants with a reported concussion, 36% reported substance use. Participants with a concussion, who used any substance, were more likely to have continued concussion symptoms than those who did not use substances (33% v. 0%). Among participants who had a concussion, there is a trend for those who use substances to also have higher rates of other sports related injuries (83%) than those who do not use substances (67%).

2. **Visual Phenomena Associated with Migraines as Depicted in Children’s Headache Drawings**
   *Staffstrom C (Baltimore, MD), Lee E*

   **Objective:** Headache diagnosis in children relies mainly on history. Children often lack the verbal sophistication to describe their headache symptoms; drawings allow self-expression of headache symptoms and provide insight into self-image. We previously showed that drawings have high specificity, sensitivity and positive predictive value (PPV) to distinguish migraine from non migraine headaches (Pediatrics 109:460, 2002). In this study, we analyzed visual phenomena in children’s headache drawings.

   **Methods:** Children ages 5-18 years seen for headache at a university hospital-based pediatric neurology clinic were asked to draw a picture of their headache (blank white paper, colored pencils). Participants were encouraged to draw any aspect of their headache; no leading questions were asked. After drawing completion, a history and examination were performed to determine headache type.

   **Results:** From our database of 1120 children’s headache drawings, 822 were migraines. 193 (23.5%) of the migraine pictures depicted visual symptoms before (aura) or accompanying the headache. 137 drawings depicted positive visual phenomena such as stars, spots/dots, zig-zag lines, or flashing lights. 40 pictures showed visual field defects. 56 pictures illustrated blurring or tunnel vision. 101 migraine drawings depicted phobia. By comparison, 4 of 298 (1.3%) pictures drawn by children with tension-type headaches illustrated visual phenomena (p<0.001). Therefore, visual symptoms on a headache drawing are specific for migraine with a PPV of 98%.

   **Conclusions:** Visual symptoms on children’s migraine drawings are remarkably creative and correlate with an extremely high predictive value. Such drawings are valuable as an adjunct to the clinical history in pediatric headache evaluations.

   **Keywords:** Headache/Migraine

3. **Predicting Post Concussion Syndrome: A Retrospective Analysis of Risk Factors for Prolonged Recovery in Adolescent and Pediatric Patients**
   *Kingry E (Charlottesville, VA), Reynolds T*

   **Objective:** The management of post concussion syndrome (PCS) in pediatrics and adolescents is not well understood. While emerging literature describes tools for evaluating mild traumatic brain injury (mTBI) in the pediatric population, methods for identification of patients at risk for prolonged
PCS have yet to be described. The purpose of this research is to examine clinical characteristics of pediatric and adolescent patients with prolonged PCS in an attempt to identify risk factors for prolonged recovery.

**Methods**: A retrospective chart review was conducted of 295 patients 0-18 years with ICD codes for concussion, PCS, and TBI seen between January 2010 and May 2014 in a general pediatric neurology clinic serving a state of ~275,000 children. Patients’ symptom recovery courses were defined as either prolonged (>1 month) or short (<1 month). Both populations were analyzed and compared on several parameters using the chi-square test for significance (p < 0.05).

**Results**: 295 individuals were identified with concussion; 207(70.2%) experienced prolonged PCS and 88(29.8%) had short symptom resolution. Population characteristics are described in Table 1.

**Conclusions**: This data identifies adolescent age as a possible risk factor for prolonged PCS. No significant difference was identified between the groups with respect to gender, mechanism of injury (sport v. other), concussion history, or pre-morbid neuropsychiatric condition. Pre-morbid medication use was significantly different however we hypothesize this is reflective of potentially significant referral bias within this data rather than neuroprotective effects of medication. Further analysis is needed to develop a model for risk-stratification for prolonged PCS in patients at the time of injury.

**Keywords**: Headache/Migraine

### TABLE 1. Abstract 3

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<tr>
<td>Adolescent (13-18)</td>
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<td>47 (53.4%)</td>
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</tr>
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</tr>
<tr>
<td>Positive Concussion History</td>
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<td>34 (38.6%)</td>
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</tr>
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<td>Pre-morbid Neuropsychiatric Medication</td>
<td>33 (15.9%)</td>
<td>24 (27.3%)</td>
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</table>

4. **Chronic Daily Headache; Focus on Younger Children Age 3-11**

**Tunc E (Cleveland, OH), Rothner A**

**Objective**: Chronic Daily Headache (CDH) was first described by Silberstein in 1993. To date there is limited information on younger children ages 3-11 with CDH.

**Methods**: We reviewed the literature of CDH in adolescents and younger children and all CCF patients presenting with headache between May 2014-May 2015.

**Results**: Literature review showed that among primary headache patients aged 3-20, CDH ranged from 8 to 30%. 28-56% of patients were under 12. In our study 327 primary headache patients were identified; 57% had CDH. Of our CDH patients 28% were under age 12. Male to female ratio was 1:1 for patients under 12 and 1:2 for over 12 both in previous studies and our study. Most common type was CDH with migraine for both younger and older patients: 81% and 66% respectively. Brain MRI was performed more in older patients (58%) than younger (38%) (p=0.013). All were within normal limits. Younger patients have significantly greater duration of illness prior to initial evaluation (p=0.002) School absenteeism (>10 days in last 3 months) was present in 30% of younger and 41% of older patients. Older children had higher PedMIDAS scores (p=0.039). 61% of younger and 52% of older patients had medication overuse. Behavioral concerns were present in 27% of both younger and older patients.

**Conclusions**: This is the first and largest study specifically dealing with CDH under age 12. Results showed that CDH is not uncommon among younger children and characteristics are surprisingly similar to older children. Earlier diagnosis in younger patients would allow for earlier treatment and decrease morbidity.

**Keywords**: Headache/Migraine

5. **Magnesium Sulfate and Ziprasidone as Treatments for Pediatric Status Migrainosus**

**Griffith J (St. Louis, MO), Hasan N, Mar S**

**Objective**: Evidence for the use of atypical agents in treatment of acute headache is limited. This study aimed to evaluate the efficacy and safety of magnesium sulfate (MgSO4) or ziprasidone (ZPS) as treatments for pediatric status migrainosus.

**Methods**: The medical records database at St. Louis Children’s Hospital was searched to identify all patients receiving MgSO4 or ZPS in the ER or inpatient setting between February 2013 and February 2016. Patients with diagnosis of headache were included in the dataset. Charts were reviewed for patient characteristics and treatment response.

**Results**: Twenty-seven patients received IV MgSO4 (dose range 500 mg – 2000 mg). Median duration of headache prior to presentation was 10 days. Fifteen of 27 patients had received at least 2 medications prior to MgSO4. Change in headache severity (on 10-point scale) was 3.3 ± 3.5 (mean ± st. dev.). Only two patients had adverse
effects of MgSO4 (abdominal pain; mild elevation of serum Mg [2.8 mg/dl]). Three patients received IM ZPS (dose range 10 – 20 mg). All patients had received at least 3 medications prior to ZPS. Only 1/3 patients had improvement in headache at discharge. No adverse effects of ZPS were reported.

Conclusions: Evidence regarding use of IV MgSO4 for treatment of acute headache is mixed, however in this retrospective chart review, IV MgSO4 was not an effective abortive treatment for pediatric migraine. Although a recent study suggests IM ZPS may be effective for status migrainosus in adults, our limited data do not suggest it is effective in adolescents.

Keywords: Headache/Migraine

6. Rapid Weight Loss Results in Stabilization of Vision in Medically Refractory Idiopathic Intracranial Hypertension
Malray P (Washington, DC), Acosta M

Objective: The annual incidences of idiopathic intracranial hypertension (IIH) have been increasing the past decade likely secondary to the obesity epidemic. In adults, weight loss over the course of months has been shown to reduce optic disc pallor and improve visual field loss. It has not been demonstrated that in cases that are not amenable to ameliorating surgeries such as ventriculoperitoneal shunts or optic fenestrations whether more rapid weight loss may be beneficial.

Methods: We present a patient of medically refractory idiopathic intracranial who underwent serial lumbar drainage and serial ophthalmologic evaluations including Goldman and Humphrey visual field testing over the course of a 2 week period.

Results: A 16 year old morbidly obese (body mass index of 52.7 kg/m2) female with rapidly worsening of her visual fields despite maximal therapy of acetazolamide and furosemide was treated with a lumbar drain. Her pressures decreased from an initial opening pressure of 43 mmH20 to intracranial pressures of 1 to 11 mmH20. A 1000 calorie restricted diet resulting in a 2.5kg (2%) reduction of weight over 7 days. Patient’s visual acuity improved from 20/60 in the right eye and 20/50 in the left eye to 20/30 and 20/20, respectively. Visual fields were stable on visual field testing with symptomatic improvement in her headaches.

Conclusions: This is the first case report of rapid weight loss on the order of days demonstrating stabilization in visual fields, improvement in visual acuity and improvement of headache symptoms in a morbidly obese teenager.

Keywords: Headache/Migraine

7. Dysautonomia: Retrospective Study of Amino Acids, Cytokines and Neurotransmitter Metabolites
Wadhwania R (Houston, TX), Butler I, Hashmi S, Numan M, Lankford J

Objective: The aim of this study is to shed light on the pathogenesis of autonomic dysfunction and identify key biomarkers. A frequently studied subject in patients with autonomic dysfunction, like Multiple System Atrophy (MSA) and migraines is the imbalance of excitatory/inhibitory neurotransmitters, amino acids and pro-inflammatory and anti-inflammatory cytokines. However, the role of amino acids, cytokines and inflammatory mediators in autonomic dysfunction remains unknown.

Methods: This study retrospectively examined a cohort of young patients (n=25) diagnosed with neurocardiogenic syncope and dysautonomia by abnormal head-up tilt table testing (HUTT). CSF amino acids and neurotransmitter metabolites were quantitated, along with CSF and serum cytokines that were collected in a subset of patients.

Results: Overall, 86% of the cohort study patients (18/21) had elevated CSF cystine, 44% (4/9) and 55% (6/11) had elevated CSF and serum IL-13 respectively, and 48% (11/23) had low CSF HVA and 5HIAA.

Conclusions: Our findings indicate chronic oxidative stress in more than 80% of our dysautonomia cohort study group as evident with elevated cystine, elevated IL-13, and depleted HVA and 5HIAA implicating the vagus nerve to spleen circuit in the pathophysiology of autonomic dysfunction.

Keywords: Headache/Migraine, Infections/Neuroimmunology, Translational/experimental therapeutics

8. Is Less More? Pediatric Intractable Migraine and Botox Treatment
Pezzuto T (Wilmington, DE), Beyderman L, Chugani D, Xie L

Objective: Chronic migraine occurs in approximately 1.75% of adolescents in United States. Preventive and abortive medication with a combination of integrative therapy is standard practice in headache programs. This approach is ineffective or limited by adverse responses in some patients. OnabotulinumtoxinA (Botox) 155-200 unit dose was approved by the FDA for treatment of Chronic Daily Headache in adults in 2010. Botox is used off-label in refractory pediatric and adolescent patients but no standard dose has been established.

Methods: A retrospective chart analysis was performed in all patients who received Botox between February 2014 and March 2016 to assess age, headache type and effectiveness of dose administered.

Results: Forty-two patients (35 females, 8 males, and age range 11-18 at time of treatment) received Botox using a modified dose approach based on location and tolerance, with parent and patient consent. Forty-seven percent had chronic migraine without aura and 53% had chronic migraine with aura. Significant improvement in migraine intensity and frequency was reported in 71% of patients. Sixty-six responded to responded to < 110 units, 16% percent responded to < 75 units and 16% responded to < 50 units. Soreness at the injection sites was the only reported side effect.

Conclusions: Botox was well tolerated using a modified dose approach and provided improvement in migraine intensity and frequency in the majority of adolescents who failed standard treatment (At least three preventative medications: topiramate, amitriptyline, divalproex, propranolol, cyproheptadine). The data supports prospective studies of optimal dosing in medically refractory pediatric migraine patients.

Keywords: Headache/Migraine
FIGURE 1: MRI findings in H-SMD (Abstract 9).

FIGURE 2: Skeletal abnormalities in H-SMD
GENETICS

9. X-linked Hypomyelination with Spondylometaphyseal Dysplasia (H-SMD)

Objective: The leukodystrophy characterized by the unusual combination of hypomyelination and spondylometaphyseal dysplasia (H-SMD) has been observed in a small number of patients. After careful clinical and neuroradiologic phenotyping of existing cases of this disease, we identified additional patients who also presented with this rare disorder.

Methods: 5 patients in two families presenting with hypomyelination with spondylometaphyseal dysplasia have previously been described, but have eluded genetic characterization to date. Additional cases of this disorder were sought to facilitate genetic characterization. Patients with similar clinical and neuroradiological features were identified through the Myelin Disorders Bioregistry Project (MDBP) and by outside institutions.

Results: An additional 6 males from 4 families were identified with H-SMD, increasing reported cases to a total of 6 families with X linked pattern of inheritance. Presentation typically occurred between 12 and 36 months. In addition to the obligate findings of hypomyelination on MRI (Figure 1) and spondylometaphyseal dysplasia (Figure 2), common phenotypic features included motor deterioration, spasticity, tremor, ataxia, nystagmus and vision loss, cognitive defects, and dysarthria. The course of the disease is slowly progressive.

Conclusions: Among patients with hypomyelination, the presence of spondylometaphyseal dysplasia has only been described twice previously (Neubauer et al., 2006, Kimura-Ohtba et al. 2013). Here, we add to the cohort of existing patients presenting with H-SMD, an X-linked, recessively inherited leukodystrophy (Neubauer et al., 2006). We hypothesize that the gene whose mutation causes this disorder encodes a mitochondrial protein that functions in both bone metabolism and in myelination.

Keywords: Genetics, Demyelinating Disorders, Neuroimaging

10. Rett Syndrome: Analysis of Memory and Attention
Djukic A, Rose S (Bronx, NY), Jankowski J, Feldman J

Objective: Rett syndrome (RTT), a severely disabling neurodevelopmental disorder caused by spontaneous mutations in the x-linked MECP2 gene, affects 1:10,000 females. Assessments of cognitive functioning have been extremely difficult because patients with RTT are nonverbal and have no or little purposeful hand use. We have pioneered using state-of-the-art eye-tracking technology to bypass these limitations and reveal the disorder’s cognitive phenotype.

Methods: Testing more than 100 genetically confirmed RTT patients, and their typically developing counterparts (TD), we have: (1) established the feasibility of using this new technique with RTT, (2) examined the extent to which memory is affected (as shown by visual preference for a novel target over a familiar one) and (3) delineated aspects of attention that are compromised.

Results: Children with RTT were able to recognize simple patterns, faces, and some emotional expressions (i.e., novelty scores were significantly above chance), although their performance was significantly poorer than that of TD children. An especially striking finding were the atypical patterns of attention, characterized by fewer and longer fixations, poorly distributed looking, less looking to key target areas (e.g., over 40% totally ignored the lower part of the face, and a striking absence of anticipatory/predictive saccades. Deficits in attention correlated with poorer recognition.

Conclusions: This new work indicates that the cognitive world of those with RTT can be unlocked using visually-based tasks, and holds promise for the assessment of therapeutic interventions. Deciphering attentional processes has already led to the design of better attention training strategies which are showing promise in pilot studies with RTT.

Keywords: Genetics, Cognitive/Behavioral Disorders

11. Rett Syndrome-Treatment with Glatiramer Acetate

Objective: To assess the efficacy of glatiramer acetate in improving gait velocity in patients with Rett syndrome (RTT). Secondary endpoints included cognition, respiratory function, electroencephalogram, and quality of life.

Methods: Phase two, open label, single center trial. Inclusion criteria: ambulatory girls with genetically confirmed RTT, 10 years or older. Pre- and post-treatment measures were compared using paired t-tests and the non-parametric Wilcoxon signed rank sum test.

Results: Ten of 11 enrolled patients tolerated the treatment well and completed the trial. Gait velocity improved significantly (improvement range 13%-95%, p=0.03) and emerged as an especially valuable outcome measure with excellent test-retest reliability of the 2 trials within sessions (r=0.94, p=0.0002). Memory, and the breath holding index also improved significantly (p=0.03). Epileptiform discharges decreased in all 4 patients who had them at baseline. There was a trend towards improved QOL, which did not reach statistical significance.

Conclusions: This prospective open-label trial provides important preliminary information related to the efficacy of GA in improving gait velocity in female patients with RTT who are 10 years or older. The results of this trial justify the need for larger scale controlled trials of GA as well as provide a template for assessing the efficacy of other interventions in RTT.

Keywords: Genetics, Translational/experimental therapeutics
12. Neurofibromatosis Type 2 in Pediatric Patients: Clinical Course

Ghosh A (Houston, TX), Slopis J

Objective: Neurofibromatosis type 2 (NF2) is considered an adult disease with onset occurring post adolescence. Study the initial presentation and clinical course in pediatric patients with NF2.

Methods: 21 Patients evaluated in the Neurofibromatosis Clinic at MD Anderson were diagnosed before age of 18 years and followed up to 15 years. Chart review of the group included clinic notes, EMG results, MRI, CT, genetic analysis, and audiology reports.

Results: Frameshift mutations were the most common germline event (6/10), with severe disease symptoms. 2/10 patients had nonsense mutation and 2/10 patients had splice consensus mutations. Vestibular schwannoma was documented in 62% (13/21) of patients but only 23% had symptoms during initial assessment. 38% (5/13) underwent surgical resection and 30% (4/13) underwent gamma knife radiation, but both the groups eventually developed complete hearing loss. Mononeuritis multiplex (MNM) was an unexpectedly common finding in these patients: 4% (1/21) presented with MNM as the initial symptom and 23% (5/21) developed during the course of the disease. EMG confirmed the diagnosis. Nearly 75% of patients developed excruciating headache and were diagnosed with sagittal sinus meningioma and pseudo-tumor cerebri. Pregnancy appears to accelerate progression of NF2 and 25% developed symptoms of MNM during the second and third trimester of pregnancy. Spinal tumors include schwannoma, meningioma, and low grade ependymoma.

Conclusions: The sensitivity of diagnostic clinical criteria for initial assessment is unknown in this population. Pediatric NF2 patients present with asymptomatic features and so greater knowledge of the clinical course in childhood and DNA diagnosis are crucial to timely diagnosis and treatment.

Keywords: Genetics, Brain Tumors/Oncology, Neuroimaging

MRI Spine at this time showed myelopathic changes in the lower spine (Fig 1A), MRI Cervical Spine showed ependymoma in C2 to C3 (Fig 1B). MRI Brain showed bilateral acoustic neuroma (Fig 1C). He was noted to have left lower extremity atrophy on examination. MRI of the thigh showed Mononeuritis multiplex (MNM) with no evidence of nerve ending schwannoma and meningioma (Fig 1D). MNM was further confirmed with EMG studies. He was diagnosed with NF2 at the age of 32 years.

His first fraternal twin daughter presented with ataxic gait at the age of 3 years, and MRI spine showed ependymoma in C2 to C3 (Fig 1E). His second fraternal twin developed cataract and was found to have intraorbital meningioma. MRI Spine of the second fraternal twin showed myelopathic changes in the lower spine (Fig 1F). MNM was further confirmed with EMG studies.

FIGURE 1: This is a case of 32 Y old man who first experienced weakness in bilateral lower extremities when he was 7 Years old. He was noted to have spinal tumor at the outside hospital and underwent surgical resection. He was discharged with no further interventions until he experienced hearing deficit and bilateral lower extremity weakness when he was 32 Y old (Abstract 12).
FIGURE 2: This is a case of a 15-year-old girl with no significant family history and past medical history of cataract (onset at the age of 4 years) who presented for the first time with excruciating headache, proptosis of left eye, and left hearing deficit. MRI Brain showed intra orbital, and cavernous meningioma (Fig 2A and Fig 2B) along with acoustic neuroma. She was diagnosed with NF 2 at the age of 15 years (spontaneous mutation). Fig 2C shows the progression of the meningioma (compared to 2A).

FIGURE 3: Shows a pie diagram explaining all the different initial presentation of the patients who presented with early onset of NF 2.
showed ependymoma in the same level C2 to C3 (Fig 1F). This is an example of Tancyciotic ependymoma in the family members diagnosed with NF 2.

During pregnancy (at the age of 22 years), she was noted to have worsening headache and left foot drop. MRI Brain showed diffuse sagittal sinus meningioma (Fig 2D) and EMG confirmed the onset of MNM.

13. Strain-specific Phenotypes in the Maternally Deficient Ube3a Angelman Syndrome Mouse Model

Anderson A (Houston, TX), Dao A, Born H

Objective: Angelman syndrome (AS) is a genetic neurodevelopmental disorder with unique behavioral phenotypes and seizures as key features of the disease. The most common genetic cause of AS is the deletion or mutation in the maternally imprinted Ube3a gene, encoding ubiquitin ligase (Ube3a). In this study, we sought to determine the effect of mouse strain background on the AS behavioral profile, electroencephalography (EEG) activity, and seizure threshold in a mouse model of AS (Ube3a gene maternal deletion).

Methods: We utilized AS C57Bl/6J (B6), AS 129Sv/Ev (129), and AS F1 hybrid mice (B6 x 129) in a battery of behavioral tests. In parallel in a separate cohort of these mice we performed video EEG and monitoring background and epileptiform activity as well as induced seizure threshold.

Results: We found strain-dependent differences in behavioral, EEG, and seizure phenotypes. The AS C57Bl/6J (B6) mice displayed hypoactivity, impaired motor coordination and learning, deficits in recognition learning and memory, abnormal marble burying activity, spontaneous spike bursting (i.e., polyspikes), and increased delta and theta and decreased gamma EEG spectral power in the hippocampus. The AS 129Sv/Ev (129) mice exhibited poor performance on the wire hang and contextual learning and memory tests and lower seizure threshold when induced with loud sound (140 dB) or the chemoconvulsant kainate. The AS F1 hybrid mice (B6 x 129) showed hypoactivity, abnormal marble burying activity, impaired rotarod performance, and infrequent spontaneous polyspikes.

Conclusions: Together, these findings indicate that mouse genetic background modifies the behavioral, EEG activity, and seizure threshold Ube3a maternal deletion phenotype.

Keywords: Genetics, Epilepsy, Cognitive/Behavioral Disorders

14. Neuropsychological Outcomes in Pediatric Patients with Genetically Confirmed Episodic Ataxia Type 2

Jindal A (Pittsburgh, PA), Thakkar K, Goldstein A, Vento J

Objective: Episodic ataxia type 2 (EA2) is caused by a heterozygous mutation in the CACNA1A gene. Cognitive delays and psychiatric disorders have been described in individuals with EA2.1,2 However, no studies to date have detailed neuropsychological testing in non-related patients with EA2. We present three patients with EA2 and review their neuropsychological profiles.

Methods: We identified 10 patients with confirmed CACNA1A gene mutations through retrospective chart review over a 10-year period at a single institution. Of these patients, three had detailed neuropsychological assessments completed.

Results: Average age at symptom presentation was 3 years and average age at diagnosis of EA2 was 7.33 years. All three children presented with paroxysmal episodes of imbalance or falling; two patients had nystagmus on examination. One child had preexisting global developmental delay, another had required speech therapy for stuttering, and the third had preexisting learning difficulties. Formal neuropsychological testing was performed at an average of 4 years after diagnosis of EA2. As determined by validated measures, all three patients were found to have cognitive delays and impairments in executive functioning—specifically, deficits in working memory, processing speed, visuospatial and visuomotor tasks. These patients were also reported to have difficulties with fine motor skills and/or tasks requiring manual dexterity.

Conclusions: EA2 is associated with developmental and academic challenges, in addition to motor issues. Delays in neuropsychological testing can lead to delays in implementing interventions and school accommodations. We advocate for early developmental assessments and comprehensive neuropsychological evaluations in children diagnosed with EA2 in order to optimize their cognitive outcomes.

Keywords: Genetics, Cognitive/Behavioral Disorders, Movement Disorders

15. Shared Bioinformatics and Research Resources Inform Clinical Interpretations of Genetic Findings in Atypical Leigh Syndrome

Walker M (Boston, MA), Anselm I, Krishnamoorthy K

Objective: To employ published data and publicly available tools to understand genetic variants in atypical Leigh syndrome (LS) and review relevant literature

Methods: “Typical” LS can has been described using the following criteria: (1) progressive psychomotor regression, (2) brainstem or basal ganglia disease, (3) elevated blood or cerebrospinal fluid lactate, (4) ≥ 1 of: (a) MRI brain abnormalities, (b) characteristic postmortem neuropathologic findings, (c) characteristic neuropathologic findings in an affected sibling. Reported median age of onset was 7 months, and median age of death was 2.4 years. We report 2 atypical cases of Leigh syndrome with genetic findings. We employ bioinformatics analysis, published literature and resources (Mitocarta 2.0, Exome Aggregation Consortium, Target P) to assess the likelihood of causality for each genetic variant. We review and summarize reports of atypical Leigh Syndrome with associated molecular diagnoses cases and summarize clinical and genetic findings.

Results: Each patient carries novel variants in Complex I assembly factors (NDUFAF3 and NDUFAF6, respectively) and exhibits atypical (age 5 and 11 years), with late onset and preserved intelligence in one. Bioinformatics
analyses, variant database and functional screen mining support causality. ≥20 atypical LS cases with molecular etiologies have been identified to date.

Conclusions: LS represents a broad genotypic and phenotypic spectrum. Publically available resources can assist in understanding genetic variants.

Keywords: Genetics

16. WARS2, Encoding Mitochondrial Tryptophanyl-tRNA Synthetase, is a Candidate Gene for Leukoencephalopathy
Theisen B (Baltimore, MD), Cohen J, Alcaraz W, Shinde D, Tang S, Srivastava S, Fatemi A

Objective: Of the 19 mitochondrial aminoacyl-tRNA synthetase genes (mt aaRSs), WARS2 is the only one that has not been associated with disease in humans to date. Here we present a patient with severe infantile-onset leukoencephalopathy who was found by whole exome sequencing (WES) to have compound heterozygous variants in WARS2.

Methods: Trio WES was performed on gDNA isolated from blood of a 24 year-old patient with profound intellectual disability, spastic quadriplegia, and epilepsy in whom extensive previous testing was negative, along with his parents. Dideoxy sequencing was used to confirm the variants and perform targeted testing in the unaffected brother.

Results: The patient was compound heterozygous for a missense variant c.938A>T (p.K313M) and an in-frame deletion c.298_300delCTT (p.L100del) in WARS2. The parents and unaffected brother were heterozygous carriers of one variant. Mitochondrial and WARS2 enzyme activity assays on patient’s fibroblasts are underway.

Conclusions: We suspect the WARS2 gene to be implicated in this patient’s phenotype, an infantile-onset leukoencephalopathy with brain MRI findings including cerebral atrophy, ventriculomegaly, periventricular white matter abnormalities. He presented with global delays and epilepsy at 6 months of age, evolving to postnatal microcephaly and profound intellectual disability. On examination he had spastic quadriplegia, tremor, contractures, muscle atrophy, and signs of peripheral neuropathy. Mutations in other mt aaRSs cause autosomal recessive disorders with diverse clinical presentations including neurologic phenotypes.

Keywords: Genetics, Movement Disorders, Neuroimaging

17. Impaired Mitochondrial Dynamics and Mitophagy in Neuronal Models of Tuberous Sclerosis Complex

Objective: Tuberous sclerosis complex (TSC) is a neurodevelopmental disease caused by TSC1 or TSC2 mutations and subsequent activation of the mTORC1 kinase. Here we aim to understand the impact of mTORC1 hyperactivity on mitochondrial dynamics, metabolism and turnover in neuronal in vitro and in vivo models of TSC.

Methods: We use a combination of genetic strategies, pharmacology, live cell imaging, microscopy, flow cytometry, and biochemistry in Tsc2-deficient neurons, human iPSC-derived neurons from TSC patients, and brain-specific Tsc1 mutant mice.

Results: We find that Tsc1/2-deficient neurons accumulate mitochondria in cell bodies but are depleted of axonal mitochondria. Axonal mitochondria show an abnormal morphology, indicating disrupted mitochondrial dynamics. Mitochondrial respiration and mitochondrial membrane potential are diminished with dysfunctional mitochondria accumulating in neurites. iPSC-derived neurons from TSC patients show similar mitochondrial dysfunction in neurites. Importantly, we find that axonal mitochondria in Tsc2-deficient neurons are progressively returned to the cell body, leading to a depletion of presynaptic mitochondria. Axonal and global turnover of damaged mitochondria via mitophagy is impaired, suggesting that deficits in mitochondrial turnover act upstream of impaired mitochondrial metabolism. Lysosome-dependent stages are deficient, indicating impaired autophagosome-lysosome fusion. Finally, we find that blocking mTORC1 (rapamycin) or inducing mTOR-independent autophagy (carbamazepine) can reverse many of the changes in mitochondrial dynamics and turnover seen in Tsc2-deficient neurons.

Conclusions: Our study clarifies the complex relationship between the TSC-mTORC1 signaling pathway, autophagy and mitophagy. Our results provide evidence for impaired mitochondrial homeostasis and thus point to novel therapeutic targets for TSC and related diseases.

Keywords: Genetics, Translational/experimental therapeutics

18. High frequency of Mosaicism in Genes Associated with Epilepsy and Neurodevelopmental Disorders
McKnight D (Gaithersburg, MD), Stosser M, Butler E, Lindy A, Richard G

Objective: New molecular diagnostic techniques, including capture and next-generation sequencing (NGS) with high read-depth, have increased sensitivity for detecting mosaic variants. We aim to determine the frequency of mosaicism in epilepsy-related disorders.

Methods: A retrospective analyses of results in >9000 probands who had undergone NGS and copy number analysis for a panel of epilepsy-related genes (2-70 genes) was conducted. Mosaicism was suspected when the variant call was observed in <35% of NGS reads for autosomal dominant genes and X-linked genes in females or when both variant and wildtype calls were detected in X-linked genes in males without sex chromosome aneuploidy.

Results: We reported mosaic pathogenic or likely pathogenic variants in 35 probands and levels of mosaicism ranged from 9-87% of reads. The majority of mosaic variants were identified in five genes and accounted for a significant frequency of positive finding for each gene: PCDH19(8.1%), CDKL5(7.1%), SCN2A(7.0%), and TSC1/TSC2(3.1%). Less frequent were mosaic variants in SCN1A, GABRG2, GRIN2B, MECP2, SLC9A6, and KCNQ2. Furthermore, targeted Sanger sequencing of parents of affected probands revealed several cases of
parental mosaicism for variants in SCN2A, SCN1A, KCNQ2, and TSC1. Based on available clinical information, half of these parents were affected with milder symptoms compared to their offspring, while the other half were unaffected.

Conclusions: In conclusion, mosaicism may represent an underappreciated disease mechanism for certain epilepsy-related genes, particularly CDKL5, PCDH19, SCN2A, and TSC1/TSC2. Detecting mosaicism provides important information regarding a diagnosis, which may alter treatment strategies, and is necessary for appropriate genetic counseling regarding recurrence risk and family planning.

Keywords: Genetics, Epilepsy, Cognitive/Behavioral Disorders

19. “Salt and Pepper Syndrome”: A Deficiency in Ganglioside Metabolism and an Under-recognized Genetic Cause of Intellectual Disability, Choreaathetosis and Failure to Thrive

Gordon-Lipkin E (Baltimore, MD), Cohen J, Srivastava S, Levey E, Fatemi S

Objective: Salt and Pepper Syndrome was originally described in a family with pigmentary changes and intellectual disability (ID). A mutation in ST3GAL5, a gene encoding a sialyltransferase that synthesizes ganglioside GM3, was later identified. Biallelic mutations result in GM3 Synthase Deficiency, an autosomal recessive condition characterized as profound ID, failure to thrive (FTT) and infantile onset epilepsy. We expand the phenotypic spectrum of this rare disorder with three siblings of Pakistani descent.

Methods: Family-based whole exome sequencing (WES) was performed by GeneDx (methods in Retterer 2015) in three affected siblings (one female, two males) with profound ID and choreoathetosis. Variants were confirmed by dideoxy sequencing. Records were retrospectively reviewed and compared to cases in the literature (Boccuto 2013, Simpson 2004, Fragaki 2013, Wang 2013).

Results: All affected siblings were homozygous for a nonsense variant, c.862C>T (p.R288*) in ST3GAL5. Unaffected parents, brothers were heterozygous carriers. Affected siblings had normal birth history, subsequent developmental stagnation, FTT, visual and hearing impairment. One cruised. Two were non ambulatory. Features newly described in our cohort include severe atopic dermatitis, self-injurious behavior (SIB), sleep difficulties. Table 1 illustrates an analysis of our cohort with 52 cases from the literature. EEG, MRI were variable.

Conclusions: GM3 Synthase deficiency is a neurodevelopmental disorder with consistent features of profound ID, choreoathetosis, deafness, FTT. Other phenotypic features have variable expressivity including epilepsy, regression, vision, skin findings. Atopic dermatitis, SIB, sleep disorder are newly described and may influence clinical management. Our analysis demonstrates a broader phenotypic range of this underrecognized disorder.

Keywords: Genetics, Cognitive/Behavioral Disorders, Movement Disorders

<p>| TABLE 1. Comparison of the Clinical Features of GM3 Synthase Deficiency With Our Patients* (Abstract 19) |</p>
<table>
<thead>
<tr>
<th>Descent</th>
<th>KKI</th>
<th>Boccuto</th>
<th>Simpson</th>
<th>Fragaki</th>
<th>Wang</th>
<th>Total (N)</th>
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<td>38/38</td>
<td>55/55</td>
<td>100</td>
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<tr>
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<td>IQ 5-18</td>
<td>IQ 2-4</td>
<td>NR</td>
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<tr>
<td>Neuro deterioration</td>
<td>0/3</td>
<td>1/4</td>
<td>8/8</td>
<td>2/2</td>
<td>NR</td>
<td>11/17</td>
<td>65</td>
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<tr>
<td>Verbal</td>
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<td>NR</td>
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<td>Choreoathetosis</td>
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<td>3/3</td>
<td>8/8</td>
<td>2/2</td>
<td>NR</td>
<td>16/16</td>
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<td>Tone</td>
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<td>Ambulates</td>
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20. Identification and Functional Annotation of Novel Autism Candidate Genes Using an in Vivo High-Throughput Drosophila Genetic Screen

Chao H (Houston, TX), Kanca O, Manivannan S, Luo X, Liu N, Saurabh S, Lagarde M, Chao Y, Wangler M, Yamamoto S

Objective: Autism spectrum disorders (ASD) are genetically heterogeneous neurodevelopmental disorders defined by impaired communication and social interaction, with restricted and repetitive behaviors. Despite large-scale genomic sequencing efforts in thousands of families with ASD probands, the identification of candidate autism genes remains limited by the incomplete functional annotation of the human genome.

Methods: Examined whole-exome sequencing data from the Simon’s Simplex Collection of 2,500 families to identify genes with \textit{de novo} missense or in-frame indels in the ASD proband. Gene conservation in the model organism \textit{Drosophila melanogaster} was determined via integration of multiple ortholog prediction algorithms. Transposable element MI\textit{MIC} lines were used to generate loss-of-function strains for molecular, neurophysiological, viability, and behavioral phenotyping. Strains were also generated expressing the corresponding human cDNA with the reference and variant allele for rescue and fluorescent reporter strains for expression analyses.

Results: Identified 2,437 candidate ASD genes with potentially deleterious variants. 1,931 genes were conserved in \textit{Drosophila}. 69 genes were selected for initial annotation with 61 genes forming an interaction network based on pathway analysis, physical and genetic interactions. 16 genes formed key interaction nodes with protein function.

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<td>Descent</td>
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<td><strong>SEIZURES</strong></td>
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<td>Abnormal EEG</td>
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<td>Vision Impairment</td>
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<td>PO Feeds</td>
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<td><strong>PHYSICAL EXAM</strong></td>
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<td>Severe atopic dermatitis</td>
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<td><strong>BEHAVIOR</strong></td>
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<td>Sleep Difficulty</td>
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<td>SIB</td>
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<td><strong>HISTORY</strong></td>
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<td>Nml Prenat, Birth Hx</td>
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<td>Nml Birth Parameters</td>
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including voltage-gated ion channels, calcium-mediated signaling, DNA-binding, cell-migration and proliferation, and kinase activity. *Drosophila* strains were generated for functional annotation of candidate disease genes and variants of interest.

**Conclusions:** Model organisms are invaluable for elucidating genetic regulation of neuronal development and function. The synergy between human genomics and functional analysis in *Drosophila* facilitates identification of novel ASD candidate genes, mediates classification of ASD by gene function, and uncovers new therapeutic avenues.

**Keywords:** Genetics, Epilepsy

21. Escaping X-inactivation: A New Perspective on KIAA2022-Related Disorder

Le Pichon J (Kansas City, MO), Thiffault I, Farrow E, Soden S, Parikh S, Saunders C

**Objective:** X chromosome inactivation is a mechanism that modulates the expression of X-linked genes in females to achieve a proper balance between X-linked and autosomal genes. In humans 15-25% of X-linked genes have been shown to ‘escape’ from X-chromosome inactivation. A significant subset of X-linked escapees are likely important contributors to human phenotype by lack of dosage compensation. To date, little is known about genes that escape inactivation. Recent genomic studies have yielded contradictory results and fueled debate over the possibility that genomic imprinting is not limited to autosomes and the X-inactivation center.

**Methods:** We report two females with intractable epilepsy caused by *de novo* loss of function variants in *KIAA2022*, an X-linked gene associated with severe intellectual disability in males. This is perplexing since the carrier mothers of such males are unaffected. Random patterns of X-chromosome inactivation have been observed in both affected females and unaffected carrier mothers so is not sufficient to explain these differences.

**Results:** We review what is known about *KIAA2022* and offer parent-of-origin mono-allelic expression as a possible mechanism for the apparent dichotomous phenotypic expression of *KIAA2022*.

**Conclusions:** The sex-specific dichotomous phenotypic expression of *KIAA2022* presents us with a pathophysiological conundrum. We propose that parent-of-origin monoallelic expression within a given cell or tissue may account for this observation. This opens the door to a novel field of X-linked intellectual disability research in females in which X-linked genes escaping X-inactivation exhibit non-random monoallelic expression, contributing to an atypical mode of inheritance.

**Keywords:** Genetics, Epilepsy

22. Next generation sequencing-based gene panel testing in childhood intractable epilepsy

Lee J (Seoul, Korea), Lee J, Lee C, Lee M

**Objective:** In this study, we try to detect genetic mutations through epilepsy gene panel using next generation sequencing (NGS) in childhood-onset intractable epilepsies.

**Methods:** We retrospectively reviewed the medical records of 48 patients (female: male = 24: 24) with childhood-onset intractable epilepsy at Samsung Seoul Hospital between June 2014 and July 2015. We designed customized NGS-based epilepsy gene panel containing total 111 genes which included 38 candidate genes for genetic generalized epilepsy syndromes and 73 genes for other genetic epilepsy.

**Results:** Twenty-eight patients (58.3%) had severe developmental delay and six had psychiatric disorders. Three sibling cases were included and 24 patients had a family history of epilepsy (n = 12) or febrile seizure (n = 12). In 16 patients (33.3%), we identified mutations which were known to be associated with genetic epilepsy disorders: *SCN1A* (n = 5, 31%), *SCN3A* (n = 4, 25%), *SCN8A*, *PCDH19*, *PRRT2* (n = 2, 13%), *ARX*, *KCNQ2*, and *FOXG1*. In six children with presumed as Dravet syndrome clinically, five were confirmed to have a *SCN1A* mutation and the other one had a *PCDH19* mutation. Two families were revealed to have *SCN3A* and *PRRT2* mutation respectively. Eight patients with mutation were sporadic cases without family history.

**Conclusions:** Our data demonstrated the clinical efficacy of NGS-based epilepsy gene panel for screening in not only patients with clinically suspicious of specific syndrome but also sporadic cases. NGS-based epilepsy gene panel makes another step forward in diagnosis and new therapeutic approaches of childhood intractable epilepsy.

**Keywords:** Genetics, Epilepsy

23. The Pitfalls and Triumphs of Whole Exome Sequencing in Rare Childhood Disorders


**Objective:** There are many limitations to whole exome sequencing (WES). Even though we sequence over 20,000 genes not all of these are well characterized or linked to disease. At TGen’s Center for Rare Childhood Disorders we have a 30-40 percent diagnostic rate. We use RNAseq data to help improve these odds but the mechanism of disease for many of our families still eludes us. On the other hand, there are times where next generation sequencing reveals mutations that were missed by specific gene or panel testing.

**Methods:** Here we present four different cases where whole exome sequencing was used to diagnose rare childhood disorders.

**Results:** Case 1: *MeCP2* testing in a female child showed two heterozygous variants. Clinicians diagnosed Rett syndrome. Whole exome sequencing revealed that the child is heterozygous for a *de novo* variant in GNAO1, causing epileptic encephalopathy. Case 2: *MeCP2* gene sequencing and MLPA testing for deletion and duplications were normal. However, WES detected an 88bp deletion in the *MeCP2* gene. Case 3: A gene panel containing *CLN3* missed the deletion of exon 7 and 8 that was only detected by WES.
after visualizing the gene in the IGV software (Broad Institute). Case 4: Reanalysis of WES data finds a rare variant in the PYCR2 gene.

Conclusions: Whole exome sequencing can be an excellent tool for diagnosing rare disorders, knowing that there are limitations that need to be recognized. Likewise, WES may shed light on disorders previously ruled out due to traditional genetic testing methods.

Keywords: Genetics

24. Analysis of Disease-Specific Bio Markers Gaucher and Niemann Pick Disease

Raymond K (Rochester, MN), Turgeon C, Gavrilov D, Matern D, Oglesbet D, Rinaldo P, Tortorelli S

Objective: Some lysosomal storage disorders (LSDs), present clinically with hepatosplenomegaly or isolated splenomegaly. Current biochemical analysis of these disorders requires study of their enzymatic activity. The ideal assay would combine analysis of several biomarkers to shorten the time to diagnose them to allow specific treatment to be started as early as possible. An assay for the detection of plasma biomarkers for Gaucher disease (GD), and Niemann Pick (NPA/B/C) disease can significantly improve the diagnostic approach.

Methods: Plasma samples from patients with abnormal beta-glucosidase activity (including confirmed GD (n=5), confirmed heterozygous carriers (n=3) and undetermined (n=5) cases), NP type A and B (n=14) and healthy individuals (59 male, 60 female) were tested using a combined liquid chromatography/tandem mass-spectrometry (LC-MS/MS) method for detection of GD and NPA/B/C biomarkers. The biomarkers analysed are: glucosylsphingosine (GD), lyso-sphingomyelin, cholestane-3β,5α,6β-triol and 7-ketocholesterol (NPD).

Results: Glucosylsphingosine proved to be highly specific and reliable biomarker to discriminate GD patients (298-1,230 nM) from carriers (<9 nM) and healthy individuals (<6 nM). In NP type A or B, plasma lyso-sphingomyelin levels were significantly higher (319-5,220 nM) as compared to the healthy control group (<17 nM).

Conclusions: This biomarker analysis is highly reliable, less invasive, and shorter turn-around time tests. We propose this combined biomarker assay as a first-line test for patients with suspected sphingolipidosis.

Keywords: Genetics, Cognitive/Behavioral Disorders

25. Human Macrophages in Adrenoleukodystrophy Show Phenotypic Specific Cytokine and Glutamate Response to Very Long Chain Fatty Acid Stimulation


Objective: Adrenoleukodystrophy is an X-linked peroxisomal disorder due to ABCD1 mutation and very long chain fatty acid (VLCFA) accumulation. Metabolic and oxidative stress are proposed central effectors of general ALD cell pathology, while microglia activation in brain has been indicated as a mediator of deadly cerebral disease. We attempted to create individual macrophage models from each ALD patient and phenotype in order to determine reaction to stimulation with VLCFAs C24:0 and C26:0.

Methods: Peripheral Blood Mononuclear Cell (PBMC) culture was derived from 21 consented ALD patients (n=21) and healthy controls (n=5) at Kennedy Krieger Institute, then differentiated into M1 polarised macrophages over 7 days. Monocyte and macrophage cultures were stimulated with VLCFA and lipopolysaccharide (LPS) at multiple time points and doses.

Results: Monocytes and Macrophages showed dose dependant response to LPS stimulation in secretion of pro-inflammatory cytokines IL-6 and TNF alpha. VLCFA stimulation showed high fold over base increase in cerebral ALD phenotype, but not heterozygote female carrier (Het) or adrenomyeloneuropathy (AMN) of TNF alpha and Glutamate.

Conclusions: A phenotypic specific PBMC in-vitro cytokine response may indicate either a cytokine profile shift after cerebral disease onset, or discernible prognostic parameter before cerebral onset. Additionally, this novel in-vitro model may serve in testing pharmacological agents in reducing pro-inflammatory cytokine production or other oxidative stress parameters in ALD.

Keywords: Genetics, Demyelinating Disorders

26. Prevalence and Geographic Distribution of SSADH Deficiency

Pearl P (Boston, MA), Wiwattanadittakul N, Hodgeman R, Goullett J, Gibson K

Objective: Succinic semialdehyde dehydrogenase (SSADH) deficiency is a rare disorder of GABA degradation featuring global developmental delay, hypotonia, epilepsy, extrapyramidal manifestations, hyporeflexia, and abnormal MRI signal involving the globus pallidus, subthalamic nucleus, and cerebellar dentate nuclei. The incidence is unknown and past estimates derive from laboratory reports of GHB aciduria, the biochemical marker. Delayed and under-diagnosis are suspected.

Methods: Cross sectional analysis using a patient database combined with literature review was used to ascertain the number of all identifiable cases, age at diagnosis, and geographic distribution.

Results: A total of 180 unique cases of SSADH deficiency were identified (91 confirmed subjects derived from our database and 89 with clinical details provided from the literature) from 39 countries, with the largest proportions from the US (24%), Turkey (10%), China (7%), Saudi Arabia (6%), and Germany (5%). The median age of diagnosis is ≤ 5 years, although 10% of cases are diagnosed in adolescence or adulthood.

Conclusions: A total of 180 unique cases of diagnosed SSADH deficiency could be confirmed, spread across 39 countries. Five reporting countries account for approximately half of all reported patients. With China and India accounting for ~36% of the world population, our data strongly suggest dramatic underreporting. Increased detection is anticipated in SSADH and similar rare disorders

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with the expansion of next generation gene sequencing. The clinical evolution of the disease is unknown, and a longitudinal study of patients is planned to address this gap in our understanding.

Keywords: Genetics


Objective: To describe and better delineate the different types of CDG in Saudi Arabia and to correlate the phenotype and genotype.

Methods: Retrospective study over the last 5 years in 5 major referral hospitals in Riyadh, KSA. All patients were confirmed biochemically and genetically.

Results: We have evaluated 29 patients from 16 families with consanguinity. ALG9-DCG(Ia) 9 patients (31%), ALG3-CDG(IId) 7 patients (24%), COG6-CDG(IIL) 7 patients (24%), MGAT2-CDG(IHa) 3 patients (10%), and one patient for each of PMM2-CDG(Ia), SLC35A2-CDG(IIm), COG7-CDG(Ile).

Conclusions: Compared to literature, PMM2-CDG(Ia) is rare in our cohort study (only one patient). In ALG9-CDG type Ia, hydrops fetalis maybe the presenting feature, adding to constant features of skeletal dysplasia, refractory epilepsy, cerebral & cerebellar atrophy and severe developmental delay. In ALG3-CDG (IId), we report a striking finding of multiple congenital anomalies and early neonatal death. In COG6-CDG (IIL), cerebral hypomyelination and hypohydrosis are common.

Keywords: Genetics, Neuroimaging, Epilepsy

28. Clinical Characterization of Mendelian Disorders that Mimic the Phenotype of Rett Syndrome


Objective: Rett syndrome (RTT) is a neurodevelopmental disorder associated with features such as postnatal microcephaly, seizures, loss of hand use/language, stereotyped hand movements, and apraxic gait. The disorder is caused by MECP2 mutations, but defects in other genes (e.g. CDKL5, FOXG1, and MEIS2) can lead to presentations that resemble, but do not completely mirror, RTT. In this study, we attempted to identify other monogenic disorders sharing features with RTT.

Methods: We performed a retrospective chart review on n=319 patients who had undergone clinical whole-exome sequencing (WES) for further etiological evaluation of neurodevelopmental diagnoses. From this group, we characterized those who (1) possessed RTT features based on clinical judgment (2) underwent MECP2 sequencing (+/- MECP2 deletion/duplication analysis) with negative results (3) ultimately arrived at a diagnosis other than RTT with WES.

Results: There were 7 patients with clinical features overlapping RTT who had negative MECP2 analysis but diagnostic WES. Two individuals had pathogenic variants in KCNB1; the remaining 5 individuals possessed pathogenic variants in these genes: WDR45, FOXG1, MEIS2, TCF4, IQSEC2. RTT-associated features included: microcephaly (n=3; WDR45, FOXG1, KCNB1); loss of hand/language skills (n=3; KCNB1 x 2, IQSEC2); seizures (n=5; KCNB1 x 2, WDR5, FOXG1, MEIS2); disrupted sleep (n=4; WDR45, KCNB1, MEIS2, TCF4); stereotyped hand movements (n=5; KCNB1 x 2, FOXG1, MEIS2, TCF4); bruxism (n=3; KCNB1 x 2; TCF4); hypotonia (n=7).

Conclusions: Clinically-based diagnoses can be misleading, evident by increasing numbers of genetic conditions associated with RTT-like features with negative MECP2 mutations. It may be prudent to restrict the definition of RTT to MECP2 mutations.

Keywords: Genetics

29. A Two-Tier Biochemical Genetic Approach to Newborn Screening for Mucopolysaccharidosis Type I

Tortorelli S (Rochester, MN), Lacey J, Raymond K, Gavrilev D, Oglebier E, Rinaldo P, Matern D

Objective: MPSI was recently added to the US Recommended Uniform (Newborn) Panel. Available screening assays for several MPS are sensitive but have high false positive rates. To improve this situation we developed and validated a 2nd tier test to measure dermatan (DS) and heparan sulfate (HS) in dried blood spots (DBS) when low iduronidase is found by the primary NBS assay.

Methods: DS and HS are extracted from DBS and enzymatically digested to disaccharides prior to LC_MS/MS analysis. Run time is 7 minutes per sample.

Results: Newborn DBS, pediatric DBS (>1 week - 18 years), and adult DBS controls were analyzed for DS and HS. DBS from 20 MPSI patients were analyzed and showed elevated DS (median: 509.3, range: 162.4-3457.9 nmol/L) and HS (range: 20.9-49.5 nmol/lL) concentrations.

Conclusions: Clinical-based diagnoses can be misleading, evident by increasing numbers of genetic conditions associated with RTT-like features with negative MECP2 mutations. It may be prudent to restrict the definition of RTT to MECP2 mutations.

Keywords: Genetics
We also analyzed specimens from other MPS disorders: eight MPSII, three MPSIII, five MPSIV, and three MPSVI.

**Conclusions:** Preliminary data show that our test is a rapid and specific method for timely diagnosis and treatment of newborns with MPSI, allowing identification of cases with low iduronidase activity due to pseudodeficiency.

**Keywords:** Genetics

### 30. Infection Unmasks POLG Disorders and Leads to New Onset Refractory Status Epilepticus (NORSE)

**Objective:** Children presenting with epilepsy or acute liver failure may have mutations in polymerase gamma 1 (POLG), the cause of Alpers-Huttenlocher syndrome, among other clinically distinct phenotypes. Although child neurologists are familiar with this condition, there are underdiagnosed children presenting with infectious etiologies that can unmask the symptoms of POLG disorders, including new onset refractory status epilepticus. Infectious presentations can delay the diagnosis of POLG mutations.

**Methods:** We review a case series of 11 patients presenting with acute liver failure or status epilepticus, who were ultimately diagnosed with POLG mutations. Four patients had infectious symptoms, with or without associated fever, up to two weeks leading to their presentation of refractory status epilepticus. Analysis was conducted examining age of onset, presenting symptoms, associated clinical features, seizure type and neurophysiology findings, liver involvement, and neuroradiological correlation.

**Results:** Four of the patients presented with acute or recent infection leading to clinical compensation as their first presenting POLG-associated illness. One patient had rhinovirus and fever, another streptococcal sepsis, and the other two patients had recent viral URIs. All had epilepsy partialis continua at some point during the course of their illness. MRI findings included perfusion abnormalities on ASL sequences of neuroimaging.

**Conclusions:** In this cohort of genetically confirmed patients with POLG mutations, a significant proportion presented with status epilepticus and infectious symptoms which shifted the focus towards infectious workup and delayed the diagnostic investigation for POLG as a primary underlying etiology. ASL imaging demonstrating perfusion abnormalities may be a helpful diagnostic clue.

**Keywords:** Genetics, Epilepsy

### 31. GATAD2B-Associated Neurodevelopmental Disorder (GAND): Distinct Phenotypic and Genotypic Features in Vitro and In Vivo

**Objective:** The GATA zinc-finger domain-containing 2B (GATAD2B) gene encodes the p66-beta protein is a part of the MeCP1 complex that is involved in methylation and transcriptional regulation. Autosomal dominant mutations in this gene result in GATAD2B-associated neurodevelopmental disorder (GAND). GAND has been associated with distinctive facial features and global developmental delays. We review the in vivo and in vitro features of GAND to further understand the clinical and molecular aspects of the disorder.

**Methods:** Retrospective record analysis and family interviews were used to identify features of the disorder. Affected individuals were assessed for developmental progress and associated neurological abnormalities. Electrophysiological, neuroimaging, and cardiac evaluations were also investigated. Induced pluripotent stem cells (IPSCs) were generated from several patients.

**Results:** Over 20 GAND-affected patients have been identified with most affected patients possessing de novo truncating mutations of GATAD2B. Two affected children were the result of parenteral somatic mosaicism, one patient had a heterozygous deletion of GATAD2B, and one missense mutation was present.

All affected individuals had cognitive disability and limited language abilities. Consistent findings included infantile hypotonia, feeding difficulties, strabismus, macrocephaly and distinct facial features. Less consistent features included hypomyelination, optic nerve hypoplasia, anisocoria, epilepsy, and cardiac valvular abnormalities.

**Conclusions:** GAND is a neurodevelopmental disorder associated with distinctive phenotypic features. Autosomal dominant mutations likely cause a decreased dosage of p66-beta function leading to transcriptional dysregulation. In vitro and in vivo modeling of this disorder with patient-derived iPSCs and rodent models of this disorder are ongoing.

**Keywords:** Genetics, Cognitive/Behavioral Disorders, Translational/experimental therapeutics

### 32. Phenotypic Variability in Tuberous Sclerosis Complex (TSC): Genetic Modifiers

**Objective:** Tuberous sclerosis complex is caused by heterozygous mutations in the TSC1 or TSC2 genes, resulting in constitutive activation of the intracellular mTOR signaling pathway. Neurocognitive phenotypes in TSC range from profound mental retardation, intractable epilepsy, and autism, to normal cognition and only a mild behavioral phenotype. Variability in phenotype can be seen even within a single family, where all affected individuals have the same gene mutation. We hypothesize that genetic variants in genes other than TSC (belonging to an “mTOR Network”) or differential expression of genes in this network account for this phenotypic variability. Our goal is to develop a molecular profile that correlates with disease severity, and will allow early treatment of patients before onset of neurological disease.

**Methods:** We have studied a cohort of affected parent-child pairs. As age is a confounding factor (seizure onset, learning disability, autistic features), we have focused on parent-child pairs where the child has a severe neurocognitive phenotype and the parent is mildly affected. We used (a) whole exome sequencing to identify genetic variants in modifier genes, focusing on TSC1/TSC2/mTOR pathway genes, and (b) RNA sequencing to characterize differential expression of genes in this network.

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33. **MAGAs, Intrauterine Environment & Fetal Growth**  
Johnson W (Piscataway, NJ), Bayoke S, Cartun Z, Surgeon J, Stenroos E

**Objective**: To test the hypothesis that MAGAs make a significant contribution to DOHaD. DOHaD, Developmental Origin of Health and Disease, involves environmental factors affecting fetal growth during gestation that are believed to be environmental in nature. Maternally acting gene alleles, MAGAs, may contribute to DOHaD, i.e., metabolic syndrome. MAGAs act in maternal tissues independently of any inheritance by the fetus. From the fetus’ perspective, MAGAs are environmental factors since they act independently of any inheritance from mother-to-fetus and since their effects result from gene action in the mother not in the fetus.

**Methods**: We identified reports of maternal effects in gestation, excluding those resulting from: maternal environmental effects acting on the fetus or interacting with a fetal genotype; mitochondrial-coded genes; microchimerism; or known genomic imprinting. We determined possible mechanisms of action and considered possible ascertainment bias.

**Results**: We analyzed 623 reports of 169 MAGAs whose categories included: detoxification/oxidative stress (14%), immune mechanisms (23%), and folate-related (12%). 48 of the 169 MAGAs, a significant fraction (28.4%) of the total, contributed to fetal growth-related categories: IUGR, low birth weight, FGR, & SGA. A few MAGAs were unique to this group, including some in lipid metabolism, blood pressure regulation, or hormone metabolism, as were a number of pathways. Maternal genes may have greatest effect on *in utero* environment when ratio of maternal-to-fetal mass is greatest, i.e., early in gestation.

**Conclusions**: Determining the specific contributions of MAGAs may help prevent fetal growth abnormalities and DOHaD-related sequellae of metabolic syndrome, e.g., hypertension, stroke, myocardial infarct, type 2 diabetes.

**Keywords**: Genetics, Cognitive/Behavioral Disorders, Epilepsy

34. **The Sabril® Registry After 6 Years: Patient Characteristics and Vision Loss**  

**Objective**: To analyze data from the Sabril® Registry, part of an FDA-mandated REMS program to monitor/detect/ describe vigabatrin-associated vision loss.

**Methods**: A physician-documented benefit-risk assessment is required for patients to receive vigabatrin maintenance therapy. Ophthalmologic assessments (OAs) must be documented during and following therapy completion. To meet predetermined criteria for visual-acuity (VA) or visual-field (VF) loss, a reduction relative to baseline OA (first OA form [OAF]) during two consecutive assessments must be demonstrated.

**Results**: Of 8,107 enrolled patients (2,337 rCPS; 5,197 IS), 6,628 were <17 years and 1,393 were ≥17 years. At enrollment, 83% and 87% of patients <17 and ≥17 years, respectively, were vigabatrin-naïve. Prior to enrollment: 1) most pediatric patients attempted ≤3 treatments (including ACTH/steroids for IS); 2) adults frequently attempted ≥4 AEDs; 3) most patients were using multiple AEDs at vigabatrin initiation; 4) 38% could not undergo baseline vision testing (per initial OAFs). Of 408 (5%) patients with a baseline exam and ≥2 follow-up acuity tests, 21 had reduced VA per pre-defined criteria; of 34 patients who could undergo consistent VF testing, 5 met pre-defined criteria for VF loss.

**Conclusions**: Patients frequently attempted several epilepsy treatments before vigabatrin and are likely to receive other AEDs with vigabatrin. Reductions in VA were detected in a small subset of registry patients; some returned to baseline after initially meeting acuity-loss criteria. Some patients met pre-defined criteria for VF loss, but the number of patients with consistent testing was too small to determine the frequency of vigabatrin-associated VF changes. Funding: Lundbeck, LLC

**Keywords**: Epilepsy

35. **The Impact of Genetic Testing in Infantile Onset Epilepsy**  
Koay A (Pittsburgh, PA), Robert S, Vento J, Yoshimi S

**Objective**: With increasing availability and knowledge of phenotype-genotype correlation, genetic tests have become routine during infantile epilepsy workup. Often these children are without a readily apparent clinical phenotype when diagnosed. To determine the genetic diagnostic yield in infantile epilepsy of unknown etiology, we performed a retrospective cohort study.

**Methods**: We reviewed all patients with infantile epilepsy seen by Neurology in 2014 at Children’s Hospital of Pittsburgh. Patients with causes for epilepsy including acquired brain injury and congenital brain anomalies were excluded.

**Results**: 47 patients met inclusion/exclusion criteria. Median ages of first seizure and epilepsy diagnosis were 5.2 and 6.1 months, respectively. 51% had normal examination and development when diagnosed. Initial EEG was abnormal in 71%. Epileptiform activity was seen in 91% of abnormal EEGs. MRI brain was abnormal in 40% with findings considered irrelevant to epilepsy. 75% of patients had genetic testing done; 62% had SNP array, 32% had epilepsy panel, 9% had targeted exome sequencing, 17% had
POLG, and 25% had other studies. SNP array was more often sent in patients with abnormal development ($p = 0.029$). Epilepsy panel was more often sent in patients without abnormalities ($p = 0.01$). Of patients who had any genetic investigation 53% had at least 1 pathogenic result. Developmental delay was predictive for positive SNP array ($p = 0.023$).

**Conclusions:** The yield of genetic testing on infantile onset epilepsy of is quite high (53%), which impacts medication selection, medical surveillance and genetic counseling and ultimately improves outcomes.

**Keywords:** Epilepsy, Genetics

**36. Clinical Characteristics and Antiepileptic Drug Effectivity in New Onset Epilepsy Patients**

**Can A (Boston, MA), Jackson M, Ojo O, Kapur K, Loddenkemper T**

**Objective:** Describe characteristics, treatment variability and seizure frequency in patients with new onset epilepsy.

**Methods:** Retrospective descriptive study of new onset epilepsy patients who were diagnosed and followed at Boston Children’s Hospital during 2013 and 2014.

**Results:** 353 patients (185 (52.4%) males, 168 (47.6%) females) were followed for a median of 14 months (range: 7-27 months). Median age at onset was 7 years (range: 0-20 years) with the characteristics are shown in table 1. Among 353 patients, 204 (57.7%) patients remained seizure free after their diagnosis or first available clinical visit, 147 (41.6%) patients continued to have seizures and the remaining 2 (0.7%) patients had seizures due to noncompliance and missed doses. Among those 147 patients who continued to have seizures; 76 (51.8%) patients had more than 50% seizure frequency decrease, 70 (47.6%) patients had less than 50% decrease, and 1 (0.6%) patient had no change in

**TABLE 1. Clinical characteristics and first treatment choice at the time of diagnosis (Abstract 36)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median, no</th>
<th>Range, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (n=353)</td>
<td>7</td>
<td>0-20</td>
</tr>
<tr>
<td>Gender (n=353)</td>
<td>Female 168 47.6</td>
<td>Male 185 52.4</td>
</tr>
<tr>
<td>Pre-perinatal complication (n=353)</td>
<td>No 267 75.6</td>
<td>Yes 78 22.1</td>
</tr>
<tr>
<td>Prior seizure history (n=353)</td>
<td>No 290 82.2</td>
<td>Yes 63 17.8</td>
</tr>
<tr>
<td>Family history (n=353)</td>
<td>No 250 70.8</td>
<td>Yes 99 28</td>
</tr>
<tr>
<td>Etiology (n=353)</td>
<td>Idiopathic 262 74.2</td>
<td>Structural 60 17</td>
</tr>
<tr>
<td></td>
<td>Genetic 26 7.3</td>
<td>Immune 2 0.6</td>
</tr>
<tr>
<td></td>
<td>Infectious 2 0.6</td>
<td>Metabolic 1 0.3</td>
</tr>
<tr>
<td>Localization (n=353)</td>
<td>Generalized 198 56</td>
<td>Focal 129 36.6</td>
</tr>
<tr>
<td></td>
<td>Multifocal 26 7.4</td>
<td></td>
</tr>
<tr>
<td>Seizure type*</td>
<td>Tonic-clonic 136 31.2</td>
<td>Arrest/Staring/Blinking 82 18.8</td>
</tr>
<tr>
<td></td>
<td>Tonic 53 12.2</td>
<td>Absence 53 12.2</td>
</tr>
<tr>
<td></td>
<td>Myoclonic 33 7.5</td>
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</tr>
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</table>
their seizure frequency compared to the initial presentation. All 204 seizure free patients were treated with a single anti-epileptic drug (Table 1). Among 149 patients who were not seizure free; 95 patients were treated with a single drug, 44 patients with 2 drugs, 8 patients with 3 drugs (2 patients received ketogenic diet) and 2 patients with 4 drugs.

**Conclusions:** We describe initial presentation characteristics, first treatment choices and seizure frequency in new onset epilepsy patients. Most patients became seizure free on their first treatment choice and remained on this treatment at a median follow up of 14 months.

**Keywords:** Epilepsy

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### TABLE 1. Continued

<table>
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<tr>
<th>Characteristics</th>
<th>Median, no</th>
<th>Range, %</th>
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<tbody>
<tr>
<td><strong>Clonic</strong></td>
<td>20</td>
<td>4.5</td>
</tr>
<tr>
<td><strong>Other focal motor</strong></td>
<td>20</td>
<td>4.5</td>
</tr>
<tr>
<td><strong>Atonic-Drop attack</strong></td>
<td>20</td>
<td>4.5</td>
</tr>
<tr>
<td><strong>Epileptic spasms</strong></td>
<td>19</td>
<td>4.4</td>
</tr>
<tr>
<td><strong>Myoclonic-Tonic</strong></td>
<td>1</td>
<td>0.2</td>
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**EEG at baseline (n=350)**

<table>
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<tr>
<th>Normal</th>
<th>Abnormal</th>
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<tbody>
<tr>
<td>67</td>
<td>283</td>
</tr>
<tr>
<td>19.1</td>
<td>80.9</td>
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**MRI at baseline (n=295)**

<table>
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<th>Normal</th>
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<tbody>
<tr>
<td>153</td>
<td>142</td>
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<tr>
<td>51.8</td>
<td>48.2</td>
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**CT at baseline (n=58)**

<table>
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<tr>
<th>Normal</th>
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<tbody>
<tr>
<td>41</td>
<td>17</td>
</tr>
<tr>
<td>70.6</td>
<td>29.4</td>
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**Motor function at baseline (n=353)**

<table>
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<tr>
<th>Normal</th>
<th>Abnormal</th>
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<tbody>
<tr>
<td>252</td>
<td>101</td>
</tr>
<tr>
<td>71.4</td>
<td>28.6</td>
</tr>
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</table>

**Cognitive function at baseline (n=353)**

<table>
<thead>
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<tr>
<td>228</td>
<td>125</td>
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<tr>
<td>64.6</td>
<td>35.4</td>
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**1st treatment choice (n=353)**

<table>
<thead>
<tr>
<th>Levetiracetam</th>
<th>Oxcarbazepine</th>
<th>Ethosuximide</th>
<th>Valproate</th>
<th>ACTH</th>
<th>Topiramate</th>
<th>Lamotrigine</th>
<th>Zonisamide</th>
<th>Vigabatrin</th>
<th>Carbamazepine</th>
<th>Phenobarbital</th>
<th>Gabapentin</th>
<th>Clonazepan</th>
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<tbody>
<tr>
<td>195</td>
<td>57</td>
<td>40</td>
<td>16</td>
<td>12</td>
<td>9</td>
<td>9</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>55.3</td>
<td>16.2</td>
<td>11.3</td>
<td>4.5</td>
<td>3.4</td>
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<td>2.5</td>
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<td>0.8</td>
<td>0.8</td>
<td>0.6</td>
<td>0.6</td>
<td></td>
</tr>
</tbody>
</table>

*Seizure type numbers do not equal to patient number as some patients presented with more than one seizure type.*

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37. **Deficit Attention Hyperactivity Disorder (ADHD) in Children with Epilepsy and their Siblings**

Velez-van-Meerbeke A (Bogota, Colombia), Romero C, Taver L, Talero-Gutierrez C, Lopez-Cabra C, Barrera C, Romero C, Angel C

**Objective:** Epilepsy is a high prevalent neurologic disease in our country (10.6 per 1000 habitants) but the real frequency of ADHD in those patients and its siblings is controversial. The purpose of this study was to establish the prevalence and risk factors of ADHD in epileptic children and their siblings in Colombia.
Methods: Observational analytic study with 156 children with epilepsy and 51 siblings aged 6 – 18 years selected from different epilepsy clinics. We used the checklist of the DSM IV for ADHD and the Behavioral Assessment System for Children (BASC) applied to parents and teachers.

Results: ADHD prevalence was 35.9% in children with epilepsy and 13.7% in their siblings. Combined sub-type was the most common in both groups (44.6% and 42.8% respectively). There was a non-significant trend in patients with partial epilepsy (n = 30) to have a higher prevalence of ADHD when compared to those with generalized epilepsy (n = 26). There was no association when age was analysed but younger patients had a greater risk to present ADHD (OR = 2.037 IC 95% = 1.943 – 3.978 p = 0.035). 82.1% of children was taking antiepileptic drugs and only 24.4% were seizure free; nevertheless, there was no association between treatment of persistence of seizures and the presence of ADHD.

Conclusions: Epileptic patients and their siblings have a higher prevalence of ADHD than general population. We did not have a representative sample to find out what risk factors will explain this association.

Keywords: Epilepsy, Cognitive/Behavioral Disorders

38. Hemispherotomy in Children with Electrical Status Epilepticus of Sleep
Jeong A (St. Louis, MO), Strahle J, Vellimana A, Limbrick D, Smyth M, Bertrand M

Objective: To describe the features of nine patients with electrical status epilepticus of sleep (ESES) and a unilateral structural lesion amenable to hemispherotomy.

Methods: We retrospectively reviewed the clinical, EEG, MRI, and neuropsychological features of nine children with ESES who underwent hemispherotomy. ESES was defined as greater than 85% of slow-wave sleep occupied by spike-waves.

Results: Mean age of seizure onset was 1.9 years (birth to 4.2 years), mean age at ESES diagnosis was 6.0 years (3.5 years to 8.8 years), and mean age at hemispherotomy was 6.8 years (3.7 years to 11.5 years). Underlying etiologies included perinatal infarct (3 patients), polymicrogyria (4 patients), hemimegalecephaly (1 patient), and focal cortical dysplasia type IIB (1 patient). Engel class I seizure outcome was observed in 9/9 children, with a mean length of follow-up of 3.0 years (6.0 months to 6.1 years). Hemispherotomy terminated ESES in 6/6 patients with available postoperative sleep EEG. All children had preoperative neuropsychological impairments. Postoperatively, none of the children continued to have developmental regression. None of the children returned to their original pre-ESES baseline.

Conclusions: ESES is often poorly responsive to traditional epilepsy treatments, and few studies have examined the role of epilepsy surgery, specifically hemispherotomy, in its treatment. Children with drug-resistant ESES and a structural lesion should be evaluated for hemispherotomy, as patients may experience cessation of seizures, termination of ESES, and improvement in neuropsychological status.

Keywords: Epilepsy, Cognitive/Behavioral Disorders

39. Characterization of the GABRB2 Variant Associated Epilepsy and Neurodevelopmental Disorder

Objective: To describe the clinical phenotype and functional consequences of de novo GABRB2 variants, a new epilepsy gene with only a single prior case report.

Methods: Patients with seizures and de novo GABRB2 variants were identified by a referring laboratory and patients were enrolled at Boston Children’s Hospital. Pheno-typing was performed by phone interviews and review of clinical records, EEG and MRI data. Variants of the human GABA_A receptor subunit beta-2 were introduced by site-directed mutagenesis and studied using the Xenopus laevis oocyte expression system and the automated two-electrode voltage-clamp recording technique.

Results: Six new patients with de novo likely pathogenic GABRB2 variants were identified (4 males, 2 females, aged 3-16 years). All patients had epilepsy, refractory in 4/6.
Seizure onset ranged from 2 days to 3 years, 5/6 before 1 year. Semioologies included generalized tonic, myoclonic, tonic-clonic, and focal dyscognitive seizures. Three patients had a movement disorder. All patients had developmental delay, 5 with severe impairment, and 3 had regression. Patients had strabismus, cerebral visual impairment or both. Four patients were microcephalic. All had axial hypotonia. Two patients had mild diffuse atrophy on MRI; a third had a Chiari malformation. EEGs suggested encephalopathy and showed generalized or multifocal epileptiform activity. Electrophysiological analysis showed decrease of GABA-induced currents for the I246T variant and no GABA-induced currents for the reported M79T variant.

Conclusions: Patients with likely or proven loss of function variants in GABRB2 have epilepsy, often infantile onset and refractory, developmental delay or regression, and variably movement disorder and microcephaly.

Keywords: Epilepsy, Genetics, Movement Disorders

<table>
<thead>
<tr>
<th>Pi</th>
<th>Age</th>
<th>Variant Classification</th>
<th>First seizure</th>
<th>Seizure types</th>
<th>Seizure severity</th>
<th>Development</th>
<th>MD</th>
<th>Functional analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/</td>
<td>10y</td>
<td>2885 Likely pathogenic</td>
<td>15m</td>
<td>Focal dyscognitive, subclinical</td>
<td>Intractable, + SE</td>
<td>Severely impaired, no regression</td>
<td>Y</td>
<td>Ongoing</td>
</tr>
<tr>
<td>2/</td>
<td>4y</td>
<td>P252L Likely pathogenic</td>
<td>2d</td>
<td>Myoclonic, tonic, GTC</td>
<td>Intractable, + SE</td>
<td>Severely impaired, no regression</td>
<td>Y</td>
<td>Ongoing</td>
</tr>
<tr>
<td>3/</td>
<td>15y</td>
<td>V282A Likely pathogenic</td>
<td>3y</td>
<td>GTC, focal dyscognitive, myoclonic</td>
<td>Seizure free on 3 AEDs, no SE</td>
<td>Severely impaired, no regression</td>
<td>Y</td>
<td>Ongoing</td>
</tr>
<tr>
<td>4/</td>
<td>3y</td>
<td>246T Likely pathogenic</td>
<td>5m</td>
<td>Focal dyscognitive, tonic</td>
<td>Intractable, + SE</td>
<td>Severely impaired, + regression</td>
<td>N</td>
<td>Significant decrease in GABA-induced currents</td>
</tr>
<tr>
<td>5/</td>
<td>8y</td>
<td>V302M Likely pathogenic</td>
<td>8m</td>
<td>Focal dyscognitive, tonic clonic</td>
<td>Seizure free on 2nd AED, +SE</td>
<td>Severely impaired, + regression</td>
<td>N</td>
<td>Ongoing</td>
</tr>
<tr>
<td>6/</td>
<td>11y</td>
<td>F245L Likely pathogenic</td>
<td>?m</td>
<td>Focal dyscognitive, tonic clonic, tonic</td>
<td>Intractable, no SE</td>
<td>Moderately impaired, + regression</td>
<td>N</td>
<td>Ongoing</td>
</tr>
<tr>
<td>*/</td>
<td>14y</td>
<td>M79T Likely pathogenic</td>
<td>9m</td>
<td>Focal seizures, tonic clonic, focal dyscognitive</td>
<td>Intractable, SE not reported</td>
<td>Moderately impaired, + regression</td>
<td>U</td>
<td>Loss of GABA-induced currents</td>
</tr>
</tbody>
</table>

Table 1: Summary of GABRB2 variants and clinical characteristics.
Variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines
P=Proband, G=Gender, M=male, F=female, SE=status epilepticus, MD=movement disorder, U=unknown

Payne E (Rochester, MN), McBain K, Sharma R, Hutchison J, Hahn C

Objective: Continuous video-EEG monitoring (cEEG) is commonly used in the intensive care unit (ICU) to detect subclinical seizures and evaluate whether paroxysmal clinical events represent seizures. We assessed the ability of ICU bedside caregivers to predict which children would demonstrate seizures on subsequent cEEG.

Methods: Children in our pediatric and cardiac ICUs underwent cEEG at the request of the attending intensivist according to predefined indications. Prior to cEEG onset, the child’s bedside nurse and physician were asked to predict whether the cEEG would identify seizures.

Results: 111 bedside nurses and 102 physicians completed surveys prior to cEEG onset. cEEG subsequently identified seizures in children (20%) of whom 7 had status epilepticus. The sensitivity for predicting subclinical seizures was 82.4% (95% CI. 56.6-96.2%) for both nurses and physicians. The specificity for predicting subclinical seizures was 53.4% (95% CI. 39.9-66.7%) for nurses and 33.3% (95% CI. 21.1-47.5%) for physicians. The false negative rate was 4% for both nurses and physicians. The sensitivity for predicting that paroxysmal events represented EEG seizures was 87.5% (95% CI. 47.4-99.7%) for nurses and 100% (95% CI. 39.8-100%) for physicians. The specificity for predicting that paroxysmal events represented EEG seizures was 16.0% (95% CI. 4.5-36.1%) for nurses and 21.1% (95% CI. 6.0-45.6%) for physicians. The false negative rate was 3% for nurses and 0% for physicians.

Conclusions: ICU bedside nurses and physicians were both quite sensitive at predicting seizures on cEEG, but this came at the expense of low specificity. False negative rates were low.

Keywords: Epilepsy
41. Adjunctive Everolimus Therapy for the Treatment of Refractory Seizures Associated With Tuberous Sclerosis Complex: Results From a Randomized, Placebo-Controlled, Phase 3 Trial

Objective: To assess the efficacy/safety of everolimus (EVE) 3-7 (low trough C_min) or 9-15 ng/mL (high trough [HT]) targeted trough concentration (C_min) ranges vs placebo as adjunctive therapy in patients with refractory seizures associated with tuberous sclerosis complex (TSC).

Methods: This is the first randomized, placebo-controlled, double-blind phase 3 study of EVE for the treatment of refractory seizures associated with TSC (EXIST-3, NCT01713946). Following an 8-week baseline phase, patients aged 2-65 years with TSC and refractory seizures on 1-3 antiepileptic drugs were randomized to EVE LT or HT C_min target ranges or placebo. Dose titrations were performed over weeks 1-6 and as needed during the subsequent 12-week maintenance period. The primary endpoints were change from baseline in average weekly seizure frequency expressed as response rate (RR) 50% reduction, and percentage reduction.

Results: Overall, 366 patients were randomized to EVE LT (n=117), HT (n=130), or placebo (n=119). The median percentage reduction in seizure frequency was significantly greater with EVE LT (29.3%, P=0.003) and HT (39.6%, P<0.001) vs placebo (14.9%). RR was also significantly greater with EVE LT (28.2%, P=0.008) and HT (40%, P<0.001) vs placebo (15.1%). The most frequent ≥20% all grade adverse events (AEs) reported with EVE LT/HT vs placebo included stomatitis (28.2%/30.8% vs 3.4%), diarrhea (17.1%/21.5% vs 5%), and mouth ulceration (23.9%/21.5% vs 4.2%). Discontinuations due to AEs (4.3%/3.1% vs 1.7%) were low.

Conclusions: Adjunctive EVE therapy demonstrated a clinically and statistically significant reduction in seizure frequency with a tolerable safety profile compared with placebo in patients with TSC.

Keywords: Epilepsy

42. Fragile X Syndrome: Review of Seizure Prevalence, Seizure Characteristics & Electroencephalogram Findings in Children With & Without Intellectual Disability
Golla S (Plano, TX), Evans P, Sirsi D, Morris M

Objective: To describe seizure prevalence, seizure characteristics & electroencephalogram (EEG) findings in children with full mutation Fragile X Syndrome (FXS) & evaluate the association between intellectual disability (ID) & epilepsy.

Methods: This was a retrospective cohort study, approved by IRB. All children with full mutation FXS, between 1 month to 18 years, seen over a period of 5 years were included. Children with mosaic pattern, premutation and those without genetic testing were excluded. Clinical data and EEG database were reviewed. Children with & without ID were compared with respect to seizure prevalence, seizure characteristics & EEG abnormalities.

Results: The FXS database had 115 patients; 78 (68 boys & 10 girls) met inclusion criteria. Seizure prevalence was higher in full mutation FXS compared to general population (15.4% vs 1%, p < 0.0001). Focal seizures were common (58.3% vs 41.6%). 50% children with seizures had abnormal EEG with focal spikes. 46% children had ID. Seizure prevalence in the ID and non-ID group was similar (13.9% vs 16.7%, p 0.77). Focal seizures were common in both ID and non-ID groups (60% vs 57.1%, p > 0.99). More patients with ID and seizures had abnormal EEG compared to non-ID patients (60% vs. 42.9%, p > 0.99).

Conclusions: Seizure prevalence is higher in full mutation FXS children compared to the general population. Focal seizures are more common. Focal spikes is the most common EEG abnormality in patients with seizures. Deficiency of FMRP (Fragile X Mental Retardation Protein) appears to lead to increased neuronal excitability and susceptibility to epilepsy.

Keywords: Epilepsy, Cognitive/Behavioral Disorders, Genetics
2. Seizure Types in FXS:

<table>
<thead>
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<th>Seizure Types</th>
<th>Number of Patients</th>
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<tbody>
<tr>
<td>Focal</td>
<td>7 (58.3%)</td>
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<tr>
<td>Generalized</td>
<td>5 (41.6%)</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
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3. Seizure Types in FXS:

<table>
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<th>Seizure Types</th>
<th>Number of Patients</th>
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<tbody>
<tr>
<td>Focal 7 (58%)</td>
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<tr>
<td>Focal seizures with impaired awareness (CPS)</td>
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<tr>
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</tr>
<tr>
<td>Focal seizures with impaired awareness (CPS) and Generalized atonic</td>
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<tr>
<td>GTC</td>
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4. EEG Findings in FXS:

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<tr>
<td>Abnormal</td>
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</tr>
<tr>
<td>Focal/multi focal spikes</td>
<td>6 (50%)</td>
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<tr>
<td>Centro temporal spikes</td>
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<td>Generalized polyspike waves</td>
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<tr>
<td>Focal/Generalized slowing</td>
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![Seizure Types in FXS](image1.png)

![EEG Findings in FXS with seizures](image2.png)
5. Association of ID to Seizure Prevalence in FXS:

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<td>7 (16.7%)</td>
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<tr>
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<td>66</td>
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p = 0.7647

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<tbody>
<tr>
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<td>3 (60%)</td>
<td>4 (57.1%)</td>
<td>7</td>
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<tr>
<td>Generalized</td>
<td>2</td>
<td>3</td>
<td>5</td>
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<tr>
<td>Total</td>
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p = 1.000

6. Association of ID to Seizure Types in FXS:

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<td>Generalized</td>
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<tr>
<td>Total</td>
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7. Association of ID to EEG Findings in FXS:

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</thead>
<tbody>
<tr>
<td>Focal/multi focal spikes</td>
<td>3 (60%)</td>
<td>3 (42.9%)</td>
<td>6</td>
</tr>
<tr>
<td>Normal or mild slowing</td>
<td>2</td>
<td>4</td>
<td>6</td>
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<tr>
<td>Total</td>
<td>5</td>
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P = 1.000
43. Role of Language Testing Prior to Left Hemispherectomy in Children Aged 5 Years or Older

Sieciechowicz D (Chicago, IL), Gupta A, Kotagal P, Pestana-Knight E, Wyllie E, Moosa A

**Objective:** To assess the role of language testing with Wada and fMRI in the management of children considered for left hemispherectomy.

**Methods:** Medical records of children ages 5-18 years old, considered for hemispherectomy were reviewed. Patients were identified from 3 databases over a 10-year period: epilepsy surgery (n=54), functional MRI (102) and Wada test (79). Data collected included: age at brain injury, age at seizure onset and at surgery, pre and post-op language skills, type and extent of lesion on brain MRI, results of Wada testing and/or fMRI when performed.

**Results:** Fifty-eight potential left hemispherectomy candidates were identified. Three patients were excluded after Wada testing; two had Rasmussen encephalitis (RE) with age of onset 7 years or older and the third had posterior dominant brain injury. One patient with posterior dominant encephalomalacia was excluded after fMRI (ipsilesional dominant). Of 54 who had left hemispherectomy, 47 had no language lateralization studies. Of these 47 children, 35 had no impact on speech/language, 9 had improvement and 3 reported worsening in postoperative language skills. Two out of the three who worsened had RE; the third patient had very few words prior to surgery.

**Conclusions:** In many children with refractory epilepsy due to early onset extensive brain injuries hemispherectomy can be safely performed without the need for Wada or fMRI. Children with RE with age of onset at 7 years or older and/or partial injury with sparing of the frontal regions may harbor language functions in the ipsilesional hemisphere.

**Keywords:** Epilepsy, Neuroimaging

44. How Predictive are Interictal Epileptiform Abnormalities of Ictal Findings in Children with Focal Epilepsy?

Wrrell E (Rochester, MN), Nickels K, Payne E, Wong-Kisiel L

**Objective:** Do interictal abnormalities correlate with ictal findings in children with focal seizures (FS) recorded on prolonged video EEG (V EEG).

**Methods:** Records of children with recorded FS on VEEG at Mayo Clinic in Rochester MN between Nov 2010 and Dec 2015 were identified, and recording duration, presence and location of interictal and ictal findings were documented.

**Results:** 370 children with FS were identified (51% male, median age 8.7 years). Median recording duration was 47.5 hours. While longer recording duration tended to correlate with higher prevalence of interictal discharges (p=0.053), discharges were seen in 93.2% recorded for <24 hours. Of 80 cases with a single interictal focus, 71 (88.8%) also had a single ictal focus, which was concordant with the interictal focus in 68/71 cases. Of 205 cases with multifocal +/- generalized interictal discharges, only 73 (35.6%) were found to have a single ictal focus. Of the 21 cases without interictal discharge, 15 (71%) were found to have a single ictal focus, 1 (5%) had two ictal foci, 3 (14%) had a non-localizing, but probable frontal focus, and in 2 (10%) a clear scalp correlate was not seen.

**Conclusions:** Most children with recorded FS had interictal discharge seen in the first 24 hours of recording. A single ictal focus is highly suggestive of a single, concordant ictal EEG focus. Although lack of interictal discharge was uncommon, the majority of these cases also had a single ictal focus. Conversely, only approximately one third of children with multifocal +/- generalized interictal discharges had a single ictal focus.

**Keywords:** Epilepsy

45. Investigator IND Trial of Cannabidiol in Sturge-Weber Syndrome

Kaplan E (Baltimore, MD), Sievers J, Comi A

**Objective:** Sturge-Weber syndrome (SWS) is a disorder caused by a somatic genetic mutation in the gene GNAQ. Cerebral blood vessel abnormalities result in epilepsy and cognitive impairments. Cannabidiol, a cannabinoid without psychoactive properties, is being investigated as adjunctive therapy in Dravet and Lennox-Gastaut Syndromes; this study is the first in SWS.

**Methods:** Five subjects (4F, ages 2, 6, 7, 19; 1M age 7) with SWS brain involvement and refractory epilepsy treated with 1-4 concomitant anticonvulsants were enrolled, with cannabidiol target dose of 5-25 mg/kg/day. Motor seizure frequency, quality of life (QoL), and adverse events were recorded at each visit. Data were compared from the 56-day pre-treatment period, the 56-day period after starting maintenance dose (Week 14), and the most recent visit. Four subjects had data through Week 14; the 2-year-old female withdrew due to lack of efficacy.

**Results:** Among those who reached Week 14, all 4 remaining subjects had a reduction in seizures (10%, 83%, 33%, and 90%, respectively). At last follow-up, three of 5 subjects reported improved QoL and remained on study drug, one worsened from baseline at time of withdrawal, and one remained unchanged and was subsequently...
withdrawn. Three subjects reported mild side effects considered related to cannabidiol (sedation and/or behavioral disturbance). Benefits reported by other patients were improvements in mood/behavior in 2 subjects and improvements in function in 3 subjects.

Conclusions: This pilot study suggests that cannabidiol is well-tolerated as adjunctive medication for seizure management. It provides preliminary data for further study of cannabidiol in SWS patients.

Keywords: Epilepsy

46. Electrographic Seizures in Neonatal Intensive Care Unit
Buraniqi E (Boston, MA), Sansevere A, Loddenkemper T

Objective: The aim of this study is to characterize the clinical and EEG characteristics of neonates undergoing continuous electroencephalography (cEEG) in the neonatal intensive care unit (NICU).

Methods: Retrospective study of all patients aged less than 1 month of corrected gestational age who underwent cEEG monitoring in the NICU at Boston Children’s Hospital between January 1st 2011 and December 31st 2013.

Results: Two hundred and ten patients with a mean age of 11.6 (±18.45) days were monitored on cEEG, of which 55% were male. The clinical indication for cEEG was primarily to characterize an event concerning for seizure (n=163), followed by encephalopathy with a concern for nonconvulsive seizures (n=40). There was a symptomatic structural etiology in 58% (n=122), systemic in 29% (n=60), symptomatic nonstructural in 11% (n=24) and unknown in 2% (n=4). Of the patients monitored 34% (72/210) had electrographic seizures and 11% (8/72) met criteria for status epilepticus. Of the seizures 38% (n=27) were electrographic only, 51% (n=37) had a mix of clinical and subclinical seizures and 11% (n=8) were electro-clinical only. The time to first seizure from initiation of cEEG has a median of 1.6 hr (IQR 0.4-4.16) and a mean of 3.5 hr (SD ±5.4). Of the patients who had seizures 65% (47/72) were treated after they had an electrographic seizure with a mean time to treatment of 7.1 hour.

Conclusions: This work highlights the high frequency of EEG only seizures in critically ill neonates focusing on the time needed to capture and treat the seizures.

Keywords: Epilepsy, Neonatal neurology

47. A Comparison of Semiologies Between Tilt-induced Psychogenic Non-Syncopal Collapse and Psychogenic Non-Epileptic Seizures
Heyer G (Columbus, OH), Albert D, Weber A, Gedela S, Vidaurre J

Objective: To compare the clinical semiologies between tilt-induced psychogenic non-syncopal collapse (PNSC) and psychogenic non-epileptic seizures (PNES) from youth cohorts.

Methods: A prospective observational study was conducted of patients referred to a pediatric neurology clinic for head-upright tilt testing with video EEG. A PNSC diagnosis was made when a clinical event occurred that the patient regarded as fainting, but associated hypotension or EEG changes were not present. The clinical signs of PNSC (n=40) were compared to the clinical signs of video-EEG-confirmed PNES (n=40), derived from a retrospective cohort of similarly-aged patients.

Results: A PNSC diagnosis was made in 17.6% of all referred patients. PNSC and PNES cohorts did not differ in age (15.5 ± 2.2 versus 14.6 ± 2.7) or female gender (80% versus 72.5%). PNSC events were briefer than PNES events (median 45 versus 201.5 seconds, p<.001). Negative motor signs (head drop, body limpness) predominated in PNSC, (85% versus 20%, p<.001); while the positive motor signs of convulsion occurred more often with PNES (90% versus 30%, p<.001). Behavioral arrest (25% versus 32.5%, p=.46) and eye closure (85% versus 72.5%, p=.21) did not differ between PNSC and PNES. Patients with PNSC were more likely to be tearful before (30% versus 7.5%, p=.02) and after (62.5% versus 7.5%, p<.001) an event.

Conclusions: Although overlap exists, the features of PNSC generally appear similar to neurally-mediated syncope, while the features of PNES generally appear similar to epileptic seizures. PNSC and PNES likely represent identical conversion disorders that differ only by clinical semiologies and referral patterns.

Keywords: Epilepsy

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<th>TABLE 1. Demographics (Abstract 46)</th>
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<tr>
<td><strong>N=210</strong></td>
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<tr>
<td><strong>Age (days)</strong></td>
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<tr>
<td>Median</td>
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TABLE 1. Pre and Post-CBD anti-epileptic drugs by patient (Abstract 48)

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TABLE 2. Alternative Therapies

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<td>vagal nerve stimulator</td>
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48. The Use of Cannabidiol for the Treatment of Febrile Infection Related Epilepsy Syndrome (FIRES)


Objective: Febrile infection related epilepsy syndrome (FIRES) is an epileptic encephalopathy affecting previously normal school aged children, characterized by a sudden catastrophic onset of status epilepticus. Current therapeutics have been met with limited results. We report the response of 7 children from 5 centers who were treated with Cannabidiol (CBD) on emergency or expanded access investigational new drug protocols. We assessed the epilepsy and functional outcomes of these seven children.

Methods: Data from 7 children with a diagnosis of FIRES given Cannabidiol (Epidiolex, GW Pharma) on expanded investigational new drug protocols was collected. Information regarding premorbid function, presentation, workup, treatment and outcomes was summarized from 5 different centers both pre and post-CBD administration. CBD was administered up to a dose of 25mg/kg/day in the setting of failed prior therapy response. Prolonged video EEG as well as clinical data was used to measure response to therapies.

Results: All children had refractory seizures with regression from normal to an encephalopathic state and failed 6 to 9 standard AEDs, plus up to 5 anesthetics. After starting CBD, 6 of 7 patients’ seizures improved in frequency and duration. One patient died due to multiorgan failure secondary to isoflurane. An average of 4 AEDs were weaned. Currently 5 subjects are ambulatory, 1 walks with assistance, and 4 are verbal.

Conclusions: Children with FIRES may respond to CBD. While this is an open label case series, only the ketogenic diet has been reported to have any efficacy in FIRES. We add CBD as a possible treatment for this condition.

Keywords: Epilepsy, Translational/experimental therapeutics, Cognitive/Behavioral Disorders

49. Efficacy and Tolerability of Perampanel in Adolescent Patients with Generalized Seizure Types: A Pooled Analysis of Six Randomized Studies

Piña-Garza E (Nashville, TN), Rosenfeld W, Sae K, Villanueva V, Yoshinaga H, Bibbiano E, Yang H, Patten A, Williams B, Laurenza A

Objective: Perampanel was investigated in adolescents across five Phase III studies involving patients with partial-onset seizures (POS; studies 304 [NCT00699972], 305 [NCT00699582], 306 [NCT00700310], 335 [NCT01618695]) or primary generalized tonic-clonic (PGTC) seizures and idiopathic generalized epilepsy (332; NCT01393743), and a Phase II cognition study in POS (235; NCT01161524).

TABLE 3. Outcomes

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<tr>
<td>Seizure-free</td>
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<td></td>
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<td>Focal seizures only</td>
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<td>X</td>
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<tr>
<td>Seizures last &lt;3 min each</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
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<tr>
<td>&lt;1 seizure/week</td>
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<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Ambulatory</td>
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<td>X</td>
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<tr>
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<td>X</td>
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<tr>
<td>Ataxia</td>
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<td>Tremor</td>
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TABLE 4. Seizure Frequency in Past 28 Days in Subjects Treated During Chronic Phase Subject Number

<table>
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<tr>
<th>Patient number</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>Mean % change</th>
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<tr>
<td>Pre-CBD Seizure counts/28 days</td>
<td>4</td>
<td>5600</td>
<td>216</td>
<td>7</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>4 weeks post-CBD Seizure counts/28 days (% change)</td>
<td>0 (100)</td>
<td>47.2 (99)</td>
<td>0.4 (99)</td>
<td>3 (57)</td>
<td>1 (99)</td>
<td>90.94%</td>
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<tr>
<td>48 weeks post-CBD Seizure counts/28 days</td>
<td>1.6 (60)</td>
<td>564(90)</td>
<td>1.6 (99)</td>
<td>6.2 (88)</td>
<td>1 (99)</td>
<td>71.8%</td>
</tr>
</tbody>
</table>
Methods: This post-hoc pooled analysis included adolescents (12 to <18 years), with secondarily generalized (SG) or PGTC seizures, randomized to adjunctive placebo or perampanel 8 mg/day over double-blind study phases (Titration, 4-6 weeks; Maintenance, 13 weeks). Efficacy was assessed in the full analysis set (placebo, n=46; perampanel, n=67) as median percent change in SG/PGTC seizure frequency per 28 days (Baseline vs Double-blind Phase); percentage of patients achieving 50% or 75% reduction in SG/PGTC seizure frequency (Baseline vs Maintenance); and study completers who were free from SG/PGTC seizures (Maintenance). Adverse events (AEs) were assessed in the safety analysis set (placebo, n=47; perampanel, n=68).

Results: Compared with placebo, perampanel improved SG/PGTC seizure control (median percent change in frequency: −25.5% vs −75.2%; 50% responder rate: 28.3% vs 67.2%; 75% responder rate: 19.6% vs 53.7%; seizure freedom: 8.7% vs 37.3%). Efficacy outcomes were broadly consistent with adults. AEs affected 66.0% placebo-treated and 76.5% perampanel-treated adolescents. With perampanel, most common AEs were dizziness (placebo, 6.4%; perampanel, 19.1%) and headache (placebo, 12.8%; perampanel, 14.7%). Most common psychiatric/behavioral AEs were aggression (placebo, 2.1%; perampanel, 8.8%) and irritability (placebo, 0.0%; perampanel, 8.8%).

Conclusions: Adjunctive perampanel improved SG/PGTC seizure control in adolescents, with outcomes similar to adults.

Keywords: Epilepsy

50. Response to Cannabidiol in Epilepsy of Infancy with Migrating Focal Seizures Associated with KCNT1 Mutations

Poison K (Winston Salem, NC), Wong M, Lee C, Cilio M

Objective: Epilepsy of Infancy with Migrating Focal Seizures (EIMFS) is an early-onset severe epileptic encephalopathy with polymorphous, migrating focal seizures that are highly treatment resistant. Mutations in KCNT1 appear to be the most frequent cause. We investigated whether treatment with cannabidiol (CBD) would decrease seizure frequency in two patients with EIMFS and KCNT1 mutations.

Methods: Both patients (47 and 21 months old) received CBD through the GW Pharma expanded access program. Treatment regimens included ketogenic diet (patient 1) and ketogenic diet, phenobarbital, and potassium bromide (patient 2). Seizure frequency was documented at baseline (4-week pre-treatment period) and over a 12-week treatment period. CBD was titrated to a maximum dose of 25mg/kg/d. Patient 2 also had prolonged EEG monitoring before and after 6 months of treatment to accurately quantify response.

Results: Both patients had no significant improvement in seizure frequency from baseline during the 12-week treatment period. During the 12-week period after CBD reached maximum dose, patient 1 had a modest reduction (−12%) in overall seizure frequency, with a marked reduction (−93%) in the most severe seizures with desaturation noted. Patient 2 did not respond to CBD during 6 months of treatment.

Conclusions: In two patients with EIMFS associated with a KCNT1 mutation, there was no significant improvement in overall seizure frequency when treated with CBD. However, Patient 1 showed a decrease in seizure intensity at the maximum dose. Further research is needed to determine whether CBD may have an impact on seizures in patients with EIMFS due to mutations in KCNT1.

Keywords: Epilepsy, Translational/experimental therapeutics, Genetics

51. Palliative Resective Surgery in Pediatric Epilepsy

Wong-Kisiel L (Rochester, MN), Wang Y, Wetjen N, Nickels K, Payne E, Wirrell E

Objective: Resective surgery for seizure reduction is an evolving concept and performed in selected pediatric cases given the developmental cost of frequent seizures. We assessed outcome of palliative resective surgery in children.

Methods: This is a single-center retrospective review of resective palliative surgery in children between 2000 and 2015. Hemispherotomy, corpus callosotomy, device implantation, and patients with <6-month follow-up were excluded. Pre- and post-operative seizure frequencies, MRI findings, etiology of structural abnormality (acquired or congenital) were abstracted. Outcome was stratified based on whether subjects achieved >50% reduction in seizures at last follow-up.

Results: Twenty-eight patients (male 46%) with median age at surgery 8.8 years (IQR 5.7-14) were identified. Preoperative seizure frequency was daily in 17 patients (61%). MRI abnormality was bihemispheric in 11, hemispheric in 13, and nonlesional in 4 patients. Etiology was acquired in 9 and congenital in 15, including 8 tuberous sclerosis (TS). Median postoperative followup was 54.8 months (IQR 30-90). Seizure reduction >50% was achieved in 17 patients (61%), including 11 who achieved seizure-freedom. Neither presence nor etiology of MRI abnormality contributed to likelihood of seizure reduction. Although outcome was favorable in TS patients (seizure reduction in 6/8 patients, seizure free in 3/8), seizure outcome was not different between TS and other etiologies combined (p=0.32).

Conclusions: Significant seizure reduction is achieved in about half of children undergoing palliative resective surgery. Although extent and etiology of MRI abnormality does not appear to affect outcome, patients with TS should be carefully investigated given favorable seizure control after resective surgery.

Keywords: Epilepsy

52. Pharmacokinetics, Safety, and Tolerability of Midazolam Nasal Spray (USL261) in Pediatric Subjects with Epilepsy

Bancke L (Maple Grove, MN), Berg A, Kapelan B, Meng T, Moe C, Van Es P

Objective: Characterize pharmacokinetics and safety/tolerability of midazolam nasal spray (USL261) in pediatric
subjects with epilepsy to inform its potential for treating bouts of increased seizure activity.

Methods: This phase 1, open-label, multicenter, inpatient study evaluated single USL261 doses. Subjects (2-13 y) with focal or generalized epilepsy received 1.25, 2.5, or 5.0 mg USL261 based on body weight (≥10-<20, ≥20-<40, or ≥40-≤60 kg, respectively). Non-compartmental pharmacokinetic parameters were calculated for midazolam and 1-hydroxymidazolam (metabolite), including: area under the plasma concentration-time curve (AUC), maximum observed plasma concentration (C\text{max}), and time to C\text{max} (T\text{max}). Safety/tolerability assessments included treatment-emergent adverse events (TEAEs), clinical laboratory evaluations, vital sign measurements, and nasal examinations.

Results: All 36 enrolled subjects (n=12/dose) completed the study. Geometric mean C\text{max} and median T\text{max} were similar for midazolam across dose groups (~35 ng/mL and ~15 minutes, respectively); midazolam AUC values were higher in the 5.0 mg versus 2.5 or 1.25 mg groups. Geometric mean C\text{max} and AUC values for 1-hydroxymidazolam were similar across groups. Twenty-five subjects (69.4%) reported ≥1 TEAE; most were mild. TEAEs reported by >10% of subjects were somnolence (n=21, 58.3%) and product taste abnormal (n=4, 11.1%). No clinically meaningful effects attributed to USL261 were observed for clinical laboratory values, vital signs, or nasal exam results.

Conclusions: Midazolam was rapidly absorbed following single doses of USL261 (1.25-5.0 mg), and no dose-dependent differences in maximum plasma concentration were observed. USL261 was generally well tolerated, with no clinically significant safety concerns. These results support the continued development of USL261 in this population. Support: Upsher-Smith Laboratories, Inc.

Keywords: Epilepsy

53. Modeling Dravet Syndrome Caused by SCN1B Mutations Using Human Induced Pluripotent Stem Cells

Dang L (Ann Arbor, MI), Swaminathan P, Tidball A, Lopez-Santiago I, Yuan Y, Hull J, Iomn L, Parent J

Objective: Dravet Syndrome is a severe childhood epileptic encephalopathy, typically caused by de novo mutations in SCN1A, which encodes the voltage-gated sodium channel, Na\text{v}1.1. Mutations in other associated genes such as SCN1B, which encodes the beta-1 subunit of the sodium channel, are also known to cause Dravet Syndrome. We aim to use patient-derived induced pluripotent stem cells (iPSCs) to model SCN1B-related Dravet Syndrome, study the underlying pathogenesis, and develop a tool to screen anti-seizure medications.

Methods: We obtained fibroblasts from a subject with Dravet Syndrome caused by a homozygous R89C mutation in SCN1B. Using episomal reprogramming of patient fibroblasts, we generated several iPSC lines. In addition, we used CRISPR gene editing to introduce frameshift mutations into the first exon of SCN1B in control cells, generating SCN1B knock-out lines with isogenic controls. The iPSCs were used to generate cortical-like neurons, as well as cerebro organoids.

Results: We successfully differentiated patient-derived iPSC lines into cortical-like neurons, with expression of various cortical layer markers, such as CTIP2 and TBR1. We performed whole-cell patch-clamp recordings as well as multi-electrode array recordings on these neurons, and demonstrated mature functional electrophysiologic characteristics. We also generated cerebro organoids from patient and control iPSCs, and these displayed markers for mature neurons and various cell layer markers, and also generated astrocytes.

Conclusions: Using iPSCs to model genetic epilepsies is a viable method to study SCN1B-related Dravet Syndrome. This platform will help us understand the underlying mechanisms of childhood genetic epilepsies, test new therapies, and develop techniques for precision medicine.

Keywords: Epilepsy, Genetics, Translational/experimental therapeutics

54. Effects of Vagus Nerve Stimulation on Sleep-related Breathing Patterns in Epilepsy Patients in the Pediatric Population: a Retrospective Chart Review

Malik M (Atlanta, GA), Karroum E, Phan H

Objective: Incidence of pediatric epilepsy is 5-8.4/1000 patients, one third are medically refractory. Alternative therapies to medication are vagus nerve stimulator (VNS), ketogenic diet and surgery. Patients with VNS can have central apneas, obstructive hypopneas, and obstructive apneas. Study by Marlow et al demonstrated correlation of OSA after VNS placement; however it accounted for patients 21-58 years of age. Our study examines the relationship between VNS and OSA in the pediatric population.

Methods: A retrospective chart review was conducted from Children's Healthcare of Atlanta Pediatric Epilepsy clinic. We identified 17 children who had VNS implantation and PSG performed from 2009-2015. Post-VNS PSG variables were extracted and analyzed. For comparison, a control group of 16 children with similar medically intractable epilepsy without VNS was selected.

Results: Ages ranged from 2–20 years (M = 11.6 SD = 5.0) and our sample consisted of 7 boys and 10 girls in the study group and 11 boys and 8 girls in the control group. 100% had intellectual disability, 82.6% of cases and 85% control were non-ambulatory. VNS group had higher AHIs as compared to non-VNS group (average AHI for VNS = 4.44, average AHI for non-VNS = 1.75), t(25) = -1.7, p = 0.05.

Conclusions: VNS is a common treatment for children with refractory epilepsy. Based on the findings of our small study, there is evidence demonstrating presence of OSA in patients with VNS. PSG before implantation of VNS should be considered to identify patients with pre-existing OSA to prevent worsening of OSA.

Keywords: Epilepsy, Cognitive/Behavioral Disorders
55. Ganaxolone Therapy Improves Interictal EEG and Seizure Control in Lennox Gastaut Syndrome in Patients with PCDH19 and CDKL5
Chez M (Sacramento, CA)

Objective: Intractable childhood cases of Lennox Gastaut (LGS) show significantly abnormal Interictal EEG patterns that may affect developmental outcome. LGS can be caused by genetic epilepsy syndromes. We present 3 genetic syndromes cases with LGS presentation (2 PCDH19 and 1 CDKL5) showing Improved Interictal EEG patterns that correlate with improved seizure control. Ganaxolone (GNX) is a CNS-selective gamma-aminobutyric acid A (GABAA) positive allosteric modulator of the GABAA receptor with anticonvulsant and anxiolytic effects, and may improve EEG and function in LGS patients.

Methods: Patients with PCDH19(2) and CDKL5(1) with LGS were allowed to participate in an open label trial with ganaxolone (Marinus Pharmaceuticals). Dosages were up to 1800mg/day. EEG 24 hr baseline tracings were available with follow-up at 8-12 weeks. Seizure control and EEG changes in spike-wave percentage were quantified. Parental and Investigator CGI were done.

Results: Patients with PCDH19 showed a reduction in seizure frequency after 8 weeks treatment with 1200 and 1800mg/day of ganaxolone of 80% and 75%, respectively and EEG improvement in slow-spike and wave frequency of (> 90%, 80%) on awake and asleep EEG. The CDKL5 patient showed seizure reduction of (>67%) and EEG changes respectively as well (50% reduction in slow-spike wave discharges). CGI-I and CGI-parent were showing much improved for global function and seizure control.

Conclusions: This is a preliminary report of ganaxolone showing promise for refractive genetic cases of LGS with PCDH19 and CDKL5. More expanded study for other genetic, symptomatic, or idiopathic cases of LGS may be warranted.

Keywords: Epilepsy, Genetics, Translational/experimental therapeutics

56. Expanding the Phenotype of CACNA1H Mutations
Chourasia N (Houston, TX), Osio-Rivera H, Von Allmen G, Koenig M

Objective: To expand the phenotypic spectrum of CACNA1H mutations and describe potential co-morbid conditions.

Methods: The phenotypic spectrum of five patients with de novo pathogenic CACNA1H mutations was explored. Included features were: age of seizure onset, seizure semiology, response to therapy, brain imaging findings, EEG characteristics, behavior, and co-morbid conditions.

Results: All patients had de novo pathogenic heterozygous mutations in CACNA1H. The mean age of seizure onset was 8 years. Seizure semiology varied with patients experiencing absence, complex-partial, myoclonic, atonic, and generalized tonic-clonic events. EEGs showed focal, multifocal or generalized discharges. One child had global developmental delay with autism and one had developmental regression following seizure onset. Two patients had failure to thrive and functional B-cell immunodeficiency.

Conclusions: CACNA1H encodes for the a1H subunit of Cav3.2 channels, a subtype of T-type channels expressed at neuronal cell bodies and dendrites. CACNA1H mutations have previously been associated with susceptibility to idiopathic generalized epilepsy. Our series demonstrates that patients are also susceptible to focal onset epilepsy. Phenotype varied from mild to intractable with fifty percent of our patients responding to anti-epileptic medication. Two
<table>
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<th>Subject:</th>
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<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
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<tr>
<td><strong>Current Age; Gender</strong></td>
<td>3 year old female</td>
<td>8 year old female</td>
<td>13 year old female</td>
<td>10 year old female</td>
<td>7 year old male</td>
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<tr>
<td><strong>Seizure History</strong></td>
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<td>Onset of seizures</td>
<td>17 months</td>
<td>2 years</td>
<td>8 years</td>
<td>8 years</td>
<td>9 months</td>
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<td><strong>MRI Brain</strong></td>
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<td><strong>Treatment</strong></td>
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<td>LTG, CLB</td>
<td>ETX, ZNS</td>
<td>OXC</td>
<td>LEV, TPM, CLBs/p VNS</td>
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<td>Frequency (preTx)</td>
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<td>Multiple times/day</td>
<td>Multiple times/day</td>
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<tr>
<td>Frequency (post Tx)</td>
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<td>Seizure free since ZNS was added</td>
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<td><strong>EEG</strong></td>
<td>* Focal discharges</td>
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<td>* Multifocal discharges</td>
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<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>* Generalized discharges</td>
<td>X</td>
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<tr>
<td></td>
<td>* Diffuse Slowing</td>
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<td>Cognitive function</td>
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<td>Recurrent infections/Poor vaccine response</td>
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patients required VNS placement and one required a ketogenic diet. The recognition of immunodeficiency in two patients may represent a co-morbidity that has not previously been recognized. Both patients with functional B-cell deficiency responded to immunoglobulin therapy. Larger studies are required to delineate further the phenotypic characteristics and to determine whether functional B-cell deficiency is part of the spectrum of CACNA1H mutations.

**Keywords:** Epilepsy, Genetics, Infections/Neuroimmunology

### 57. Extrapolating Anti-Epileptic Drug Efficacy Data from Adults to Children: Results from the PEACE Initiative

O’Neill D (Chapel Hill, NC), Pellock J

**Objective:** Initial approval of anti-epileptic drugs (AEDs) for seizure types common in adults and children is based on trials conducted in adults; off-label use limits enrollment in pediatric clinical trials. Pediatric Epilepsy Academic Consortium for Extrapolation (PEACE) investigated the scientific basis for extrapolation of efficacy of AEDs from adults to children with the goal of expediting AED approvals for pediatric use.

**Methods:** The PEACE initiative was a collaborative effort between academic, regulatory and industry partners to formulate the biological basis of extrapolation, compare clinical trial findings and assess placebo effects and concentration-response relationships for various AEDs. Trial data for various seizure types, age range for extrapolation, and regulatory guidelines were reviewed to develop scientific consensus and propose revision of regulatory policies.

**Results:** Biological basis for extrapolation of efficacy from adults to children 4 years and older for focal seizures was supported by preclinical, neuropathological and clinical data. Clinical trial data showed comparable treatment effect sizes between adults and children for adjunctive therapy of focal seizures with five drugs (gabapentin, oxcarbazepine, lamotrigine, topiramate and levetiracetam); placebo responses and concentration-response relationships between adults and children for individual drugs were comparable. Findings were reviewed by the ILAE Regulatory Affairs Task Force (RATF) and European, US and Japanese regulatory agencies.

**Conclusions:** PEACE proposal for extrapolation of efficacy from adults to children 4 years and older for adjunctive AED therapy of focal seizures was endorsed by the ILAE RATF. Regulatory agencies revised and updated policies to accept extrapolation as proposed by the PEACE initiative.

**Keywords:** Epilepsy

### 58. Children with Epilepsy have a Remarkable Number of Convulsive Seizures with Loss of Consciousness

Camfield P (Halifax, Nova Scotia), Camfield C

**Objective:** Generalized tonic-clonic seizures (GTCs) (primarily generalized or focal with secondary generalization) frighten families, are a risk factor for SUDEP and dominate the public’s image of epilepsy. We studied how many children with epilepsy have GTCs and how often they recur during 25 years of follow up.

**Methods:** We selected 463 children from the prospective Nova Scotia population-based cohort of children with new onset epilepsy and ≥10 years follow up. We then studied those with ≥1 GTC.

**Results:** Overall 362/463 (78%) had ≥1 GTC. Age of epilepsy onset averaged 6.2 ± 4.8 years with 25.6 ± 5 years follow up. The number of GTCs was: 136/463 (29%) had 1-10 GTCs, 54 (12%) had 11-20, 69 (15%) had 21-99 and 96 (21%) had >100. The proportion with >20 GTCs (n=165, 36%) in broad epilepsy syndrome groupings were: focal epilepsy 95/235 (40%), JME 11/21 (52%), symptomatic generalized epilepsy 45/73 (62%). Of those with >20 GTCs, 80 (48%) were intellectually disabled compared with 23/197 (12%) of those with 1-20 GTCs (p<0.00001). Terminal remission off AEDs occurred in 288/463 (62%) for the overall cohort, 145/197 (74%) of those with 1-20 GTCs but only 55/165 (33%) of those with >20 (p<0.0001). One patient died from SUDEP after >100 GTC.

**Conclusions:** Three quarters of children with epilepsy have GTCs: 40% have >20 and 20% >100. Only half with >20 GTCs have normal intelligence, most have focal epilepsy and the chance of eventual remission is only 1/3. It is not surprising that families and the public fear GTCs even though SUDEP is rare.

**Keywords:** Epilepsy
59. Long-term Seizure Outcomes in Cortical Dysplasia (CD) Patients with Seizure Recurrence after Epilepsy Surgery
Javarayee P (Cincinnati, OH), Arya R, Holland K, Horn P, Greiner H, Mavagano F

**Objective:** Pre-surgical MRI status predicts long-term seizure outcomes in CD

**Methods:** Chart review was performed for CD patients with ≥1 seizures after resective surgery, and ≥3 year follow-up. Study period: January 2007 to December 2012.

**Results:** A total of 12 CD patients with post-operative seizure recurrence were identified. Subjects had failed an average of 4.3 AEDs before surgery. Two patients (16%) achieved terminal remission and were off AEDs at the end of 3 year follow-up, while 4/12 (33%) achieved good outcome (ILAE classification 1-3). Mean monthly seizure frequency had decreased from 33 (SD39) to 2 (SD15) at the end of follow up (p<0.002). Demographic variables, pre-surgical MRI, type or location of CD, and concordance of functional imaging with the site of surgery, did not predict long-term seizure outcome.

**Conclusions:** This study suggests a trend for good eventual seizure outcomes in CD patients with post-operative seizure recurrence. Small sample size limited ability to explore potential determinants of the outcome.

**Keywords:** Epilepsy

### TABLE 1. Pre-surgical factor predicts long-term seizure outcomes in CD (Abstract 59)

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<th>Factor</th>
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60. EEG Spike Localization in BECTS: Correlates with Neuropsychological Outcomes
Gelineau-Morel R (Cincinnati, OH), Tenney J, Maloney T, Vannet J

**Objective:** Benign epilepsy with centrotemporal spikes (BECTS) is termed “benign”, although recent evidence has shown adverse cognitive and behavioral effects, specifically in areas of language and attention. However, previous studies have failed to identify a consistent predictor for which patients will have the poorest outcomes. In this study, we examined the 24-hour EEGs of 29 patients with a new diagnosis of BECTS to correlate spike localization with neurobehavioral outcomes.

**Methods:** Spike localization was defined as the lead(s) with a phase reversal in the AP bipolar montage of the EEG and spread defined within the same montage as any lead with a visible deflection from the background at the time of the spike.

**Results:** Patients with spike localization extending to areas outside of the centrotemporal region (n=9) were found to have significantly lower scores in multiple areas of language testing than the patients with spikes localized only to centrotemporal regions (n=20) (mean scores: CELF core 86.75 vs 99.58, p=0.05; CTOPP phonological awareness 90.78 vs 102.17, p=0.01; Woodcock Johnson letter-word 99.33 vs 108.28, p=0.03; and NEPSY verbal fluency 7.17 vs 9.64, p=0.05). Additionally, patients with greater left-sided spread had a trend towards decreased language performance (NEPSY semantic, r²=0.11, p=0.08; CTOPP naming, r²=0.14, p=0.06).

**Conclusions:** These results suggest that BECTS patients with epileptic spikes occurring in extra-rolandic areas and increased left hemispheric spread are at higher risk for impaired language outcomes and may benefit from early screening and intervention.

**Keywords:** Epilepsy, Cognitive/Behavioral Disorders

61. Epilepsy and Cognition in Infants with Tuberous Sclerosis: Do Timing and Nature of Epilepsy Severity Relate to Cognitive Outcomes?

**Objective:** To evaluate the association between epilepsy severity and intellectual disability (ID) in children with Tuberous Sclerosis Complex (TSC).

TSC is a leading genetic cause of epilepsy. Approximately 85% of these individuals have refractory epilepsy (Curatolo et al. 2012). Early seizure onset and infantile spasms (IS) are associated with increased risk of cognitive problems in children with TSC (Bolton et al. 2015). The prevalence of epilepsy and ID in TSC lends to the importance of appropriately quantifying the severity of epilepsy in TSC.

**Methods:** These data represent the endpoint analysis from a multi-site longitudinal investigation of neurodevelopmental disorders in infants with TSC. At 24 and 36 months of age, the Mullen Scales of Early Learning and medical questionnaires were collected. Epilepsy data included age of seizure onset and history of IS. T-tests compared cognition in the IS and Non-IS groups. Linear regressions analyzed the association between cognition and age of seizure onset.
Results: 21/36 patients had a history of IS. Developmental Quotient (DQ) was significantly lower in the IS group versus the Non-IS group (p=0.04). Verbal-IQ (VIQ) and Nonverbal-IQ (NVIQ) were lower in the IS group (p=0.1). There was a significant association between earlier age of seizure onset and lower DQ (R²=0.3, p=0.006), VIQ (R²=0.2, p=0.006), and NVIQ (R²=0.2, p=0.02).

Conclusions: IS and early age of seizure onset are associated with increased risk of cognitive impairment. Ongoing analysis is focused on evaluating delays in specific cognitive domains and detailed epilepsy characteristics, in order to better understand the relationship between epilepsy and ID.

Keywords: Epilepsy, Genetics, Cognitive/Behavioral Disorders

62. Time is Neuron - Pediatric Status Epilepticus Protocol: Implementation and Measuring Effectiveness

Objective: To assess the improvement of care provided after implementation of Status Epilepticus Alert Protocol at children hospital through multidisciplinary approach, timely escalation of care and second line anti-epileptic drug administration. A prior study from our institution showed delay in escalation of care and administration of second line anti-epileptic drug.¹

Methods: This is prospective study with pre and post implementation surveys. Before implementation of protocol, pre implementation survey and mock codes were conducted to quantify awareness, knowledge and time regarding escalation of care, disposition and administration of 2nd line anti-epileptic drugs. Written protocol and EHR order set was designed after multidisciplinary consensus. Four months after implementing protocol (June/16) post implementation survey and second series of mock codes will be conducted. Protocol will be adjusted based on the post implementation. Actual patient data will be reviewed retrospectively before and after implementation to assess improvement.

Results: Pre Implementation survey and mock codes showed more than 50% residents did not chose 2nd line anti epileptic drug in timely manner and did not escalate the care. Retrospective chart review showed delay averaging 70 minutes in 2nd line epileptic drugs availability. Post protocol results are pending and will be presented at CNS conference.

Conclusions: We hypothesize that enterprise wide Status Epilepticus alert protocol can help in better patient care through timely escalation of care, disposition and administration of 2nd line drugs.

Keywords: Epilepsy

63. Clinical and Neuroradiological Differences Between Epileptic Children With Agenesis of Corpus Callosum or Aicardi Syndrome
Govil-Dalela T (Detroit, MI), Kumar A, Rahman E, Roberts M, Agarwal R, Chugani H

Objective: Agenesis of corpus callosum (ACC) can be seen in patients with epilepsy, either in isolation (iACC) or as part of various neurologic syndromes, such as Aicardi syndrome (AS). In this study we evaluated the clinical/neuroradiological differences between children with iACC or AS.

Methods: Clinical and neuroradiological data were analyzed in 26 epileptic children with ACC [17 females; median age: 4 years; 11 with AS (all females)].

Results: The median age at seizure onset was lower (2 vs 3.5 months; p=0.005) and seizure frequency higher in children with AS. The predominant seizure type was complex-partial in iACC (60%) and infantile spasms in AS children (100%); 91% AS and 33% iACC children were non-ambulatory until median age of 30 and 14 months, respectively (p=0.005), while 80% AS and 29% iACC patients were non-verbal until median age of 24 and 11 months, respectively (p=0.04). MRI as well as FDG-PET abnormalities were more extensive in AS children. FDG-PET showed more extensive abnormalities compared to MRI. Four children (2 from each group) underwent epilepsy surgery with moderate-to-significant reduction in seizure frequency and some improvement in cognitive development; the outcome was worse in those with FDG-PET abnormalities on the non-surgical hemisphere despite their normal-MRI appearance.

Conclusions: Seizure onset was earlier, its frequency higher and developmental impairment/extent of cortical abnormality worse in AS compared to iACC children. The functional abnormality was consistently larger than structural involvement; therefore, FDG-PET may be useful in surgical planning or prognostication, as benefit from epilepsy surgery is possible in carefully selected patients.

Keywords: Epilepsy, Neuroimaging

64. Predicting Frequent ED Use Among Children With Epilepsy: A Retrospective Cohort Analysis using Electronic Health Data from Two Centers, and Statewide Data from Two States
Grinspan Z (New York, NY), Patel A, Hafeez B, Johnson P, Abramson E, Kern L

Objective: For children with epilepsy, past emergency department (ED) use roughly predicts future use. The additive predictive value of insurance coverage and disease severity is underexplored.

Methods: Using 2013-2014 electronic records from two centers, we conducted a retrospective cohort study to predict ED use. We used logistic regression, benchmarked against machine learning algorithms. For robustness, we fit models on half the data, and evaluated performance on the other half, 100 times.

Results: We tested generalizability with statewide administrative data from California and New York from 2010-11. We estimated the break-even cost of an intervention to reduce ED visits by 10% among the 10% highest risk individuals, using median ED and inpatient reimbursements from one center.

Results: A three-concept prediction rule (prior ED use, insurance status, number of anti-epileptic drugs) predicted frequent ED use with performance similar to machine learning (center1, N=2730; median AUC 0.82 [interquartile-interval 0.8-0.82] vs. best machine learning algorithm 0.84 [0.83-0.85]; center2, N=786: 0.74 [0.70-0.76] vs. 0.73 [0.72-0.75]). A two-concept model (prior ED use, insurance status) also performed well (center1: 0.88 [0.79-0.81]; center2: 0.84 [0.72-0.75], NY: N=11,711, AUC=0.72; CA:
N=12,384, AUC=0.70). Estimated yearly per-patient break-even intervention costs ranged from $51-246 if only ED discharges are preventable, and $734-3543 if ED-to-inpatient admissions are also preventable. For small potential cohorts (20-50) at one center, the three-concept model meaningfully outperformed the two-concept model.

Conclusions: Prior ED use and insurance status accurately predict future use among children with epilepsy in multiple datasets. Consideration of disease severity may meaningfully improve predictions in limited circumstances.

Keywords: Epilepsy

65. Barriers to Genetic Testing for Pediatric Medicaid Beneficiaries with Epilepsy: A National Survey
Grinspan Z (New York, NY), Patel A, Kutscher E, Hafeez B, Joshi S

Objective: Understanding barriers to obtaining genetic testing for children with epilepsy with Medicaid insurance can inform initiatives to improve their care.

Methods: We sent a web-based survey to a convenience sample of child neurology clinicians throughout the US.

Results: 302 clinicians responded from 47 states, including 249 board-certified child neurologists, 17 residents, 10 nurses, and 9 nurse practitioners. Among respondents who answered definitively about reimbursement for specific testing, 69% (92 of 134) indicated Medicaid paid for microarray, 49% (60 of 122) single gene testing, 28% (32 of 115) epilepsy genetic panel testing, and 10% (15 of 147) exome sequencing. In a subgroup of 156 respondents, a plurality (43%) felt genetic testing was easier for commercial patients than for Medicaid patients. Fewer (12%) thought testing was easier for Medicaid patients. In free text responses, 170 respondents cited insurance as a major barrier to obtain testing for children with Medicaid (particularly denials). Other frequently cited barriers include: insufficient staff and time (24 responses), cost to families (9), and physician uncertainty about the clinical relevance of testing (8). Cited facilitators include availability of genetics specialists (32 responses), support from private testing companies (27), and increased willingness by insurance to pay (19).

Conclusions: Compared to children with commercial insurance, children with epilepsy with Medicaid insurance have poor access to genetic testing, particularly for more advanced testing. Potential strategies to improve access include: improve coverage, improve access to genetics specialists, improve clinician education, reduce paperwork, reduce co-pays, disseminate guidelines, and encourage ongoing assistance from private labs.

Keywords: Epilepsy, Genetics

**Demyelinating Disorders**

66. Interrogation of the Visual System in Pediatric Multiple Sclerosis: Relative Insights Gained by Optical Coherence Tomography and Visual Evoked Potentials

Objective: To determine the relative capacity of optical coherence tomography (OCT) and visual evoked potentials (VEP) to detect clinical and subclinical optic pathway pathology in pediatric MS.

Methods: Pediatric MS subjects (onset <18 years) and healthy controls were recruited. Clinical optic neuritis (ON) diagnosis was confirmed by a neuro-ophthalmologist and abstracted from the medical record. OCT (Cirrus HD-OCT) and pattern reversal VEP were obtained and included after passing quality control. Subclinical disease in unaffected eyes was defined as parameters beyond 2 standard deviations. Generalized estimating equation models were used to compare the groups, adjusting for age and inter-eye correlations.

Results: Twenty-four pediatric MS patients (20 ON eyes, 8 fellow eyes, 20 non-ON eyes) and 24 healthy controls (48 eyes) were enrolled. RNFL thinning (<83 microns) occurred in 50% of ON eyes, 25% of fellow eyes, and 5% of non-ON eyes. GCL-IPL thinning (<71 microns) occurred in 33% of ON eyes, 25% of fellow eyes, and 10% of non-ON eyes. Prolonged VEP latency (>109 msec) occurred in 55% of ON eyes, 43% of fellow eyes, and 55% of non-ON eyes. A clinical history of ON predicted RNFL (p<0.001) and GCL-IPL thinning (p<0.001) whereas prolonged VEP latency occurred independent of ON history (p<0.001).

Conclusions: VEP abnormalities occurred more frequently in pediatric MS eyes than RNFL thinning. RNFL abnormalities were rare in clinically unaffected eyes, indicating that RNFL in pediatric MS patients is sensitive to retinal changes in the context of clinical ON but does not appear to serve as a more global metric of MS pathology.

Keywords: Demyelinating Disorders

67. ABCD1 Deficiency Causes White Matter Microvascular Perfusion Abnormalities

Objective: X-linked Adrenoleukodystrophy (ALD) is a devastating neurodegenerative disorder that results from mutations in the ABCD1 gene and leads to rapidly progressive cerebral inflammatory demyelination (CALD) in ~50% of affected males. The exact mechanisms leading to conversion to cerebral disease are unclear. Based on recent data suggesting that ABCD1 deficiency directly alters brain endothelial function, we set out to assess changes in capillary flow using dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI).

Methods: Fifty-one patients with ALD were evaluated between 2006 and 2015 at MGH. Microvascular flow patterns, Oxygen extraction capacity, upper limit of O2 metabolic rate (CMRO2max) and contrast leakage rate were estimated from a total of 161 perfusion scans using an algorithm that applies vascular models to the raw data. Regional, lesional and whole white matter perfusion was compared to 24 matched controls.
FIGURE 1: ABCD1 deficiency related changes in white matter microvascular perfusion (Abstract 67)

FIGURE 2: ABCD1 deficiency has spatial and temporal effects upon microvascular flow
Results: We found that complete lack of function of ABCD1 causes abnormal perfusion in white matter regions and developmental stages with highest susceptibility for conversion to CALD (Fig.1, Fig.2). High flow heterogeneity followed by an increase in BBB permeability predicts lesion progression in patients with CALD. These abnormalities normalize after treatment with hematopoietic stem cell transplantation.

Conclusions: We demonstrate that ABCD1 deficiency causes perturbation in cerebral perfusion with peaks during the developmental period and in anatomical regions with highest susceptibility for conversion to CALD. The exact mechanisms underlying the detected alternations in vascular physiology remain to be elucidated but DSC MR perfusion may provide a powerful biomarker for risk certification, monitoring of treatment and earlier identification of high-risk patients.

Keywords: Demyelinating Disorders, Genetics, Neuroimaging

68. Pediatric Onset Multiple Sclerosis: A Single Center Experience
Yamamoto E (Cleveland, OH), Ginsberg M, Rensel M, Moodley M

Objective: To describe the epidemiologic, clinical, neuroimaging, laboratory features and therapeutic management and outcome of a growing pediatric onset MS (POMS) patient population seen at a single center.

Methods: A retrospective chart review of 60 children, under 20 years of age, with POMS who initially presented to the Cleveland Clinic from 2002-2015. Data on demographics, presenting symptoms, clinical features, neuroimaging, laboratory studies, treatment and outcomes were analyzed.

Results: 78.3% were Caucasian; ages 2-19 years, mean of 15.7 years; 68.3% female in both under and over 12-year old subsets; 49% were overweight; 63% were vitamin D deficient. Most frequent reported symptom was sensory dysfunction (78.3%); fatigue and impaired memory (15.8% and 17.5%, respectively). Abnormal saccadic pursuit was identified in 35.0%. CSF IgG index was elevated (76.4%) and oligoclonal bands were present (67.0%). MRI lesions in non-diagnostic locations were common including brainstem, cerebellar, cortical lesions (46.7%, 28.0%, 15.0%). 72.4% of patients were started on Avonex therapy. At last consultation, 42.1% remained on Avonex, 10.5% on Copaxone, and 26.3% on Tecfidera. Annual relapse rate was 0.63 relapses per person-years.

Conclusions: These data support associations between MS and environmental triggers such as obesity and vitamin D deficiency. Presenting symptoms, MRI and laboratory findings were largely consistent with that in the existing literature; however, the prevalence of cortical lesions and abnormal saccadic pursuit is higher than other reports. Such non-characteristic findings highlight difficulties in recognition and diagnosis of POMS. Management is also challenging, as many patients require second-line disease modifying therapies that have not been appropriately evaluated in children.

Keywords: Demyelinating Disorders

69. NEDA is Rare in Pediatric Onset MS treatment. Can We Do Better with Higher Potency Disease Modifying Therapies?
Rosman I (Cleveland, OH), Moodley M, Rensel M

Objective: No evidence of disease activity, or NEDA, is an emerging clinical trial endpoint and treatment goal in multiple sclerosis (MS). Defined as no clinical relapses, new or enlarging T2 hyperintense lesions, nor gadolinium enhancement, NEDA is difficult to achieve in adult-onset MS, and rarely sustained. However, NEDA at 2 years predicts better clinical outcomes. NEDA estimates in adult clinical trials of disease modifying therapies (DMTs) range from 20-40% at 2 years, and 7% at 7 years. The highest NEDA rates were achieved using highly potent therapies, alemtuzumab (40% at 3-5 years) and hematopoietic stem cell transplant (78% at 3 years). NEDA has not been thoroughly evaluated in pediatric onset MS (POMS). Accounting for 5% of MS cases, POMS has more early clinical and radiographic disease activity, but less disability progression compared to adult onset MS. We previously found NEDA to occur rarely in our POMS population (8%). We now aim to compare NEDA rates between standard injectable DMT versus higher-potency oral and infusion DMTs in our POMS cohort.

Methods: Retrospective chart review of POMS patients presenting to Cleveland Clinic from 2006-2016.

Results: Overall, NEDA was achieved in 8% of office visits, and occurred more frequently with older age of MS onset. In the minority of patients receiving dimethyl fumarate or natalizumab, NEDA rates were higher, 37.5% and 67%, respectively, though numbers were small and follow up limited.

Conclusions: This retrospective evaluation suggests higher potency DMTs achieve better clinical outcomes, though prospective, multicentered, blinded studies will be needed to better ascertain NEDA in POMS.

Keywords: Demyelinating Disorders, Infections/Neuroimmunology, Neuroimaging

70. Multiple Sclerosis: Association Between Radiological Burden and Headache Severity
Singh I (St. Louis, MO), Wu E, Mar S

Objective: To study prevalence of migraine-like headaches in pediatric multiple sclerosis and to see if there is any association between radiological burden of multiple sclerosis with headache severity.

Methods: We conducted a retrospective chart review of 49 patients from our multiple sclerosis data base at Saint Louis Children’s hospital. The patients with headache reported at the time of MS diagnosis were identified. The mean age was 16 yrs at the time of diagnosis.

Results: The prevalence of headache was found in 32 patients (65%) of the pediatric MS patients with comorbid migraine-like headaches. 20 of 32 patients (62%) had daily headache with MRI showing greater than 15 supratentorial T2/FLAIR lesions. 5 of 17 (29%) had occasional headache in the beginning with mean supratentorial T2/FLAIR lesions of 8, which progressed to greater than twice a week headache associated with progression of radiological burden of greater than 15 supratentorial T2/FLAIR lesions.
patients had greater than 10 supratentorial T2/FLAIR lesions and headaches remained occasional.

**Conclusions:** Migraine-like headaches is a common comorbidity in patients with pediatric MS as seen in adult MS patients. Headache was reported in 65% of Pediatric MS patients at the time of diagnosis. 10% had worsening of headache with progression of radiological disease. There is an association of radiological burden of MS disease with headache severity in pediatric MS patients.

**Keywords:** Demyelinating Disorders, Headache/Migraine, Neuroimaging

71. Evaluation of Revised 2015 Neuromyelitis Optica Spectrum Disease (NMOSD) Diagnostic Criteria in a Pediatric Demyelinating Cohort


**Objective:** Identification of Aquaporin-4 (Aq4) seropositivity in neuromyelitis optica (NMO) broadened the classic phenotype of optic neuritis (ON) plus longitudinally-extensive transverse myelitis (LETM) to include brain lesions. Revised 2015 criteria enables NMO spectrum disease (NMOSD) diagnosis if Aq4-seropositive with isolated ON, TM, brainstem, diencephalic or cerebral syndromes or, if Aq4-seronegative, if ≥2 of these regions affected. Goal: Evaluate revised 2015 NMOSD diagnostic criteria in a pediatric demyelinating cohort.

**Methods:** Pediatric demyelinating database of >500 patients evaluated in tertiary children's hospital and followed prospectively since 2000 was queried for ON, TM or brainstem syndromes. Cases were reviewed to determine whether they fulfilled LETM+ON only or 2015 expanded criteria.

**Results:** NMOSD was diagnosed in 65 patients, with 32 (49%) having LETM+ON (47% Aq4 positive, n=15) and 33 (51%) meeting 2015 criteria (42% Aq4-positive, n=14). Aq4-Ab positive patients were 90% female (n=26) and 72% non-Caucasian (n=21) with mean onset age 11.9 ±4.2 years. In contrast, Aq4-Ab negative patients were significantly younger (8.7 ±3.6, p<0.004), Caucasian (68%, p<0.001) and less predominantly female (56%, p<0.05). Brainstem symptoms were experienced by two-thirds of the entire cohort (n=43), with 17 presenting with area postrema syndrome of vomiting and hiccups (26%). Encephalopathy was present at some point in >50% of Aq4 seronegative patients (n=20) but only 7% (n=2) seropositive patients (P<0.0001).

**Conclusions:** Application of revised 2015 NMO criteria was associated with significant differences in age, race, sex and presence of encephalopathy. These findings suggest that Aq4-Ab seropositivity may distinguish biologically distinct sub-groups.

**Keywords:** Demyelinating Disorders, Infections/Neuroimmunology

72. Adrenoleukodystrophy Phenotypes Show Reduction of Superoxide Dismutase in Blood Plasma Over Time, Correlating With Leses Score in Cerebral Disease


**Objective:** Adrenoleukodystrophy (ALD) is an X-linked peroxisomal disorder, due to ABCD1 dysfunction and very long chain fatty acid (VLCFA) accumulation. ALD presents as multiple phenotypes with unknown genotype correlation; Slow progressive adrenoleukodystrophy (AMN), or rapid, deadly cerebral ALD (cALD) amongst others. No identified triggers for phenotype shift from AMN to cALD have been established. Superoxide dismutase (SOD) polymorphisms, have been associated with cALD. In this study, predictive values of antioxidant parameters including SOD were analyzed in human blood plasma and other tissues.

**Methods:** Total radical antioxidant capacity (TRAP), Glutathione (GLT), Superoxide dismutase (SOD) 1 and 2, prostaglandin E2 were measured in ALD patient blood plasma, monocytes, macrophages and fibroblasts of cALD (n=28), AMN (n=18) and Heterozygote females (n=12)

**Results:** cALD patients monocytes, blood plasma and fibroblasts show significantly lower (p<0.0003) SOD activity and TRAP levels than AMN patients, who in turn show significantly lower levels (p<0.005) than healthy controls. SOD activity in cALD inversely correlates with cranial MRI Loes score severity (p<0.005, r2=0.81). SOD activity sees a reduction over time in individual patients, sharply dropping to very low activity around cerebral onset.

**Conclusions:** We demonstrate reduced SOD and antioxidant capacity in cALD which appears to evolve over time as patients develop cerebral demyelination. This finding is consistent with previous findings of specific SOD polymorphisms in cALD. Correlation of cMRI Loes score and individual patients over time may support future endeavor of determining prognostic value of SOD in early determination of cerebral disease onset.

**Keywords:** Demyelinating Disorders, Genetics

73. The Evolving Clinical Picture of Leukodystrophies: Cases of Atypical Presentations of Metachromatic Leukodystrophy in Children

*Adang L (Philadelphia, PA), Waldman A*

**Objective:** Metachromatic Leukodystrophy (MLD) should be considered in the differential for GBS, CMT, and motor delay, even in the absence of typical MRI findings.

**Methods:** We describe 3 cases of early infantile MLD with atypical presentation and imaging.

**Results:** Patient 1 presented with early gross motor delay. After a plateau in skills, she began to lose her motor milestones. Electrodiagnostic testing was consistent with a diagnosis of GBS and the patient showed minimal improvement post-IVIG. A repeat brain MRI was suggestive of MLD. Patient 2 presented with intermittent esotropia, bilateral facial weakness, and subtle ataxia following a fever with later MRI showing enhancement of cranial nerves and the leptomeninges. Patient 3 presented to his pediatrician with delayed gross motor skills and a positive Gower’s maneuver. The EMG was consistent with a peripheral demyelinating polynuropathy.

**Conclusions:** This case series illustrates that MLD can initially be misdiagnosed as peripheral nervous system disease. As novel therapeutics emerge for MLD, it is increasingly important to diagnosis MLD early in the disease course.
These examples reinforce the isolated, early peripheral manifestations of MLD, even in the absence of MRI changes. It is important to add this rare leukodystrophy to the differential diagnosis of peripheral nervous system diseases and motor delay.

**Keywords:** Demyelinating Disorders, Genetics, Cognitive/Behavioral Disorders

74. **Brainstem Presentations in Pediatric Multiple Sclerosis**  
_Shelton L. (Pittsburgh, PA), Zuccoli G, Alper G_

**Objective:** Isolated brainstem symptoms have been reported in 13-40% of children with multiple sclerosis at disease onset; however specific information regarding clinical and

---

**TABLE 1. Characteristics of brainstem syndrome in pediatric onset multiple sclerosis (Abstract 74)**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (year)</th>
<th>Gender</th>
<th>Symptoms</th>
<th>Cranial Nerve Exam</th>
<th>Exam - Other</th>
<th>MRI Brainstem Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>Female</td>
<td>Diplopia, Bilateral facial weakness</td>
<td>INO; 1 1/2 syndrome, Bilateral LMN facial palsies</td>
<td>Normal</td>
<td>Central Medulla, Right Pons</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>Female</td>
<td>Diplopia</td>
<td>Left 6th nerve palsy</td>
<td>Normal</td>
<td>Right pons/MCP</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>Female</td>
<td>Diplopia</td>
<td>Bilateral 6th nerve palsies</td>
<td>Normal</td>
<td>Left ventral pons, Left pontomedullary junction</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>Female</td>
<td>Right facial myokymia and weakness, dysarthria</td>
<td>Right LMN facial palsy, right facial myokymia</td>
<td>Normal</td>
<td>Right pons</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>Female</td>
<td>Right facial numbness, Right hand weakness</td>
<td>Right V1-V3 decreased sensation</td>
<td>Right hand weakness</td>
<td>Right pons, left pontomedullary junction</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>Female</td>
<td>Left facial paraesthesias, Left tongue paraesthesia, Left hand paraesthesia</td>
<td>No neurologic examination while symptomatic</td>
<td>Normal</td>
<td>None in brainstem, left cerebellum/MCP</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>Female</td>
<td>Diplopia, Right facial weakness</td>
<td>Right 6th nerve palsy, mild right facial weakness, right hyperacusis</td>
<td>Normal</td>
<td>Medial medulla, left pons MLF, right pons facial colliculus</td>
</tr>
<tr>
<td>7</td>
<td>17</td>
<td>Female</td>
<td>Left facial numbness</td>
<td>Left V1-V3 decreased sensation</td>
<td>Normal</td>
<td>Left pons (trigeminal fascicula, left MCP</td>
</tr>
<tr>
<td>8</td>
<td>17</td>
<td>Male</td>
<td>Diplopia, Right facial weakness, Dysarthria, Dysphagia</td>
<td>Right INO, mild right LMN facial palsy, left decreased gag, left decreased taste</td>
<td>Normal</td>
<td>Right caudal midbrain</td>
</tr>
<tr>
<td>9</td>
<td>13</td>
<td>Male</td>
<td>Diplopia, Vertigo</td>
<td>Right &gt; Left INO, vertical nystagmus</td>
<td>Normal</td>
<td>Left mid pons</td>
</tr>
<tr>
<td>10</td>
<td>18</td>
<td>Female</td>
<td>Left facial/hemibody numbness/paraesthesias, Left facial weakness</td>
<td>Right LMN facial palsy, right hyperacusis, Left V1-V3 decreased sensation</td>
<td>Left hand weakness, Left pronator drift, left hemibody decreased sensation</td>
<td>None in brainstem, left cerebellum/MCP</td>
</tr>
</tbody>
</table>

LMN – lower motor neuron; INO – internuclear ophthalmoplegia; MCP – middle cerebellar peduncle; SCP – superior cerebellar peduncle; MLF – medial longitudinal fasciculus

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radiologic features of brainstem involvement in multiple sclerosis attacks has not been well described in children.

**Methods:** Patients were identified from the Pittsburgh Pediatric Demyelinating Registry. The clinical presentation, neurological examination, laboratory data, MRI findings and outcomes are described in a series of 10 children who had MS attacks clinically involving only the brainstem.

**Results:** Two males and eight females aged 12–18 years-old presented with symptoms of brainstem dysfunction. Five patients had an established diagnosis of multiple sclerosis, while brainstem presentation was the initial attack in the other five children. All patients had cranial nerve involvement, two had focal extremity weakness and one had sensory findings (table). Eight of ten patients had corresponding brainstem lesions on MRI. Multiple sclerosis lesions were seen in pons (n=8), medulla and pontomedullary junction (n=5), and midbrain (n=3). Additional supratentorial lesions consistent with multiple sclerosis were seen in all patients although clinical presentations solely represented brainstem symptoms. All patients were treated with five days of IV methylprednisolone. Nine children had complete resolution of symptoms within 1 to 10 weeks. One patient presented with symptoms of brainstem dysfunction. Five patients although clinical presentations solely represented brainstem lesions consistent with multiple sclerosis were seen in all patients (n=8), medulla and pontomedullary junction (n=3), and midbrain (n=1). Additional supratentorial lesions consistent with multiple sclerosis were seen in all patients although clinical presentations solely represented brainstem symptoms. All patients were treated with five days of IV methylprednisolone. Nine children had complete resolution of symptoms within 1 to 10 weeks. One patient had resolution of facial palsy but had persistent facial myokymia.

**Conclusions:** Brainstem involvement occurs both at onset and during the course of disease in pediatric multiple sclerosis. In this limited case series, cranial nerve deficits were the most common. The majority of patients had corresponding MRI lesions involving intrapontine fascicular fibers and the internuclear connections.

**Keywords:** Demyelinating Disorders, Neuroimaging

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**TABLE 1. Treatment and outcome measures in pediatric Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) (Abstract 75).**

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Case</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Disease Duration (months)</th>
<th>IVIG</th>
<th>R-ODS score</th>
<th>Grip Strength (kg)</th>
<th>Nerve Conduction Study (Median mv. amplitude)</th>
<th>Special Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DE</td>
<td>18</td>
<td>F</td>
<td>64</td>
<td>1</td>
<td>4</td>
<td>5.3</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>AOG</td>
<td>18</td>
<td>M</td>
<td>41</td>
<td>1</td>
<td>3</td>
<td>1.9</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>3</td>
<td>PMP</td>
<td>10</td>
<td>F</td>
<td>32</td>
<td>1</td>
<td>3</td>
<td>1.6</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>4</td>
<td>DR</td>
<td>18</td>
<td>M</td>
<td>9</td>
<td>1</td>
<td>3</td>
<td>0.75</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>5</td>
<td>GM</td>
<td>11</td>
<td>F</td>
<td>15</td>
<td>1</td>
<td>2</td>
<td>1.25</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>6</td>
<td>MP</td>
<td>8</td>
<td>M</td>
<td>10</td>
<td>1</td>
<td>2</td>
<td>0.41</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
variable (range 2-4 weekly). R-ODS and hand grip strength were useful to show interval improvement.

Keywords: Demyelinating Disorders

STROKE

76. Prevalence of Acute Seizures and Subsequent Epilepsy Among Critically-Ill Children with Acute Ischemic Stroke
Payne E (Rochester, MN), Yau I, Frndova H, Hutchinson J, deVeber G, Mahatir M, Hahn C

Objective: Acute seizures are known to accompany pediatric stroke. We examined the prevalence of acute seizures and subsequent epilepsy among critically-ill children with acute stroke admitted to a tertiary children’s hospital.

Methods: We studied children, including neonates, with radiographically confirmed ischemic stroke admitted to our ICUs and evaluated by our pediatric stroke service between 2010-2012. Clinical details were abstracted from our institutional pediatric stroke registry and electronic medical records. Neuroimaging and EEG data were re-analyzed in a blinded fashion. Outcomes were assessed through follow-up in our pediatric stroke clinic.

Results: Ninety-two patients (50% male; mean age 3.25y (IQR: 0-4.25); 37 (40%) neonates) were included: 75 (82%) with acute ischemic stroke and 17 (18%) with cerebral sinovenous thrombosis. Seventy-four patients (80%) underwent EEG, including 38 (41%) who underwent continuous video-EEG monitoring (cEEG) (mean duration 37 hours (IQR: 18-48)). Acute clinical seizures were observed in 19 children (21%), all of whom subsequently underwent cEEG. EEG seizures were detected in 17 children (18%), 16 (94%) of which experienced subclinical seizures. The mean time to first EEG seizure was 13.5h (range: 0-110). Status epilepticus occurred in 5 children (5%). Survivors (n=58, 92%) were followed for an average of 26m (IQR: 12, 39). At last follow-up, 17 children (20%) remained on anti-epileptic medication, and 11 (13%) had active epilepsy.

Conclusions: Among critically-ill children with acute stroke, acute seizures and status epilepticus were common and frequently subclinical. Accurate assessment of seizures in this population requires cEEG monitoring. Whether seizure detection and treatment improves outcomes requires further study.

Keywords: Stroke, Epilepsy

77. Inflammatory Cytokines Distinguish Perinatal Stroke Syndrome Subtypes
Mineyk A (Calgary, Alberta), Nettle-Aguirre A, Qi W, Kamran Y, Mark F, Benseler S, Kirton A

Objective: Perinatal stroke causes lifelong disability. Imaging-defined diseases include neonatal arterial ischemic stroke (NAIS), arterial presumed perinatal ischemic stroke (APPI), and fetal periventricular venous infarction (PVI). Pathophysiology for each is poorly understood though placental inflammation is suspected in NAIS. We hypothesized that abnormal neonatal inflammatory signatures are recognizable in NAIS but not PVI or controls.

Methods: MRI-defined cases of NAIS, APPI, and PVI were identified within a population-based research cohort (Alberta Perinatal Stroke Project). Neonatal blood spots were obtained for all index cases. The next 3 chronological cases served as controls. Using bioplex technology, a panel

TABLE 1. Continued

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Case Age (yrs)</th>
<th>Sex</th>
<th>Disease Duration (months)</th>
<th>IVIG Dose (gm/kg)</th>
<th>Frequency (weekly)</th>
<th>Duration (years)</th>
<th>R-ODS score</th>
<th>Grip Strength (kg)</th>
<th>Nerve Conduction Study (Median sv. amplitude)</th>
<th>Nerve Conduction Study (Median motor conduction vel)</th>
<th>Special Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>RTL</td>
<td>18</td>
<td>M</td>
<td>48</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>7</td>
<td>45</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>8</td>
<td>MRF</td>
<td>18</td>
<td>F</td>
<td>40</td>
<td>1</td>
<td>3</td>
<td>3.33</td>
<td>15</td>
<td>48</td>
<td>4.08</td>
<td>7.7, 4.08, 9.07</td>
</tr>
<tr>
<td>9</td>
<td>LGH</td>
<td>9</td>
<td>M</td>
<td>11</td>
<td>1</td>
<td>2</td>
<td>0.9</td>
<td>19</td>
<td>48</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>10</td>
<td>CL</td>
<td>12</td>
<td>F</td>
<td>8</td>
<td>1</td>
<td>3</td>
<td>0.66</td>
<td>33</td>
<td>31</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>11</td>
<td>TBC</td>
<td>11</td>
<td>M</td>
<td>69</td>
<td>1</td>
<td>4</td>
<td>5.75</td>
<td>10</td>
<td>47</td>
<td>N/A</td>
<td>N/A, Additional treatment-Prednisone</td>
</tr>
</tbody>
</table>

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of 65 cytokines were quantified on all samples. Fisher linear discriminant analysis and classification trees explored cytokine patterns across groups to define sensitivity, specificity, positive and negative predictive values (PPV, NPV).

Results: A total of 188 subjects were analyzed (27 NAIS, 6 APPIS, 11 PVI, 132 controls). Cytokines were quantifiable with internal quality control measures including standards testing, decay analysis, and positive controls. Linear discriminant analysis was able to accurately define disease classification. PVI and control samples were comparable. NAIS identification was highly accurate: sensitivity 77%, specificity 97%, PPV 83%, NPV 96%. APPIS patterns were distinct from NAIS with similar accuracy (sensitivity 86%, specificity 99%). Classification tree analysis generated similar diagnostic accuracy. Fifteen cytokines demonstrated the most discriminatory power.

Conclusions: Unique inflammatory biomarker signatures are associated with arterial (but not venous) perinatal stroke syndromes. Findings support increasing evidence for acquired pathophysiology and suggest the possibility that at-risk pregnancies might be identifiable.

Keywords: Stroke

78. Expanding the Neurological Phenotype of Adenosine Deaminase 2 Deficiency (DADA2 Syndrome) Due to Biallelic Mutations in the CECR1 Gene: A Treatable Pediatric Lacunar Stroke Syndrome

Objective: To describe the expanding neurological phenotype of DADA2 syndrome and treatment implications.

Methods: 22 patients with DADA2 syndrome have been followed at the NIH Clinical Center with serial neurological and MRI evaluations.

<p>| TABLE 1. Neurological features of DADA2 patients evaluated at the National Institutes of Health Clinical Center (Abstract 78) |
|---|---|---|---|
| Age (yrs) | Gender | Neurological Involvement | STROKE (yes/no) | Immunotherapy (with onset dates for TNF-blockers) | Duration of TNF-blockade |
| 28 | F | multiple stroke episodes infancy; L central retinal artery occlusion; L hemisphere hemorrhagic stroke while on warfarin leading to expressive aphasia requiring use of augmentative communication device, dense right hemiparesis/non-ambulatory and right visual field deficits, oromandibular dystonia and blepharospasm (secondary Meige syndrome) | Y | ivIG, etanercept 1/2015 | 16 months |
| 15 | F | at 2 yrs of age midbrain lacune with CSF WBC 20 and protein; then thalamic lacune; myelitis; seizure onset 5/2014; current epilepsy and severe behavioral dysregulation | Y | prior cyclophosphamide and anakinra; etanercept since 10/2013 | 31 months |
| 8 | M | mild intellectual disability, 6 prior strokes (brainstem, thalamus, corpus callosum, internal capsule, basal ganglia), elevated CSF opening pressure, s/p conventional angio and brain biopsy, petechial hemorrhages on SWI | Y | prior cyclophosphamide; etanercept since 6/2013, also on anakinra and prednisone | 35 months |
| 10 | F | first stroke at 1 yr of age, then basal ganglia and corpus callosum lacunes, ICH and subdural from head trauma while on anticoagulation requiring craniotomy, and also recurrence of bleed subsequently without trauma, last stroke 9/2012 | Y | prior cyclophosphamide, MMF, steroids; currently on hydroxychloroquine, anakinra, ivIG and etanercept since 6/2013 | 35 months |</p>
<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Gender</th>
<th>Neurological Involvement</th>
<th>STROKE (yes/no)</th>
<th>Immunotherapy (with onset dates for TNF-blockers)</th>
<th>Duration of TNF-blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>M</td>
<td>Thalamus and midbrain lacunes; right fronto-temporal hemorrhage 11/2010 in context of plavix/ASA, s/p EVD and brain biopsy, 10/2012 seizure onset, 2016 s/p right frontal lobectomy for refractory lesional epilepsy</td>
<td>Y</td>
<td>prior cyclophosphamide; current anakinra and etanercept 6/2013</td>
<td>35 months</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>midbrain and thalamic lacunes, orbital pseudotumor</td>
<td>Y</td>
<td>prior steroids and MTX; etanercept 1/2014</td>
<td>28 months</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>midbrain lacune, s/p conventional angio</td>
<td>Y</td>
<td>etanercept 4/2015</td>
<td>13 months</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>febrile myositis, migranes, one spell of confusion/headache/blinkling/slurred speech with hand paresthesias? TIA/sz/complicated migraine, EEG neg</td>
<td>N</td>
<td>etanercept 4/2014 switched to adalimumab 9/2014, also on ivIg</td>
<td>25 months</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>OCD/tics, ADHD</td>
<td>N</td>
<td>etanercept 6/2014</td>
<td>23 months</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>ADHD and mild behavioral dysregulation; muscle biopsy consistent with inflammatory myopathy and marked vasculitis; paramedian midbrain and thalamic lacune</td>
<td>Y</td>
<td>etanercept 7/2014</td>
<td>22 months</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>None (tested prompted by sibling)</td>
<td>N</td>
<td>10/2015 etanercept</td>
<td>7 months</td>
</tr>
<tr>
<td>25</td>
<td>M</td>
<td>stroke onset at age 14 yrs with possible INO, then caudate lacune, left retinal infarct, clinical dysexecutive syndrome</td>
<td>Y</td>
<td>etanercept 9/2015 switched to golimumab 1/2016</td>
<td>8 months</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>hemorrhagic right cortical insular stroke while on warfarin, bilat thalami and paramedian medullary stroke, no strokes since TNF-blockade in 2007</td>
<td>Y</td>
<td>prior cyclosporine, MMF, cyclophosph; TNF-blockade in 9/2007 initially infliximab then adalimumab 8/2008-3/2012 and then resumed 9/2012 to current, also MTX</td>
<td>98 months</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>at age 16 yrs isolated episode of right vestibular and acoustic neuropathy (? neuronitis); tested prompted by sibling</td>
<td>N</td>
<td>untreated</td>
<td>N/A</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>at 8 yrs internal capsule stroke, at 13 yrs paramedian midbrain stroke, s/p conventional angio</td>
<td>Y</td>
<td>s/p Ritux and steroids; etanercept 2/2016</td>
<td>3 months</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>seizures in the context of PRLES/acute HTN in 2013, f/u normal MRI</td>
<td>N</td>
<td>prior azathioprine and steroids; etanercept 9/2014</td>
<td>20 months</td>
</tr>
</tbody>
</table>
**Results:** Most had lacunar strokes; sometimes these were radiologically isolated; 7/22 patients have not had strokes. Other presentations included retinal artery occlusion, myelitis, epilepsy, behavioral dysregulation and dysexecutive syndrome. Many of these patients had undergone invasive diagnostic testing such as cerebral angiograms and/or brain biopsies. Some patients had large hemorrhagic strokes, in the context of antiplatelet or anticoagulant therapies. Despite varied empiric immunomodulatory treatments, often including prolonged steroids or cyclophosphamide (for presumed childhood primary angiitis of the CNS), breakthrough strokes continued. Since being started on TNF-blockade, none of the 21 treated patients in the NIH cohort have had occurrence of stroke clinically or radiologically, median duration of 20 months (IQR 6-29.5), longest treatment follow-up 8 years.

**Conclusions:** In young patients with lacunar stroke, even without fever, neurologists should consider the diagnosis of DADA2. ADA2 is a growth factor promoting endothelial cell integrity and also development of M1 macrophages, such that deficiency of ADA2 in addition to endothelial cell dysfunction, skews towards a predominance of M2 (inflammatory) macrophages. The treatment implications include avoiding anti-platelets and anticoagulant therapies. TNF is present perivascularly on skin biopsy stains from patients with PolyArteritis Nodosa. TNF-blockade with etanercept has been effective in suppressing the systemic inflammation in DADA2 and moreover, no further strokes have been noted over a median treatment duration of nearly 2 years in this cohort.

**Keywords:** Stroke, Infections/Neuroimmunology, Genetics

### Table 1. Continued

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Gender</th>
<th>Neurological Involvement</th>
<th>STROKE (yes/no)</th>
<th>Immunotherapy (with onset dates for TNF-blockers)</th>
<th>Duration of TNF-blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>M</td>
<td>brainstem and corpus callosum lacunes</td>
<td>Y</td>
<td>prior steroids and azathioprine; etanercept 9/2014 switched to adalimumab 1/2016</td>
<td>20 months</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>placental pathology with umbilical cord vasculitis but normal perinatal course</td>
<td>N</td>
<td>etanercept 3/2016</td>
<td>2 months</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>INO, brainstem and internal capsule lacunes, elevated CSF opening pressure, no fevers</td>
<td>Y</td>
<td>etanercept 4/2016</td>
<td>1 month</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>radiologically isolated lacunar infarcts (corpus callosum and thalamus), s/p muscle biopsy</td>
<td>Y</td>
<td>etanercept 6/2014</td>
<td>23 months</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>first stroke at age 3 years (midbrain), 1/2016 (midbrain), headaches</td>
<td>Y</td>
<td>steroids, etanercept 3/2016</td>
<td>2 months</td>
</tr>
<tr>
<td>24</td>
<td>F</td>
<td>Vasovagal syncope</td>
<td>N</td>
<td>etanercept 12/2015</td>
<td>5 months</td>
</tr>
</tbody>
</table>

**79. Anatomical Venous Variants and Physiological Adaptive Changes in Children with Cerebral Sinovenous Thrombosis**
Kouzmitcheva E (Toronto, Ontario, Canada), Andrade A, Pontigon A, Mathusami P, Shroff M, Moharir M

**Objective:** Cerebral venous vessels have a unique morphology. We aim to describe the frequency of anatomical variants, and physiological changes, in children with CSVT. We hypothesize that these variations impact in the re-distribution of venous drainage in the presence of stressors such as dehydration.

**Methods:** We retrospectively reviewed children (1 month–18 years), with CSVT over 5 years (Jan 2008–Dec 2013). We excluded children with arterial ischemic stroke, trauma, compressive intracranial lesions and systemic venous hypertension. We reviewed for symptoms at presentation, risk factors, sinus involved, parenchymal lesions, antithrombotic therapy, outcome using the Paediatric Stroke Outcome Measure and recanalization rate at follow-up.

**Results:** Thirty-four children were identified. 17 boys (50%), with mean age at CSVT of 13.5 years (0.2–17.6 years). 11 had anatomical variations (32%) vs. 23 (68%) with typical anatomy. These included 6 (54%) children with abnormal sinus morphology (hypoplasia/absence of a major dural sinus), 3 (27%) children with persistent fetal structures and 6 (54%) with prominent collateralization. Most of the cases had > 1 anatomical variant together. Signs of increased intracranial pressure were seen more frequently in children with anatomical variants 7(63%) than in those without 7(30%), although not statistically significant.
5 children (45%) with variants had brain parenchymal involvement vs. 5 (22%) with normal anatomy.

**Conclusions:** The presence of anatomical variants in the cerebral venous structures may be associated with a more severe initial presentation in children with CSVT. Variant venous anatomy may be less efficient in compensating for the obstruction to venous outflow due to thrombosis.

**Keywords:** Stroke, Neuroimaging

80. **Stroke and Headache in a Pediatric Population: Establishing Connections**
**Barmherzig R (Toronto, Ontario, Canada), MacGregor D, deVeber G**

**Objective:** Pediatric arterial ischemic stroke (AIS) is a significant cause of long-term morbidity in childhood. A proposed causal relationship between migraine headache and AIS has been debated in the adult literature; however, there is a paucity of literature regarding the association between pediatric AIS and headache. We aim to determine the frequency and characteristics of post-stroke headache in children, and whether a causal relationship can be determined for migraine-type headaches in pediatric AIS.

**Methods:** This is a single center cohort study of patients diagnosed with acute AIS from 1992-2012 at the Hospital for Sick Children, Toronto, Canada. Data was collected using the Pediatric Stroke Outcome Measure (PSOM) and Pediatric Stroke Recurrence and Recovery Questionnaire (RRQ) until 2015.

**Results:** 411 patients met inclusion criteria. Data regarding the presence or absence of headache was available for 255. Of those, 56% described post-stroke headache, in contrast to the 3-4% frequency of headache in healthy school-aged children. Post-stroke headache was found to be more prevalent in children with a personal or family history of migraine, with high statistical significance ($p < 0.0001$).

**Conclusions:** There is strong suggestion that headache occurs with greater frequency in the AIS pediatric population. The above data will be further analyzed evaluating the characteristics and subtype of headache to determine whether a relationship between migraine headache and AIS can be identified. If determined, the mechanism of this causal relationship will be of considerable interest in managing post-stroke patients and in the ongoing care of children with AIS.

**Keywords:** Stroke, Headache/Migraine

81. **Fetal Vascular Origins of Schizencephaly**
**Khalid R (Kansad City, MO), Krishnan P, Blaser S, Andres K, Miller S, Moharir M, Dlamini**

**Objective:** Schizencephaly is a rare congenital brain abnormality characterized by a cerebral mantle cleft lined by

![FIGURE 1: DWI images of the fetal brain at 21 weeks gestation shows areas of acute diffusion restriction within the right MCA distribution (Abstract 81)](image_url)
heterotopic gray matter, extending from the pial surface to the lateral ventricles. Late first and early second trimester vascular disruption is a proposed pathogenetic mechanism. We present a case of schizencephaly supporting this theory.

Methods: A 27-year-old primigravida mother had abnormal echogenicity detected in the right anterior parietal region of the brain on routine fetal ultrasound at 19-weeks' gestation. Fetal MRI at 21-weeks' gestation demonstrated acute diffusion restriction in the same region in a right middle cerebral artery territory distribution suggestive of ischemic infarction. Additionally, a susceptibility focus was noted in the right fronto-temporal lobes and basal ganglia representing hemorrhagic transformation of infarct. Follow-up MRI at 35-weeks gestation identified focal volume loss in the region of previously documented ischemic injury with a parenchymal cleft extending to the ventricular margin, consistent with open lip schizencephaly. TORCH and thrombophilia screens were normal. MRI at 4-weeks postnatal age showed parenchymal volume loss, porencephaly and schizencephaly in affected regions. The combination of ischemic and hemorrhagic brain injury prompted COL4A1 mutation analysis, which was positive.

Results: To our knowledge, this is the first report linking an acute in-utero ischemic brain injury with subsequent development of schizencephaly. COL4A1 mutation associated capillary fragility likely played a role in the causation of stroke, subsequent schizencephaly and porencephaly.

FIGURE 2: HASTE images reveal increased signal intensity within the entire thickness of the cortical mantle with obscuration of the cortical layers in the affected zone. Abstract 81

FIGURE 3: Serial follow up at 35 weeks gestation reveals focal volume loss in the right cerebral hemisphere with parenchymal cleft extending to the ventricular margin. Abstract 81
Conclusions: Our case supports the theory of vascular disruption leading to in-utero stroke as a pathogenetic mechanism of schizencephaly. COL4A1 testing should be strongly considered in such cases.

Keywords: Stroke, Neonatal neurology, Neuroimaging

82. Pediatric Reversible Cerebral Vasoconstriction Syndrome: A Case Series and Review
Coffino S (New York City, NY), Fryer R

Objective: Reversible cerebral vasoconstriction syndrome (RCVS) is a rare but well-described syndrome in adults. We review cases of pediatric RCVS.

Methods: We present 2 pediatric cases of RCVS and review the previous 10 reported pediatric cases in the literature.

Results: The clinical and radiographic findings in the pediatric cases are similar to adults, including triggers, risk factors, clinical course, prognosis and treatment. Surprisingly, the majority of cases in pediatrics (10 out of 12) occur in adolescent males, as compared to the preponderance of females in adult cases. Triggers include trauma, serotonergic medications, hypertension, exercise and diving or swimming.

Conclusions: Interestingly, several of these triggers point to a possible mechanism behind RCVS as most can lead to increased pressure in cerebral blood vessels triggering an autoregulation response. While the pathophysiologic basis of reversible cerebral vasospasm remains unclear, we suspect that the high incidence in adolescent boys reflects an alteration in cerebrovascular tone due to the presence of androgens, with failure of some vessels to properly vasodilate when the systemic blood pressure returns to normal.

Keywords: Stroke, Neuroimaging, Headache/Migraine

83. Risk Factors for Childhood Stroke in the Kids’ Inpatient Database
Taylor J (Cincinnati, OH), Horn P, Sucharew H, Khouy J

Objective: Childhood stroke is well known among neurologists despite low incidence. The etiologies underlying stroke in children and adolescents are vastly different from the adult population. Mackay and IPSS colleagues proposed a classification system for childhood stroke risk factors. We applied this categorization scheme to describe risk profiles for children hospitalized with and without arterial ischemic stroke (AIS).

Methods: The 2000 and 2009 Kids’ Inpatient Database (KID) were used for analysis. AIS were identified by predefined discharge ICD9 codes. We adapted a published list of risk factors (Lo et al.) to fit the IPSS categories of atherosclerosis, cardiac, chronic systemic, acute systemic, chronic head/neck, acute head/neck, atherosclerosis, and other. The number of risk factor classes per child was counted; a class was counted if at least one of the factors in the class was present.

Results: The weighted frequency of AIS was 795 in 2000 and 1157 in 2009 both less than 0.02% of the hospitalized
84. Predicting Ischemic Risk using Blood Oxygen Level Dependent (BOLD) MRI in Children with Steno-occlusive Arteriopathy

Dlamini N (Toronto, Canada), deVeber G, Armstrong D, Kirkham F, Logan W

Objective: Arteriopathy, including Moyamoya (MM), is common in childhood stroke and predicts recurrence and poor outcome. The ischaemic risk (IR) attributable to each arteriopathy is variable and not reliably quantifiable. Cerebrovascular reactivity, a marker of brain vascular reserve, predicts IR in adults. Our objective was to investigate whether qualitative hypercapnic challenge BOLD-MRI CVR (CVR) predicts IR in children with arteriopathy.

Methods: Children with MM and Non-MM arteriopathy were enrolled and had MRI/MRA brain and CVR

Results: Forty seven (25 male; 37 MM: 23/37 bilateral, 6/37 right, 8/37 left MM; 10 Non-MM: 4 bilateral, 6 unilateral/Transient cerebral arteriopathy) were studied. Mean age MM diagnosis (8.6 years) was higher than Bilateral Non-MM (3.7 years) and Unilateral Non-MM groups (4.5 years), p = 0.02, p = .012 respectively. Impaired CVR was limited to the infarct zone and adjacent white matter in Unilateral Non-MM whereas, as in adult studies, it went beyond the region of angiographic abnormality in MM. CVR was worse in MM compared to Non-MM; worse in the right hemisphere in MM and Bilateral Non-MM; and worst in the Radiation vasculopathy-MM and Chromosomal-MM groups. CVR was significantly affected by comorbidity ($\chi^2(4) = 10.5$, p = 0.021). MM laterality and CVR abnormality was predominantly left sided in the Neurofibromatosis-1-MM group.

Conclusions: The greater impairment of CVR in the MM compared with Non-MM; right hemisphere compared with left; and Chromosomal compared with other MM groups is suggestive of varying levels of IR not explained by the presence of arteriopathy alone. BOLD-MRI CVR may predict IR.

Keywords: Stroke, Neuroimaging

85. Successful Mechanical Embolectomy in Five Pediatric Stroke Cases

Pergami P (Washington, DC), Khan M, Duru B, Boo S, Carpenter J

Objective: Mechanical embolectomy in pediatric stroke has been described through case reports and case series, due to limited options for clinical trials in this rare disease. New RCT data supporting endovascular therapy in selected adults resulted in updated guidelines including a statement that this therapy may be reasonable in children. All single-arm trials conducted so far using FDA–cleared devices excluded patients <18, and therefore there remains a lack of safety and efficacy data in children. Our aim is to contribute to increasing knowledge about used of intravascular intervention in pediatric stroke.

Methods: We retrospectively identified five pediatric arterial ischemic stroke (AIS) cases (age 7-17) treated at West Virginia University with mechanical intervention.

Results: One patient had basilar artery (BA) occlusion, and four had large, occlusive middle cerebral artery (MCA) and ICA/MCA clots (TIMI 0). Initial NIH stroke scale ranged form 15 to 22. Mechanical embolectomy resulted in recanalization in all five cases (TIMI 2 to 3), without significant complication related to the procedure. Four patients had good outcome at 3 months with Modified Rankin Scale = 1-2. One patient with congenital cardiac abnormalities had multiple episodes of ventricular arrhythmia and the parents decided to withdraw care. This complication was not related to the procedure.

Conclusions: Mechanical embolectomy can be an acceptable approach in older children with large cerebral artery occlusion, but the risk-to benefit ratio remains to be determined in this population. Pediatric patients undergoing any type of acute revascularization treatment should be included in national or international registries.

Keywords: Stroke
false-negative results. Our results suggest that MRI is indicated whenever fetal stroke is suspected. The actual incidence of this condition may be underestimated due to limited availability of fetal MRI. Acknowledgements: FASO Russia (project #0333-2014-0003) for data acquisition, Russian Science Foundation (project #14-35-00020) for image analysis.

Keywords: Stroke, Neuroimaging, Neonatal neurology

NEUROIMAGING

87. Role of Tryptophan Metabolism in Predicting Long-Term Tic Outcome in Children with Tourette Disorder: Evaluation with Serial α-[11C]-methyl-L-tryptophan Brain Positron Emission Tomography

Kumar A (Detroit, MI), Behen M, Pilli V; Roberts M, Chugani H

Objective: Previously, we reported cortical/subcortical abnormalities of tryptophan metabolism, assessed with α-[11C]-methyl-L-tryptophan (AMT) positron emission tomography (PET) in children with Tourette Disorder (TD). We found an association between pattern of AMT uptake in the fronto-striatal-thalamic circuit and tic severity. Although 75% of children outgrow their tics by early adulthood, there are currently no predictors of tic outcome. We repeated AMT-PET scans in adults, previously scanned as children, to determine whether abnormalities seen in childhood persisted and to correlate them with tic outcome.

Methods: Four patients with diagnoses of TD (mean age=11.6 ± 3.2 years; 3 males), underwent repeat neuropsychological evaluations and AMT-PET at the mean age of 19.6 ± 2.9 years. The images were analyzed visually for AMT increases/decreases in prefrontal cortex, caudate, putamen and thalamus and quantitatively using regions-of-interest analysis to determine asymmetry index.
88. Recipe-Based Creation of a NeuroDebian Virtual Machine Lowers the Cost of Entry for Neuroimaging Research in the Clinical Setting

Cohen A (Rochester, MN), Kenney-Jung D, Batha H, Tillemann J

Objective: The past two decades have seen tremendous advances in neuroimaging capabilities as well as maturation of freely available software for neurologic research. While not FDA-approved for clinical use, these have capabilities that are often more flexible than those available in day-to-day clinical practice. Using this software, however, can be daunting for clinical trainees, requiring: 1) access to preconfigured computers, 2) availability of local expertise, online tutorials, or off-site workshops, and 3) a basic level of Unix/command-line knowledge. Here, we present our efforts to address the first of these challenges.

Methods: We created a recipe and video tutorial for rapidly building a virtual computing environment that conforms to current research standards and can exist within a HIPAA-compliant system. We used freely available tools, including NeuroDebian and Oracle’s VirtualBox, and generated a list of standard commands and “connector” scripts to simplify the visualization and analysis of single subject data.

Results: A standardized computing environment can be easily created within a HIPAA-compliant system without compromising network security or requiring new hardware. This allows for retrieval of clinical imaging data from DICOM nodes (where permitted), conversion to standard research file formats, and visualization/quantification of individual patients’ cortical and subcortical anatomy using FSL, FreeSurfer, and/or the recently created Connectome Workbench

Conclusions: Here, we present one approach to overcoming the most significant barrier to using modern neuroimaging techniques, i.e., creation of a Linux/Unix/OSX environment and neuroimaging software configuration. Our hope is that this generates broader research interest in clinical neuroimaging and the creation of novel clinical/translational research questions.

Keywords: Neuroimaging, History/Teaching of Child Neurology, Translational/experimental therapeutics
spectroscopy (MRS) how the biochemical levels of N-acetylaspartic acid, glutamine, glutamate, creatine, choline, myoinositol, lactate, and lipids vary from the norm in a child experiencing HA.

**Methods:** This was an IRB approved, retrospective study in which 8 patients with genetic defects in the urea cycle were identified. A chart review was conducted to collect MRI, MRS, and plasma glutamine and ammonia levels.

**Results:** MRS data showed that brain levels of myo-inositol are decreased in patients with hyperammonemia. Levels of lactate, glutamate, glutamine, choline, and lipid are increased. MRI data showed that areas of the brain most affected by high ammonia are the peri-insular region, the globus pallidus, the brainstem, and the frontal, temporal, and parietal lobes.

**Conclusions:** The findings indicate distinct chemical footprints occurring in the brain during HA. MRI data suggest that there are distinct regions of the brain that are more sensitive to the effects of HA and can be used to identify patients at risk for ongoing neurological damage and can be used to make treatment decisions.

**Keywords:** Neuroimaging, Genetics, Translational/experimental therapeutics

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**91. Clinical Correlates of Calcified Brain Volume in Sturge-Weber Syndrome**

**Juhasz C (Detroit, MI), Pilli V, Behen M, Hu J, Xuan Y, Chugani H**

**Objective:** Calcification is common in the affected hemisphere of children with Sturge-Weber syndrome (SWS). However, the role of calcification in SWS neuro-cognitive progression is not well understood. In this study we used longitudinal MRI with susceptibility-weighted imaging (SWI) to: (i) quantify changes in calcified brain volume during the early SWS disease course, and (ii) evaluate if calcified brain volume is associated with clinical seizure or cognitive variables.

**Methods:** Fifteen children (median age: 3.5 years) with unilateral SWS underwent a baseline and follow-up MRI including SWI (mean follow-up: 20 months). All children had a formal neuropsychology evaluation within 24 hours of the imaging. Volume of calcified brain tissue was measured on SWI images both at baseline and follow-up and correlated with clinical variables.

**Results:** Nine patients had calcified brain regions on baseline and 11 on follow-up SWI. In these 11 children, mean calcified brain volume increased from 1,530 mm³ to 2,470 mm³ during follow-up (p = 0.03, Wilcoxon test); the volume increase was more robust in those with younger age at epilepsy onset (Spearman’s rho = –0.62, p = 0.04). Larger calcified brain volume at baseline was associated with longer duration of epilepsy and may predict poor cognitive functions in SWS.

**Keywords:** Neuroimaging, Cognitive/Behavioral Disorders, Epilepsy

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**92. Decreased White Matter Integrity of the Corpus Callosum in Children with NF1 Compared to Age-Matched Controls**

**Campen C (Palo Alto, CA), Monje M, Yeom K**

**Objective:** Children with NF1 have neurocognitive challenges that are not organ specific, require significant extrapolation, or are not organ specific. As children have many decades of expected life ahead of them, repeated use of ionizing radiation is of special concern. Moreover, these systemic therapeutics may be due to alterations in oligodendroglial lineage precursor differentiation. Investigation of DTI in other WM tracts and in neoplasms of children with NF1 is warranted.

**Keywords:** Neuroimaging, Cognitive/Behavioral Disorders, Brain Tumors/Oncology

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**93. Continuous, Bedside Monitoring of the Vulnerable Neonatal Brain with Diffuse Optics**

**Busch D (Philadelphia, PA), Ko T, McCarthy A, Lynch J, Mavroudis C, Licht D**

**Objective:** The neonatal brain undergoes substantial development during childhood, generating considerable metabolic demand. If the oxygen supply to the brain is insufficient to meet these demands, irreversible brain damage may result. Currently, clinicians lack tools to directly and quantitatively monitor cerebral oxygen metabolism and therefore rely on systemic proxies. Unfortunately, these tools have are not organ specific, require significant extrapolation, or are otherwise inadequate. As children have many decades of expected life ahead of them, repeated use of ionizing radiation is of special concern. Moreover, these systemic therapeutics may be due to alterations in oligodendroglial lineage precursor differentiation.
parameters often change quite slowly, preventing clinicians from dynamically following the efficacy of interventions. We and our collaborators seek to develop non-invasive tools for continuous bedside monitoring of cerebral perfusion, metabolism, and health.

Methods: Diffuse optical and correlation spectroscopies provide continuous measurement of cerebral blood oxygenation, volume, and flow without ionizing radiation at a patient’s bedside utilizing a diffusion approximation to the radiation transport equation.

Results: In this contribution, we review work at the June and Steve Wolfson Laboratory for Clinical and Biomedical Optics designing, developing, and translating optical tools into clinical use in the context of the vulnerable pediatric brain. Unlike commercially available cerebral oximeters, we rapidly quantify hemodynamic parameters continuously throughout routine care and interventions.

Conclusions: We have applied these tools to children with severe congenital heart disease, on extra-corporeal membrane oxygenation therapy (ECMO), extremely premature infants, pediatric stroke, and sleep apnea. The unique insights provided by diffuse optical tools have the potential to significantly impact pediatric care.

Keywords: Neuroimaging

94. Cerebral Blood Flow Response to Orthostatic Challenges in Healthy and Diseased Populations

Objective: Management of ischemic stroke is focused on maximizing cerebral blood flow (CBF) to minimize further damage to the ischemic penumbra. However, management strategies are generally empirical due to the absence of bedside CBF monitoring. For example, most stroke patients are kept flat after stroke onset to increase perfusion pressure. This position can be uncomfortable and increase the risk of aspiration, a particular concern in children. Previous studies have shown that CBF is generally higher in the supine vs. sitting position. This is consistent with guidelines that a patient should be kept supine as much as possible. However, prior work demonstrated CBF response to supine positioning is heterogeneous with ~20-25% showing a paradoxical decrease when the head-of-bed is lowered from an elevated position. A supine position may be detrimental to these subjects.

Methods: In this study, we describe findings from 126 subjects: stroke patients, chronic obstructive sleep apnea patients and controls 5 to 93 years of age. Additionally, we study alterations in final supine CBF due to temporary head-of-bed elevation, followed by a return to a supine position.

Results: We observe lower blood flow in the supine, compared to the seated, position in ~25% of subjects across a wide range of ages and diagnoses. Further, we observe that postural manipulation raises blood flow.

Conclusions: Bedside monitoring of microvascular cerebral blood flow can identify patients for whom the standard of care supine position is deleterious. Additionally, the suggestion that postural manipulation can itself raise cerebral blood flow rates further investigation.

Keywords: Neuroimaging

95. It is Worth a Second Look - MRI Findings in Vitamin Responsive Neonatal Seizures
Appalla D (New Brunswick, NJ), Venkat A

Objective: Pyridoxine dependent seizures (PDE) due to deficiency of α-aminoadipic semialdehyde dehydrogenase (antiquitin) encoded by ALDH7A1 is a rare cause of early onset epileptic encephalopathy. Less than 100 cases have been reported. Specific neuroimaging criteria for diagnosis have not been established. Our case adds to the literature of brain MRI findings with PDE.

Methods: A term baby with normal perinatal history developed early onset refractory electro-clinical seizures...
requiring treatment with Phenobarbital, Phenytoin and Lev-
etiracetam. Routine work up for neonatal seizures was nega-
tive. MRI of the brain showed no evidence of hypoxic ischemic encephalopathy but revealed a mega cisterna magna, mild inferior cerebellar vermian hypoplasia and thinning of corpus callosum. IV pyridoxine (B6) treatment resulted in cessation of clinical seizures and improvement in EEG background. A 76 gene focus epilepsy panel identified a pathogenic homozygous variant in the ALDH7A1 gene and established a definitive diagnosis of PDE. Repeat imaging showed interval prominence of the subarachnoid spaces and increase in size of the ventricular system consistent with atrophy.

Results: Significant MRI findings was present in our patient similar to what has been described. Mega cisterna magna and cerebellar hypoplasia have been described in 5 other patients in association with PDE. Other documented findings include gray and white matter cortical atrophy, thinning of the corpus callosum and progressive brain atrophy.

Conclusions: Vitamin responsive seizures should be high in the differential diagnosis if such characteristic MRI findings are recognized. Identifying a definitive genetic basis is valuable for estimating prognosis, recurrence risks and specific treatment choices.

Keywords: Neuroimaging, Epilepsy, Genetics
2) begin to evaluate its ability to predict neurologic progression.

Methods: TCD was performed either once (n=5, 2F, 8 mos-9 yrs) or twice in one day (n=9, 5F, 3 yrs-20 yrs). Reproducibility was evaluated using Spearman’s correlation between the two sets of measurements done on the same day on the same subjects (n=9, see Figure 1). Percent side-to-side differences (PSSDs) of reproducible TCD values for participants with two sessions in one day were averaged for correlations with SWS clinical neuroscores one year later.

Results: Figure 1 shows the three reproducible TCD measurements when comparing same-day sessions: MCA velocity, PCA velocity, and ACA pulsatility index. Lower PCA velocity on affected brain hemisphere was correlated with worse hemiparesis score (r=0.81, p=0.027, n=7). Lower ACA pulsatility index (PI) on affected side was correlated with worse seizure frequency one year after TCD (r=-0.72, p=0.029, n=9). Lower ACA-PI on affected side was significantly associated with uncontrolled seizures one year after TCD (Fisher’s Exact, p=0.0476, two-tailed). Lower MCA velocity on affected side was correlated with a worsening of seizure score between time 1 and 2, however not statistically significant (r=-0.69, p=0.06, n=8).

Conclusions: These data suggest that MCA-V, PCA-V, and ACA-PI are reliable measures with potential clinical value in SWS subjects. Larger studies are needed to determine the utility of TCD as a safe, non-invasive tool for predicting neurologic progression in SWS and aiding clinical care.

Keywords: Neuroimaging, Epilepsy, Stroke

Percent side-to-side differences (PSSDs) were calculated between the affected and unaffected side of the brain for each subject as their own control. Middle Cerebral Artery (MCA); Distal Internal Carotid Artery (DICA); Posterior Cerebral Artery (PCA); Anterior Cerebral Artery (ACA); Velocity (V); Pulsatility Index (PI); Not all TCD measurements were able to be collected for each participant at both time points due to subject cooperation. A clinical severity score (frequency of seizures, extent of hemiparesis, assessment of visual field cut, degree of cognitive functioning, and total) was assigned for each participant approximately the same day as TCD and approximately one year later.

97. Brain Abnormalities in Children with Congenital Cytomegalovirus Infection Identified through Newborn Hearing Screening

Hranilovich J (Salt Lake City, UT), Park A, Bale J

Objective: To characterize the brain magnetic resonance imaging (MRI) findings in children with congenital cytomegalovirus (CMV) who first present to care due to hearing deficits. Background: Utah has passed legislation requiring all infants who fail their newborn hearing screen to be tested for congenital CMV infection. Thus, there are increasing numbers of CMV infected infants identified because of hearing deficits. The brain MRI findings in this group have not been characterized to date.

Methods: Retrospective medical record review identified infants and children who were found to have congenital CMV infection after a failed newborn hearing screen and subsequently underwent brain MRIs.

Results: Fifteen infants and children were identified. The age at imaging ranged from 0.8 to 130 months with a median of 2 months. Hearing loss was mild in 20%, moderate in 33%, severe in 13% and profound in 33%. White matter abnormalities were found in three (20%) of the subjects. On record review two were small for gestational age (SGA), and one had facial petechiae at birth. The two SGA infants also had polymicrogyria.

Conclusions: Although most CMV-infected infants and children had normal MRIs, white matter and other brain

FIGURE 1: Analysis Flowchart (Abstract 96)
abnormalities can be present in those identified by hearing screening. Such children may represent a unique subgroup of CMV infected children, differing from those who are considered asymptomatic at birth and those who are overtly symptomatic.

**Keywords:** Neuroimaging, Neonatal neurology, Infections/Neuroimmunology

98. Preliminary Evidence of Contralateral Pippocampal Network Reorganization Associated with Post-operative Memory Decline in Children with Temporal Lobe Epilepsy

*Kim J (Sterling Heights, MI), Juhasz C, Asano E, Lee Y, Chugani H, Jeong J*

**Objective:** To investigate if axonal reorganization pattern of contralateral hippocampal network is associated with compensatory mechanism of cognitive memory after temporal lobe resection.

**Methods:** 3-Tesla DTI data of 7 children with focal epilepsy (age: 11.0 ± 3.5 years, 4/3 with left/right temporal lobe resection including hippocampus) and 33 healthy controls (age: 10.0 ± 4.5 years) were acquired using 55 encoding gradient directions at b-value=1000 sec/mm^2. Average months of pre-/post-operative DTI were 4.1/8.2, respectively. All 7 epilepsy children underwent pre-/post-operative memory function evaluation within a week of DTI acquisition. In contralateral hippocampus on each DTI, betweenness centrality (which indicates the number of neighboring paths that pass through the hippocampus) was calculated to evaluate the potential association between post-operative increase of this DTI parameter and memory preservation.

**Results** The postoperative betweenness values of contralateral hippocampus were significantly higher in comparison to pre-operative values and also healthy control values (One-way ANOVA, F=4.02, p=0.025). Such increases were apparent in 5 of 7 epilepsy children; the most prominent increases occurred in 2 memory-preserved patients, whereas milder increases were seen in 3 children with only mild post-operative memory decline, suggesting a significant association between post-operative increase in betweeness and memory preservation (r=0.76, p=0.046). Interestingly, larger resection volume was associated with greater increase in post-operative betweenness value (r=0.79, p=0.036).

**Conclusions:** Temporal lobe resection including hippocampus may alter the number of neighboring paths in the contralateral hippocampal network to compensate for potential memory deficit; betweeness value on DTI may be a biomarker for the neural substrate of memory preservation.

**Keywords:** Neuroimaging, Epilepsy, Translational/experimental therapeutics

99. White Matter Differences in Children with Developmental Coordination Disorder

*Zwicker J (Vancouver, British Columbia), Brown-Lum M, Fitzpatrick K, Kim D, Oberlander T, Rauscher A, Giaschi D, Bjornson B*

**Objective:** Developmental coordination disorder (DCD) is a neurodevelopmental disorder of unknown etiology characterized by poor motor coordination and difficulty learning motor skills. Our objective was to extend our pilot work (Zwicker et al., 2012) using diffusion tensor imaging (DTI) to further characterize white matter differences in children with and without DCD. We hypothesized that the corticospinal tract, posterior thalamic radiations, corpus callosum and cerebello-cortical pathways would be implicated in the disorder.

**Methods:** DTI data were collected from 28 children between 8-12 years of age (12 DCD; 16 TD) who had an MRI scan at a mean age of 10.12 years. Voxel-wise statistical analysis of FA data using tract-based spatial statistics (TBSS) (Smith, 2006) was conducted, using a two-group comparison design matrix with age and attention as covariates. Data were corrected for multiple comparisons across space and statistical significance was set at p<0.05.

**Results:** Mean FA in TD children was greater compared to children with DCD in regions associated with sensorimotor function: cerebellar peduncle, cerebral peduncle, corpus callosum (particularly the splenium), corticospinal tract, and posterior limb of the internal capsule.

FIGURE 1: TBSS results. A: cerebellar peduncle B: corpus callosum, cerebellar peduncle C: corpus callosum, corticospinal tract, cerebral peduncle D-E: posterior limb of the internal capsule, corpus callosum (Abstract 99)
Conclusions: Our findings suggest that children with DCD show altered microstructural development in white matter pathways associated with sensorimotor function. Our next steps are to determine predictors of white matter development in these regions and whether rehabilitation can improve brain development and motor function.

Keywords: Neuroimaging, Movement Disorders

100. MRI Biomarker and Natural History in Alexander Disease

Objective: To develop an MRI score in AxD as a prognostic biomarker for future clinical trials.

Methods: MRIs from individuals with Type I AxD were scored according to a custom modified Loes score. A binary outcome (poor functional status = Gross Motor Function Classification System (GMFCS) > 2) was assigned at time of MRI and after > 2 years. Logistic binary regression established best predictive models.

Results: 20 individuals with Type I AxD with MRI and clinical data were studied. Median age at onset was 10.5 months (2-48 months), and time of initial MRI was 22 months (4-242 months). The majority of scored criteria were present in all individuals regardless of functional

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<td>INTERNALCAPSULE*</td>
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<td>20% 0.013</td>
</tr>
<tr>
<td>. CENTRAL</td>
<td>Bs% 0.089</td>
<td></td>
<td>5.Nigra</td>
<td></td>
<td>65%</td>
</tr>
<tr>
<td>. SUBCORTICAL*</td>
<td>15% 0.038</td>
<td></td>
<td>N.Gracilis</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>. CE (N=12)</td>
<td>25% 0.005</td>
<td></td>
<td>N. Olivary</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Occipital</td>
<td>80%</td>
<td></td>
<td>Periaqueductal Gray Matter</td>
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<td>70%</td>
</tr>
<tr>
<td>. periventricular</td>
<td>50%</td>
<td></td>
<td>. Swelling</td>
<td></td>
<td>45%</td>
</tr>
<tr>
<td>. central</td>
<td>75%</td>
<td></td>
<td>CE (N =12)</td>
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<td>17%</td>
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<tr>
<td>SUBCORTICAL*</td>
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<td></td>
<td>Hypothalamus</td>
<td></td>
<td>95%</td>
</tr>
<tr>
<td>. CE (N=12)</td>
<td>8% 0.141</td>
<td></td>
<td>. Swelling</td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>Corpus Callosum</td>
<td>75%</td>
<td></td>
<td>Garlands</td>
<td></td>
<td>90%</td>
</tr>
<tr>
<td>. SPLENIUM ATROPHY</td>
<td>25% 0.069</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optic radiations</td>
<td>75%</td>
<td></td>
<td>Any CE (N=12)</td>
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<td>92%</td>
</tr>
<tr>
<td>Optic tracts</td>
<td>15%</td>
<td></td>
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</table>
outcome. Twelve MRI features were found to correlate with functional outcome \((p<0.15)\). A subset of 4 points, the AxD MRI scale, was established as a predictive model for functional disability: subcortical white matter T2 abnormalities in the temporal and frontal white matter, the internal capsule and basal ganglia atrophy. AxD MRI Scale scores \(\geq 2\) are correlated with poor functional outcomes at the time of MRI, and more than 2 years later.

**Conclusions:** Specific features of the Loes score (developed for Adrenoleukodystrophy) involving the subcortical white matter, the projection tracts and the basal ganglia were correlated with functional disability in AxD, predictive of short and long term functional outcomes.

**Keywords:** Neuroimaging

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**TABLE 2. Best MRI Predictive Model of Poor Functional Status in Alexander Disease (see Figure 2 for examples) (Abstract 100)**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Computer Involvement of Anterior Temporal Subcortical White Matter (1 point)</td>
<td></td>
</tr>
<tr>
<td>Computer Involvement of Frontal Subcortical White Matter Involvement (1 point)</td>
<td></td>
</tr>
<tr>
<td>Computer Involvement of Internal Capsule (1 point)</td>
<td></td>
</tr>
<tr>
<td>Basal Ganglia Atrophy (1 point)</td>
<td></td>
</tr>
</tbody>
</table>

Total possible points \(4\)
- If \(>2\) points, poor functional outcome (GMFCS>2): Prediction of GMFCS >2 \((N=20)\), at time of MRI: Sensitivity 78%, Specificity 100%, Correct Classification 80%
- Prediction of GMFCS >2 \((N=n)\), several years after MRI (median 5 year, range 2.56 years after MRI): Sensitivity 67%, Specificity 100%, Correct classification 73%

---

**FIGURE 1:** Gross Motor Functional Classification System (GMFCS)(5) demonstrating levels of function in children > 2 years associated with the scale; a slightly different functional scale is in place for children < 2 years appropriate for developmental level. Images: Cerebral Palsy Affiance, https://www.cerebralpalsy.org.au/what-is-cerebral-palsy/severity-of-cerebral-palsy/gross-motor-function-classification-system/

**FIGURE 2:** MRI Scoring in Alexander Disease. T2 weighted MRI images in individuals with GFAP mutations \((A=$LD_{oa54}$, 6 yo male, $B=LD_{oa35}$, nmo female, $C=LD_{0309}$ 4mo female, $D$ and $E=LD_{0270}$, 15mo female, and $F=LD_{0168}$, 20 mo female). Demonstration of involvement of the anterior temporal subcortical white matter (small white arrow, spared in $A$ and involved in $D$), the frontal subcortical white matter (small black arrow, spared in $B$ and involved in $E$), the internal capsule (long white arrow, spared in $B$ and involved in $C$) and the basal ganglia (asterisk, swollen and non atrophic in $C$ and atrophic in $F$) (Abstract 100)

**FIGURE 1:** (Arterial spin labeling measurements) (Abstract 101)
and imaging findings in atypical migraine with aura in children.

**Methods:** Retrospective review was performed of patients with atypical migraine at a single institution. All patients were evaluated with a stroke-protocol brain MRI within 12 hours of symptom onset. We assessed clinical symptoms, timing of MRI from onset of symptoms, and headache severity, when available. The MRI modalities included quantitative analysis of diffusion weighted imaging, susceptibility weighted imaging, non-contrast MR angiography and arterial spin labeling to assess cerebral blood flow (image 1).

**Results:** From 2012 to 2016, 7 patients met eligibility criteria. A strong linear trend was found between time of onset and relative perfusion difference between hemispheres; measurements obtained with closer proximity to symptom onset demonstrated relative hypoperfusion; measurements with longer latency showed hyperperfusion (image 2). Measurements suggesting hypoperfusion in the affected hemisphere were accompanied by SWI changes showing prominence of venous structures indicative of deoxygenation. MRA revealed cutoff of the distal branches of the MCA on the affected side in all cases with relative hypoperfusion (image 3).

**Conclusions:** Our results are consistent with current hypotheses of hypoperfusion and reperfusion in migraine imitating stroke. Systematic use of multimodal imaging techniques offers the opportunity for improved understanding of the time course of perfusion recovery accompanying symptoms in these unusual patients with complicated migraine. Detailed quantification of the perfusion recovery profile may identify patients who are more likely to have identifiable channelopathies or increased risk of future ischemic stroke.

**Keywords:** Neuroimaging, Headache/Migraine, Stroke

102. Correlation of Cerebral Artery Growth and Biometric Parameters in Healthy Children

**Taylor J** (Cincinnati, OH), Chang M, Nguyen T, Linscott L, Vadivelu S, Zhang B, Abruzzo T

**Objective:** Arterial size and tortuosity is an important biomarker of cerebrovascular disease. Establishing diagnostic criteria for pathological enlargement or narrowing requires knowledge of the normal range of metrics across different age groups.

**Methods:** Patients who underwent MRI for headache or seizure without structural anomaly of the brain or cerebral vasculature were selected for analysis. Screening of the medical record excluded confounders to normal vascular development (e.g., congenital heart defect). Biometric data including age, sex, height, weight, and head circumference acquired at the time of imaging were recorded. The luminal diameter of the basilar artery and cavernous internal carotid arteries was measured in axial and coronal planes on T2 weighted images, and the average luminal diameter was calculated for each vessel. Age-related changes in absolute lumen diameter and lumen diameter relative to patient-specific biometric data was then analyzed according to age and compared with standard growth curves.
Intracranial Arterial Growth During Childhood

Average luminal diameter of cavernous carotid (●, n=590) and mid-basilar artery (■, n=293) shown with standard deviation over time. Dashed lines show Nellhus 50% head circumference for age (—— male —— female).

FIGURE 1: Abstract 102

Results: Data were obtained on 295 children ranging in age from 3 days to 18 years. Comprehensive patient-specific biometric data was collected at imaging when available. Figure 1 shows absolute and relative lumen diameter for intracranial arteries over time contrasted against the Nellhus standard head circumference curve. Basilar arterial lumen size stabilizes after 2-4 years while carotid growth proceeds into the second decade.

Conclusions: The diameter of normal cerebral arteries correlates closely with age and head circumference. Normative data can be used to establish diagnostic criteria for abnormally large or abnormally small cerebral arteries in children with suspected cerebral arteriopathies.

Keywords: Neuroimaging, Stroke

103. Microstructural White Matter Abnormalities in Isolated Ventriculomegaly Decrease During Pre- and Post-Natal Brain Maturation

Korotyshkevskaya A (Novosibirsk, Russian Federation), Karganova A, Savolov A, Yarnyk V

Objective: Isolated ventriculomegaly (IVM) is a common perinatal brain abnormality potentially associated with delayed neurodevelopment. Recent studies utilizing diffusion-based MRI identified microstructural changes in developing white matter (WM) in the presence of IVM. The goal of this study was to compare temporal trajectories of both fetal and post-natal WM maturation between normal controls and subjects with IVM.

Methods: Diffusion-weighted MRI was performed on a 1.5T MRI scanner for 22 fetuses and 16 children with IVM, 24 control fetuses, and 42 control children. Apparent diffusion coefficient (ADC) was measured in the pons, thalamus, frontal and occipital WM, and cerebellum. Distinctions between controls and IVM were assessed across four age groups (fetuses with gestational age of 20-27 and 28-35 weeks and children with age ranges of 0-2 and 2-6 years) using ANOVA.

Results: ADC significantly (p<0.001) decreased with age in both control and IVM groups. Significant (p<0.05) increase of ADC in IVM compared to controls was found in frontal and occipital WM for all age groups except for children of 2-6 years. The mean difference in ADC in cerebral WM between IVM and controls declined with age from 0.08 to 0.02x10^{-3} mm^2/s.

Conclusions: Microstructural WM abnormalities associated with IVM are more pronounced in the fetal brain and decrease with maturation. Spatial-temporal patterns of an increased ADC in IVM suggest that it may be related to edema or alterations in axonal development and is unlikely to be associated with myelination. Acknowledgements: FASO Russia (project 0333-2014-0003) for data acquisition, Russian Science Foundation (project # 14-35-00020) for image analysis.

Keywords: Neuroimaging, Neonatal neurology

104. Aberrant Reorganization of Inter-Hemispheric Connections After Traumatic Brain Injury

Pergami P (Washington, DC), Nanavati T, Lewis J, Frum C

Objective: An 11-year-old boy with severe traumatic brain injury developed an abnormal gait pattern with flexion/abduction of the non-affected leg while running (video) after an intense rehabilitation regimen. Using multimodal MRI methods we investigated his brain motor functional reorganization in order to explain the mechanism of his gait abnormality. We hypothesized: a) an aberrant activation of the non-affected hemisphere during high-demand task of the affected M1; or b) a movement-induced dystonia.

Methods: For fMRI acquisition, a three-minute video depicting age/gender-equivalent subject standing, walking, and running was filmed; using a block paradigm, the patient viewed four consecutive runs of the video. Resting state functional connectivity (rs-fcMRI), and DTI data were also obtained.

Results: Prominent activation of the leg area of non-affected (right) M1 and minimal activation of the affected (left) M1 was evident while watching ‘run’ action versus ‘stand’. Activation of the VLPFC was observed in the less-affected hemisphere.

Conclusions: The aberrant reorganization of the cortical motor area resulted in abnormal activation of the intact hemisphere for tasks of high-demand such as running, and overflow of signal from the non-affected to the affected side. VLPFC activation during a simple functional task reflects recruitment of regions involved in redirection of higher-complexity tasks and in go-no-go action; we speculate that this could suggest an attempt to limit the overactivity of the non-affected hemisphere. No activation or abnormal connectivity between cortex and basal ganglia was observed, excluding movement-activated dystonia. Combination of advanced MR imaging can provide insight into functional reorganization and guide therapeutic approach.

Keywords: Neuroimaging, Movement Disorders

105. Cortical Thickness and Cerebrovascular Reactivity: Potential Biomarkers of Hypoperfusion Injury in Moyamoya

Dlamini N (Toronto, Canada), Poublanc J, Kirkham F, Dirks P, Logan W, deVeer G

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Objective: In children with moyamoya (MM) and no stroke, chronic hypoperfusion may result in a penumbral-like state causing apoptosis, cell involution and neuronal loss with consequent thinning of the cortical rim. Cerebrovascular reactivity (CVR) is an indicator of cerebrovascular reserve and tissue at risk of ischaemia. Adult studies have demonstrated an association between CVR abnormality and cortical thickness. Hence our objective was to determine whether in children with MM, abnormality in CVR is associated with reduced cortical thickness.

Methods: Using Freesurfer, cortical thickness was measured on high resolution 3D T1 anatomic sequences in children with MM and no cortical infarcts on FLAIR MRI. Association between CVR and cortical thickness was explored.

Results: Twelve children (7 male, 10 unilateral MM; mean age at diagnosis 7.93 ± 3.47 years; mean age at first CVR 9.05 years ± 4.29 years; 7 white matter ischaemic injury (WMI); 9 revascularization surgery (surgery)) were included. Five had headache; 3 were asymptomatic; 1 each had seizures, paroxysmal sensory symptoms, movement disorder or transient ischaemic episodes. Five (5/7; 71%) with no surgery preceding first CVR had decreased cortical thickness in the hemisphere with impaired CVR and MM. Of those with serial measures cortical thickness increased in 3/5 with, and decreased in 2/2 without surgery. However, there was no significant association between surgery nor WMI and cortical thickness (p = 0.43; p = 0.143).

Conclusions: CVR abnormality and cortical thickness may be useful biomarkers of hypoperfusion injury in MM. However, further exploration of the predictors and mechanisms underpinning the apparent cortical thinning and post-surgical reconstitution is required.

Keywords: Neuroimaging, Stroke

106. Patterns of Intracranial Venous Thrombosis on MRI in a Cohort of Neonates
Buch K (Boston, MA), Caruso P, Krishnamoorthy K, Duhaime T, Chang J, Kim G, Rincon S

Objective: The imaging appearance and clinical prognosis of neonates with intracranial venous thrombosis (IVT) is varied. The purpose of this study was to investigate IVT and associated findings in a cohort of neonates undergoing MR imaging.

Methods: Between 2006-2016, 27 neonates undergoing MR imaging of the brain on either a 1.5T or 3T scanner were identified to have IVT. The extent of IVT and presence of hydrocephalus, intraventricular hemorrhage (IVH), parenchymal hemorrhage, extra-axial hemorrhage, cerebral edema, and infarction were recorded.

Results: 17 males and 10 females with a mean gestational age of 37 weeks (range 26-41 weeks) were included. The majority of babies were scanned at 1-10 days of life (average = 10.2 days, range 0-66 days). Gestational age did not significantly correlate with severity of IVT, presence of IVH or hydrocephalus (P = 0.38, P = 0.63 and 0.57, respectively). In our cohort, the degree of IVH ranged from none to severe. Patients with more severe IVT, involving a large number of central veins (greater than 6), were more likely to have severe IVH and hydrocephalus (n = 8). Dural venous sinus thrombosis was seen, but occurred only in the...
presence of medullary venous involvement. Hydrocephalus was observed in 13/27 (48%) patients and these patients all had severe IVT with 5/13 (39%) patients required shunt placement. Associated findings included diffuse cerebral edema (n=5), and coexistent arterial infarction, most commonly in the MCA territory (n=5).

Conclusions: The imaging presentation of neonates with IVT is varied; however, more severe IVT was associated with hydrocephalus and IVH.

Keywords: Neuroimaging

107. Does Abnormal EEG Predict MRI Abnormalities in Patients with Complex Febrile Seizures
Hodgeman R (Boston, MA), Nagarajan E, Kimia A, Kapur K, Bergin A, Loddenkemper T, Harini C

Objective: The role of imaging in complex febrile seizures (CFS) is unclear. Neurologists may consider neuroimaging in patients with CFS in the setting of abnormal EEG findings; however there is no evidence to support this association. Our aim was to examine the non-urgent MRI results in patients with CFS and correlate with EEG findings.

Methods: We retrospectively reviewed 156 patients with CFS at Boston Children’s Hospital between 1996 and 2011. Subjects were required to have an EEG and a minimum 2-year follow-up.

Results: We reviewed 156 patients (70 female), who were neurologically healthy or mildly delayed at onset of first CFS. Out of 156 patients, 43 had an abnormal EEG. MRI was completed in 28 (65%) patients with an abnormal EEG and only 6 (21%) had abnormal MRI results. This was comparable to the 14 (24%) patients with normal EEG and an abnormal MRI (P = 0.812; graph 1). Median age at CFS onset was 1.5 years (IQR: 0.5–4.58). Median duration of follow-up was 6.3 years (IQR: 3.8–10.4). MRI results did not correlate with developmental delay (P = 0.295) or development of epilepsy (P = 0.918) during follow-up.

Conclusions: Abnormal MRI findings were uncommon and did not correlate with EEG abnormalities in neurologically normal or mildly delayed children presenting with CFS. Additionally, the abnormal MRI did not lead to changes in management. The utility of MRI in children with CFS requires further scrutiny.

Keywords: Neuroimaging, Epilepsy

108. Rhomboencephalosynapses and Neurodevelopmental Outcomes: A Review of 4 Cases
Agarwal S (Houston, TX), Clark G, Emrick L

Objective: Rhomboencephalosynapses is a rare brain malformation characterized by fusion of cerebellar hemispheres and dentate nuclei and vermis hypogenesis. This case series discusses four children with rhomboencephalosynapses (RES) and their clinical presentation, thus highlighting a wide spectrum of neurodevelopmental profiles.

Methods: We discuss the imaging, clinical findings and genetic testing of four children with RES presenting with diverse neurological issues at a tertiary care Fetal Center and Neurology clinic.

Results: The study includes two children in the adolescent age group, one with behavioral disorders, ADHD, and gait and balance issues and the second with shunted hydrocephalus and developmental delay since an early age. The third infant is a 12 month old male with prenatally diagnosed RES and is developmentally normal with a prenatal amniocentesis showing unbalanced rearrangement of 18p11.3 chromosome. The fourth infant is a 13 month old female with multiple congenital anomalies in the VACTERL spectrum that include aqeductal stenosis secondary to rhomboencephalosynapsis, shunted hydrocephalus and has global developmental delay, with a normal chromosomal microarray.

Conclusions: Rhomboencephalosynapses is rare malformation of the posterior cranial fossa with characteristic imaging findings and is increasingly being diagnosed prenatally. The clinical presentation may be on a wide spectrum of neurological issues. The associated genetic aberration, other congenital malformations and the severity of the condition help prognosticate the neurodevelopmental outcomes.

Keywords: Neuroimaging, Cognitive/Behavioral Disorders, Neonatal neurology

109. Reduced Cortical and Thalamic Cerebral Blood Flow in Adolescents with Chronic Post-Concussive Symptoms
Ashwal S (Loma Linda, CA), Barnes S, Bartnik-Olson B, Holshouser B

Objective: 14% of children with sports-related concussions (SRC) remain symptomatic 3 months after injury. Studies have shown regions of hypoperfusion in symptomatic patients in the chronic phase of mild TBI. In this study we used whole-brain spatial mapping and a voxel-wise statistical approach to investigate the extent and anatomical distribution of cerebral hypoperfusion in chronic symptomatic pediatric concussion.

Methods: 23 adolescents (15y) who previously sustained a SRC (3–24 months) and 13 controls (15y) were enrolled. Subjects were referred if they reported cognitive, behavioral, or emotional symptoms. Conventional 3D T1 weighted (T1WI) and DSC-perfusion weighted images were acquired (3.0T Siemens Tim Trio scanner). Relative CBF maps were generated and then deformably registered to the T1WI template. Segmentation identified the regional cortical and thalamic regions.
thalamic structures. Voxel-wise analysis determined significant differences (p<0.05) in regional CBF.

**Results:** We identified multiple areas of reduced CBF in cortical and subcortical regions, including the left medial temporal gyrus, left inferior frontal lobe, left posterior frontal lobe and left posterior cingulate cortex and bilateral thalamus.

**Conclusions:** Our findings identified multiple cortical and subcortical regions of reduced CBF. We speculate that hypoperfusion in the temporal lobe, posterior cingulate cortex and thalamus may be implicated in cognitive deficits after SRC. Compared to our previous results [Barnik-Olson et al., J Neurotrauma 2014;3:921-32] using ROI analysis, we detected a greater number of areas of hypoperfusion suggesting that whole-brain spatial mapping and voxel-wise analysis improved detection of CBF abnormalities.

**Keywords:** Neuroimaging, Cognitive/Behavioral Disorders, Headache/Migraine

**110. Hemorrhagic MRI Brain Lesions are associated with One-Year Outcomes after Pediatric TBI**


**Objective:** Susceptibility weighted imaging (SWI) is an advanced MRI technique that improves the ability to detect/quantify micro- and macro-hemorrhagic lesions after TBI. There are few studies in children and most have been acute and not included repeated long-term imaging, combined with neuropsychological or neuropsychological measures. We report the relationship of these acute lesions with one-year MRI, neurologic and neuropsychological outcomes.

**Methods:** Patients with moderate/severe (GCS score <13) or complicated mild (with hemorrhagic intracranial injury on CT) TBI underwent MRI (3T), acutely (6-18 days) and at 1 year. The number and volume of hemorrhagic brain lesions on SWI were compared to 1-year neurologic (PCPCS) and neuropsychological (memory, attention, IQ), outcomes.

**Results:** We studied 75 children (54M/21F; mean age 12 years), who were injured in vehicle/bike accidents (48), falls (20), sports (6), or assaults (1). GCS scores were mild (28), moderate (11) or severe (36). Severely injured patients had the highest number or volume of brain lesions. Lesion number/volume showed significant negative correlations with one-year neurologic outcomes (p=0.000/p=0.001) and neuropsychologic assessment related to memory (p=0.000/p=0.005) and attention (p=0.000/p=0.002). There was no significant correlation with IQ. 70 patients returned for follow-up MRI. ~50% of hemorrhagic lesions persisted at one year. Improvement in lesion volume correlated with improved one-year neurologic scores (p=0.000).

**Conclusions:** The extent of hemorrhagic brain lesions on acute MRI correlate with one year neurologic and neuropsychological (memory and attention) outcomes. Although 50% of hemorrhagic lesions persisted, improvement in lesion volumes correlated with improved neurologic outcomes [Support from NIH/NINDS:R01-NS054001].

**Keywords:** Neuroimaging, Cognitive/Behavioral Disorders, Headache/Migraine

**111. Early NAA Reductions Predict Neuropsychological Outcomes after Pediatric TBI**

_Ashwal S (Loma Linda, CA), Pivonka-Jones J, Tong K, Oyoyo U, Ghosh N, Holshouser B_

**Objective:** Advanced MRI methods are increasingly used to assess pediatric patients with traumatic brain injury (TBI) to predict outcome. Previous studies have been retrospective, lacked age-appropriate controls and have not included repeated long-term imaging, neurological or neuropsychological measures. We present our findings involving a prospective study of MR spectroscopic imaging (MRSI) in pediatric TBI patients studied acutely and at 1-year.

**Methods:** Hospitalized patients (ages 4 to18) were enrolled if they sustained a mild to severe TBI (GCS <13 or CT evidence of intracranial injury). Age-matched controls underwent identical imaging, neurological and neuropsychological testing. Subjects underwent 3T MRI with proton 3D MRSI acutely (6-17 days) and at 1 year. Regional MRS ratios (NAA/Cr, NAA/Cho, Cho/Cr) for the initial studies were correlated and regression analyses were done to determine which variables predicted neurologic (PCPCS) and neuropsychological (memory, attention and intelligence) outcomes at 12 months.

**Results:** We studied 68 children (50M/18F); age 11.9±3.6 yrs; initial GCS-Mild; n=25; Moderate=9; Severe=34) and 72 control children (36M/36F); age 12.7±3.3 yrs. Initial studies were done at 12±4 days and follow-up studies at 12±1 months for TBI patients and 13±1 months for controls. Total and regional NAA/Cr and NAA/Cho ratios were significantly 1) reduced initially compared to controls; 2) correlated with PCPCS, FSIQ, General Memory and General Attention scores; and 3) predicted dichotomized PCPCS (93%), FSIQ, General Memory and General Attention (p=.000).

**Conclusions:** NAA reductions detected acutely are indicative of neuronal loss or dysfunction and predict long term neurologic and neuropsychologic outcomes [Supported by NIH/NINDS:R01-NS054001].

**Keywords:** Neuroimaging, Cognitive/Behavioral Disorders, Headache/Migraine

**112. Brain Morphology in Children with Gorlin Syndrome**

_Shiohama T (Chiba-shi, Japan), Fujii K, Miyahita T, Uchikawa H, Mizuochi H, Ikebara H, Fukuhara T, Shimojo N_

**Objective:** Brain morphology is tightly regulated by diverse signaling pathways. Hedgehog signaling is a candidate pathway for brain morphology because Gorlin syndrome (GS), which is caused by a PTCH1 mutation in this signaling component, occasionally exhibits macrocephaly and medulloblastoma. Although cerebellar enlargement occurs in ptch1 heterozygous-deficient mice, its impact on human brain development remains unknown. We herein investigated the brain morphological characteristics of GS children.
Objective: We herein examined the brain morphology of GS children. The sizes of the cerebrum, cerebellum, and cerebral ventricles were larger in GS children than in NC, suggesting that constitutive active hedgehog signaling affects human brain morphology as well as the PI3K/AKT and RAS/MAPK pathways.

Keywords: Neuroimaging, Genetics, Brain Tumors/Oncology

113. Disorganized Sulcal Pattern in Fetal Brains with Agenesis of Corpus Callosum
Tarui T (Boston, MA), Mada N, Farhat N, Kitano R, Tanriranir A, Graham G, Rollins C, Ortinau C, Bianchi D, Grant E, Im K

Objective: Prenatal diagnosis of isolated agenesis of the corpus callosum (iACC) is challenging because conventional fetal MRI may not detect the full extent of anatomical abnormalities relevant to prognosis until birth. We determined altered cerebral sulcal development in fetuses with iACC by using novel post-acquisition quantitative fetal MRI analyses.

Methods: We used quantitative fetal MRI analyses implementing sulcal pattern matching and sulcal pattern similarity analysis to compare the sulcal development pattern between 7 fetuses with iACC (25.5 +/- 4.3 week of gestation, mean +/- SD) and 16 typically developing (TD) fetuses (25.4 +/- 2.8). Gyrification indices, measures of complexity of cerebral surface convolution determined by amount of cortex buried within the sulcal folds, were also compared between groups. Statistical analysis was performed using a two sample t-test and linear regression, with significance set at 0.05.

Results: Fetuses with iACC had different cerebral surface development in the second and third trimester compared to TD fetuses. The absolute position (left and right hemispheres, respectively in following data, p-value=0.0009 and <0.0001, t-test.) and relative inter-sulcal relationship (p-value=0.0014 and 0.0005, t-test) of overall evolving sulci were different in fetuses with iACC. Fetuses with iACC also have slower evolution of cerebral gyriification compared to TD fetuses (p-value=0.03 and 0.08, linear regression).

Conclusions: In fetuses with iACC, associated alterations in sulcation and gyrification have already begun as early as the second trimester and continue to be a factor throughout the fetal period. Broader developmental alteration beyond callosal dysgenesis may explain broad and heterogeneous neuropsychological impairments in affected individuals.

Keywords: Neuroimaging, Neonatal neurology, Genetics

114. Evidence for Postnatal Development of Enlarged Medullary Veins in Children with Sturge-Weber Syndrome
Pilli V (Detroit, MI), Beben M, Xuan Y, Chugani H, Juhasz C

Objective: Enlarged deep medullary veins are common MRI findings in children with Sturge-Weber syndrome (SWS) and are considered to be congenital vascular abnormalities. The goal of this study was to determine if enlarged deep medullary veins may develop in the postnatal period, during the early SWS clinical disease course.

Methods: From a cohort of 35 children with SWS, who were followed by longitudinal imaging study and had no interval epilepsy surgery, 15 children had MRI with repeated post-gadolinium T1 images (T1-Gad) and susceptibility-weighted imaging (SWI), an MRI sequence exquisitely sensitive to fine details of cerebral veins. Deep medullary veins were evaluated at baseline and follow-up MRI. Changes in brain glucose metabolism were also assessed by positron emission tomography (PET).

Results: Twelve children (80%) showed enlarged deep medullary veins on the baseline SWI. Two of these children (age 7 and 21 months at baseline) showed additional, newly visualized enlarged deep medullary vein(s) in the frontal lobe of the affected hemisphere at follow-up (on SWI in both children and on T1-Gad in one), at 31 and 36 months of age, respectively. Longitudinal PET showed relatively stable cortical glucose metabolism in these frontal lobe regions. Both children had relatively mild neuro-cognitive abnormalities.

Conclusions: These data provide imaging evidence for the postnatal formation of additional, enlarged deep medullary veins in the frontal lobe in SWS. Such a venous remodeling may facilitate collateral drainage through the deep venous system and provide a vascular compensatory mechanism to preserve the functional integrity of the frontal lobe in SWS.

Keywords: Neuroimaging, Epilepsy

115. Volumetric Studies of Submandibular and Parotid Glands May be Used as Indicators of Efficacy of Intraglandular Botulinum Toxin Type A Injections for Refractory Sialorrhea in Neurologically-Impaired Pediatric Patients
Benko W (York, PA), Triapeni J, McClain M, Tibbett A, Drake M

Objective: To assess the potential correlation of the trend of serial volumetric studies of submandibular glands (SLG) after Botulinum Toxin A (BoNT-A) injections regarding both clinical efficacy and future dosing.

Methods: 19 prospective patients (age range=4-26 years) were injected with ultrasound guidance from July 2011-
April 2016. Serial volumetric SLG biometric studies were obtained in 5 patients. Dose range was 10-45 Units of BoNT-A to each gland. 3 of 5 patients had SLG injected, while 2 patients had both SLG as well as parotid glands injected. During the inter-injection intervals, family was contact at 2 weeks post injection for safety assessment and at least one month post-injection to report toxin effects.

**Results:** We found, that overall there was a trend of a decrease in the overall volume (in cm3) of both the SLG as well as in the parotid glands. Whether or not there were specific decreases in glandular size from one injection time to the next, there was generally a positive effect in decrease of sialorrhea. Additionally, even after considering inter/intra-investigator variance (of ultrasound technician), the mean decrease in the right submandibular gland volume was 25%, and the mean decrease in the left submandibular gland volume was 30.5%.

**Conclusions:** Though very small and limited (n=5), this study not only supports previous studies that chronic injection of BoNT-A decreases the size of the glands measured via ultrasound technique, allowing a proposal of possible glandular atrophy as an explanation, but also supports molecular studies that show both presynaptic ANP-25 cleavage and postsynaptic AQP5 redistribution.

**Keywords:** Neuroimaging, Translational/experimental therapeutics, Neuromuscular disorders

**116. Beyond the ER: Selected Sequence Brain Magnetic Resonance Imaging for Evaluation of Non-traumatic Pediatric Neurological Indications**

*Yang Y (Jacksonville, FL), Shah C*

**Objective:** Current widespread use of CT Head limits our ability to evaluate for acute stroke, brainstem and posterior fossa lesions, demyelination, as well as DAI, vascular injury,
ischemia and hypoxia especially in the trauma setting, and more. A modality that is at once accurate, efficient, and cost effective, in addition to eliminating risks such as radiation and sedation, would be a breakthrough in neuroimaging. 4-pulse sequence brain MRI protocol: axial FLAIR, axial DWI, mid-sagittal SSFSE, and axial susceptibility-weighted images may be effective to evaluate a new neurological complaint except where contrast or angiography is indicated.

Methods: Blinded interpretations will be obtained for retrospective analysis of selected sequence MR. These findings will be compared to CT and full sequence MR and missed findings generated, including Level I findings that may require immediate change in patient management.

Results: Intracranial findings were disparate in 37.5%. In 9%, this resulted in a definitive treatment decision obtained through selected sequence MRI and not through CT. In one half of these cases, this resulted in a level I finding. In another 9% MRI findings were not seen on CT, with no apparent treatment implications, and variable clinical implications. In 2%, findings on CT were not noted on MRI and this had no apparent treatment implications, and no apparent clinical implications.

Conclusions: Selected sequence MR will be an invaluable tool in emergency settings and beyond, enabling us to avoid sedation, ionizing radiation from CT, and stratifying patients who need more detailed brain MRI.

Keywords: Neuroimaging

NEUROMUSCULAR DISORDERS

117. Peripheral Neuropathy (PN) Profile at a Tertiary Care Children’s Hospital in Atlanta, Georgia
Malik M (Atlanta, GA), Pochiraju S, Verma S

Objective: Ouvrier et al 1999 pooled Peripheral Neuropathy (PN) data on 125 children and classified 71% inherited, 10% inflammatory and 19% unclassified. In recent years, advancements/availability of molecular genetics, improved training in electrophysiology/neuromuscular medicine made us revisit the trend of PN at a tertiary care pediatric hospital.

Methods: Retrospective chart review of PN cases from the pediatric neuromuscular and electromyography clinics at a tertiary care Children’s Hospital was performed from 2013 to 2016. Available clinical history, neurological examination findings, electrophysiological reports, genetic/metabolic test results, neuroimaging, CSF studies and muscle/nerve biopsies were reviewed.

Results: Three hundred ninety five subjects were screened and 126 children (64 girls, 62 boys) with PN were identified. Mean age was 10.6 ± 5.3 years (range 3 months to 20 years). Clinical history, neurological examination, electrodiagnostic testing and laboratory results suggested 48% (60) to have inherited polyneuropathy; genetic confirmed 36% (45; CMT 36, Metabolic 2, Mitochondrial 2, ataxia-SCA 3, Friedrich’s 1) and no genetic confirmation in 12% (15), followed by traumatic in 27% (34; MVA 8, bone tumors 7, dog bite 4, gunshot 4), inflammatory 19% (21; CIDP 10, Bell’s 3), toxic/metabolic in 4% (5; chemotherapy 3, vitamin deficiency 1, unknown 1) and unclassified in 2% (2).

Conclusions: Our study results show a changing trend in pediatric PN with an increase in traumatic and inflammatory neuropathies. Inherited neuropathies were the largest group with 12% without genetic confirmation. Study limitations include short duration of study and single center experience.

Keywords: Neuromuscular disorders, Genetics, Demyelinating Disorders

118. Copy Number Analysis Using Next-Generation Sequencing: Comprehensive Genetic Testing and its Application to Testing of Neuromuscular Conditions
Entezam A (San Francisco, CA), Rabideau M, Tan C, Winder T, Aradhya

Objective: While the majority of mutations in Mendelian disorders are detected by sequence analysis, intragenic deletions and duplications (i.e. copy number variants; CNVs) are an increasingly significant factor in elucidating the genetic etiology of many conditions, particularly neuromuscular conditions. Some genes have a relatively high frequency of intragenic CNVs (e.g., DMD) while others typically have recurrent whole-gene CNVs (e.g., PMP22). To supplement methods that detect sequence changes in diagnostic genetic testing, quantitative PCR, MLPA, or exon-focused array CGH have been used to detect gene-level copy number variants. We present a method for detecting both sequence changes and gene-level CNVs simultaneously using a single next-generation sequencing (NGS) assay.

Methods: We have validated custom-built algorithms that use depth of coverage information and split-read detection to identify CNVs from NGS gene panels. We summarized positive CNV results from our clinical neuromuscular testing.

Results: Among clinical samples tested, our bioinformatics pipeline has identified 85 pathogenic CNVs in genes associated with neuromuscular disorders. These genes include DMD, PMP22, SPAST, PLP1, SPG7, KIAA0196, MFN2, and REEP1. Seventy-three patients had whole gene CNVs (the majority were in PMP22), 9 had CNVs spanning multiple exons, and 3 had single-exon CNVs, the latter of which are often difficult to detect by traditional methods.

Conclusions: The development and validation of this method for clinical diagnostic testing requires a considerable investment in bioinformatics. An NGS-based CNV detection method allows for integrated simultaneous sequence and copy number calling which enables lower costs, faster turnaround times, reduced sample input requirements, and higher resolution.

Keywords: Neuromuscular disorders, Genetics
119. Muscle Eye Brain Phenotype Associated with Compound Heterozygous Variants in the NRAP (Nebulin Anchor Related Protein) Gene and Reduced NRAP Protein Expression in Muscle: A Potential New Dystroglycanopathy Gene

Harper A (Charlotte, NC), Lu Q, Hedge M, Nallamilli B, Lavigne J, Sparks S, Lu P, Dollar J, Keramis E

Objective: Dystroglycanopathies are a group of genetically heterogeneous muscular dystrophies. Previously, there were only 6 known α-Dystroglycanopathy-related genes. In more recent years, this number has grown to 18 reported genes. However, many cases without identifiable genes remain. We report such a case with a Muscle Eye Brain phenotype.

Methods: Muscle biopsy showed severe myopathy and immunostaining indicated as dystroglycanopathy. Commercially available genetic testing failed to demonstrate a pathogenic variant consistent with the patient’s findings, nor were variants found in genes known to be involved in dystroglycanopathies by exome sequencing performed on a research basis.

Results: Exome sequencing identified two heterozygous variants in the NRAP (Nebulin Related Anchoring Protein) gene, c.360 + 1G>A and c.3808G>A (p.A1270T). This was confirmed by Sanger sequencing. Parental studies
detected the heterozygous splice variant c.360+1G>A in father and heterozygous missense variant c.3808G>A (p.A1270T) in mother. Immunostaining of the patient’s muscle using rabbit anti-NRAP and monoclonal anti-NRAP antibodies demonstrated decreased staining and abnormal NRAP distribution in the patient’s muscle as compared to

FIGURE 3: Two variants in NRAP gene were detected in exome sequencing with high confidence and also further confirmed by Sanger sequencing. Left side sequencing panels indicates the variants conformations by exome sequencing. Right side sequencing panels indicates the variants conformation by Sanger sequencing. (Abstract 119)

FIGURE 4: cDNA functional studies in a patient with clinical features of congenital muscular dystrophy (CDG). Pictorial representation of exon 4 deletion (105bp deletion) due to altered splicing induced by splice mutation c.360+1G>A in NRAP gene. RNA isolated from patient muscle tissue was used for the cDNA synthesis. cDNA sequencing was performed with the help of primers specific to exonic region close to the detected splice variant: c.360+1G>A. Sequencing results clearly indicated altered splicing in the patient. Splice variant c.360+1G>A induced complete deletion of Exon 4 from the transcript. As a result of altered splicing new transcript is 105bp shorter than the regular transcript. NM_001261463.1 was used as a reference sequence for the mapping sequence coordinates in this study. (Abstract 119)
FIGURE 5: NRAP detection with rabbit polyclonal antibody against NRAP (R-A-NRAP) (Sigma) by immunohistochemistry. DYS1, monoclonal antibody to dystrophin (left panel). Both middle (cross section) and right panel (with some longitudinal fibers) were stained with R-A-NRAP. Blue nuclear staining with DAPI. (Abstract 119)

FIGURE 6: NRAP detection with mouse monoclonal antibody against NRAP (M-A-NRAP) (SantaCruz) by immunohistochemistry. DYS1, monoclonal antibody to dystrophin (left panel). Both middle (cross section) and right panel (with some longitudinal fibers) were stained with M-A-NRAP. Blue nuclear staining with DAPI. (Abstract 119)
normal and dystrophic controls. Western blot revealed that NRAP was barely detected in the patient’s muscle

Conclusions: In conclusion, we report a case of a Muscle Eye Brain phenotype with 2 inherited unique heterozygous variants in the NRAP gene and reduced muscle NRAP expression in an atypical distribution. This suggests NRAP as a potentially new z-Dystroglycanopathy-related gene requiring further investigation with mouse models to confirm its pathogenicity and molecular studies to better discern its role in the glycosylation pathway.

Keywords: Neuromuscular disorders, Genetics, Neuroimaging

120. The DuchenneConnect Registry Experience with a Pain Interference PRO
Lucas A (Charlotte, NC), Lavigne J, Martin A, Kinnett K, Peay H

Objective: Chronic pain can be a problem for many with neuromuscular disorders, including Duchenne and Becker muscular dystrophy (DBMD). Pain is intended to be self-reported and a wide range of pain patient-report outcome measures (PROs) exist. Only a single study was found focused on pain in children with DBMD (N=53) and one of adults (N=80).

Methods: In February 2016 the online DuchenneConnect Registry integrated items from the pediatric and adult
PROMIS<sup>™</sup> Pain Interference Banks to explore pain interference in DBMD. Since this represented the Registry’s first use of a pediatric PRO, we included a question to assess who responded. From February 5-March 22, 2016 we obtained 148 pediatric and 52 adult surveys.

**Results:** Adults reported a mean pain score of 2.0 (SD 1.3), which is below the midpoint on a 1-5 scale. 13.5% (n=7) of adults reported a mean of >4. Children reported a mean of 2.2 (SD 1.0) and 3.4% (n=5) reported a mean of >4. There was no significant correlation between pain interference and age. Preliminary results show relatively low pain interference, though 6% report high pain.

**Conclusions:** While the survey instructs self-report of data, 85.8% of caregivers answered without input from the child and 40.4% answered without input from the adult participant. This demonstrates a potential limitation in self-report research, identified due to a non-standard practice of adding a reporting item to the measure. Consistently asking who is providing answers to PRO measures will improve their integration into self-report registries, allow for data quality checks and indicate when education is needed.

**Keywords:** Neuromuscular disorders, Genetics

1.21. The European Prospective and Longitudinal Natural History Study of Patients with Type 2 and 3 Spinal Muscular Atrophy: Baseline Data
Marquet A (Biel, Switzerland), Seabrook T, Hermosilla R, Czech C, Rumey G, Jordan P, Annoosamy M, Servais L, Khwaja O

**Objective:** Spinal muscular atrophy (SMA) is a rare disease and caused by loss-of-function of the survival motor neuron 1 gene (SMN1) leading to motor neuron degeneration, progressive muscle weakness and loss of motor function. Several therapeutic strategies are currently under clinical investigation. Currently, no effective treatment has received market approval. Given the variability in SMA clinical phenotypes, there is significant need to determine the best clinical outcome measures, surrogate biomarkers and identify prognostic factors to inform the design of clinical trials. We have established a prospective multicenter study to characterize the disease course of patients with type 2 and type 3 SMA by using standardized evaluations. We present baseline data from this study.

**Methods:** 70 patients aged 2 to 30 years were enrolled in France, Germany and Belgium.

**Results:** 61% of enrolled patients are SMA type 2 and 39% type 3. Assessments are adjusted to age and ambulatory status. Evaluations include clinical exam, motor and pulmonary function tests, electrophysiology and MRI, device-based measurement of strength, function and activity and quality of life assessment. Patients’ usual follow-up care data include psychomotor development, orthopedic status, respiratory function and feeding status. Blood samples have been collected to determine SMN2 gene copy number, expression of SMN2 mRNA, SMN protein, and exploratory biomarkers.

**Conclusions:** The outcomes will be further analyzed as changes from baseline. Data generated in this study will help to characterize the SMA spectrum and to identify relevant assessments for future clinical trials.

**Keywords:** Neuromuscular disorders, Translational/experimental therapeutics

122. Meta-Analyses of Ataluren in Patients with Nonsense Mutation Duchenne Muscular Dystrophy

**Objective:** Ataluren is the first drug approved in the EU for the treatment of nonsense mutation Duchenne muscular dystrophy (nmDMD). The aim of this meta-analysis was to evaluate the efficacy of ataluren in patients with nmDMD across a phase 2b (NCT00592553) and a phase 3 study (NCT01826487).

**Methods:** Patients in the phase 2b study who met the phase 3 inclusion criteria were included in this analysis. Boys (7–16 years) with nmDMD, baseline 6-minute walk distance (6MWD) of ≥150 m and ≤80% of that predicted for their age and height, and ≥6 months of steroid use, received ataluren (orally, dosed 10, 10, 20 mg/kg/day) or placebo for 48 weeks. The primary endpoint was week 48 change from baseline in 6MWD. Week 48 changes in timed function tests (TFTs) were also assessed. The meta-analysis was repeated using all patients in the phase 2b study.

**Results:** Overall, 291 patients were included in this analysis (phase 2b: ataluren, n=144; placebo, n=147; phase 3: ataluren, n=114; placebo, n=117). A benefit of 21.1 m in 6MWD (p=0.0193) was observed in patients who received ataluren compared with placebo. Patients receiving ataluren also showed statistically significant improvements in time to run/walk 10 m (−1.4; p=0.0251), time to climb 4 stairs (−1.6 s; p=0.0184), and time to descend 4 stairs (−2.0 s; p=0.0044) versus placebo. Similar results were obtained when all patients were included (all endpoints, p<0.05).

**Conclusions:** Patients who received ataluren over 48 weeks experienced a statistically significant clinical benefit, as measured by 6MWD and TFTs, compared with placebo.

**Keywords:** Neuromuscular disorders

123. Safety of Ataluren in Ambulant and Non-Ambulant Patients in the Initial 48-Week Period of a Long-Term Open-Label Extension Trial of Patients Previously Enrolled in Ataluren Clinical Trials for Nonsense Mutation Duchenne Muscular Dystrophy (nmDMD)
Campbell C (London, Ontario, CA), McIntosh J, Fengbin J, Souza M, Riebling P, Luo X, Ong T, Spiegel R, Peliz S

**Objective:** This ongoing, open-label access trial in Europe, Israel, Australia, and Canada assessed the safety and tolerability of ataluren in patients with nmDMD (NCT01557460).

**Methods:** Males with nmDMD who had received ataluren in previous trials were enrolled. Patients were to receive ataluren 40 mg/kg/day for up to 240 weeks. Safety results from the first 48 weeks are reported.

**Results:** Overall, 94 patients were enrolled; 50 (53.2%) were ambulant and 83 (88.3%) were receiving corticosteroids at study entry. At baseline, mean (standard deviation
age was 12.8 (2.31) years and mean (SD) body mass index was 23.64 (4.67) kg/m². At least 1 treatment emergent adverse event (AE) occurred in 42 (84.0%) ambulant and 34 (79.1%) non-ambulant patients (Table 1). Treatment-related AEs were observed in 13 (26%) ambulant and 5 (11.6%) non-ambulant patients. Overall, 7 (7.4%) patients discontinued: 3 withdrew consent; 2 discontinued due to AEs (cardiac failure and aspiration pneumonia, resulting in death; and non-fatal, life-threatening myocardial infarction, the only serious AE considered treatment-related); 2 were lost to follow-up. There were no Grade 3 laboratory value abnormalities. Lipid values were raised in some patients, the majority of whom were on corticosteroids. No clinically meaningful changes were observed in any other laboratory tests, vital sign measurements or physical examinations at any post-baseline assessment. No new safety signals were identified.

Conclusions: Ataluren was well tolerated in the first 48 weeks of the long-term, open-label extension study; these data are consistent with its known safety profile and are similar in ambulant and non-ambulant patients.

Keywords: Neuromuscular disorders

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Ambulant n=50</th>
<th>Non-ambulant n=43</th>
<th>Overall N=93</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one TEAE</td>
<td>42 (84.0%)</td>
<td>34 (79.1%)</td>
<td>76 (81.7%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>18 (36.0%)</td>
<td>16 (37.2%)</td>
<td>34 (36.6%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (24.0%)</td>
<td>6 (14.0%)</td>
<td>18 (19.4%)</td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>5 (10.0%)</td>
<td>4 (9.3%)</td>
<td>9 (9.7%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2 (4.0%)</td>
<td>7 (16.3%)</td>
<td>9 (9.7%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (4.0%)</td>
<td>5 (11.6%)</td>
<td>7 (7.5%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>19 (38.0%)</td>
<td>15 (34.9%)</td>
<td>34 (36.6%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>10 (20.0%)</td>
<td>6 (14.0%)</td>
<td>16 (17.2%)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>3 (6.0%)</td>
<td>6 (14.0%)</td>
<td>9 (9.7%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4 (8.0%)</td>
<td>1 (2.3%)</td>
<td>5 (5.4%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>12 (24.0%)</td>
<td>6 (14.0%)</td>
<td>18 (19.4%)</td>
</tr>
<tr>
<td>Headache</td>
<td>12 (24.0%)</td>
<td>5 (11.6%)</td>
<td>17 (18.3%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>7 (14.0%)</td>
<td>7 (16.3%)</td>
<td>14 (15.1%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (6.0%)</td>
<td>5 (11.6%)</td>
<td>8 (8.6%)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>3 (6.0%)</td>
<td>11 (25.6%)</td>
<td>14 (15.1%)</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (2.0%)</td>
<td>5 (11.6%)</td>
<td>6 (6.5%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>2 (4.0%)</td>
<td>4 (9.3%)</td>
<td>6 (6.5%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>7 (14.0%)</td>
<td>6 (14.0%)</td>
<td>13 (14.0%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3 (6.0%)</td>
<td>4 (9.3%)</td>
<td>7 (7.5%)</td>
</tr>
</tbody>
</table>

a a patient who reported ≥2 AEs with the same preferred term was counted only once for that term. A patient who reported ≥2 AEs with different preferred terms within the same system organ class was counted only once in that class.

AE, adverse event; TEAE, treatment-emergent adverse event

124. The Natural History of Type 1 Spinal Muscular Atrophy in Taiwan
Jones C (Cambridge, MA), Ou S, Jong Y, Ho C, Lee W, Lin K, SMA Study Group

Objective: Spinal muscular atrophy (SMA) is a progressive autosomal recessive neuromuscular disease resulting from a defect in the survival of motor neuron 1 (SMN1) gene. The objective of the Cooperative Study of the Natural History of Type 1 SMA in Taiwan is to describe the natural history of SMA in Taiwan, not reported previously.

Methods: The study followed 111 SMA type 1 patients (onset ≤6 months) between 1979 and 2015. Data include demography, clinical course, genetic confirmation, correlation between genotype and phenotype, SMN2 copy number, feeding and breathing support, comorbidities, and survival.

Results: By the end of the study period, 95 infants had died, 13 were living and 3 were lost to follow-up. 57 patients were male; 54 were female. The age of onset (mean±SD) was 1.2 ± 1.5 months. Patients with onset before 2 months had worse prognoses than those with onset after 2 months. Age at confirmed diagnosis was 4.9 ± 3.7
months. Over the 36-year period, age at death was 21.2 ± 32.7 months (median 11.6 months, range 2.4–157.3 months). SMN1 gene deletion/mutation was identified in 70 (63%) infants. Of the 31 infants with an available SMN2 copy number, 20 (65%) had 2 copies and 11 (35%) had 3 copies. The prognosis of type 1 SMA patients with 3 SMN2 copies was better than those with 2 SMN2 copies.

Conclusions: The longitudinal nature of this observational cohort allows for the characterization of disease onset and trajectory, with the overarching objective of improving outcomes and survival for patients with type 1 SMA and informing future clinical studies.

Keywords: Neuromuscular disorders, Genetics

125. Interim Safety, Efficacy and Achievement of Developmental Milestones in this Phase 1, First-In-Human Study of the Systemic Delivery of AVXS-101, an AVAA9-Mediated Gene Therapy for Children with Spinal Muscular Atrophy (SMA) Type 1

Objective: Spinal muscular atrophy (SMA) is the most common lethal neurodegenerative disease in infants, caused by mutations of the survival motor neuron 1 gene (SMN1). AVXS-101 is a gene therapy designed to deliver a functional copy of the SMN gene. In preclinical studies, systemic delivery of AVXS-101 rescues the severe SMA mouse model extending survival from 15.5 days to >250 days (~90%), with approximately 30% surviving beyond 400 days.

Methods: Here we report interim data as of 4/1/2016 of this ongoing first-in-human study. The study is evaluating the safety of AVXS-101 administered at two different doses for 15 patients with SMA type 1 (two copies of SMN2 only). The secondary outcomes include time-to-death or need for ≥16 h/day of ventilator assistance continuously for ≥2 weeks in the absence of an acute reversible illness. CHOP INTEND scores and motor milestone development are also determined as clinically relevant exploratory outcomes.

Results: Overall, there have been no significant tolerability concerns reported with this IV administered gene therapy in SMA type 1. Currently, all patients from both cohorts are alive; none have required persistent ventilation as defined in the secondary outcome.

Conclusions: Patients have reached 5.6–28.9 months of age and preliminary analyses of exploratory clinical outcomes suggest that patients treated at a younger age and having a high baseline CHOP-INTEND score (>30 points) show the greatest progression in motor function with the therapeutic dose. Furthermore, some patients have reached developmental milestones that SMA type 1 patients essentially never achieve, such as crawling, sitting without support, and rolling over.

Keywords: Neuromuscular disorders, Movement Disorders

126. Efficacy and Safety of AbobotulinumtoxinA (Dysport®) in Children with Dynamic Equinus Foot Deformity Previously Treated with Botulinum Toxins
Dabrowski D (Detroit, MI), Boniowski M, Gormley M, Grandoulier A, Picaut P, Delgado M

Objective: Describe the effect of abobotulinumtoxinA (Dysport®) in children with cerebral palsy (CP) previously treated with another Botulinum Toxin (BoNT), compared with the total study population.

Methods: Post-hoc responder analyses of a Phase III study conducted in ambulatory CP children (aged 2–17) with equinus foot. Patients were randomized (1:1:1) to single doses of abobotulinumtoxinA 10U/kg, 15U/kg or placebo injected into the gastrocnemius-soleus complex. Responders were defined as those achieving ≥1 grade improvement in the Modified Ashworth Scale (MAS), and ≥1 grade improvement in the Physicians Global Assessment of treatment response.

Results: Of the 241 randomized patients, 86 were previously treated with another BoNT. Mean age±SD was 6.9 ± 3.1y in the previously-treated group and 5.9 ± 3.1y in the total-group. Eighty patients had previously received onabotulinumtoxinA (mean±SD dose 207 ± 105U) and 6 patients had received incobotulinumtoxinA (190 ± 73U). At Week-4, the proportions of MAS responders (abobotulinumtoxinA 10U/kg/leg, 15U/kg/leg vs. placebo, respectively) were 70.0%, 82.8% vs. 55.6% in the previously-treated groups and 60.8%, 68.4% vs. 45.5% in the total-groups. TEAEs that were reported (Dysport groups 63.8%, placebo 53.2%) with majority being mild. In the total group, the most common treatment-related AE were localized muscular weakness (10U/Kg/leg=2; placebo=1) which was not reported in previously-treated patients and two injection site reactions occurred one in each Dysport group.

Conclusions: The proportion of responders was consistently higher in patients treated with both doses of abobotulinumtoxinA versus placebo, whether or not patients had been previously treated with onabotulinumtoxinA/incobotulinumtoxinA. The safety profile of Dysport was similar in non-naïve subjects as compared to the whole patient population.

Keywords: Neuromuscular disorders

127. Ambulatory Outcome Measures after the Initial 48-week Period of a Long-Term, Open-Label Treatment with Ataluren in Patients Previously Enrolled in Ataluren Clinical Trials for Nonsense Mutation Duchenne Muscular Dystrophy (nmDMD)
Mercuri E (Rome, Italy), McIntosh J, Fengbin J, Souza M, Panaggio G, Riebling P, Luo X, Ong T, Spiegel R, Peitz S

Objective: In this ongoing, long-term open-label access trial in Europe, Israel, Australia, and Canada, physical function was assessed in patients with nmDMD receiving ataluren (NCT015557400).

Methods: Males with nmDMD who had received ataluren in previous trials were enrolled; the gap between last prior exposure and entry to this trial ranged from 801–1334 days. Patients are to receive ataluren 40 mg/kg/day for
up to 240 weeks. Results from the first 48 weeks for ambulant patients (able to run/walk 10 m in ≤30 s upon study entry) are reported. Study assessments were performed at baseline and every 12 weeks during treatment. Change from baseline in 6-minute walk distance (6MWD), timed function tests, and North Star Ambulatory Assessment (NSAA) total score were summarized.

**Results:** Overall, 94 patients were enrolled, 50 (53.2%) of whom were ambulant at study entry. Of those, 49 completed the week 48 observation. At baseline, mean (standard deviation [SD]) age was 12.1 (2.08) years, body mass index was 22.8 (4.63) kg/m², and 6MWD was 341.6 (108.1) meters. Corticosteroids were used by 47 (94.0%) ambulant patients. Mean (SD) change from baseline in 6MWD, time to stand from supine, time to run/walk 10 m and NSAA score are shown in Table 1. One patient lost ambulation during these 48 weeks of treatment.

**Conclusions:** The results for this relatively older and potentially more severely affected ambulant DMD males, suggest a slowing of disease progression in patients receiving...
ataluren for the first 48 weeks of treatment, compared with the current understanding of natural history.

Keywords: Neuromuscular disorders

128. Results of North Star Ambulatory Assessments in the Phase 3 Ataluren Confirmatory Trial in Patients with Nonsense Mutation Duchenne Muscular Dystrophy (ACT DMD)
Muntoni F (London, United Kingdom), Luo X, Elfring G, Kroger H, Riebling B Ong T, Spiegel R, Pelts S, McDonald C

Objective: To examine the efficacy of ataluren in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD), as measured by the North Star Ambulatory Assessment (NSAA).

Methods: This phase 3, randomized, double-blind, placebo-controlled trial of ataluren (ACT DMD; NCT01826487) enrolled boys (7–16 years) with nmDMD and a baseline six-minute walk distance (6MWD) ≥150 m and ≤80% of that predicted for their age and height. Eligible patients were randomized 1:1 to receive ataluren (10, 20 mg/kg) or placebo orally three times daily for 48 weeks. The NSAA is a validated functional scale to measure disease progression in ambulant boys with DMD. It consists of 17 activities ranging from standing up from a chair to jumping. Each activity is scored (0−100); the sum of these 17 scores forms the total score, which is linearized to a 0−100 (worst−best) score.

Results: The intent-to-treat population consisted of 228 patients (ataluren, n=114; placebo, n=114). Patients who received ataluren gained a 1.5-point advantage in NSAA observed score versus patients who received placebo (mean NSAA scores: ataluren, −7.0; placebo, −8.5; p=0.268). Fewer patients who received ataluren changed from a score of 1 or 2 (able to perform activity) to 0 (unable to perform activity) across all 17 activities compared with those who received placebo. Between-group differences across each of the 17 activities consistently favored ataluren, ranging from 1% (lift head) to 12% (rise from chair).

Conclusions: Ataluren is the first drug to demonstrate a benefit to patients with nmDMD compared with placebo, as assessed by the NSAA.

Keywords: Neuromuscular disorders

129. Pediatric Charcot-Marie-Tooth Disease in the Era of Genomics
Acsadi G (Farmington, CT), Soltigis N, Fullam A, Bow K, Ounpuu S, Pierz K

Objective: Our goal was to examine the impact of next-generation exome sequencing (NES) in the diagnosis and care of pediatric Charcot-Marie-Tooth (CMT) patients.

Methods: Retrospective data collection from electronic records was carried out in a cohort of pediatric CMT patients diagnosed between 2011 and present. Genetic testing was performed by commercial laboratories.

Results: 38 out of 48 patients with non-acquired length dependent neuropathy had sufficient data for this study. Three patients, who were initially diagnosed with CMT, were excluded from the CMT group after NES showed mutations in genes unrelated to CMT (BICD2 causing lower extremity dominant SMA, paraplegin causing HSP, and FAM1 related to HSAN2B). Two siblings with prior clinical diagnosis of distal SMA were found to have CMT2A caused by mutation in MFN2 gene. 22 patients (64%) had demyelinating form (CMT1) from which, 17 (50%) had the most common CMT1A (PMP22 duplication) form. 8 patients (23%) had axonal CMT from which, 5 (15%) had CMT2A caused by MFN2 mutations. 2 patients (6%) had CMT4 forms. Only a single CMT2 patient had no genetic cause identified by NES. Children with CMT2 typically had an earlier onset and a faster progression of the disease. EMG correlated well with CMT type.

Conclusions: Exome sequencing has provided genetic diagnosis in the majority of our CMT patients. CMT1A and CMTX are less frequent in the pediatric age group compared to adults. Genetic testing for PMP22 duplication and MFN2 sequencing will provide genetic diagnosis of about 65% of all pediatric CMT patients.

Keywords: Neuromuscular disorders, Genetics

130. Effect of Deflazacort and Prednisone versus Placebo on Pulmonary Function in Boys with Duchenne Muscular Dystrophy Who Have Lost Ambulation
Dubow J (Northbrook, IL), Cunniff T, Wanaski S, Meyer J

Objective: To assess the effects of deflazacort and prednisone on pulmonary function in boys with DMD who have lost ambulation

Methods: This randomized, double-blind, placebo-controlled, Phase 3 study evaluated the efficacy of two deflazacort doses (0.9 mg/kg/day and 1.2 mg/kg/day) compared to prednisone (0.75 mg/kg/day) and placebo for the treatment of DMD. The first segment compared deflazacort and prednisone to placebo over 12 weeks. The second segment compared the two doses of deflazacort to prednisone from 12 to 52 weeks. We conducted a post-hoc subgroup analysis of pulmonary function (FVC, MVV) in patients who were non-ambulatory at baseline.

Results: A total of 196 participants were randomized to the 4 treatment groups; 45 patients were non-ambulatory at baseline. At 12 weeks, both doses of deflazacort demonstrated improvement over placebo on FVC and MVV (p=0.065 for 0.9 mg/kg/day on FVC and p=0.02 for 1.2 mg/kg/day on MVV) while prednisone had larger numerical declines than placebo in both measures. Over 52 weeks of treatment deflazacort at 0.9 mg/kg/day had a 0.128 L improvement in FVC and an 11.1 L/min improvement in MVV compared to prednisone (NS) while deflazacort at 1.2 mg/kg/day demonstrated a 13.6 L/min improvement in MVV over prednisone (p=0.065). More patients on deflazacort showed improvement in pulmonary function compared to prednisone.

Conclusions: This is the first prospective, randomized, blinded study to demonstrate the benefits of deflazacort and prednisone on pulmonary function in non-ambulatory boys with DMD. Although some measures appeared to favor
deflazacort over prednisone, well-powered clinical studies are needed to better assess these differences.

**Keywords**: Neuromuscular disorders, Genetics, Translational/experimental therapeutics

### 131. Safety of AbobotulinumtoxinA (Dysport) in Children Aged 2-17 Years Old with Lower Limb Spasticity Due to Cerebral Palsy: Data from Clinical Trials and Pharmacovigilance Reporting


**Objective**: Evaluate the safety of abobotulinumtoxinA (Dysport) in the management of pediatric lower limb spasticity due to cerebral palsy (PLLS-CP).

**Methods** Presented here are pooled adverse event (AE) data from three double-blind, randomized, placebo-controlled trials (single injections) and five open-label, repeat-cycle studies of abobotulinumtoxinA for the management of PLLS-CP. All clinical trial subjects (2-17y) received abobotulinumtoxinA injections (≤30U/kg & ≤1000U) into the distal (gastrocnemius with/without soleus) and/or proximal (hamstring/adductors) muscles. In addition, data from the manufacturer’s post-marketing database are described.

**Results**: In the single-cycle studies, 57.9% of abobotulinumtoxinA-treated subjects (n=280) reported ≥1 AE versus 47.8% with placebo (n=136). The most common AEs (both groups) were childhood infection related. Treatment-related AEs (TRAEs) were more common with abobotulinumtoxinA versus placebo (11.8% vs. 5.9%); the most common TRAE was pain in extremity (2.1% with abobotulinumtoxinA). Fewer serious AEs (SAEs) were reported in abobotulinumtoxinA-treated subjects (1.8%) versus placebo (4.4%). There were no treatment-related SAEs, and no subject withdrew due to an AE. In the open-label studies, where subjects (n=476) received ≤7 injections and were followed for up to 28 months, TRAEs were reported in 21% of subjects; the most frequent TRAEs included: pain in the extremity and muscular weakness. Only two treatment-related SAEs (ataxia due to walking on tiptoes and head injury resulting from a fall) were reported.

Detailed review of the post-marketing safety database showed consistent reporting with the clinical studies; no unexpected safety concerns for abobotulinumtoxinA (varying doses) were identified.

**Conclusions**: These data demonstrate a low incidence of TRAEs for abobotulinumtoxinA in the management of PLLS-CP.

**Keywords**: Neuromuscular disorders

### 132. A Review of the Health-Related Quality of Life in Pediatric Patients with Cerebral Palsy and Associated Spasticity

Clarke N (Bethesda, MD), Stephens J, Pulgar S, Bains S, Marchese D, Tilton A

**Objective**: To evaluate the health related quality of life (HrQoL) associated with pediatric spasticity cerebral palsy patients (CP).

**Methods**: A comprehensive literature review from 2005-2015 was conducted in PubMed and Embase on pediatric spasticity due to CP.

**Results**: 25 studies used validated instruments to capture HRQoL including: SF-36, SF-6D, Child Health Questionnaire, and Questionnaire on Pain caused by spasticity, and others. Consistently reported domains impacting CP patients with spasticity included physical functioning, bodily pain, mental health, and social functioning. Health state utility values from the SF-6D (range 0.741 to 0.797) were lower than the population norm (0.82) for young adults aged 20-29 years. The pain domain maximally impacted HrQoL in spastic CP patients and was the highest reported symptom, followed by tightness due to spasticity. Those with lower limb spasticity experienced a high impact on disability domains. Caregivers were more likely to over-report pain, and provide lower HrQoL compared to those reported by CP patients. Gait speed was important for the caregiver, but correlated less with self-perceived HrQoL for children. Interventions to reduce spasticity such as botulinum toxin type A injections, intrathecal baclofen therapy, or selective dorsal rhizotomy improved HrQoL. A reduction in parental stress levels and caregiver burden was reported for treatments that reduced spasticity, with both patient and parents likely to request these treatments.

**Conclusions**: Studies suggest treatments to reduce spasticity improve overall HrQoL, measured by various instruments, and improve self-reported pain scores. Future areas of research should include humanistic value of new treatments based on CP sub-type and severity.

**Keywords**: Neuromuscular disorders

### 133. Interim Results of a Phase 2 Clinical Study of Nusinersen (ISIS-SMNRx) in Patients with Infantile-Onset Spinal Muscular Atrophy


**Objective**: To assess the safety, tolerability, pharmacokinetics and clinical effects of nusinersen (ISIS-SMNRx) in patients with infantile-onset SMA. Twenty participants (4 in a multicenter, open-label, Phase 2 clinical study designed to evaluate the safety/tolerability, pharmacokinetics, and clinical effects of multiple intrathecal doses of nusinersen in patients with infantile-onset SMA. Twenty participants (4 in a lower-dose cohort, 16 in a higher-dose cohort) were enrolled. Autopsy tissue in 3 participants enabled pharmacodynamic analyses.

**Methods**: This is an interim analysis of an ongoing multicenter open-label, Phase 2 clinical study designed to evaluate the safety/tolerability, pharmacokinetics, and clinical effects of multiple intrathecal doses of nusinersen in patients with infantile-onset SMA. Twenty participants (4 in a lower-dose cohort, 16 in a higher-dose cohort) were enrolled. Autopsy tissue in 3 participants enabled pharmacodynamic analyses.

**Results**: As of an interim analysis performed in January 2016, the study has been ongoing for 32 months. Nusinersen has been well tolerated with no safety concerns identified. Sixteen of 19 participants in the evaluable population remain alive (median age 20.1 months) and demonstrate significant (p=0.01) improvements in motor function.
scores, incremental achievement of motor milestones such as head control (10 participants), rolling (9 participants), sitting (6 participants), and improvements in neuromuscular electrophysiology compared to baseline and published natural history data. Pharmacodynamic data support drug delivery, enhancement of full-length SMN2 transcript, and an increase in SMN protein in target neurons.

Conclusions: In this open-label Phase 2 study, nusinersen exhibits good safety and tolerability, pharmacology that is consistent with its intended mechanism of action, and encouraging evidence supporting meaningful clinical response. Importantly, a pivotal, sham-controlled Phase 3 clinical study of nusinersen in infantile-onset SMA is currently ongoing.

Keywords: Neuromuscular disorders, Translational/experimental therapeutics, Genetics

134. The Usefulness of the Six Minute Walk Test in Myasthenia Gravis
Andrew S (New York City, NY), Montes J, Young S, DeVivo D

Objective: Traditionally, patients with myasthenia gravis (MG) are monitored by qualitative clinical observations, most of which lack standardization. The six minute walk test (6MWT) captures weakness and fatigue in MG but its ability to evaluate responsiveness to treatment has not been explored. Our objective is to evaluate 6MWT performance as a monitor of disease progression and treatment response in MG.

Methods: Fourteen patients diagnosed with MG ages 3-15 years with serial visits were included. Anthropometric measures, medical history and performance on 6MWT were collected. 6MWT distance and fatigue were calculated. Correlations were determined using Pearson correlation coefficients.

Results: Forty follow-up visits with 6MWT assessments were identified. At first visit, mean distance and fatigue was 361.1 meters and 32%, respectively. There were 9 visits in which patients showed minimal change. In twenty-two visits, patients exhibited a change between 30-100 meters, attributed to concurrent changes in medication (n=12), weight (n=6), lifestyle (n=2), thymectomy (n=1), or intercurrent illness (n=1). In nine visits, patients exhibited changes greater than 100 meters, attributed to thymectomy (n=4) or changes in medication (n=4) and weight (n=1). There was a significant negative correlation between changes in distance walked and fatigue (r=-0.460; p=0.003).

Conclusions: This study suggests that the 6MWT is sensitive to disease status in MG. Changes in medication, weight, thymectomy, intercurrent illness, and lifestyle were reflected in interval performance. Improvements in 6MWT distance correlated with reduced fatigue. Studies are needed to determine the sensitivity of the 6MWT and the causal role of these factors on test performance.

Keywords: Neuromuscular disorders, Genetics, Cognitive/Behavioral Disorders

135. Neurological Complications in Pediatric Cardiac Surgery: Incidence, Predictors and Outcome
Hakami W (Riyadh, Saudi Arabia), Elwy A, Tabarki B, Alheberi R, Alorwan K, Ababaker M, Abuzaid A

Objective: To study the incidence, risk factors and spectrum of acute neurological complications associated with congenital heart disease surgery.

Methods: This is a retrospective case-control analysis of the intra-operative and immediate postoperative period of children underwent cardiac surgery from January 2010 to December 2015. We selected 2 control patients for each case, matched for surgical complexity.

Results: During the 6 year-study period, a total of 3043 patients were reviewed. We found 140 neurological complications (4.6%), of which (78.7%) were in the central nervous system and (21.3%) in the peripheral nervous system. The complications involving the central nervous system include: seizures (N=55), intracranial bleed (N=34), cerebrovascular accidents (N=13), hypoxic-ischemic insult (N=15), neuro-ophthalmic defects (N=25), spinal cord infarction (N=2). The complications involving the peripheral nervous system include: neuropathy/myopathy (N=4), phrenic nerve palsy (35). Mortality was 2.8% (4 patients).

Patients with neurological complications had a complex cardiac lesion, longer bypass time, longer aortic cross time, longer hospitalization in intensive care, longer duration of mechanical ventilation and an increased number of days under inotropic support.

Conclusions: Our incidence of neurological complications in the context of pediatric cardiac surgery is similar to other studies, but still high with high morbidity rate. Units caring for patients with congenital heart disease must implement neurological monitoring during and after cardiac surgery to prevent and to detect these complications earlier.

Keywords: Neuromuscular disorders

MOVEMENT DISORDERS

136. Treatment Outcomes in Children Diagnosed with Tourette Syndrome
Kumnick A (Chagrin Falls, OH), Bhatia P, Ostrowski S

Objective: Tourette’s Syndrome is a chronic nervous system disorder characterized by multiple motor and one or more vocal tics lasting for more than 1 year, diagnosed before 18 years of age (DSM V). It occurs 3 to 4 times more often in males than females. The purpose of this study was to assess the clinical characteristics and comorbidities of Tourette’s and examine treatment outcomes for patients at Akron Children’s Hospital, Ohio.

Methods: In a retrospective chart review of 50 patients seen in the Neurodevelopmental Science Center at Akron Children’s Hospital between 2009 and 2014 for Tourette’s Syndrome, data was collected on the following criteria: demographics, comorbidities, clinical characteristics, family history, medications and psychosocial treatment.
Results: Results showed that 82% of patients had at least one comorbidity, compared to a national average of 86%. In addition, 6% and 10% reported coprolalia and echolalia respectively, and 42% patients had family history of tics or comorbidities. Clonidine, Guanfacine, and Topamax were the most commonly prescribed drugs; no drug was found to be more effective than the others (average 54% improvement). While 14% of patients received Comprehensive Behavioral Intervention for Tics (CBIT) and 100% showed improvement, another 34% were referred but never received therapy.

Conclusions: A recommendation was made to investigate barriers to patients receiving CBIT. Prospective studies should include a comparison between drug treatment alone, CBIT alone, and a combination of both.

Keywords: Movement Disorders

137. A Curious Case of Paroxysmal Spells and Developmental Delay: Report of an Infant with a Rare Defect in Neurotransmitter Metabolism

Lakhotia A (Cleveland, OH), Waldron J, Schillaci L, Zinn A, Bass N

Objective: Case report of a 7 month old infant who presented with dystonic spells and developmental delay, subsequently diagnosed with sepiapterin reductase deficiency (SRD)

Methods: Chart review

Results: Four month old boy presented to medical attention with brief paroxysmal episodes of hemibody stiffening, eye rolling, tongue protrusion and irritability. Electroencephalogram (EEG), Magnetic Resonance Imaging (MRI), lumbar puncture, pH probe were normal. He presented to our center at 7 months of age. Examination was significant for hypotonia and head lag, inability to roll over or sit. Spells were captured on EEG and found to be non-epileptic (Video1) CSF neurotransmitter testing was consistent with SRD (Fig 1) Molecular genetic testing was confirmatory with two pathogenic compound heterozygous mutations in the SPR gene - c.595 + 1G>A and c.501-526del (p.Try167Cysfs*3). He was started on levodopa/carbidopa (25/100). Significant clinical improvement was seen within 4 weeks (Video2) During course of treatment he developed “rage attacks”, poor sleep and worsened irritability. He was started on 5-hydroxytryptophan (5-HTP) which improved these symptoms. He is currently 11 months old, and can babble, wave, pull to stand.

Conclusions: SRD is a rare cause of dystonia along with hypotonia and developmental delay in infancy. It is a defect in BH4 synthesis, a cofactor required for dopamine and serotonin synthesis, leading to deficiency of these neurotransmitters in the CNS (Fig 2) It is responsive to treatment with levodopa, and 5-HTP. It is crucial to consider SRD and other monoamine neurotransmitter disorders in infants presenting with dystonic spells and developmental delay, as these are potentially treatable conditions.

Keywords: Movement Disorders, Genetics
138. Incidence and Etiologies of Pediatric Asterixis

Anavamuthan B (Boston, MA), Waugh J

Objective: Asterixis (negative myoclonus) is associated with generalized encephalopathies or structural brain lesions in adults. We examined whether the relative incidence and etiologies of asterixis differ in children.

Methods: We conducted a retrospective chart review of all inpatient and outpatient notes at a large tertiary care children’s hospital (Boston Children’s Hospital, Boston, MA) over a seven month period (9/30/2014-4/30/2015) containing the words “asterixis” or “negative myoclonus” as an analogue of all patients formally evaluated for asterixis.

Results: One hundred fifty patients were evaluated for asterixis over a seven month period. Of these, 30 patients were age 18 or older and thus excluded. The remaining 120 patients had a mean age of 11.7 (SD 4.3) years. Only 2 of these patients demonstrated asterixis on examination. Patient 1: A 6 year old girl with focal-onset epilepsy without an underlying brain lesion presented for second opinion regarding her epilepsy. Some of her seizures manifested as negative myoclonus of predominantly her left arm. Patient 2: A 12 year old boy presented for treatment of relapsed Hodgkin’s lymphoma. Neurology was consulted for weakness. He was found to have ifosfamide-associated generalized negative myoclonus. Neither patient was encephalopathic. Of the encounters with chief complaints of twitching/tremors/tics/spasms/fasciculations (n=8), altered mental status/encephalopathy/sleepiness (n=9), or valproate-associated hyperammonemia (n=5), none documented asterixis.

Conclusions: Asterixis is a rare finding in the pediatric population, can be present without encephalopathy or an underlying brain lesion, and should prompt comprehensive investigation for etiologies including epilepsy and medication side effects.

Keywords: Movement Disorders

139. Efficacy of Parent-Delivered Behavioral Therapy for Primary Complex Motor Stereotypies

Singer H (Baltimore, MD), Specht M, Mahone E, Kline T, Waranch H, Brabson L, Thompson C

Objective: “Primary” Complex motor stereotypies (CMS) are persistent, patterned, repetitive, rhythmic movements (hand/arm flapping, waving, wriggling) in normally developing youth. Anecdotal data suggests pharmacotherapy has little benefit whereas a psychologist-directed behavioral treatment (awareness training and differential reinforcement of successful inhibition) was beneficial. This study evaluated the efficacy of an instructional DVD as a home-based, parent-administered, behavioral therapy for primary CMS.

Methods: Eighty-one children with primary CMS were enrolled. Primary outcome measures included the Stereotypy Severity Scale (SSS)—Motor and Impairment scores, and Stereotypy Linear Analog Scale (SLAS). Mean CMS onset was 13.4 months (±13.1). Eligibility required observed
complex stereotypies. Psychiatric disorders were not exclusionary and a stable medication regimen was required. Intellectual disability, neurological disorder, autism spectrum disorder and tics were exclusionary. Initial assessments were completed via REDCap prior to receipt of the DVD. Fifty-four of the 81 (34 boys, mean age ± sd = 8.19 ± 1.42 years) completed assessments at 1, 2, or 3 months after receiving the DVD.

Results: Reductions (baseline to last assessment) in SSS Motor, SSS Impairment, and SLAS scores (all \( p<0.001 \)) represented change ratios of \(-15\%\), \(-24\%\), and \(-20\%\), respectively. Greatest relative treatment benefit was observed by younger children (ages 7-8), and by one month following receipt of DVD, while a parent global assessment scale showed progressive improvement throughout the study. A post-treatment parent completed questionnaire showed that 96% would "recommend it to others". Conclusions: An instructional DVD for parent-delivered behavioral therapy is a safe, effective intervention for primary CMS.

Keywords: Movement Disorders, Demyelinating Disorders

140. Palliative Use of Intrathecal Baclofen in Leukodystrophy: A Review of Two Cases Riordan H (Kansas City, MO), Le Pichon J, Aalbers B

Objective: Leukodystrophies are neurodegenerative disorders resulting in progressive spasticity and dystonia. Oral and intravenous medications have dose-limiting side effects and administration can be difficult at end-stages. Intrathecal baclofen may offer an alternate palliative option. We present two patients with leukodystrophy treated with intrathecal baclofen.

Methods: We reviewed the pertinent literature and the records of all patients in our baclofen pump database.

Results: Most literature on management of leukodystrophies focuses on disease modification. There is a paucity of research on symptomatic treatment. We did not find any information on intrathecal baclofen in leukodystrophies. We identified two patients with leukodystrophy treated with intrathecal baclofen. The first had Pelizaeus Merzbacher. A baclofen trial showed improvement in the average modified Ashworth scale (aMAS) from 1.31 to 0.1 - 0.2 over 5 hours. Complications include a chronic spinal leak. His most recent aMAS was 2.0 one year after implantation. The second patient had metachromatic leukodystrophy. Her pre-trial aMAS was 2.4. Post-trial aMAS ranged from 0.3-0.95. Her most recent aMAS 1 week after implantation was 1.0, with improved spasticity and dystonia.

Conclusions: Intrathecal baclofen improved spasticity and dystonia in our patients with leukodystrophy. It did not prevent worsening aMAS's over time. Further studies are needed to determine which patients will most benefit, the optimal time in the disease course to place a pump, and outcome measures for patient comfort, ease of care and quality of life.

Keywords: Movement Disorders, Demyelinating Disorders

141. Juvenile Parkinsonism in Neuronal Intranuclear Inclusion Disease Cialone J (Rochester, NY), Srinivasan J, Johnson M, Mink J

Objective: Parkinsonism is characterized by tremor, rigidity, bradykinesia, and postural instability. While common in adults, juvenile parkinsonism (JP) is rare. We report a case of JP due to Neuronal Intranuclear Inclusion Disease (NIID) and review the literature on JP and NIID.

Methods: Single case natural history over 10 years and comprehensive reviews of JP and of NIID.

Results: The male patient was initially seen at the University of Rochester at age 12 years for four year of progressive dysarthria, dysphagia, and clumsiness. He had a history of congenital nystagmus. His examination was notable for tremor, rigidity, bradykinesia and postural instability, consistent with JP. He had negative testing for many causes of JP including Wilson disease, Huntington disease, and mutations in PINK1 and PARKIN genes. The family declined rectal biopsy. He had excellent initial response to levodopa, but subsequently developed dopa-induced motor fluctuations, dyskinesias, psychosis, and dystonia. He also developed autonomic symptoms, seizures, constipation, and sleep disturbance later in the disease course. He ultimately died from respiratory failure. Neuropathology demonstrated large eosinophilic nuclear inclusions, confirming the diagnosis of NIID.

Conclusions: NIID, also known as neuronal intranuclear hyaline inclusion disorder, is a rare neurodegenerative condition. Symptoms usually start in childhood and affect the central, peripheral, and autonomic nervous systems. NIID can be sporadic or familial. In addition to parkinsonism, NIID may cause cerebellar ataxia, chorea, dystonia, nystagmus, pyramidal signs, seizures, cognitive impairment, peripheral neuropathy and autonomic instability. Levodopa-induced dyskinesias are common. Diagnosis is confirmed by antemortem rectal or skin biopsy or postmortem neuropathology.

Keywords: Movement Disorders, Cognitive/Behavioral Disorders

142. A Study of Restless Legs Syndrome in Children James L (Columbus, OH), Lehwald L, Ghosh D

Objective: Characterize pediatric patients with Restless Legs Syndrome (RLS) to add to the pediatric literature, to distinguish from other pediatric and adult cases.

Methods: Retrospective chart review of all patients < 18 years, diagnosed with RLS following consensus diagnostic criteria for children, seen at our institution in last 5 years. Patient demographics, clinical features, investigations, management and follow-up were recorded and analyzed.

Results: 79 patients (F: M = 2.2); Age at diagnosis 15.5 ± 2.1 years; 62% presented with other neurological features including migraine in 21, migraine and chronic daily headache 7, unqualified headache 14, epilepsy 9, postural orthostatic tachycardia syndrome 6, and tic disorder 6. 77% had mental/cognitive/behavioral diagnoses including anxiety 12, bipolar disorder 12, ADHD 12, oppositional defiance 10, and depression 6. 21/79 had a positive family history of
RLS. Non-restorative sleep reported in 47 patients. 8/17 with polysomnography had periodic limb movement index (PLMI) > 5. Serum ferritin < 50 ng/ml observed in 44/64 (69%); 48 received iron; 9/18 (50%) improved on iron mono-therapy.

**Conclusions:** Female preponderance in our series mimics adults; possibly due to older mean age. Mental/cognitive/behavioral comorbidities (77%) are higher than other pediatric series. Comorbid headache (53%) is not previously reported in children. Most presented with non-RLS symptoms, and RLS diagnosis was made later. Hitherto undiagnosed RLS might have worsened the neurological or psychiatric comorbidities. PLMS was less compared to adults. Serum ferritin and response to iron (50%) were similar to those in adults or other childhood series.

**Keywords:** Movement Disorders

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### TABLE 1. Clinical Findings in Patients with GNAO1 Mutations (Abstract 143)

<table>
<thead>
<tr>
<th>Nakamura patient series</th>
<th>Female</th>
<th>Female</th>
<th>Female</th>
<th>Female</th>
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<tbody>
<tr>
<td>Gender</td>
<td>Age</td>
<td>Age</td>
<td>Age</td>
<td>Age</td>
<td>8 years</td>
<td>8 years</td>
</tr>
<tr>
<td></td>
<td>13 years</td>
<td>4 y 1m</td>
<td>Died 11m</td>
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<td></td>
<td>6 years</td>
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<tr>
<td>Mutation</td>
<td>c.836T&gt;G (p.Ile279Asn)</td>
<td>c.521A&gt;G (p.Asp174Gly)</td>
<td>c.572_592 del (p.Thr191_Phe197 del)</td>
<td></td>
<td>c.607G&gt;A (p.Arg209His)</td>
<td>c.626G&gt;A (p.Arg209His)</td>
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<tr>
<td>Inheritance</td>
<td>De Novo</td>
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<td>Epileptic Encephalopathy</td>
<td>Movement Disorder</td>
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<td>Initial Symptom</td>
<td>Tonic seizure at 4 days</td>
<td>Series of tonic seizures at 29 days</td>
<td>Series of tonic seizures at 2 weeks</td>
<td>Ophistotonic posture, development delay at 7 months</td>
<td>Hypotonia at 18 mo</td>
<td>Hyperkinesis at 2 years</td>
</tr>
<tr>
<td>Initial EEG</td>
<td>Suppression burst pattern at 4 days</td>
<td>Suppression burst pattern at 29 days</td>
<td>Suppression burst pattern at 2 weeks</td>
<td>Diffuse irregular spike and slow wave complex at 5 years</td>
<td>No irregularities other than diffuse slowing</td>
<td>No irregularities other than diffuse slowing</td>
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<td>Course of seizures</td>
<td>Tonic seizures at 5 years</td>
<td>Series of tonic seizures at 9 months</td>
<td>Tonic seizure at 10 months</td>
<td>Focal seizure (tonic upgaze), tonic seizure at 5 years</td>
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<td>Course of EEG</td>
<td>Multifocal sharp waves at 1 year, 4 months; suppression burst pattern at 5.5 years</td>
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<td>MRI</td>
<td>Normal at 1 month; cerebral atrophy at 5 years 6 months</td>
<td>Delayed myelination and thin corpus callosum at 10 months</td>
<td>Normal at 3 months</td>
<td>Delayed myelination at 1 year 3 months, reduced cerebral white matter, thin corpus callosum at 4 years 8 months</td>
<td>Normal MRI at 3 years</td>
<td>Normal MRI at 3 years and 6 years</td>
</tr>
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**143. Progressive Movement Disorder in Brothers Carrying a GNAO1 Mutation Responsive to Deep Brain Stimulation**

*Kulkarni N (Phoenix, AZ), Grebe T*

**Objective:** GNAO1, located on chromosome 16q12.2, encodes for 1 of the heterotrimeric guanine binding proteins subunits (G proteins), specifically Ga o, which has been implicated as having an important role in brain function. GNAO1 mutations have been shown to impart oncogene properties as well as cause epileptic encephalopathy. The authors report 2 cases of brothers with a severe movement disorder and hypotonia without epilepsy who have been confirmed by whole exome sequencing to have a novel mutation in GNAO1. Their movement disorder improved significantly with deep brain stimulation.
Methods: Genomic DNA was isolated from the patients’ whole blood, as well as from their parents.

Results: Whole exome sequencing revealed the same heterozygous novel variant in the GNAO1 gene in both boys. The alteration c.626G>A (p.R209 H) is located in exon 6 of the coding region of the gene, resulted from a G to A substitution at codon position 626.

Conclusions: The authors report 2 cases of brothers with an atypical presentation of a GNAO1 mutation as well as propose an effective treatment for this disorder. The authors’ patients exhibited a movement disorder that was refractory to pharmacological modalities. Implantation of a globus pallidus deep brain stimulator has been effective in relieving the majority of their symptoms, and has prevented further hospital admissions. These patients have broadened the phenotype of GNAO1 mutations and identified a treatment that could prove effective for patients with this movement disorder.

Keywords: Movement Disorders, Genetics, Neuromuscular disorders

144. Dopamine Deficiency Promotes L-Dopa-Induced Dyskinesias Through HCN Channels
Bamford N (New Haven, CT), McKinley J, Kavikova I, Angeles C, Darvas M

Objective: Segawa and acquired forms of Parkinsonism reduce striatal dopamine availability and increase striatal acetylcholine production. Treatment with L-Dopa improves motor function but elicits incapacitating L-Dopa-induced dyskinesias (LIDs) via an unknown mechanism. We examined if dopamine-depletion could modify the expression of hyperpolarized cation (HCN) channels in pacemaking cholinergic interneurons (ChI) to promote LIDs by modifying cholinergic regulation of striatal activity.

Methods: We created novel parkinsonian mice that encode the human diphtheria toxin (DT) receptor (DTR) with the dopamine transporter (DAT). Treatment with DAT-DTR mice with DT progressively reduces dopamine availability. A quadruple mutant mouse expressing DAT-DTR, RiboTag, choline acetyltransferase (ChAT-Cre), and conditional tdTomato was prepared. RiboTag and ChAT-Cre allowed quantitative real-time PCR measures of ribosomal-associated mRNA from ChIs in the motor striatum; while tdTomato fluorescently marked these rare, but influential striatal interneurons for slice electrophysiology. Stria from quadruple mutant DAT-DTR and control mice (DAT-WT; 30-day-old; n=10) were removed following DT when rotarod performance declined. Results were compared with rapid dopamine depletion over 12 hr using reserpine in DAT-WT mice (n=8).

Results: Dopamine depletion reduced HCN channel activity and expression levels of HCN2, HCN3, and choline-acetyltransferase. A dopamine challenge using amphetamine in vitro depressed ChI activity in controls but excited ChIs from dopamine-depleted mice.

Conclusions: Dopamine depletion reduced HCN channel expression and activity in ChIs from the motor striatum. The paradoxical rise in ChI firing following a dopamine challenge increases striatal activity to promote LIDs. Together, these findings suggest that supplementing HCN channel transcripts by viral vector may lead to improved clinical outcome.

Keywords: Movement Disorders, Translational/experimental therapeutics, Genetics

145. Clinical Profile of Children with Cerebral Palsy Born Term Compared to Late- and Post-Term: A Retrospective Cohort Study
Frank R (Montreal, Quebec, CA), Garfinkle J, Oskoui M, Shevell M

Objective: In comparison to full term children with cerebral palsy (CP), the clinical profile of children with CP born late term and post-term is unknown. Our objective is therefore to determine whether cerebral palsy risks factors, neurologic subtype, GMFCS severity, and comorbidities differ between early/full-term-born children with cerebral CP compared to those born late/post-term.

Methods: Using the Canadian Cerebral Palsy Registry (n = 1692), the clinical profile of children with CP born at 37 to 40 weeks gestation (n = 686) was compared to those born at 41 weeks and later (n = 116) using the Pearson chi-square test (or Fisher’s exact test) for univariate analyses of categorical data. A P value of < 0.05 was considered significant a priori.

Results: Neonatal encephalopathy was found in 23.9% of children with CP born early/full-term and in 33.6% of those born late/post-term (P = 0.026). Neonatal hyperbilirubinemia was found in 2.6% of children born in the earlier period and in 10.2% of those born in the later period (P = 0.008). Rates of CP subtype, severity, and comorbidities did not differ significantly between the two gestational periods.

Conclusions: In children with CP, neonatal encephalopathy was significantly less frequent and neonatal hyperbilirubinemia significantly more frequent in those born early/full-term compared to their later-born counterparts. However, clinical outcomes of CP were not significantly different between these two gestational epochs.

Keywords: Movement Disorders

146. Hereditary Manganism in a Saudi Child: Mild Neurologic Phenotype and a Novel SLC30A10 Mutation
Gulab Khan S (Jeddah, Saudi Arabia), Kayyali H, Tamim A

Objective: Mutations in the manganese transporter gene SLC30A10 were recently described to cause hypermanganeseemia and brain manganese (Mn) accumulation. Affected individuals present with extrapyramidal dysfunction, polycythemia, extreme elevation of blood manganese levels, and characteristic magnetic resonance imaging findings of T1 hyperintense signals in the basal ganglia. Hepatic involvement is variable.

Methods: We describe the clinical features, laboratory and neuroimaging characteristics, and genetic analysis of Hereditary Manganism in a 6 years old Saudi Child. The beneficial effect of early treatment on clinical course and resolution of MRI lesions are described.

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**T1 Weighted MRI brain**

FIGURE 1: Initial MRI brain (T1 weighted sagittal image) showing T1 hyperintense signals in basal ganglia and cerebellum. (Abstract 146)

FIGURE 2: T1 weighted sagittal image; 6 months after EDTA chelation therapy, showing decreased signal intensity in the same regions.

Results: Age of onset was 5 years with hypotonia and mild dystonia. Brain MRI showed bilateral symmetrical T1-hyperintense signals in the globus pallidi and other regions, suggestive of brain Mn deposition. Characteristic laboratory features included marked polycythemia, iron deficiency, and markedly elevated blood Mn levels (154.8 ng/ml; Reference range 4.7-18.3 ng/ml). SLC30A10 gene sequencing identified a novel mutation c.359 G > A p. gly > asp, confirming the diagnosis of hereditary manganism. Early chelation therapy with disodium calcium edetate (EDTA) and iron supplementation halted progression of neurologic disease and led to resolution of polycythemia and improvement of MRI changes.

**Conclusions:** We wish to emphasize the variable and mild neurologic phenotype of hereditary manganism. Early Diagnosis and prompt institution of EDTA chelation therapy is the key to preventing severe neurologic disability.

**Keywords:** Movement Disorders, Neuroimaging, Genetics

147. **Status Dystonicus in Newly Diagnosed Dystonia Secondary to Intrathecal Methotrexate-Induced Leukoencephalopathy**

**Chopade T** (Louisville, KY), **Barton C, Puri V**

**Objective:** To describe a rare case of status dystonicus in newly diagnosed dystonia secondary to intrathecal methotrexate-induced leukoencephalopathy.

**Methods:** Status dystonicus (SD) is a rare, but life threatening movement disorder emergency characterized by an acute onset of intense and frequent episodes of severe generalized dystonia in a patient who is already diagnosed with dystonia. Currently, lack of a standard definition for the disease along with an absence of widely accepted therapeutic guidelines with no validated assessment tools, contribute to underdiagnosis and underreporting of this life threatening disorder and need to be addressed in the future.

**Results:** A 16-year-old male with history of trisomy 21 and acute lymphoblastic leukemia presented with myoclonic jerking as well as generalized stiffening with back arching after developing leukoencephalopathy following intrathecal methotrexate and diagnosed with acquired dystonia secondary to intrathecal methotrexate-induced leukoencephalopathy. He later developed continued severe involuntary generalized muscle spasms of limbs and trunk with severe back posturing and respiratory insufficiency after starting mercaptopurine and diagnosed with status dystonicus (SD) secondary to febrile illness. This episode eventually subsided with use of baclofen, tetrabenazine, clonazepam, cyclobenzaprine, and levetiracetam. Further use of intrathecal methotrexate has been held and he has not had any episodes since.

**Conclusions:** SD is a rare and life threatening movement disorder emergency that can have a high rate of mortality and morbidity if not quickly identified. This case presents SD as a secondary dystonia with intrathecal methotrexate-induced acute leukoencephalopathy that has not been previously reported.

**Keywords:** Movement Disorders, Brain Tumors/Oncology, Demyelinating Disorders

148. **Phenotypic Spectrum of GABA-Transaminase Deficiency: A Rare Early Onset Epileptic Encephalopathy and Movement Disorder**

**Hodgeman R** (Boston, MA), **Koenig M, Bonnen P, Riviello J, Chung W, Bain J, Chiriboga C, Gibson K, Pearl P**

**Objective:** GABA-transaminase (GABA-T; ABAT) deficiency is a rare disorder of GABA degradation. Previously reported in three patients from two families, we report five additional patients and the current phenotypic spectrum.

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Methods: Newly reported patients were seen clinically to obtain medical history. We contacted the authors of previously reported cases to obtain follow-up information.

Results: Clinical manifestations include developmental impairment, hypotonia, generalized tonic-clonic seizures, choreoathetosis, and subcortical myoclonus. Whole exome sequencing in the two previously unpublished cases revealed ABAT compound heterozygosity (case 1) and homozygous mutations (case 2)—see table. Case 1 had significant choreoathetosis and was unresponsive to auditory and visual stimuli at 20 months of age (Video 1). At 21 months, he initiated treatment with flumazenil infusion and is maintained on a regimen of 1.7 mg/kg/day with clinical improvement (Video 2 - 30 months). EEG recordings post-flumazenil show improved background. The three remaining patients are treated with the ketogenic diet and a combination of AEDs without clear benefit (see table), and remain without mobility or language.

Conclusions: While diagnosis previously relied on CSF GABA quantification or MR spectroscopy, this disorder is likely to be detected more frequently with increased use of advanced generation sequencing. The effect of long-term flumazenil treatment is unclear, but warrants further investigation and Case 1 could represent a less debilitating form of the disorder. We describe two previously unreported patients and a series of 8 patients in whom the phenotype is known, including three who have survived infancy contrary to earlier descriptions of the disorder.

Keywords: Movement Disorders, Genetics, Translational/experimental therapeutics

149. Deep Brain Stimulation in Pediatric Dystonias
Marks W (Fort Worth, TX), Bailey L, Reed M, Honeycutt J

Objective: At Cook Children’s Medical Center, we have performed DBS since 2007

Methods: An IRB approved retrospective review was performed on all DBS patients. Dystonias were characterized as primary progressive (PP) or non-progressive (PNP). Acquired dystonias were sub-classified as secondary progressive (SP) or non-progressive due to cerebral palsy (DCP) or other etiology (SNP). All patients were assessed using Burke Fahn Marsden motor (BFM-M), disability (BFM-D) and Barry Albright scales.

Results: Ninety-five patients with dystonia have had lead implants at our institution. Mean age at lead activation was 13.96 (7.09-30.14 years). Thirty-five were classified as primary dystonia (17 with Dyt-1) vs 60 with secondary dystonias (39 with DCP). Seventy-six patients had at least 1 follow-up data point (range 2-87 months). Across all scales and all times, the mean scores for patients with primary dystonia DYT-1 were significantly lower than for patients with DCP. All groups demonstrated improvement in rating scales over time; no single group improved more significantly than any other. Overall, patients with primary dystonia demonstrated significantly greater improvement in disability scores (BFM-D) than those with secondary dystonias ($F_{(1,73)} = 5.57, p = .021$).

Conclusions: DBS is an effective treatment for primary and secondary dystonias. Response rates to DBS are similar among primary and secondary non-progressive dystonias. Even incomplete responses have generally, but not universally, been helpful for patients and caregivers. Only through shared experience can we refine the role of DBS in pediatrics. An international registry has been established. Information is available at www.PEDiDBS.org

Keywords: Movement Disorders

150. PEDiDBS: The International Pediatric DBS Registry
Marks W (Fort Worth, TX), Bailey L, Sanger T, Koy A, Liu J, Mink J, Timmerman L.

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Objective: To describe the new international registry for pediatric patients undergoing deep brain stimulation.

Methods: An international registry has been developed to capture experience regarding pediatric patients undergoing DBS implantation. Any center implanting a child aged 21 years or younger with DBS may participate. There is no restriction with regard to the underlying disorder, implant site, surgical technique. A limited data set is utilized and data is stored securely in accordance with privacy laws. Sites are identified only by number and retain access to their own data. Each site may use its own IRB approval process, and is responsible for data safety and retains access to its own data. A data oversight committee is responsible for the management of access to collective data for research purposes.

Results: Deep brain stimulation (DBS) has been available for the treatment of pediatric patients with dystonia since 2003 with FDA-HDE status in the US. Although a few centers have developed significant experience with pediatric patients, most children worldwide are implanted in adult centers or pediatric centers with small surgical volumes. Additionally, there is a low incidence of disorders for which DBS is currently accepted. There may be other disorders of childhood in which DBS might have a role. This, and many other questions about the role of DBS in children, can best be answered by the collective sharing of information and experience.

Conclusions: Thus far more than a dozen sites from he US and worldwide have visited the website. Information and request for participation is available at www.pedidbs.org.

Keywords: Movement Disorders

BRAIN TUMORS/ONCOLOGY

151. Brainstem Gliomas (BSGs) in Neurofibromatosis Type 1 (NF-1): The Children’s National Health System Experience
Sato A (Washington, DC), Vezina G, Packer R

Objective: To determine demographics, clinical course, and outcomes of children with NF-1 and BSGs.

Methods: A retrospective clinical and central neuroradiographic review was performed on 26 consecutive patients with NF-1 and presumed BSGs diagnosed from 2000 through 2015. BSGs were confirmed using standardized neuroradiographic criteria. Clinical characteristics included gender, age at diagnosis, family history of NF-1 and a previous or concurrent optic pathway glioma (OPG). Radiographic progression, treatment response, progression free survival, and overall survival were assessed.

Results: 17 of 26 patients met strict criteria of having a BSG; 12 male and 5 female. 9 patients did not meet radiographic criteria. Diagnosis occurred at a mean/median of 8/8 years, range 2-15, without gender difference. All patients survived, a mean of 8.6 (2-14) years from diagnosis. Mean progression free survival was 36 (0-108) months. 10 of the 17 patients (59%) received chemotherapy (primarily carboplatin/vincristine); 6 ultimately needed retreatment or alternative chemotherapeutic/biologic therapy. No patient received radiation therapy. Patients requiring chemotherapy tended to be older at diagnosis. Female gender, older age, family history of NF-1 and previous or concurrent OPG were associated with a higher risk of progression.

Conclusions: BSGs that occur in children with NF-1 occur later than OPGs and compared to children without NF-1, have a more indolent natural history. However, some require multiple treatments for disease control, but do not require radiation therapy.

Keywords: Brain Tumors/Oncology, Neuroimaging, Cognitive/Behavioral Disorders

152. Facial Nerve Palsy as the Presenting Symptoms of Leptomeningeal Carcinomatosis Resulting from Malignant Peripheral Nerve Sheath Tumor
Barton C (Louisville, KY), Evans R, Puri V

Objective: To describe a rare case of facial nerve palsy as the presenting symptom of LC resulting from a L3 malignant PNST.

Methods: Facial nerve palsy is a common diagnosis with a wide array of etiologies, including tumor in 5% of patients. In rare cases this is associated with peripheral nerve sheath tumor (PNST), such as in cases of leptomeningeal carcinomatosis (LC), where malignant tumor cells infiltrate the meninges.

Results: A 15 year old previously healthy female presented with 1.5 years of back pain and 3 months of right sided facial weakness. She developed worsening right sided facial weakness with increased right eye tearing and progressive back pain. MRI of the spine was performed showing an intradural lesion involving the L3 nerve root extending to the lateral margin of the L3 neural foramen. Pathology confirmed the mass to be a malignant PNST. Follow up PET scan post-operatively revealed increased uptake at C7-T1 in addition to the known lesions at L3, suggestive of LC. She underwent total craniospinal radiation with proton radiation followed by chemotherapy, and was started on gabapentin and pulse steroids. Subsequent MRIs of the spine have demonstrated stable lesions and she still has some residual right facial nerve palsy.

Conclusions: Leptomeningeal carcinomatosis can be a rare cause of peripheral facial nerve palsy. The onset whether acute, sub-acute and accompanying symptoms should help guide the initial diagnosis and work up which ultimately impacts the treatment and prognosis.

Keywords: Brain Tumors/Oncology, Infections/Neuroimmunology

153. Midbrain Gliomas: A Large Series of Clinically and Radiographically Heterogeneous Tumors
Segal D (New York, NY), Rao H, Thomas C, Cohen B, Snuderl M, Karajannis M, Allen J

Objective: Midbrain gliomas are a group of slow-growing, low-grade tumors that arise from the tectum and/or tegmentum. Clinical symptoms at diagnosis are usually due to
aqueductal compression resulting in non-communicating hydrocephalus and managed by an endoscopic third ventriculostomy. In the majority of patients, diagnosis is based on imaging characteristics, and only a subset undergo biopsy or resection. As a result, little is known about the histopathological and molecular genetic spectrum of midbrain gliomas.

Methods: We reviewed a series of 60 consecutive patients (age range birth-52 years) with midbrain gliomas treated at our institution over more than 30 years. Anatomically, these tumors appear to fall into two distinct radiographic categories: limited to the tectum and/or the periaqueductal gray matter of the tegmentum (Group A) and diffuse tumors that include the tectum and infiltrate the pons and/or thalamus (Group B).

Results: Twenty-eight of our patients (Group A – 7, Group B – 21) had biopsies or surgical resection, providing tissue for histologic and molecular analyses including methylation profiling and BRAF mutation analysis. Most tumors with available tissue, regardless of radiographic group, were found to be low-grade gliomas, primarily pilocytic astrocytomas (17 pilocytic astrocytomas, 4 other low grade gliomas).

Conclusions: Midbrain gliomas are a clinically heterogeneous group of tumors, albeit with similar histology, a subset of which behave quite aggressively with extensive regional extension and require multiple interventions. We describe the clinical, radiographic, histopathologic and molecular genetic characteristics of this large series of midbrain gliomas in order to identify features that may indicate a more aggressive course.

Keywords: Brain Tumors/Oncology

154. Utility of Post-Contrast Volumetric FLAIR Imaging in Leptomeningeal Disease
Zuccoli G (Pittsburgh, PA), Utz M

Objective: Volumetric contrast enhanced T1-weighted spoiled gradient echo (SPGR) is a routinely used imaging technique in pediatric neuroimaging. Contrast-enhanced volumetric fluid attenuated inversion recovery (FLAIR, PC-FLAIR) is a newer technique which has both T1 and T2 weighted effects with nulling of the CSE. PC-FLAIR has reduced vascular enhancement compared to SPGR. The volumetric technique features significantly reduced flow artifacts compared to traditional 2D FLAIR imaging. These two advantages may allow improved visualization of leptomeningeal disease processes. While most of our experience has been in pediatric neuro-oncology, it may also improve depiction of infectious and autoimmune/inflammatory processes. Our goal was to compare SPGR and PC-FLAIR imaging in a variety of infectious, inflammatory, and oncologic conditions.

Methods: PC-FLAIR and SPGR were added to routine post-contrast imaging protocols. In addition an IRB approved retrospective database search was performed to identify pediatric patients with brain tumors. The PC-
Results: PC-FLAIR and SPGR were both able to identify leptomeningeal disease in many pediatric oncology patients. However, several lesions were only visible on PC-FLAIR (see supplementary Figure 1). Many more were only visible on SPGR in retrospect after looking at PC-FLAIR images (see supplementary Figure 2). This was most apparent in small anatomic spaces such as the Meckel cave and the internal auditory canals.

Conclusions: PC-FLAIR is a complementary technique to SPGR in the evaluation of a variety of pediatric neoplastic, infectious, and inflammatory conditions for the evaluation of leptomeningeal disease.

Keywords: Brain Tumors/Oncology, Infections/Neuroimmunology

155. Neurofibromatosis Type 2 in Children: A Single Center Experience

Quist K (Cleveland, OH), Rothner A, Moodley M

Objective: To describe the earliest clinical presentation, clinical course and complications of NF2 in children.

Methods: A retrospective chart review (1975-2016) of all children between ages 0-21 years seen at the Cleveland Clinic with a diagnosis of NF 2.

Results: 30 children fulfilled the Manchester criteria for NF 2: 11 males and 19 females; all were Caucasian; mean age of 8.3 years; 33% patients had a family history of NF 2. The most common presentation at onset of NF-2 were:ocular complaints - 11 patients; skin schwannomas~5 patients, motor weakness- 4 patients; hearing loss ~4 patients and café au lait macules(CALM)- 1 patient; hearing loss - 15 (50%); Neuroimaging revealed bilateral vestibular schwannomas in 16 patients (53%) and unilateral schwannomas in 7 patients (23.3%). Other symptoms at presentation included headaches, musculoskeletal pain and paresthesias. Mean follow up was 9.6 years; males were diagnosed earlier than females (10.5 years vs.14.5 years); 23(77%) developed severe hearing loss; bilateral vestibular schwannomas was present in 28 (93%); 25 patients (83%) developed skin lesions-CALM 10(33%) and schwannomas 15(50%) were the commonest skin lesions. CNS tumors developed in 24 patients (80%).

Conclusions: NF 2 is more frequent in adults and its presentation and natural history differs in children. Early recognition in children with multiple CNS or skin tumors and confirmation by neuroimaging and appropriate counseling with follow up leads to a better final outcome.

Keywords: Brain Tumors/Oncology

156. Molecular Profiling in Pediatric Brain Tumors: The Memorial Sloan Kettering (MSK) Experience

Dalvi N (New York City, NY), Dunkel I, Gilheeney S, De Braganca K, Berger M, Ladanyi M, Khakoo Y, Shukla N

Objective: The recent development of clinical next-generation sequencing (NGS) assays for molecular profiling of tumor samples has led to precision medicine efforts across numerous tumor types through the use of targeted therapies. Identifying specific and therapeutically vulnerable genetic alterations as key oncogenic drivers may lead to direct improvements in patient outcomes. While survival rates in patients with pediatric malignancies have increased overall, central nervous system (CNS) tumor survival rates remain dismal. We present our experience in molecular profiling of pediatric CNS tumors which may identify targeted drug choices.

Methods: Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT), a hybridization capture-based NGS assay for targeted deep sequencing of all exons and selected introns of 410 key cancer genes, was performed on pediatric CNS tumors of 23 patients (14 with primary and 9 with recurrent tumors) from 2014-present. Primary tumors included glioblastoma (n=4), astrocytoma (n=3), ependymoma (n=3), neuroepithelial (n=2), glioneuronal (n=1), and diffuse intrinsic pontine glioma (n=1). Recurrent tumors included glioblastoma (n=2), astrocytoma (n=1), and ependymoma (n=3).

Results: Actionable oncogenic mutations were identified in 13/24 (54%) of cases. A small subset of these patients received targeted therapies based on profiling results.

Conclusions: Our results demonstrate the feasibility and potential benefit of MSK-IMPACT for pediatric CNS tumors. While still too soon to report outcome in these patients, the use of rational therapeutics is a logical approach to treating patients with otherwise incurable disease. Furthermore, ongoing tumor profiling efforts are critical for development and patient stratification in early phase trials of targeted therapies.

Keywords: Brain Tumors/Oncology, Translational/experimental therapeutics

157. Infantile Lhermitte Duclos Syndrome Treated Successfully with Rapamycin

Maertens P (Mobile, AL)

Objective: Lhermitte Duclos syndrome (LDS) is a rare hamartomatous tumor of the cerebellum due to PTEN gene mutation: it has only been previously reported in less than 10 children. Most cases are treated surgically. Treatment with Rapamycin has not been previously reported in childhood onset LDS.

Methods: Diagnosis of LDS was suggested based on serial MRI findings and recognition of tiger stripe sign and family history of early onset colon cancer. Brain biopsy confirmed the diagnosis. Rapamycin was given per G tube at dose of 0.6 mg/kg/day.

Results: The infant underwent shunting procedure shortly after birth because of aqueductal stenosis. At 3 month, gastrostomy was placed. At 6 month, she was still interacting with surroundings. Her regression started at 8 months of age. She progressively became more irritable and started having seizures. At 10 month, she presented progressively more frequent episodes of posturing with eventual loss of respiratory drive. Before Rapamycin, the brainstem was compressed and pituitary stalk was stretched causing pituitary insufficiency. Rapamycin was started at 18 months. Within one month episodes of posturing had subsided. The
child regained interest in her surroundings within 2 months. After 3 months, she regained spontaneous breathing. Repeat MRI after 4 months of treatment showed no more brainstem compression and pituitary stalk was back to normal.

**Conclusions:** Rapamycin should be considered in cases of LDS where surgical removal is not an option, as in our case where cerebellum was entirely involved.

**Keywords:** Brain Tumors/Oncology, Genetics, Translation/ experimental therapeutics

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**158. Race and Timing of Tuberous Sclerosis Complex Recognition**

Gipson T (Baltimore, MD), Desai S, Nonyane B, Thomas E, Puttgen K, Grasberg A, Cohen B

**Objective:** Racial disparities in the recognition of Tuberous Sclerosis Complex by medical professionals have not been previously studied. We hypothesized that the diagnosis of TSC may have been delayed among African Americans as compared to other races and designed the current study to test our hypothesis.

**Methods:** We conducted a retrospective chart review of patients in our TSC Center of Excellence at Kennedy Krieger Institute to examine the timing of TSC diagnosis by race. Chi square tests for independence between race and age at diagnosis, and features identified were conducted. A multivariable logistic regression model was used to investigate the effect of race on timing of diagnosis, adjusting for age and the number of major features identified.

**Results:** Fifty-two (52) individuals contributed to the analysis. Despite similarity of the diagnostic features across the races, African Americans were more commonly diagnosed at later ages. Specifically, 19% (4/21) of African Americans were diagnosed at age 18 or older as compared to 3.2% (1/31) of Caucasians. A logistic regression model showed that Caucasians had reduced odds of being diagnosed later than age 1 year, but this association was not significant. Furthermore, there was no significant difference in the number of major features identified between the races. However, when adjusting for age, the reduction in the odds of being diagnosed later among African Americans was statistically significant (OR 0.14, p-value < 0.001). The results suggest that the diagnosis of TSC may have been delayed among African Americans as compared to Caucasians.

**Conclusions:** These findings suggest a specific role for the globus pallidus and caudate nucleus in the pathogenesis of SIB in children with TSC.

**Keywords:** Brain Tumors/Oncology, Epilepsy, Genetics

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**160. Brain Tumors as a Cause of Epileptic Spasms: Natural History and Outcomes**

Benitez V (Boston, MA), Harini C, Manley P, Ulrlich N

**Objective:** While brain tumors are a known cause of seizures, they are a rare etiology of infantile spasms (IS). The objective of this study was to investigate features of tumor-associated ES.

**Methods:** We conducted a retrospective, single-institution review of patients with ES and a brain tumor. Patients with tuberous sclerosis were excluded. Demographics, pathologic, radiologic, EEG data, treatment response and long-term outcome were collected.

**Results:** Twenty-four patients were identified; 11 met inclusion criteria. Glioblastomas predominated (8/11). Tumor location involved cortex (11/11), subcortical regions (5/11) and brainstem (6/11). Five patients had focal features to both span semiology and ictal EEG. ACTH and vigabatrin were used in 4 and 1 patients, with 2 of the patients treated with ACTH showing favorable response. In 7 patients, ES preceded tumor diagnosis; 2/6 had tumor resolution prior to resection, 3/6 had tumor resolution post resection, 2/6 had persistent spasms post resection. At last follow up, 10 patients developed additional seizure types; 8 experienced refractory epilepsy, and 9 had a Modified Rankin Scale of 3.

**Conclusions:** Brain tumors are a rare cause of ES. In tumor-associated ES, EEG often demonstrates focal features. Tumor-directed surgery can lead to spasm resolution. Most
patients ultimately develop refractory seizures and experience adverse developmental outcome.

**Keywords:** Brain Tumors/Oncology, Epilepsy

### 161. Targeting Microtubule Severing ATPase Spastin in Glioblastoma


**Objective:** We previously reported Spastin overexpression in clinical glioblastoma (GBM) samples and demonstrated that Spastin depletion inhibits cell motility of human GBM cells in vitro (J Neuropathol Exp Neurol 2011;70:811-826). The objective of this study was to elucidate the role of Spastin in GBM tumorigenic potential in vitro and in vivo GBM growth, invasion and survival.

**Methods:** U87MG and T98G human GBM cell lines were infected with lentivirus containing small hairpin (sh)RNA targeting Spastin. Tumor cells were seeded into soft agar to assess their anchorage-independent growth (tumorigenic potential). The effect of Spastin depletion was also investigated in vivo using an orthotopic xenograft mouse model where U87MG cells expressing luciferase (targeted to reduce Spastin) were stereotactically implanted into mouse brains. Tumor growth was monitored by bioluminescence imaging for 21 days.

**Results:** Anchorage-independent growth in U87MG shControl cells displayed a mean colony formation (Mean±SEM; n=3) of 52.07±1.89, compared to shSpastin1 and shSpastin2: mean colony formation of 32.26±2.47 (p<0.005) and 34.66±2.14 (p<0.005), respectively. Similar inhibition of colony formation was seen in T98G human GBM cell line containing stable Spastin knockdown compared to controls. Preliminary studies suggest that knockdown of Spastin leads to a significant decrease of tumor growth in vivo.

**Conclusions:** Spastin plays a role in the tumorigenic potential of GBM cell lines U87MG and T98G in vitro and in preliminary in vivo imaging studies, thus making Spastin a promising novel therapeutic target in GBM. (Supported by a CURE Program Grant [240742-6301] to CDK and MJR)

**Keywords:** Brain Tumors/Oncology, Translational/experimental therapeutics

### COGNITIVE/BEHAVIORAL DISORDERS

#### 162. Visual Art Intervention in the Neurodevelopmental Disabilities Outpatient Clinic

Ley A (Washington, DC), Turnacioglu S

**Objective:** This study aims to determine if placement of visual art in the outpatient clinic helps ease fear and anxiety in patients with neurodevelopmental disabilities. Children with autism spectrum disorder and attention deficit hyperactivity disorder have increased risk for anxiety, and often experience greater stress in medical settings. Little is known about the effect of visual art on easing pediatric patient fear and anxiety, particularly in children with neurodevelopmental disabilities. However, research to date has shown that visual art in adult clinical environments reduces anxiety and perception of pain. We hypothesize that installing visual art in the clinic will reduce patient anxiety, and will result in improved behaviors with the ability to obtain vital signs more frequently. We also hope to see reductions in physiologic markers of stress and anxiety, such as elevated blood pressure and heart rate.

**Methods:** This is a prospective, non-randomized study. Participants evaluated before the art installation are the control group; participants evaluated after the installation are the intervention group. A caregiver questionnaire largely derived from the Screen for Child Anxiety Related Disorders will be scored and used for comparative analysis. Ability to obtain vital signs, vital sign values, other pertinent clinical exam findings, medication use and neurodevelopmental diagnosis will also be reviewed. The t-test will be the primary statistical model used. RxArt, a non-profit organization that commissions visual art from contemporary artists, is sponsoring this project.

**Results:** Results pending: Art installation to be completed in Summer 2016.

**Conclusions:** Conclusions pending: We expect to have significant results by September 2016

**Keywords:** Cognitive/Behavioral Disorders, Translational/experimental therapeutics

#### 163. Earlier Stage I Operation in Neonates with Hypoplastic Left Heart Syndrome is Not Associated with Worse Short-Term Outcomes


**Objective:** We have previously reported that earlier stage I palliation (S1P) is protective against White Matter Injury (WMI) for term infants with hypoplastic left heart syndrome (HLHS). The present study compares clinical outcomes from the acute hospitalization between neonates who had early (≤4 days) versus late surgery (>4 days).

**Methods:** A retrospective chart review was performed on all neonates with HLHS or variants who underwent S1P at a single institution between 10/2008-03/2013. Excluded were a preterm (<37 weeks gestation), left-ventricle physiology, prior operations and international referral. Anthropometric data, pre- post- and intra-operative factors, postoperative complications, and both intensive care unit (ICU) and hospital length of stay were evaluated for differences between early vs. late surgery. Analysis was performed excluding patients who had either early, or late surgery for non-elective diagnoses.

**Results:** A total of 145 infants, 114 (73 with early surgery, 41 late) met inclusion criteria. The mean day of surgery was 4.2 days (early 2.7 ± 0.1 days, late 6.9 ± 3.7 days). There were no significant differences between the groups’
post-operative complications or operative factors. Neonates who had earlier surgery had significantly longer post-operative ICU stay (median 9 days vs. median 13 days, \( p = 0.02 \)).

**Conclusions:** Early surgery for neonates with HLHS was not associated with either protection against or greater risk for post-operative complications. Neonates who have earlier surgery have a longer initial post-operative ICU stay, but total ICU and hospital stay was not different than that for infants with surgery after day four.

**Keywords:** Cognitive/Behavioral Disorders, Translational/experimental therapeutics

### 164. Depressed Cerebral Blood Flow Response To Hypercapnia in Children with Obstructive Sleep Apnea Syndrome


**Objective:** Obstructive sleep apnea syndrome (OSAS) affects 2-3% of children and is characterized by repetitive upper airway collapse during sleep which results in hypercapnia, hypoxemia and arousal from sleep. Children with OSAS may be habituated to hypercapnia due to their chronic exposure while asleep: children with untreated OSAS exhibit neurobehavioral deficits while awake. However, no polysomnographic measure has been shown to predict these outcomes. We hypothesize that habituation to hypercapnia will reduce waking cerebrovascular reactivity.

**Methods:** We have applied near-infrared diffuse optical and diffuse correlation spectroscopy to provide non-invasive measurement of cerebral blood oxygenation, volume, and flow. We utilized a rebreathing technique to induce a significant change in end tidal CO\(_2\) (\( \Delta \text{EtCO}_2 \sim 25 \) mmHg). We computed blood flow changes relative to a pre-hypercapnic baseline. This combination of a significant hypercapnic challenge with a non-invasive continuous monitor of cerebral blood flow provides a unique window into the impact of pediatric OSAS on cerebral reactivity.

**Results:** We observed no significant differences in baseline cerebral blood oxygenation and tissue hemoglobin concentration between groups. However, the relative change in cerebral blood flow, normalized by \( \Delta \text{EtCO}_2 \), was significantly greater in controls compared to children with OSAS and snorers. No correlations between sleep architecture and rCBF/\( \Delta \text{EtCO}_2 \) were found in any group.

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**TABLE 1. Abstract 163**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All ((n = 114))</th>
<th>Early ((n = 73))</th>
<th>Late ((n = 41))</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Gestational Age, wk (SD)</td>
<td>38.8 (0.9)</td>
<td>38.8 (0.9)</td>
<td>38.8 (0.9)</td>
<td>0.94</td>
</tr>
<tr>
<td>Birth Wt, kg (SD)</td>
<td>3.3 (0.5)</td>
<td>3.3 (0.5)</td>
<td>3.2 (0.4)</td>
<td>0.51</td>
</tr>
<tr>
<td>Aortic Stenosis, n (%)</td>
<td>21 (18)</td>
<td>11 (15)</td>
<td>10 (24)</td>
<td>0.31</td>
</tr>
<tr>
<td>Genetic Syndrome, n (%)</td>
<td>12 (11)</td>
<td>8 (11)</td>
<td>4 (10)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Surgical Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHCA time, min (SD)</td>
<td>46.2 (10.9)</td>
<td>46.9 (11.2)</td>
<td>45 (10.3)</td>
<td>0.35</td>
</tr>
<tr>
<td>Total bypass time, min (SD)</td>
<td>94.9 (28)</td>
<td>94 (21.4)</td>
<td>96.5 (37.2)</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Post Operative Complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac arrests, n (%)</td>
<td>17 (15)</td>
<td>13 (18)</td>
<td>4 (10)</td>
<td>0.29</td>
</tr>
<tr>
<td>ECMO, n (%)</td>
<td>12 (11)</td>
<td>10 (14)</td>
<td>2 (5)</td>
<td>0.21</td>
</tr>
<tr>
<td>Catheterization with Intervention, n (%)</td>
<td>23 (20)</td>
<td>14 (19)</td>
<td>9 (22)</td>
<td>0.81</td>
</tr>
<tr>
<td>Delayed sternal closure, n (%)</td>
<td>30 (26)</td>
<td>18 (25)</td>
<td>12 (29)</td>
<td>0.66</td>
</tr>
<tr>
<td>Surgical re-exploration, n (%)</td>
<td>9 (8)</td>
<td>7 (10)</td>
<td>2 (5)</td>
<td>0.49</td>
</tr>
<tr>
<td>Initial Ventilation post-op, median days (IQR)</td>
<td>2 (1-3)</td>
<td>2 (1-4)</td>
<td>2 (1-3)</td>
<td>0.37</td>
</tr>
<tr>
<td>Reintubation, n (%)</td>
<td>25 (22)</td>
<td>18 (25)</td>
<td>7 (17)</td>
<td>0.48</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>15 (13)</td>
<td>12 (16)</td>
<td>3 (7)</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Discharge</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-operative hospital days, median (IQR)</td>
<td>20 (13-35)</td>
<td>20 (14-39)</td>
<td>19 (12-31)</td>
<td>0.19</td>
</tr>
<tr>
<td>Post-operative ICU stay days, median (IQR)</td>
<td>10 (7-19)</td>
<td>13 (7-25)</td>
<td>9 (7-13)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Conclusions: We have demonstrated a blunted cerebral blood flow response to hypercapnia in children with OSAS and snorers compared to healthy control subjects during wakefulness. This finding suggests that OSAS in children is associated with impaired cerebrovascular reactivity even during wakefulness.

Keywords: Cognitive/Behavioral Disorders

165. ADHD in Autism and Their Association with Other Treatable Comorbidities From a National Autism Registry
Gordon-Lipkin E (Baltimore, MD), Marvin A, Law J, Lipkin P

Objective: To compare phenotype and comorbidity of Autism Spectrum Disorder (ASD) children with and without Attention-Deficit/Hyperactivity Disorder (ADHD).

Methods: Data was obtained from the Interactive Autism Network (IAN), an internet-mediated autism research registry containing parent-report data on >20,000 children with ASD. Eligibility criteria: professional diagnosis of ASD; IAN Child with ASD Questionnaire (CAQ) completed between ages 6-17 years; Social Communication Questionnaire with score ≥12 and Social Responsiveness Scale (SRS) T-Score ≥60 to verify ASD diagnosis. Information was obtained from CAQ regarding diagnosis or treatment of ADHD, anxiety disorder, mood disorder (depression or bipolar), intellectual disability. ASD severity was measured by SRS Total Score.

Results: 3319 children met inclusion criteria; 45.3% had ADHD. Table 1 contains demographics. ADHD was associated with an increase in ASD severity (p<0.001) but with a small effect size (Cohen's d=0.22). Comparison of comorbid anxiety and mood disorders in ASD, with and without ADHD, are found in Figures 1 and 2, respectively. Comorbidity rates increased with age. Overall, a generalized linear model controlling for gender, race, ethnicity and intellectual disability showed that children with both ASD and ADHD had increased risk of anxiety disorder (Relative Risk=2.37, CI95[2.12,2.64]; p<0.001) and mood disorder (Relative Risk=3.17, CI95[2.65,3.79]; p<0.001) compared to children with ASD alone.

Conclusions: Children with both ASD and ADHD have an increased risk of comorbid anxiety and mood disorder, increasing with age. Physicians caring for children with ASD should be aware of the coexistence of these treatable conditions and monitor for them as the children age.

Keywords: Cognitive/Behavioral Disorders

<table>
<thead>
<tr>
<th>TABLE 1. Demographics (Abstract 165)</th>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Total ASD</strong></td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Gender: % Male</td>
</tr>
<tr>
<td>Age (in years): Mean (SD)</td>
</tr>
<tr>
<td>Race: % White</td>
</tr>
<tr>
<td>Ethnicity: % Hispanic</td>
</tr>
<tr>
<td>ASD Severity (SRS Total Score): Mean (SD)</td>
</tr>
</tbody>
</table>
166. Measuring the Family Experience of Care Integration In Child Neurology: The Pediatric Integrated Care Survey

Objective: The Pediatric Integrated Care Survey (PICS), a family-reported experience measure of care integration, was created to assess gaps in care and drive transformation to achieve high value outcomes of better care, better health, and less cost.

Methods: The PICS was developed in partnership with families of children and youth with chronic conditions. Exploratory factor analysis of the pilot data was used to determine experience items and the underlying care integration measurement domains they represented. Psychometric properties of the final questionnaire were evaluated through assessment of construct validity, concurrent criterion validity, internal consistency, and test-retest reliability.

Results: In the pilot sample, the PICS revealed that 51.8% of the respondents (n=251) reported that their child’s care team members did not create short term goals (ie, time bound goals up to six months) and 19.6% of the respondents (n=255) reported that their child’s care team members were never or rarely aware of the results of tests and evaluations their child had recently had. We will present the components of the PICS, including the core survey of 19 validated questions representing five underlying constructs: Access to Care; Care Goal Creation/Planning; Family Impact; Communication between Health Care Provider and Parent; and Team Functioning/Performance/Quality/Connectivity.

Conclusions: Current PICS activities in the Department of Neurology at Boston Children’s Hospital will also be presented, including how the PICS is being implemented in a pre-and-post intervention study assessing the efficacy of interventions to improve care integration, coordination, and communications.

Keywords: Cognitive/Behavioral Disorders, History/Teaching of Child Neurology

167. The Effect of Care Integration on Patient Outcomes and Costs in a Population with Rett Syndrome

Objective: Patients with Rett Syndrome have complex medical needs; in our institution they see an average of twelve different specialties over the course of a year. This can lead to surveillance laboratory data failing to be obtained (everyone’s responsibility is no one’s responsibility), families being unclear which provider should be called for which problem, and a general lack of effective communication between various primary and specialty care providers. This fragmentation of care leads to poorer clinical outcomes and families who are frustrated. In addition, higher costs result, particularly for unplanned admissions and readmissions.

Methods: We developed and instituted a set of care integration measures designed to improve care coordination. Focusing on care transitions between clinic visits, we tracked rates of completion of lab testing and consultations, and notification of the family and referring provider of the results. We also implemented the Care Coordination Measurement Tool, designed to capture the value of non-billable care coordination activities.

Results: Over the first year of the intervention, inpatient charges dropped from 48% total spend ($1.59 M) to 41% ($1.42M). Unanticipated admissions went from an average of 2.06 per patient per annum to 1.32 per patient per annum. Admissions from the ED dropped from 28 per year over the cohort to 15 per year.

Conclusions: Previous work suggests that enhanced care coordination improves all three elements of the IHI Triple Aim: patient/family experience, reduced unnecessary costs, and quality of care. These data suggest that care integration improves outcomes and reduce costs in persons with complex neurological disease.

Keywords: Cognitive/Behavioral Disorders

168. Improving Access to Specialty Care for Underserved Children With Neurodevelopmental Disorders Using Telemedicine

Objective: Children and youth with special healthcare needs (CYSHCN) residing in rural and medically underserved regions of the country experience a disparity in accessing specialty care due to both distance, poverty and transportation. The objectives in this study were to demonstrate the feasibility and reliability of conducting neurodevelopmental screening using telemedicine, to assess the acceptance of families to this new model of service, to assess the family benefits

Methods: Telemedicine clinic was started between Kennedy Krieger Institute (Tertiary Center) in Baltimore, MD and Atlantic General Hospital (AGH) to provide direct evaluation and developmental testing by a neurodevelopmental physician at KKI interacting directly with patient sat the remote site using secure video conferencing. Referral reasons included DD, language delays, severe behaviors and possible autism. Standardized Developmental testing done for assessment of language, problem solving skills

Results: Total scheduled evaluations = 142 patients
Show rate = 83 to 95%. Diagnoses = Autism, ADHD, Conduct/disruptive behavior disorder, language delay, Intellectual disability, specific learning disability Age + > 0-3 years (8%); 3-5 years (22%); 5 to 11 yo (55%) and > 12 years (15%). Family satisfaction = 75-80%. Average mileage =210 to 300 miles round trip

Conclusions: Telemedicine is a replicable and valid method for a comprehensive Neurodevelopmental examination for CYSHCN. Accepted by practitioners and families, improved access to care for families with CYSHCN, early diagnosis helped to improve the care provided to the CYSHCN

Keywords: Cognitive/Behavioral Disorders, Translational/experimental therapeutics, History/Teaching of Child Neurology
169. The Subcortical Band Heterotopia/Lissencephaly (SBH/LIS) Spectrum: Phenotypic, Molecular, Functional, and Structural Analysis of Causative DCX, LIS1 and DYNCH1H1 Variants

Objective: To report and interpret the phenotypic, molecular, and functional/structural analysis of DCX, LIS1 and DYNCH1H1 variants causing the SBH/LIS spectrum and epilepsy.

Methods: Clinical, radiological and genetical review of three patients with SBH/LIS spectrum. Assays with dynamic microtubules, to measure in vitro the ability of recombinant mutated DCX protein to interact with microtubules. Bioinformatic analysis for structural interpretation of the LIS1 and dynein variants.

Results: All three patients presented with severe developmental delay and epilepsy. Patient 1 had a double cortex predominating in the frontal regions, with a pathogenic DCX variant. This variant was found to be defective in its ability to promote microtubule nucleation and polymerization, and showed impaired cooperative binding to microtubules. Patient 2 had a predominantly posterior lissencephaly, with a pathogenic LIS1 variant. Patient 3 had a predominantly posterior pachygyria, with a potentially pathogenic DYNCH1H1 variant. The change in LIS1 introduces a five residue stretch of altered sequence followed by a premature stop codon at residue 250, early in the fourth WD repeat of the Lis1 beta propeller, while the change in dynein is located at its microtubule binding domain and is predicted to weaken dynein’s affinity for the microtubule.

Conclusions: We report two novel variants and one known variant causing severe SBH/LIS. Our functional analyses show that the DCX variant disrupts microtubule binding as well as the cooperative interaction between DCX molecules. Our structural interpretation shows that the mutant LIS1 is likely degraded, while the mutant DYNCH1H1 is predicted to weaken dynein’s affinity for the microtubule.

Keywords: Cognitive/Behavioral Disorders, Epilepsy, Genetics

170. Learning and Memory in Children with Perinatal Stroke (PS)
Trauner D (La Jolla, CA), Evans T

Objective: To determine the effects of PS on learning and memory in children with left hemisphere (LH) or right hemisphere (RH) lesions.

Methods: Forty-five subjects with a single unilateral PS (ages 6-16 years, 22 RH, 23 LH) and 33 typically developing controls (ages 6-15 years) completed the Children’s Memory Scale (CMS), Recalling Sentences from the Clinical Evaluation and Language Fundamentals (CELF-3) 3rd Edition, and Digit Span from the Wechsler Intelligence Scale for Children 3rd Edition (WISC-3). Statistical analyses utilized ANOVA and t-tests.

Results: Subjects with LH or RH lesions scored significantly lower than controls on all sections of the CMS Stories and Dots subtests which test verbal and non-verbal learning and memory respectively. Subjects with LH or RH lesions also scored significantly lower than controls on the CELF Recalling Sentences and WISC Digit Span subtests. Lesion groups did not differ from each other on any subtests.

Conclusions: Unilateral PS impairs verbal and non-verbal learning and memory. Attentional deficits may play a role in the poorer performance on some of the tasks, but are not likely the only reason for impaired learning and memory in PS children. Importantly, side of the lesion did not affect learning and memory performance, as both LH and RH damage produced similar impairments. These results are important both for understanding the consequences of aberrant brain development in the face of an early lesion, and also for planning appropriate clinical management including academic and rehabilitative therapies for the child and anticipatory guidance for parents. Funded by NIH RO1 NS42584 (to DT)

Keywords: Cognitive/Behavioral Disorders, Stroke

171. Auditory Neglect in Children After Perinatal Stroke
Trauner D (La Jolla, CA), Martin K

Objective: Children with perinatal stroke (PS) demonstrate patterns of neglect in visual and tactile domains that differ from what is found in adults after stroke. Auditory neglect has been studied in adults with strokes but not in children after PS. This study assessed auditory neglect in children with PS compared with typically developing controls (TD).

Methods: 13 children with left hemisphere (LH) damage from PS, 8 children with right hemisphere (RH) damage, and 20 matched controls participated. Task: Children were seated in a room with 5 speakers attached to the walls, 2 to the left, 2 to the right, and 1 directly facing the subject. Pure tones were presented from each speaker in random order, and subjects asked to point to the speaker from which the tone came as soon as they heard it. (hearing was normal in all subjects). Data were analyzed for number of correct responses and time to respond to the tone on the left or right side.

Results: Children with LH lesions were significantly better at localizing sounds on the left side than the right. Children with RH lesions were worse at localizing sounds on both sides compared with TD.

Conclusions: Results suggest that LH lesions following PS result in contralateral auditory neglect, while RH lesions result in bilateral auditory neglect. Unlike previous reports for visual and tactile neglect, auditory neglect appears to follow a similar pattern in children with PS as is found in adults after stroke, possibly suggesting less plasticity in auditory pathways. NIH P50 NS22343 (to DT)

Keywords: Cognitive/Behavioral Disorders, Stroke, Neonatal neurology
172. Spatial Attention in Children with Perinatal Stroke Using a Posner-Based Cueing Task
Trauner D (La Jolla, CA), Adams T, Chukoskie L, Townsend J

Objective: Perinatal stroke (PS) can result in neurological deficits that affect development and behavior. Previous PS research has revealed patterns of neurological sequelae that differ from known adult stroke outcomes.

This study examined visual perception, hemispatial neglect and aspects of attention in children with unilateral PS in left (LH) or right hemisphere (RH) compared with controls (TD).

Methods: 11 children with LH lesions, 11 with RH lesions, and 34 controls participated. Two tasks were used. In the first study, a visual perception task was used to assess the speed of visual perception. The second was a Posner-based spatial attention cueing task (the Etask), which measured ability to discriminate the direction of a target stimulus (block letter “E”) presented on the left or right side of the screen. This task provided indices of performance for attention orienting, disengagement and reorienting.

Results: Slowed visual perception was found in LH but not RH children compared to TD. On the Etask, both LH and RH children demonstrated lower accuracy on both left and right sides compared to controls. LH children showed impaired attention orienting and disengagement on the left and right sides compared to TD, while RH children were most impaired in orienting and disengagement on their contralateral side.

Conclusions: These results differ from adult stroke outcomes where damage to the RH usually results in more severe neglect symptoms than LH damage. The results have implications for altered pathways of brain development following unilateral perinatal stroke and for potential interventions to improve outcome. Funded by NIH NS22343

Keywords: Cognitive/Behavioral Disorders, Stroke, Neonatal neurology

173. Early Morning Functioning in School-Age Children with Attention-Deficit/Hyperactivity Disorder
Sallee F (Cincinnati, OH), Komelova M, DeSousa N

Objective: This study examined the temporal occurrence and severity of inadequate attention-deficit/hyperactivity disorder (ADHD) symptom control throughout the day, and related early morning functioning (EMF) impairments and their impact on caregivers in school-age children with ADHD currently treated with stimulant medications.

Methods: An on-line, primary caregiver-completed questionnaire (n=201) was designed to determine if inadequately controlled ADHD symptoms exist in stimulant-treated school-age children with ADHD. Caregivers who identified inadequately controlled ADHD symptoms (Likert severity rating ≥2) during the early morning routine (EMR) were asked to continue the survey by answering a series of questions.

Results: On a 10-point scale, with 1 denoting no ADHD symptoms and 10 denoting significant ADHD symptoms, inadequately controlled ADHD symptoms were rated as equally severe during the EMR (6.45) and evening homework time (6.46). The majority of caregivers reported early morning ADHD symptoms (74%) and impairment of EMF (76%) as moderate-to-severe (Likert rating score 5–10). Easily distracted (74%) and does not listen (73%) were the ADHD symptoms reported most frequently during the EMR, and being impulsive (49%) and failing to finish things (49%) were the most frequent unwanted behaviors appearing during the EMR. Caregivers reported that they often: felt overwhelmed and exhausted (41%), raised their voice more (37%), and felt constantly stressed (30%) as a result of their child’s ADHD symptoms during the EMR.

Conclusions: Despite early morning administration of stimulants, caregivers of school-age children with ADHD report a high prevalence of inadequately controlled early morning ADHD symptoms, which has a negative impact on caregivers.

Keywords: Cognitive/Behavioral Disorders

174. EEG Endophenotypes in Autism Spectrum Disorder
Capal J (Cincinnati, OH), Carosella C, Pattanaik E, Dominick K, Thomas C, Lieberman R, Horn P, Manning-Courtney P

Objective: To identify the presence of epilepsy and EEG abnormalities among children with autism spectrum disorder (ASD) to determine the relationship to specific disease-associated impairments.

Methods: Clinical and phenotypic data, including EEG, was collected from patients with ASD ages 2 to 6 years. For analysis, patients were sub-divided into groups: ASD/abnormal EEG, ASD/normal EEG, and ASD/epilepsy. Groups were then compared to determine if clinically meaningful differences were present between groups.

Results: 322 ASD patients had an EEG and/or diagnosis of epilepsy. Out of 283 patients without epilepsy, 58 (20.5%) had an abnormal EEG (58.6% with epileptiform activity and the remainder with slowing). The abnormal EEG group exhibited worse motor function on the VABS when compared to the normal EEG group (p=0.023). Patients with abnormal EEGs scored higher on the expressive language domain on the MSEL (p=0.01) and socialization domain on the VABS (p=0.05) in comparison to those with epilepsy. Patients with normal EEGs were significantly better in all domains on the VABS and expressive language domain on the MSEL compared to the epilepsy group.

Conclusions: Presence of an abnormal EEG or epilepsy in ASD suggests worse cognitive and behavioral outcomes. Further analysis is needed to clarify these associations.

Keywords: Cognitive/Behavioral Disorders, Epilepsy

175. Abnormalities in Slow Wave Oscillations in Sleep are Associated with Externalizing Behavior in Children with Autism Spectrum Disorder (ASD)
Nguyen J (Boston, MA), Hanson E, Spence S, Maski K

Objective: Sleep difficulties and externalizing behaviors (EB), e.g., aggression and hyperactivity, are common comorbid conditions among children with Autism Spectrum
Disorder (ASD). The inter-relationship between these disturbances is unclear. Slow wave oscillations (SWO) at 0.5-1 Hz occurring during NREM sleep mirror the integrity of the thalamocortical system and cortical connections, and may serve as a biomarker of neuronal connectivity. We hypothesized that frontal SWO power would be reduced among children with ASD compared to controls, and this sleep measure would correlate with EB in the ASD group.

Methods: 19 children with ASD and 17 typically developing (TD) children ages 9-16 years had an overnight home polysomnogram including 7-channel EEG (F3, F4, C3, C4, Cz, O1, O2). SWO power in F3 and F4 leads was extracted using fast Fourier transformation. EB were reported by parents on the Child Behavior Checklist.

Results: Greater SWO power in the F3 lead was found in the ASD group with a trend toward significance [ASD = 649.4 (354.9), TD = 444.9 (217.7), p = 0.065]. A negative correlation between F3 SWO power and EB was detected only in the ASD group (r = -0.515, p = 0.049). Results retained significance after adjusting for age and medication use.

Conclusions: Counter to our hypothesis, children with ASD showed higher SWO activity in the left frontal lobe, perhaps reflecting altered connectivity. Higher SWO activity was associated with less EB in the ASD group, suggesting altered connectivity is associated with behavioral dysfunction. Our results highlight a potential sleep biomarker of behavior problems among children with ASD. Study Sponsored by Autism Speaks, Inc.

Keywords: Cognitive/Behavioral Disorders, Neuroimaging

176. Reversal of Cerebral Atrophy in a Four Year Old African Immigrant with Infantile Onset Cerebral Folate Deficiency

McLaren J (South Burlington, VT), Conus S, Craig A

Objective: The cerebral folate deficiency (CFD) syndromes are a rare group of neurodevelopmental disorders defined by low levels of cerebrospinal fluid (CSF) 5-methyltetrahydrofolate (5-MTHF) in the context of normal serum folate. Infantile-onset CFD, a phenotype of the CFD syndromes, typically presents around 4-6 months of age and is amenable to treatment with high dose folinic acid. Thus far, only twenty cases of this phenotype have been described in the literature. With this case report, we aim to provide radiologic evidence and further demographic diversity to supplement existing guidelines that support simple vitamin supplementation to treat this rare but devastating condition.

Methods: A 4-year-old Somali female presented to our hospital with a history of long-standing failure to thrive, seizures, movement disorder and developmental delay without a clear etiology. A MRI of the brain showed global gray and white matter volume loss (Figure 1a, 1b). CSF 5-MTHF levels were reported as abnormally low (19 nmol/L). The patient was subsequently started on folinic acid (0.5 mg/kg/day).

Results: Eight months after treatment, the patient showed cessation of seizure activity, improved social interaction (smile reciprocity, eye contact, excited vocalizations) and greater mobility (purposeful movements, decreased appendicular hypertonia, decreased spasticity). A repeat CSF 5-MTHF level was within the normal reference range. A repeat MRI showed reversal of previously seen cortical atrophy (Figure 1c, 1d).

Conclusions: This is the first reported case of an African patient with infantile-onset CFD and the first to demonstrate dramatic clinical and radiological improvement after vitamin supplementation.

Keywords: Cognitive/Behavioral Disorders, Epilepsy, Neuroimaging

177. Case Series: Pitt Hopkins and Pitt-Hopkins-Like Syndrome

Goodspeed K (Dallas, TX)

Objective: Pitt Hopkins Syndrome is a rare genetic disorder with an estimated incidence of five hundred patients worldwide. It is caused by an autosomal dominant mutation in the TCF4 gene, which is involved in neuronal differentiation in early brain development. Individuals with this syndrome have a characteristic facies, psychomotor delay, intellectual disability, early onset myopia, seizures, constipation, and spells of hyperventilation followed by apnea. Pitt-
Hopkins-Like Syndrome is phenotypically similar, but caused by mutations in either NRXX1 or CNTNAP2. Here, we present a series of eleven patients with Pitt Hopkins Syndrome and five patients with Pitt-Hopkins-Like Syndrome.

**Methods:** Clinical data was collected on sixteen patients with Pitt Hopkins or Pitt-Hopkins-Like Syndrome, and analyzed for phenotypic similarities. A literature review on Pitt Hopkins Syndrome and Pitt-Hopkins-Like Syndrome was also completed.

**Results:** 62.5% had seizures, 25% have apnea spells, 31% have vision impairment, 50% have behavioral problems, 50% have constipation or feeding problems, and 12.5% have sleep disturbances.

**Conclusions:** Based on this case series, seizures, behavioral problems, and GI problems are most prevalent. Spells of hyperventilation followed by apnea are fairly unique to this population, however only seen in 25% of our patient population. Additionally, sleep problems were not as common as anticipated. Based on these results, it is evident that patients with these syndromes should be screened for these conditions. Future studies could continue to define the natural history of each syndrome as well as attempt to clarify the clinical impact of genotypic variations.

**Keywords:** Cognitive/Behavioral Disorders, Genetics, Epilepsy

### 178. Time Lag from Initial Developmental Concern to Final Diagnosis of Fragile X Syndrome

**Gabis L (Tel Hashomer, Israel), Hochberg O, Leon Attia O, Banet-Levi Y, Mula D, Shefer S**

**Objective:** Fragile X syndrome (FXS) is the most prevalent known genetically inherited cause for autism and intellectual disability in males and occasionally in females. Prevalence of carrier state (55-199 CGG repeats) in Israel is high 1:140. Presenting symptoms and physical features might be non-specific, hence evaluation, especially in girls, might render different paths until specific genetic diagnosis is made. We assessed the lag between parental concerns and presenting symptoms until genetic diagnosis was made.

**Methods:** Interviews with families attending the Fragile X clinic.

**Results:** Initial 117 screened patients (25 females), from 87 families revealed that 27 families (20%), had more than one child with FRAX. In less than 20% diagnosis was made below first year. Mean age of first concern was 12.3 months boys, 23 months girls, definitive diagnosis made-boys 4 years, girls 9 years. Presenting symptoms, raised in 72% by parents and 27% by health care professionals, were motor delay in 44%, communication delay in 21%, language delay in 19%, poor eye contact in 10%, behavioral difficulties in 10% (girls). Only 60% were subsequently referred to specialist while 20% parents were reassured. 84% of multiplex families had another child with FXS before index case diagnosed.

**Conclusions:** Fragile X syndrome is prevalent and highly symptomatic, however, diagnosis is frequently deferred and less recognized in girls. Sometimes diagnosis is delayed until a second sibling is born with the disorder. In view of research advances and medical needs across ages, increased awareness to early diagnosis in non-specific delays- is warranted.

**Keywords:** Cognitive/Behavioral Disorders, Genetics

### 179. Fragile X Carrier Epidemiology and Symptomatology Derived from Index Cases, from a Tertiary Child Developmental Center

**Gabis L (Tel Hashomer, Israel), Gruber N, Berkenstadt M, Shefer S, Leon Attia O, Mula D, Cohen Y, Elitzur S**

**Objective:** Fragile X syndrome (FXS) is the most prevalent known genetically inherited cause for autism and intellectual disability. Carriers of the syndrome (premutation) were once thought to be clinically insignificant but it is now well-documented that the premutation state can cause several clinical disorders. We aimed to perform a nesting approach to acquire data with regard to direct relatives from the index Fragile X cases.

**Methods:** Seventy-nine women were referred due to a related Fragile X Syndrome patient, mainly offspring or sibling.

**Results:** Of the women who were referred as “carrier”, 17% were proven to be full mutation and not premutation. The years of education were in the range of 12-17 years (average of 14 ± 1.51 SD). Twenty-seven percent reported Tunisia as their country of origin, mainly from the island of Djerba. High incidence of prolonged pregnancy, above 41 weeks, was reported in 13% of the mothers. Of the premutated group, 22% reported symptoms consistent with learning difficulties, mainly dyscalculia, and 14% reported ADHD symptoms. Awareness of the clinical disorders of the carriers was documented in only 25% of the patients.

**Conclusions:** Increased awareness and knowledge dissemination in regard to premutation symptomatology and risks are warranted. We suggest a national registry to be installed in different countries that will accumulate genetic and clinical information in regard to Fragile X carrier state.

**Keywords:** Cognitive/Behavioral Disorders, Genetics

### 180. Computerized Working Memory Training for Children with Neurofibromatosis Type 1 (NF1): A Pilot Resting-State Study of Changes in Intrinsic Functional Connectivity

**Acosta M (Washington, DC), Yoncheva Y, Hardy K, Lurie D, Somandepalli K, Packer R, Milham M, Castellanos F**

**Objective:** Children with neurofibromatosis type-1 (NF1) commonly have deficits in executive function. Computerized training programs are increasingly being used in neuropsychiatric disorders, but empirically evaluated interventions are lacking for NF1. This pilot study examined training effects on cognition and resting-state functional connectivity (RSFC) in children with NF1.

**Methods:** In an open pre-/post-test design, we provided 25 sessions (6-10 weeks) of computerized visuo-spatial working memory training at-home with phone-based coaching assistance (Cogmed®). Sixteen participants (9 males; 11.1 ± 2.3 years) had analyzable pre-and post-test resting-
state fMRI scans and cognitive task data. Standard data pre-
processing and calculation of RSFC indices used the Con-
figurable Pipeline for the Analysis of Connectomes v. 0.3.3.
Two voxel-wise RSFC measures, fractional amplitude of low
frequency fluctuations (fALFF) and regional homogeneity
(ReHo), were contrasted pre- vs. post-test using paired t-
tests.

Results: Both RSFC measures showed statistically signifi-
cant (p < 0.05 corrected) regionally specific differences.
Decreased fALFF following treatment was found in a large
cluster spanning thalamus, globus pallidus, lingual and para-
hippocampal gyr, brainstem and cerebellum; a second clus-
ter encompassed precentral cortex, supplementary motor
area, extending into middle and superior frontal gyr. In-
creased ReHo following training was observed in predom-
nantly visual areas (intra- and supra-calcarine cortex, occipi-
tal pole and lingual gyrus). Changes in RSFC significantly
correlated with facets of behavioral improvement after
cogmed training completion and with performance on tasks
tapping executive function and visuo-spatial working
memory.

Conclusions: These pilot findings suggest that regionally
specific RSFC changes may capture treatment-related
improvements in cognitive dysfunction in NF1 and moti-
vate independent controlled replication.

Keywords: Cognitive/Behavioral Disorders, Neuroimag-
ing, Translational/experimental therapeutics

181. A Treatment Optimization Study of HLD200 in
Children with Attention-Deficit/Hyperactivity Disorder
McDonnell M (Marshfield, MA), Wigal S, Childress A,
Kollins S, DeSousa N, Komolova M, Sallee F

Objective: This 11-week Phase III trial examined the safety
and efficacy of HLD200, a novel delayed- and extended-
release methylphenidate formulation designed to be taken in
the evening to control early morning attention-deficit/hyper-
activity disorder (ADHD) symptoms before school and
throughout the day, in children.

Methods: Children (6–12 years) with ADHD were
enrolled. At the start of the 6-week open-label, treatment
optimization phase (Visit 2 [V2]), subjects received
HLD200 at their previous methylphenidate dose equivalent
for 1 week. Five subsequent weekly dose adjustments were
permitted to determine optimal daily dose and evening dos-
age administration time prior to the double-blind phase at
V8. Optimal dose and evening dosage administration time
were defined as ≥30% improvement from baseline on the
ADHD Rating Scale (ADHD-RS-IV) and Before School
Functioning Questionnaire (BSFQ), respectively. ADHD-
RS-IV, BSFQ, and Daily Parent Ratings of Evening and
Morning Behaviors-Revised (DPREMB-R) findings during
open-label treatment are reported herein.

Results: Forty-three subjects were included in this analy-
sis. Mean starting dose was 33.0 mg and mean optimal dose
achieved was 65.6 mg. Modal evening administration time
was 9 p.m. Mean ADHD-RS-IV and BSFQ scores (±SD)
at V2 were 38.2 ± 8.9 and 36.2 ± 13.3, and 12.5 ± 6.6 and
10.1 ± 7.3 at V8, respectively (p < 0.0001). DPREMB-R
AM and PM scores (±SD) were 4.9 ± 2.4 and 15.1 ± 5.9
at V2, and 1.2 ± 1.2 and 7.7 ± 5.7 at V8, respectively
(p < 0.0001). The majority of TEAEs were mild or moderate
in severity.

Conclusions: Evening administration of HLD200 dem-
onstrated statistically significant improvements of ADHD
symptoms and functioning in the early morning and
throughout the day.

Keywords: Cognitive/Behavioral Disorders

182. Auditory Hypersensitivity Issues in Children with
Autism Spectrum Disorders (ASD): Characteristics and
Burden
Lipkin P (Baltimore, MD), Law J, Marvin A, Rubenstein E,
Toroney J

Objective: Auditory hypersensitivity is common in ASD,
affecting 30–50%, and is unpredictable with potential for
challenging behaviors and injury. The objective is to
describe auditory hypersensitivity issues (AHI) in children
with ASD.

Methods: The Interactive Autism Network (IAN), a US-
based research registry, invited families of children with
ASD aged 3–17 years to complete a survey about current
and past AHI, and how AHI affects their child’s behavior
and their family.

Results: Surveys were completed for 497 children; 400
children (80.5%) had AHI in the previous six months. The
sample was majority male (83.0%), white (90.3%), mean
age = 11.1 years (SD = 3.5). Most common frequency was
‘a few times a week’ (30.0%) and ‘a few times a month’
(21.2%). Responses to sound caused at least a somewhat
unsafe situation (41.4%), with 14.4% physically injuring
themselves and 25.5% hurting others. Children with AHI
were more likely to have seizures than all children in the
registry (11.3% versus 7.3%, χ < 0.001); 37.1% with
AHI and seizures reported having AHI-provoked seizures.
Parents observed increased anxiety (89.4%), fear (70.9%),
impulsivity (65.6%), and difficulty controlling (71.5%).
Behaviors included covering ears (86.3%), yelling (58.4%),
orbit outbursts (82.6%), and escape (57.2%). AHI often led to
frequently (25.4%) or sometimes (38.7%) missing school,
family, or community activities.

Conclusions: AHI occur frequently among children with
ASD and are associated with safety concerns, challenging
behaviors, and loss of social opportunities. AHI may be
associated with seizure activity. Better understanding of AHI
will help lead to effective therapies to prevent AHI and its
consequences, including injury.

Keywords: Cognitive/Behavioral Disorders

183. Neural Maturational Trajectories Underlying
Risky Decision Making in Youth with Neurofibromatosis
Type 1
Jonas R (Los Angeles, CA), Rosser T, Roh E, Montejo C,
Congdon E, Pacheco L, Silva A, Bearden C

Objective: The cognitive phenotype in Neurofibromatosis
type 1 (NF1) is characterized by impairment in
prefrontally-mediated functions which encompass attention,
working memory and inhibitory control. Due to this neuro-behavioral profile, we hypothesized that the NF1 population would show abnormal behavior on a task of risk-taking shown to be reliant on the orbitofrontal cortex and striatum. We anticipated that neural activity during risky decision-making would be irregular in the NF1 group.

Methods: Youth with NF1 (N = 28, mean age = 11.96 ± 2.69 years) and typically developing (TD) controls (N = 22, mean age = 12.55 ± 3.45 years) were administered a developmentally sensitive gambling task in which they chose between low-risk gambles with a high probability of obtaining a small reward and high-risk gambles with a low probability of obtaining a large reward. Primary behavioral analyses included assessing how risk-taking changes as potential reward increases. We used functional MRI (fMRI) to investigate neural activity associated with risky decision making, as well as age-associated changes in these behavioral and neural processes.

Results: Youth with NF1 made fewer risky decisions, particularly when the potential reward was high. Neuroimaging analyses revealed a significant age by group interaction during risky decision-making in the medial prefrontal cortex (mPFC); in TD controls increased age was associated with diminished mPFC activity, whereas the opposite relationship was found in the NF1 population.

Conclusions: Youth with NF1 show risk-averse behavior, particularly during high-reward conditions. Neuroimaging findings suggest that developmental trajectories of prefrontal neural activity during risky decision-making may be disrupted in youth with NF1.

Keywords: Cognitive/Behavioral Disorders, Neuroimaging, Genetics

184. Clinical Characteristics and Symptom Profiles of Autism Spectrum Disorder (ASD) in Toddlers with Tuberous Sclerosis Complex (TSC)


Objective: To determine the extent to which deficits associated with autism spectrum disorder (ASD) in toddlers with Tuberous Sclerosis Complex (TSC) overlap with those in non-syndromic ASD (nsASD) and to examine cognitive function, adaptive skills, and epilepsy severity in toddlers with TSC and comorbid ASD. This is the endpoint analysis from a longitudinal investigation of ASD risk factors in infants with TSC.

Methods: Measures included the Autism Diagnostic Observation Schedule (ADOS), the Mullen Scales of Early Learning (MSEL) and clinical epilepsy variables. A repeated measures analysis of variance (ANOVA) was performed with between subjects factor of group [TD (n = 18), TSC/no ASD (n = 18), TSC/ASD (n = 18), nsASD (n = 82)] and within subjects factors of individual ADOS algorithm item scores. Within TSC group comparisons of epilepsy characteristics, cognitive and adaptive domains were performed using independent-samples t-tests and Chi-square tests.

Results: Children with TSC/ASD demonstrated a profile of social communication impairment that had complete convergence with nsASD. Toddlers with TSC/no ASD exhibited preserved social communication skills that matched those of typically developing children, despite the presence of cognitive impairment (see figure). ASD diagnosis was associated with greater cognitive and adaptive skills impairment.

Conclusions: TSC is a model disorder to study the emergence of ASD in early development, with remarkable convergence of autism symptoms between TSC/ASD and non-syndromic ASD. Our results strongly support the need for early intervention in TSC that targets social communication function before the onset of autism symptoms. Compensatory mechanisms that result in preserved social communication function in a subset of toddlers also warrant further examination.

Keywords: Cognitive/Behavioral Disorders, Genetics

NEONATAL NEUROLOGY

185. Rewarming Affects EEG Background in Cooled Asphyxiated Neonates

Birca A (Montreal, Quebec, CA), Lortie A, Birca V, Debarre J, Veilleux A, Gallagher A, DeHaes M, Lodgenysk G

Objective: Therapeutic hypothermia (TH) is the only proven neuroprotective intervention that improves survival and neurodevelopment in term neonates with hypoxic-ischemic encephalopathy (HIE). However, animal data suggest that rapid rewarming after hypothermia can reduce its beneficial effects. Remarkably, the neurological impact of rewarming has not been systematically studied in humans. EEG background evolution during TH reflects HIE severity. The objective of this study was to determine whether rewarming affects EEG background in hypothermic HIE neonates.

Methods: We recruited a retrospective cohort of 15 consecutive neonates with moderate (9) and severe (6) HIE submitted to continuous EEG monitoring during TH and
at least 12 hours after its end. We evaluated EEG background using conventional visual analysis and computational methods, including EEG discontinuity, absolute and relative spectral magnitudes. One neonate with seizures on rewarming was excluded from the analyses.

**Results:** Visual and computational analyses demonstrated significant changes in EEG background from pre- to post-rewarming, characterized by an increase in EEG discontinuity, more pronounced in neonates with severe compared to moderate HIE. Neonates with moderate HIE also had an increase in the relative magnitude of slower delta and a decrease in higher frequency theta and alpha activities with rewarming.

**Conclusions:** Rewarming affects EEG background in HIE neonates undergoing TH, which may represent either a transient adaptive response or reflect evolving brain injury. EEG background impairment induced by rewarming may represent a biomarker of evolving encephalopathy in HIE neonates undergoing TH and underscores the importance of continuously monitoring the brain health in critically ill neonates.

**Keywords:** Neonatal neurology

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**186. Development of a Scoring System to Track Disease Burden in Molybdenum Cofactor Deficiency and Isolated Sulfite Oxidase Deficiency**

**Misko A (Boston, MA), Loes D, Musolino P, Gonzalez A, Aziz-Bose R, Caruso P, Eichler F**

**Objective:** We report on a uniquely large cohort of isolated sulfite oxidase deficiency (ISOD) and molybdenum cofactor deficiency (MOCOD) patients and develop a scoring system to track disease burden on brain MRI.

**Methods:** Twenty patients were screened and 18 patients (3 with ISOD and 15 with MOCOD) with MR imaging (T1, T2 and DWI sequences) were included. A visual scoring method based on a point system (range: 0 to 16) was developed with the following disease features in mind: (1) hypoplasia of the corpus callosum or cerebellum; a score of “0” for normal appearance and “1” for hypoplasia, (2) white and gray matter lesions or cavitations; “1” for unilateral or “2” for bilateral occurrence and (3) cerebral atrophy; scored as either moderate (“2”) or severe (“4”) (Fig 1).

**Results:** On initial imaging the average score was 6.2 points (range 3-12) increasing to 9.8 (range 5-13) on latest imaging. Presence of diffusion restriction portended the

![FIGURE 1: Evolution of brain MRI abnormalities in a patient with MOCOD A. T2 weighted (A) and DWI (B) images of a 1.5 month-old child with infantile MOCOD reveals bilateral injury to caudate and thalamus as well as diffuse abnormalities in the white matter. In addition, there are focal cavities to the gray matter. T1 weighted (C) images display cerebellar hypoplasia. One week later there are diffuse cavities within the white and gray matter as well as atrophy displayed on T2 weighted (thin arrowhead, D) and T1 weighted (thin arrowhead, E) images. Two weeks thereafter, subdural effusions have developed (thick arrowheads, G, H). Despite the severe cavitation and atrophy, myelination has progressed (thin arrows, G). Cerebellar hypoplasia remains unchanged on follow-up imaging (F, I) (Abstract 186)
greatest change in score. No image that scored <6 points showed cavitations and no image scored <9 point showed cortical atrophy. Progression beyond the score of 9 points only occurred in relation to worsening cortical atrophy.

Conclusions: Our study suggests that catastrophic changes occur rapidly early in the course of disease and then plateau. Implementation of therapeutics could be guided by our scoring system which suggests early intervention before a score of 6 would be imperative to preventing severe cerebral damage. Our scoring system could also be valuable in tracking accumulation of disease burden during therapeutic trials to assess efficacy.

Keywords: Neonatal neurology, Neuroimaging

187. Patterns of Burst Suppression in Electroencephalograms of Neonates Undergoing Deep Hypothermic Circulatory Arrest

Objective: The use of intraoperative EEG in neonates and children undergoing congenital heart surgery that involves deep hypothermic circulatory arrest (DHCA) is not standardized due to a dearth of data concerning its predictive value. Electrocerebral silence (ECS) is assumed to be the point where cerebral metabolism has reached a nadir, permitting brief interruption of circulation. There are very few studies delineating patterns of burst suppression and ECS in neonates, and there has never been a correlation between the attainment of ECS prior to DHCA and the incidence of postoperative neurological complications. Clarifying these assumptions is necessary to optimize neurological protection in these vulnerable patients.

Methods: We recorded two channel scalp EEG (C3/P3, C4/P4) from 9 patients following induction of anesthesia, all of whom underwent DHCA for 37.4 ± 9.4 mins initiated after 15 minutes of cooling and/or 17°C Celsius core temperature reached, and analyzed the number of bursts recorded during sequential, 5 minute epochs of cooling. Postoperatively, all neonates were monitored for 24-48 hours according to ACNS guidelines using 10-20 electrode placement.

Results: While the number of bursts declined throughout cooling, no patient achieved ECS prior to DHCA. There was no evidence of postoperative electrographic or clinical seizures in any patients.

Conclusions: Our data indicates that current strategies of cooling are not sufficient to eliminate all electroencephalogram activity prior to DHCA. Because there were no postoperative seizures, our study questions the importance of attaining ECS prior to circulatory arrest for this duration in this neonatal patient population.

Keywords: Neonatal neurology, Neuroimaging

188. Neurodevelopmental Outcomes in Infants with Microcephaly
Gordon-Lipkin E (Baltimore, MD), Gentner M, Leppert M

Objective: In light of the recent Zika Virus epidemic and the inferences of microcephaly in neonates, we examined longitudinal neurodevelopmental outcomes in a series of infants with microcephaly.

Methods: Retrospective review of NICU follow-up clinic patients with a diagnostic code of microcephaly from 2006 to 2016 was conducted. Microcephaly diagnoses were verified by head circumference <5%ile by WHO growth curves. Data regarding prenatal, perinatal, and neonatal course was obtained. Data from NICU follow-up assessments including Capute Scales (fine motor, language) and gross motor age equivalent to yield developmental quotients (DQ) were collected. DQs were age adjusted up until 2 years for preterm infants. Delay was defined as DQ <70.

Results: 22 infants had microcephaly: 41% male, 55% preterm, and 41% IUGR/SGA. Etiologies (figure 1) were: unknown (23%), HIE (23%), ICH (14%), and migration anomalies (14%). At latest follow up (3-66 months, mean 26.8), 73% of patients had delay in one or more area of development: gross motor 65% (mean DQ 58.4), fine motor 59% (mean DQ 63.2), and language 59% (mean DQ 65.4). Mean DQs for the entire cohort and subsets based on time of etiologic onset are depicted in Figure 2.

Conclusions: Infants with microcephaly are at significant risk for delay across all aspects of development and at risk for long term disability. In this sample, postnatal etiologies of microcephaly had worse outcomes than congenital or unknown etiologies, but all groups showed significant delays. To help prognosticate outcomes for infants with microcephaly, further prospective studies are required.
Keywords: Neonatal neurology, Cognitive/Behavioral Disorders, Genetics

189. Sedation and Anesthesia in Pediatric Neuro-Critical Care
Benedetti G (Ann Arbor, MI), Rau S, Silverstein F, Shellhaas R

Objective: Sedatives, paralytics, and anesthesia are frequently administered to treat pain and agitation in critically ill infants and children. These agents limit clinical neurological assessment and may exert deleterious effects on the developing brain. We assessed current neuroactive medication use in the intensive care unit (ICU).

Methods: We systematically evaluated exposure to sedatives, paralytics, and anesthetics in consecutive ICU patients for whom neurological consultation was requested.

Results: From 11/1/2015-3/31/2016, 125 patients were evaluated (66 pediatric ICU, 34 neonatal ICU, 25 cardiothoracic ICU). Fifty-two (41.6%) were receiving ≥1 sedative infusion at the time of consultation (51 midazolam, 30 dexmedetomidine, 25 morphine, 20 lorazepam). Sedation use was independent of patient age (p = 0.12). Fifty-three (42.4%) received general anesthesia prior to consultation (29 within the preceding 24h). Forty-nine (39.2%) received ≥1 paralytic agent within the preceding 24h. EEG monitoring (cEEG) was initiated in 90/125 (72%) and 21/90 (23%) had seizures within 24h of monitoring. Sedative infusion (47/52 vs 43/73, p < 0.001) and receipt of paralytic agents within 24h of consultation (41/49 vs 49/76, p = 0.02) influenced rates of cEEG, but preceding anesthesia did not (21/29 vs 61/96, P > 0.9).

Conclusions: Critically ill infants and children are frequently treated with sedatives, paralytics, and anesthetics. There are substantial gaps in knowledge regarding risks and benefits of these medications, alone and in combination, on brain development. Neuroactive medication infusions limit clinical neurological assessments which may increase cEEG use. This has significant implications for resource utilization, but may have important clinical utility as one quarter of patients had electrographic seizures.

Keywords: Neonatal neurology, Epilepsy

190. Fourth Ventricle Size in Relation to Outcome of Preterm Infants with Posthemorrhagic Hydrocephalus
Basan H (Tel Aviv, Israel) Shiran S, Roht J, Constantini S, Ben Sira L, Alon G

Objective: Fourth ventricle (FV) dilatation is increasingly diagnosed in premature infants with posthemorrhagic hydrocephalus (PHH) following ventriculoperitoneal shunt (VPS) insertion. Information is limited, however, on its incidence, risk factors and long term clinical manifestations. To determine the incidence of FV dilatation in preterm infants with PHH following VPS, describe its MRI features, identify neonatal and neurological risk factors, and determine neuro-developmental outcome.

Methods: We retrospectively evaluated 31 infants, who developed PHH and required a VPS insertion. On follow-up MRI (age >2 years), we measured the diameter and/or area of the FV, pons, medulla, and cerebellar hemispheres. We then performed neuromotor and developmental evaluation (Batelle Developmental Inventory II).

Results: A moderate to severe FV dilatation (area >70 mm²) was found in 19 (61%) infants. Mean FV area was larger in infants who manifested neurosurgical complications in comparison to those without (674.2 ± 817 mm² vs. 193.1 ± 178.7 mm², P = 0.03). Mean FV area was significantly correlated to total developmental score (r = -0.4, p = 0.014), and cognitive sub scores (r = -0.4, p = 0.035), but not to motor sub scores. Pons diameter and the cerebellar area were significantly correlated to total developmental score (pons: r = 0.6, p = < 0.001, cerebellum: r = 0.5, p = 0.005, cognitive sub score (pons: r = 0.6, p = 0.001, cerebellum: r = 0.4, p = 0.015), and motor sub score (pons: r = 0.6, p = 0.01, cerebellum: r = 0.4, p = 0.02).

Conclusions: FV dilatation is relatively common in infants with PHH following VPS insertion. It is accompanied by reduction in cerebellar and brainstem dimensions and correlates with poor neurodevelopmental outcome. The value of FV drainage should be assessed in future prospective trials.

Keywords: Neonatal neurology, Neuroimaging, Cognitive/Behavioral Disorders

191. Seizures Among Preterm Neonates: A Multicenter Cohort Study

Objective: Seizure characterization in preterm neonates is limited by small, single-center studies and lack of EEG monitoring. The primary objective of this study was to characterize seizures among preterm neonates in the Neonatal Seizure Registry, a prospective cohort of neonates with seizures at 7 American pediatric centers that follow the American Clinical Neurophysiology Society’s neonatal EEG monitoring guideline.

Methods: From 01/2013-11/2015, 92/611 (15%) of enrolled infants with seizures were preterm. Seizure characteristics were evaluated for extremely preterm (<28 weeks, N = 18), very preterm (28 to < 32 weeks, N = 18), and moderate/late preterm (32 to < 37 weeks, N = 56) neonates.

Results: Hypoxic-ischemic encephalopathy (HIE, 33%) and intracranial hemorrhage (ICH, 27%) accounted for etiology in ≥50%. ICH was more common in <32 weeks; 15 moderate/late preterm subjects received hypothermia for HIE at a median age of 36 (range 33¹/₇-36⁶/₇) weeks. Presence of subclinical seizures and distribution of seizure burden, including status epilepticus, were similar across preterm gestational ages. However, exclusively subclinical seizures were more common in preterm than term neonates (24% vs 14%, p = 0.01). Phenobarbital was the most common initial loading medication for all age groups (>80%). Extremely preterm neonates were most likely to receive levetiracetam as the initial loading medication (25% p = 0.02). Mortality was similar among the preterm age groups but was more than twice that of term neonates (34% vs 14%, p < 0.005).
Conclusions: Preterm neonates accounted for 15% of 611 consecutive neonates with seizures. Subclinical seizures were more common and mortality was higher for preterm than term neonates. These data underscore the contribution of EEG monitoring in preterm neonates.

Keywords: Neonatal neurology, Epilepsy, Neonatal neurology

192. Risk Factors for Post-Hemorrhagic Hydrocephalus Among Infants with Intraventricular Hemorrhage
Tidly H (Seattle, WA), Rue T, Traudt C, Oron A, Saltzman B, Simon T, Kukull W, Doherty D

Objective: Post-hemorrhagic hydrocephalus (PHH) is a common complication of intraventricular hemorrhage (IVH), but the risk factors that predispose infants with IVH to PHH have not been fully elucidated.

Methods: Retrospective cohort study of infants diagnosed with IVH between 2004 and 2014, with and without PHH, from the Pediatric Hospital Information System, which contains data from 44 American children’s hospitals. Poisson regression was used to calculate adjusted risk ratios (RRs) and 95% confidence intervals (CIs) for potential risk factors. Medications with statistically significant associations in individual analyses were evaluated in a combined analysis.

Results: Among 19,077 infants with IVH who lived at least 60 days, 2,422 (12.7%) developed PHH. Hispanic and Asian ethnicity were associated with a reduced risk of PHH compared to whites (RR: 0.84, 95%CI: 0.75, 0.93; RR: 0.63, 95%CI: 0.43, 0.92, respectively). Meningitis was associated with an increased risk of PHH (RR: 2.42, 95%CI: 2.25, 2.61). Patent ductus arteriosus was associated with reduced risk, (RR: 0.80, 95%CI: 0.75, 0.86), as were the NSAIDs indomethacin and IV ibuprofen, used to treat PDA (RR: 0.73, 95%CI: 0.65, 0.83; RR: 0.71, 95%CI: 0.53, 0.96). Dexamethasone was associated with increased risk (RR: 1.68, 95%CI: 1.54, 1.83; RR: 1.26, 95%CI: 1.16, 1.37), but methylprednisolone and prednisolone were associated with reduced risk (RR: 0.78, 95%CI: 0.62, 0.98; RR: 0.79, 95%CI: 0.64, 0.98, respectively).

Conclusions: Several innate and acquired factors are associated with the development of PHH among infants with IVH. The reduced risk associated with certain classes of medication such as NSAIDs and steroids warrants further investigation.

Keywords: Neonatal neurology

193. Effect of Anesthesia on Cerebral Oxygenation and Blood Flow in Neonates with Critical Congenital Heart Disease
Lynch J (New York, NY), Ko T, Newland J, Winters M, Busch D, Nicolao S, Montenegro L, Yodh A, Licht D

Objective: Infants with critical congenital heart disease exhibit a high prevalence of hypoxic-ischemic white matter injury (WMI). Recent work has shown that in infants with hypoplastic left heart syndrome there was an increased risk for post-operative WMI with lower cerebral oxygen saturation (ScO2), measured immediately prior to surgery and after induction with anesthesia. However, the effect of duration and type of anesthesia used on cerebral hemodynamics has yet to be elicited. Understanding the effect of anesthesia on preoperative ScO2 and cerebral blood flow (CBF) in this population will help shed light on the role of anesthesia on the correlation between pre-operative cerebral hemodynamics and WMI.

Methods: Term neonates (N=36) with complex congenital heart defects were recruited. Frequency domain diffuse optical spectroscopy and diffuse correlation spectroscopy were employed to noninvasively quantify ScO2 and CBF immediately before and after induction with fentanyl (5-10 µg/kg) and pancuronium (0.2mg/kg).

Results: We observed a wide range of changes in ScO2 and CBF. On average, there was a decrease in CBF and ScO2 due to anesthesia that was not significantly correlated with diagnosis. The change in ScO2 due induction was significantly correlated with the patient’s weight. Patients with a lower weight exhibited a drop in ScO2 with anesthesia while larger patients exhibited an increase in ScO2.

Conclusions: On average, ScO2 and CBF decreased in all subjects due to anesthesia, and this response did not correlate significantly to cardiac diagnosis.

Keywords: Neonatal neurology

194. Cerebral Tissue Oxygen Consumption Under Deep Hypothermia

Objective: Hypoxic-ischemic white matter brain injury commonly occurs in neonates with hypoplastic left heart syndrome (HLHS). Approximately half of the HLHS survivors exhibit neurobehavioral symptoms believed to be associated with this injury, though the exact timing and risk factors of the injury are not known. Previous studies have shown duration of deep hypothermic circulation arrest (DHCA) to be a risk factor for this injury, while our group has previously shown cerebral tissue oxygenation saturation (StO2) measured on the morning of surgery and time-to-surgery to be the most significant predictors of injury. In
this study, we investigated the effect of DHCA on StO2 in infants with HLHS.

Methods: Term neonates (N=5) with HLHS were recruited. Frequency domain diffuse optical spectroscopy was employed to noninvasively quantify cerebral tissue oxygen saturation (StO2) during deep hypothermic circulatory arrest.

Results: We observed a decrease in StO2 during DHCA in all patients. A linear fit of the data yielded an average (±SD) slope of −2.1 ± 1.4%/min. The average initial StO2 at the start of DHCA in these subjects was 67.1 ± 6.7%, and thus the average time for StO2 to decrease to 0% was approximately 32 minutes.

Conclusions: Even in deep hypothermia, cerebral tissue still continues to extract oxygen, leading to a steady decrease in StO2.

Keywords: Neonatal neurology

195. Neuromotor Score is Predictive of Motor Outcome at 18 Months in Very Preterm Infants

Objective: To determine whether the Neuromotor Score (NMS) predicts motor outcomes of very preterm infants at 18 months corrected age (CA).

Methods: In a prospective cohort of 182 very preterm infants [median gestational age (GA): 27.9 weeks; median birth weight: 1025 grams], the NMS was conducted at a median GA of 32.0 weeks and/or at median GA of 40.2 weeks. Infants were assessed with the Peabody Developmental Motor Scales-2 at 18 months CA; poor motor outcome was defined as 1 SD below the mean (<85). Analyses included Fisher’s exact tests, cross-tabulations, and logistic regression.

Results: 83/175 (47%) of infants assessed early in life and 105/174 infants (60%) at term-equivalent age had an abnormal NMS. Compared to infants with a normal NMS at term, infants with an abnormal NMS were more likely to have postnatal infection (17% versus 36%, P=0.01), severe white matter injury (1% versus 9%, P=0.05), and chronic lung disease (13% versus 34%, P=0.002).

At 18 months CA, 39/175 (22%) of infants assessed early in life and 37/174 (21%) of infants assessed at term-equivalent age had poor gross motor outcomes. NMS showed good sensitivity at both time points (85% and 84% respectively) but less specificity (63% and 46% respectively). NMS early in life (OR 2.7, P=0.001) and at term-equivalent age (OR 2.78, P=0.001) predicted motor outcomes at 18 months CA.

Conclusions: The NMS is a sensitive predictor in identifying very preterm infants who are at risk of poor motor outcomes at 18 months CA.

Keywords: Neonatal neurology

196. Antiepileptic Drug Use for Neonatal Seizure Therapy in United States Neonatal Intensive Care Units (NICUs) from 2005 - 2014
Ahmad K (San Antonio, TX), Desai S, Bennet M, Ahmad S, Ng Y, Clark R, Tolia V

Objective: Seizures are the most common neurological condition in the NICU. Previous surveys have found that phenobarbital and phenytoin are the most prescribed antiepileptic drugs (AEDs) in neonates although use of levetiracetam and topiramate may have recently increased. To evaluate national trends of NICU AED use from 2005-2014

Methods: Using a retrospective cohort design, we identified a subset of NICU infants who were assigned a diagnosis of seizure or seizure disorder. Data were extracted from the Pediatrix Clinical Data Warehouse.

Results: From 778,395 infants across 341 facilities, we identified 10,405 infants with a seizure diagnosis. Of these, 1,039 infants were excluded due to acute transfer leaving 9,366 infants for analysis across 275 facilities. Between 84-94% of patients received at least one AED while use of multiple AEDs increased from 34% to 48% (p<0.0001). At least 11% of patients each year required 3 or more AEDs with a peak of 19% in 2012. Phenobarbital was the most commonly used AED with annual rates of use between 82-91% of infants with seizures. Phenytoin or fosphenytoin use remained stable annually with 10-14% treated. Levetiracetam use substantially increased from <1% of infants in 2005 to 14% of infants by 2014 (p<0.0001).

Conclusions: AED use was common in the treatment of seizures in the NICU and almost half of these patients were exposed to multiple AEDs. Use of multiple medications has become more frequent. Levetiracetam use, for which little efficacy data exists in neonates, increased 20-fold, surpassing phenytoin as the second most widely used AED.

Keywords: Neonatal neurology, Epilepsy
197. Circulating Inflammatory-associated Proteins in the First Month of Life Predict Cognition at 10 Years in Children born Extremely Preterm

Objective: To consider the hypothesis that children born extremely preterm (EP) with cognitive impairment are more likely than those without cognitive impairment to have indicators of sustained systemic inflammation in the first postnatal month of life.

Methods: We evaluated the relationship between concentrations of 25 inflammation-associated proteins in blood spots obtained during the first two postnatal weeks (early proteins), and 16 proteins from samples taken at 21 and 28 days (late proteins), with neurocognition in 889 EP10-year olds.

Results: Early elevated concentrations of CRP, TNF-alpha, IL-8, ICAM-1, and EPO were significantly associated with intelligence quotient (IQ) more than 2 SD below the expected mean (OR: 2.0-2.3) and with moderate and severe impairment on a composite measure of IQ and executive function (EF)) (OR: 2.1-3.6). Additionally, severely impaired cognition was associated with late protein elevations of CRP (OR: 4.0; 1.5, 10), IL-8 (OR: 5.0; 1.9, 13); ICAM-1 (OR: 6.5; 2.6, 16); VEGF-R2 (OR: 3.2; 1.2, 8.3); and TSH (OR: 3.1; 1.3, 7.3). IL-8, ICAM-1, and VEGF-R2 also were significantly elevated in mildly impaired children compared to unimpaired children. Impaired IQ, EF, and overall cognition were associated with 4 or more early elevated inflammatory protein elevations (OR: 2.1-2.4) and with four or more late protein elevations (impaired IQ: OR: 3.2; impaired EF: OR: 2.9; and severely impaired cognition: OR: 4.8).

Conclusions: EP children who had sustained systemic inflammation in the first postnatal month are more likely than their EP peers without inflammation to have cognitive impairment at 10 years.

Keywords: Neonatal neurology, Cognitive/Behavioral Disorders

198. Anticoagulation Therapy and the Risk of Brain Injury in Neonates with Transposition of the Great Arteries
Leijier L (Toronto, Ontario, Canada), Chau V, Seed M, Blaser S, Poskit K, Synnes A, Hickey E, Campbell A, McQuillen B, Miller S

Objective: Neonates with transposition of the great arteries (TGA) are at increased risk of brain injury, particularly stroke. As the management of pre-operative stroke or thrombosis in neonates with TGA may include anticoagulation to minimize the risk of subsequent stroke, we sought to determine the relationship between anticoagulation therapy following pre-operative brain MRI with the risk of post-operative brain injury.

Methods: In this two-centre cohort study, 61 term-born neonates with TGA undergoing an arterial switch operation were prospectively studied with pre- and post-operative brain MRI and scored for: stroke, white matter injury (WMI) and subdural/intraventricular hemorrhage (SDH/IVH). Relative risks (RR) of post-operative brain abnormalities were calculated for pre-operative stroke and anticoagulation following pre-operative stroke or thrombosis.

Results: Pre-operative stroke was detected in 13(21%) neonates, of whom 12 had septostomy. Other pre-operative brain injury included WMI in 9(15%), IVH in 9(15%) and SDH in 9(15%). Post-operatively additional injury was common: stroke in 5(8%), WMI in 16(26%), SDH in 9(15%) and IVH in 5(8%). In 9(15%) neonates anticoagulation was started for stroke (n=3) or thrombosis (n=6) between pre-operative MRI and arterial switch. Among neonates with pre-operative stroke none had new strokes on post-operative MRI, whether treated with anticoagulation therapy (n=3) or not (n=10). Among the 9 neonates treated with anticoagulation, there were trends to more post-operative WMI (RR 1.9; 95%-CI 0.8-4.7) and SDH (RR 2.8; 95%-CI 0.9-9.3).

Conclusions: Recurrent stroke is uncommon in neonates with TGA. Rigorous clinical trials are needed to determine the appropriate use of anticoagulation therapy in neonates with TGA.

Keywords: Neonatal neurology, Stroke, Neuroimaging

199. Cranial Ultrasonography in Term Infants and Stroke: When is it Useful?
Mondok L (Cleveland, OH), Friedman N

Objective: To report the diagnostic sensitivity and accuracy of cranial ultrasonography in detecting ischemic infarct and intraparenchymal hemorrhage in term infants in a tertiary pediatric center

Methods: Term neonates and infants from 2005-2015 with evidence of infarct (arterial or venous) or hemorrhage in brain CT or MRI and preceding cranial ultrasound results were analyzed in a retrospective cross-sectional study.

Results: Thirty patients were identified in the ischemic infarct group (24 arterial, 4 mixed, 2 venous) with only 5/30 (16% sensitivity, 95% CI 0.06-0.35) found to have abnormal cranial ultrasound results prior to confirmatory neuroimaging. Lesion size did not correlate to increased ultrasound findings. Congenital heart disease was present in 12/30 patients (40%) and 15/30 (50%) had no significant risk factors for stroke. There were 11 patients in the hemorrhage group and all except 2 had abnormal cranial ultrasound results (81% sensitivity, 95% CI 0.47-0.96). Etiology of intraparenchymal hemorrhage was more variable. EEG monitoring performed showed abnormalities in 20/30 (66%) patients in ischemic group and 7/9 (77%) in hemorrhage group. Time between cranial ultrasound and confirmatory brain CT or MRI was 4.9 days for ischemic infarct versus 1.8 days for hemorrhage.

Conclusions: Cranial ultrasonography has poor sensitivity in detecting ischemic infarcts in term infants. Advanced neuroimaging should be pursued if there is high clinical suspicion for ischemic infarcts in the neonatal period.

Keywords: Neonatal neurology, Stroke, Neuroimaging
200. Equipment in Management of Electrographic Seizures in Neonates with Hypoxic Ischemic Encephalopathy
McNally M (Baltimore, MD), Hartman A

Objective: Neonatal seizures (NSs) are commonly seen after hypoxic ischemic encephalopathy (HIE). Preclinical models suggest that NSs are harmful to the developing brain, but controversy remains regarding treatment of non-status NSs. However, growing clinical evidence suggests that electrographic seizures (ESzs) may be independently harmful in neonates with HIE. The objective of this study is to determine the scope of practice nationally regarding management of ESzs in neonates with HIE.

Methods: A case-based survey was distributed nationally through the Child Neurology Society and American Academy of Pediatrics Section on Neonatal-Perinatal Medicine list serves.

Results: Total years in practice among providers who responded (N=131) ranged from 0-40 with a median of 10 (1st quartile 4, 3rd quartile 25). For an ESz with mild HIE, 18% would observe, 67% would administer phenobarbital (PHB), and 14% would administer levetiracetam (LEV). If the ESzs persisted, 97% would initiate treatment (76% PHB, 17% LEV, 4% fosphenytoin (PHT)). If the ESzs were associated clinical correlates, 90% said their management would not change. In a case of severe HIE with initial electrographic status epilepticus on PHB, if there were ongoing intermittent ESzs, 14% would observe, 26% would increase PHB, 41% would add LEV, and 19% would add PHT.

Conclusions: Results from our national sample demonstrate equipoise in how ESzs are managed in neonatal HIE. Further studies looking at the immediate consequences of ESzs, their optimal treatment, and their effect on long-term neurodevelopmental outcomes are needed to optimize and universalize management of ESzs in this patient population.

Keywords: Neonatal neurology, Epilepsy

201. Comparing Fetal and Postnatal MRI Findings in Congenital Aqueductal Stenosis: Incidence of Rhombencephalosynapsis and Outcomes
Arroyo M (Cincinnati, OH), Thomas C, Kline-Fath B, Jawish R

Objective: Congenital aqueductal stenosis (CAS), a cause of fetal ventriculomegaly, may be associated with rhombencephalosynapsis (RES), a rare malformation of the cerebellum. The association of these findings may have prognostic implications for fetal counseling. This study aims to: 1) Determine incidence of co-occurring CAS and RES in a prenatally diagnosed CAS cohort, 2) Determine correlation between fetal and postnatal imaging for diagnosis of RES, 3) Describe morbidity and mortality outcomes.

Methods: Charts of fifty-five patients diagnosed by fetal MRI with CAS between 2005-2015 were reviewed for: Demographic data: maternal age, parity, delivery mode, gestational age, birth weight, prenatal genetic testing. Morbidity in NICU: need for shunt, tracheostomy, gastrostomy tube or seizure treatment. Mortality: pregnancy termination, intrauterine fetal demise (IUFD), death in NICU or still living.

Postnatal images were compared to corresponding fetal MRIs.

Results: Medical records were available for 48/55 (87%) patients. Mortality: 9 elective terminations (19%), 4 IUFD (8%), 1 died in NICU (3.5%), 35 live births (73%). Morbidity in NICU: 22 required shunt (79%), 1 required tracheostomy (3.5%), 4 required gastrostomy tube (14%), and 7 had seizures (25%). Initial review of fetal MRIs revealed 7 cases of CAS with RES (incidence 13%). Comparisons to postnatal scans are in process. All patients with prenatally diagnosed RES in original fetal MRI required shunt placement.

Conclusions: The incidence of RES in our cohort is similar to other published literature though we suspect when review of postnatal imaging is complete this incidence will increase. The presence of RES in conjunction with CAS affects morbidity and mortality.

Keywords: Neonatal neurology, Neuroimaging

202. Relationship Between Sociodemographics, Prenatal Care and Brain Injury in Preterm Newborns
Tavassoli M (Irvine, CA), Ferriero D, Barkovich A, Gano D

Objective: To evaluate the association of sociodemographic factors, and prenatal care with brain injury on magnetic resonance imaging (MRI) in a prospective cohort of preterm infants.

Methods: 284 infants <33 weeks gestation were prospectively studied with MRI soon after birth. A blinded pediatric neuroradiologist evaluated the severity of intraventricular hemorrhage (IVH) and white matter injury (WMI) using validated scoring systems. Infant race and ethnicity were collected via parental self-report. Prenatal care was classified as absent/delayed or routine. Clinical characteristics and brain injury were compared by level of prenatal care. The association between prenatal care, race, ethnicity and brain injury was evaluated using logistic regression adjusting for quintiles of propensity for routine prenatal care.

Results: Prenatal care was absent/delayed in 22, and routine in 262 infants. Routine prenatal care was associated with higher parity, older maternal age, and twin gestation(all P<0.01). Absent/delayed care was associated with an increased risk of moderate/severe IVH(RR 4.2, 95% CI 2.1-8.1, P<0.001) but was not associated with WMI. Adjusting for predictors of IVH and propensity for routine prenatal care, absent/delayed prenatal care was independently associated with increased odds of moderate/severe IVH(OR 3.82, 95% CI 1.09-13.39, P<0.036). Moderate/severe IVH was increased among African American infants(OR 4.95, 95% CI 1.07-23.3, P<0.04).

Conclusions: Absent/delayed prenatal care and African American race were independently associated with increased odds of moderate/severe IVH in this prospective cohort of premature newborns. Unmeasured factors such as maternal nutrition and socioeconomic status may account for the observed association of prenatal care and race with IVH.

Keywords: Neonatal neurology, Neuroimaging
203. Fetal Central Nervous System Malformations: A Ten Year Review of Prenatal Consultations at a Tertiary Care Center
Agarwal S (Houston, TX), Keller J, Clark G, Emrick L

Objective: Congenital malformations of the central nervous system (CNS) are increasingly being recognized prenatally due to better fetal imaging modalities. Prenatal counseling includes critical prognostication for the future neurodevelopmental outcomes, based on the anomaly, associated genetic aberrations and perinatal infections, with careful consideration of parental anxiety and ethical decision making. The study provides a profile of various fetal CNS malformations and helps identify associated perinatal risk factors, genetic abnormalities, perinatal infections and the neurodevelopmental outcomes.

Methods: The study reports data from a retrospective and prospective chart review of CNS abnormalities detected in the prenatal period from 2006 to 2016. All prenatal neurologic consultations presenting to the Fetal Center, Texas Children’s Hospital were reviewed for studying the prevalence of various CNS malformations based on our referred cohort, their association with perinatal risk factors and the postnatal outcomes. Genetic testing and other prenatal testing results were also reviewed.

Results: The results reviewed records from pregnant women presenting over these years and looked at prevalence of CNS abnormalities and the association with high risk maternal and perinatal factors. Postnatal imaging and prenatal imaging results were correlated. The neonatal follow up was correlated to the prenatal and postnatal imaging diagnoses and prognosis.

Conclusions: The study identifies prenatal CNS malformations and associated perinatal risk factors, genetic abnormalities, perinatal infections and the neurodevelopmental outcomes. This data will provide preliminary results to develop a standardized and comprehensive approach to fetal neurologic consultations and to prognosticate for neurodevelopmental outcomes, for timely decision making in the prenatal period and postnatal care of the infant.

Keywords: Neonatal neurology, Neuroimaging, Genetics

204. Brain Maturation and Neurodevelopmental Outcomes in Infants with Congenital Diaphragmatic Hernia

Objective: Total maturation score (TMS), a quantitative assessment of brain immaturity using magnetic resonance (MR) imaging, has been consistently validated in premature infants and in congenital heart disease. The aim of this study was to investigate the impact of brain maturation on short-term neurodevelopmental (ND) outcomes in congenital diaphragmatic hernia (CDH) survivors.

Methods: This is a single-center retrospective study of brain MRI and one-year neurodevelopmental assessment (Bayley Scores of Infant Development – III) in a prospective

TABLE 1. Total maturation score (TMS) is the sum of four parameters of cerebral maturation as described by Childs et al (Abstract 204)

<table>
<thead>
<tr>
<th>Myelination (M)</th>
<th>Cortical infolding (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1 Myelination evident in brain stem, cerebellar peduncle, inferior colliculus, cerebellar vermis</td>
<td>C1 Frontal and occipital cortex completely smooth, insula wide open; thin bright cortical rim on T1, generally low-intensity white matter (WM) on T1</td>
</tr>
<tr>
<td>M2 + Subthalamic nuclei, globus pallidus, ventrolateral thalamus</td>
<td>C2 Frontal cortex still very smooth, some sulci evident in occipital cortex; insula still wide with almost smooth internal surface; WM low intensity on T1</td>
</tr>
<tr>
<td>M3 + Caudal portion of the posterior limb of the internal capsule (PLIC)</td>
<td>C3 Frontal and occipital cortex similar number of convolutions; frontal sulci still quite shallow; internal surface of insula more convoluted; WM still somewhat low intensity on T1</td>
</tr>
<tr>
<td>M4 + Complete PLIC</td>
<td>C4 Frontal and occipital cortex folded and rich in sulci; frontal sulci obvious along interhemispheric fissure; occipital WM separated into strands by deeper sulci; insula more convoluted and infolded; WM still slightly low intensity on T1</td>
</tr>
<tr>
<td>M5 + Optic radiation</td>
<td></td>
</tr>
<tr>
<td>M6 + Corona radiata</td>
<td></td>
</tr>
<tr>
<td>M7 + Anterior limb of internal capsule</td>
<td></td>
</tr>
</tbody>
</table>

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### TABLE 1. Continued

**Cortical infolding (C)**
- **C5**: Frontal and occipital WM separated into strands by deeper sulci; insula completely infolded; WM still distinguishable from gray matter on T1
- **C6**: As above but WM now isointense with gray matter on T1

**Germinal matrix (G)**
- **G1**: Matrix seen in posterior horn, at caudothalamic notch (CTN) and anterior horns of lateral ventricles
- **G2**: Matrix evident at CTN and anterior horns only
- **G3**: Matrix at anterior horns alone
- **G4**: No matrix evident

**Bands of migrating glial cells (B)**
- **B1**: Broad band with additional narrower bands
- **B2**: Broad band alone
- **B3**: Narrow band alone
- **B4**: No bands seen

---

### TABLE 2. TMS and neurodevelopmental outcome (N = 32)

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>Cognitive scores</th>
<th>Language scores</th>
<th>Motor Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>TMSb</td>
<td>Normal</td>
<td>27</td>
<td>104.0 ± 6.5 (105, 95-111)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>5</td>
<td>93.7 ± 17.0 (95, 55-120)</td>
<td></td>
</tr>
</tbody>
</table>

a. Data are presented in mean ± SD (median; range).
b. Normal TMS value is 14. Low TMS value ends at 13.5.

---

### TABLE 3. Structural brain abnormalities and neurodevelopmental outcome (N = 83)

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>Cognitive scores</th>
<th>Language scores</th>
<th>Motor Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periventricular leukomalacia</td>
<td>No</td>
<td>78</td>
<td>92.6 ± 13.6 (95, 55-130)</td>
<td>87.0 ± 11.2 (86, 56-109)</td>
</tr>
<tr>
<td></td>
<td>Yesa</td>
<td>5</td>
<td>92.5 ± 13.2 (90, 80-110)</td>
<td>88.2 ± 18.4 (91, 62-109)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>No</td>
<td>79</td>
<td>92.5 ± 13.4 (95, 55-130)</td>
<td>87.3 ± 11.7 (89, 56-109)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>4</td>
<td>92.5 ± 17.6 (93, 75-110)</td>
<td>81.8 ± 9.6 (81, 71-94)</td>
</tr>
</tbody>
</table>

a. One patient with only language score available.
cohort of survivors of CDH surgery. MR images were analyzed for brain injury and overall brain maturation using TMS, validated for infants ≤41 post-conceptual weeks of age (PCA).

**Results:** Between September 2004 and December 2014, 83 of the 215 CDH survivors were studied. Thirty-two patients (39%) underwent brain MRI between the age of 36 and 41 PCA allowing for TMS evaluation. Total maturation scores were dichotomized to low (<14) and normal (≥14, average score for healthy historical controls). A low TMS was associated with lower cognitive scores (93.7 ± 17.0 vs 104.0 ± 6.5, p = 0.03) and lower language scores (85.6 ± 13.4 vs 97.0 ± 3.7, p = 0.001). All patients (n = 83) were assessed for structural brain abnormalities. Patients with evidence of acquired brain injury (periventricular leukomalacia, intracranial hemorrhage) generally had lower ND scores compared to those without brain injury; however, low numbers prevented statistical analysis.

**Conclusions:** Brain immaturity, as quantified on MRI, is associated with delayed ND outcomes at one year of age among CDH survivors.

**Keywords:** Neonatal neurology, Neuroimaging, Cognitive/Behavioral Disorders

### 205. Bumetanide Suppresses Biomarkers of Neuroinflammation in the Neonatal Rat Brain Exposed to Hyperoxia


**Objective:** Bumetanide (B) is a diuretic; NaKCl co-transporter; and NKCC1 and aquaporin (AQP) inhibitor that is currently being considered for treatment of neonatal seizures and autism. The mechanism for possible benefits of B remains to be elucidated. We tested the hypothesis that B suppresses biomarkers of neuroinflammation in the developing brain exposed to hyperoxia.

**Methods:** Neonatal rats were exposed to 50% O2 or room air (RA) during which they received IP injections of low-dose (0.4 mg/kg, Lo-B) and high-dose (10 mg/kg, Hi-B) from birth (P0) to P3. Control animals received equivalent volume saline (NS). Hyperoxia groups were exposed to 50% O2 from P0 to P14, and RA from P14 to P21. At P14 and P21, biomarkers of neuroinflammation (IL6, IL10, MCP1, TGFβ), neurotransmission (GAD65, GAD67, AQP1, AQP11, NKCC1, GABA_A) and astroglial activation (GFAP, connexin 43) were examined in the brain at P14 and P21 using ELISA and immunofluorescence staining.

**Results:** Lo-B and Hi-B substantially decreased IL-6, TGFβ and AQP-1 (p<0.05). More significantly, B suppressed MCP-1 in a dose-dependent manner (p<0.01). B increased AQP-11 at P14 and P21 in RA (p<0.01), and reduced it in 50% O2 (p<0.05). In the cerebral cortex, B decreased all biomarkers, except KCC2, which was robustly elevated.

**Conclusions:** B had significant effects on all markers in neonatal cortical neurons. Data demonstrate that B at the right doses may be protective against NKCC1, which has been shown to be involved in many brain disorders during early development.

**Keywords:** Neonatal neurology, Translational/experimental therapeutics, Infections/Neuroimmunology

### 206. Implementation of a Neonatal Neuro-Critical Care program (N-NCC): Improved Seizure Detection and Management in Neonates with Hypoxic Ischemic Encephalopathy (HIE)

** Bashir R** (Calgary, Alberta, Canada), Espinoza L, Vayalbrikkovil S, Irvine L, Buchhalter J, Bello-Espinosa L, Mohammad K

**Objective:** To report the impact of implementing continuous video electroencephalography (CVEEG) monitoring for neonates with HIE in the context of a N-NCC.

**Methods:** Neonates with HIE were studied retrospectively two years pre & post implementing CVEEG for 72 hrs as a routine. Before CVEEG, 60 minute routine EEG (rEEG) was performed at the discretion of the provider. Primary outcome: electrographic seizure detection; secondary outcomes: use of maintenance anti-epileptic drugs (AEDs), discharge AEDs, and cumulative dose defined as AED burden (total mg/kg during hospital stay).

**Results:** Total N=157; median gestation 40 weeks; 103 (66%) cooled. Baseline and clinical characteristics including disease severity and cooling were similar. Pre-CVEEG (N=86):44 (51.2%) had clinical seizures, of those, 35 had available rEEG; 12/35 (34%) had electrographic seizures. None of the infants without clinical seizures showed electrographic seizures. Post CVEEG (N=71): 34 (47.9%) had clinical seizures, of those 18/34 (53%) had electrographic seizures. 5/37 (14%) of infants with no clinical seizures had electrographic seizures. The introduction of CVEEG significantly increased electrographic seizure detection (p<0.016). Though there was no significant difference in the initiation of AED and maintenance use, post CVEEG, fewer infants were discharged on any AED (p=0.008) and mean phenobarbital burden reduced (p=0.034) without increase in other AEDs use.

**Conclusions:** Routine use of CVEEG as part of N-NCC program improved electrographic seizure detection; decreased phenobarbital burden and AEDs use at discharge.

**Keywords:** Neonatal neurology, Epilepsy, Translational/experimental therapeutics

### 207. Quantitative Neonatal Sleep Analyses Predict Neurodevelopmental Outcomes

**Shellhaas R** (Ann Arbor, MI), Burns J, Hassan F, Carlson M, Barks J, Chervin R

**Objective:** For newborns who require intensive care, sleep patterns reflect neurological function. We evaluated the predictive value of quantitative newborn sleep parameters for 18-month neurodevelopmental outcomes.

**Methods:** Term newborns with suspected seizures underwent a 12-hour bedside polysomnogram (PSG). For each infant, the distribution of sleep-wake stages, entropy of the sequence of state transitions, and delta power from the electroencephalogram (EEG) portion of the PSG were
calculated. Neurological examination (Thompson) scores were assigned on the day of the PSG. Surviving infants completed Bayley Scales of Infant Development, 3rd edition (BSID), at 18-22 months. Spearman correlations were used to evaluate associations between sleep measures and BSID subscale scores.

Results: Twenty-eight newborns completed the BSID. In univariate analyses, worse Thompson score ($\rho = -0.48$, $p = 0.016$) and higher sleep-wake entropy ($\rho = -0.47$, $p = 0.015$) were associated with lower BSID motor scale scores. Increased EEG delta power (0.5-2Hz) during quiet sleep ($\rho = 0.6$, $p = 0.0013$) and active sleep ($\rho = 0.48$, $p = 0.013$) was associated with better BSID motor scores. Predictors of motor scores remained significant after adjusting for neonatal Thompson score and gestational age. Delta power during quiet sleep ($\rho = 0.46$, $p = 0.016$) and the percent difference in delta power between active and quiet sleep ($\rho = 0.44$, $p = 0.02$) were also associated with BSID language scores in univariate analyses, but were not significant after adjusting for Thompson score and gestational age.

Conclusions: These novel, longitudinal data suggest that inefficient neonatal sleep – characterized by more disrupted sleep and lower EEG delta power – is an informative and independent predictor of adverse long-term outcome for newborns with neurological dysfunction.

Keywords: Neonatal neurology

209. Erythropoietin Decreases the Volume of Brain Injury in Newborns with Hypoxic-Ischemic Encephalopathy


Objective: To determine effect of erythropoietin (EPO) on the volume of acute brain injury and to determine the association of brain injury volume with neurodevelopmental outcome in newborns with hypoxic-ischemic encephalopathy (HIE).

Methods: Fifty newborns at 7 U.S. sites with moderate to severe HIE were randomized to EPO 1000 U/kg IV or placebo on days 1, 2, 3, 5 and 7 in addition to hypothermia. Whole brain volumes were measured from T1 images for infants who had MRI at ≤7 days of age. The volume of brain injury (defined as apparent diffusion coefficient <800) was measured on diffusion weighted imaging (DWI). Infants had the Warner Initial Developmental Evaluation (WIDEA) and the Alberta Infant Motor Scale (AIMS) at 12-months.

Results: Forty-four newborns, 84% moderate HIE, mean ± SD birth weight 3.3 ± 0.7 kg, gestational age 38.7 ± 1.7 weeks, 5-min Apgar 3.4 ± 2.0, initial pH 7.0 ± 0.2, had MRI at 4.4 ± 1.3 days of age. All received hypothermia. Two infants died before MRI and 4 had MRI >7 days. Twenty-one had DWI injury. There were no baseline characteristic or whole brain volume differences between infants with and without DWI injury. DWI injury volume was lower in the EPO (25.1 ± 73.8 cm³) than placebo group (68.8 ± 107.1 cm³, $P = 0.004$). DWI injury volume negatively correlated with WIDEA ($P < 0.01$) and AIMS ($P < 0.001$) scores.

Conclusions: EPO treatment reduces DWI injury volume in newborns treated with hypothermia for HIE. DWI injury volume correlates with 12-month neurodevelopmental outcome.

Keywords: Neonatal neurology, Neuroimaging

210. EEG Recording of a SIDS-like Event Followed by Loss of Heart Rate Variability in a Cooled Newborn

Anwar T (Washington, DC), Al-Shargabi T, Tsuchida T, Scarfidi J, Duplessis A, Govindan R, Chang T

Objective: We report the case of a 2-day-old male infant with a SIDS-like event captured on continuous video EEG.

Methods: We reviewed the medical records, EEG recordings and neuroimaging studies of this case. EEG with heart rate (HR) recording was reviewed for background and analyzed for heart rate variability.

Results: An infant was born at 35 weeks via emergent C-section secondary to placental abruption. He was transferred to our center for therapeutic hypothermia for presumed hypoxic ischemic encephalopathy. EEG initially was almost normal for age. At 29.3 hours of life (HOL), the infant had outcomes relative to non-identical twins. These data suggest that adverse neurodevelopmental outcomes in preterm neonates relate more strongly to acquired perinatal adversity (e.g. infection, brain injury) than to genetic factors alone.

Keywords: Neonatal neurology, Neuroimaging
suppression of EEG activity. He was given a loading dose of Phenobarbital at 30.5 HOL for seizure concerns, causing an excessively discontinuous EEG background pattern. At 37.5 HOL, the EEG changed in background to a pattern consistent with electrocerebral inactivity and then was followed by sustained bradycardia of less than 50 and desaturation to less than 40%. Positive pressure ventilation was initiated, and he received one dose of epinephrine before heart rate and saturations stabilized. HR variability did not return to baseline after returning to normothermia (p<0.05) and could not be explained by the Phenobarbital load (see Figure).

Conclusions: To our knowledge, this may be the first SIDS-like event captured on EEG and is reminiscent of SUDEP events occasionally captured on continuous EEG.

Keywords: Neonatal neurology

211. Post-Operative Recovery of Cerebral Metabolism in Neonates with Critical Congenital Heart Disease
Objective: Infants with critical congenital heart disease (CHD) experience a high incidence of peri-operative hypoxic-ischemic diffuse white matter injury, specifically periventricular leukomalacia (PVL), which may underlie adverse neurodevelopmental outcomes at school age[1,2]. Using non-invasive diffuse optical measurements of cerebral hemodynamics, we recently uncovered an important link between time-to-surgery, the decline of cerebral oxygen saturation (ScO2), and risk of new or worsened post-operative PVL[3]. This work aims to elucidate the peri-operative timing of cerebral metabolism and desaturation to pinpoint vulnerable periods for injury.

Methods: Near-infrared diffuse optical spectroscopy (DOS) and diffuse correlation spectroscopy (DCS) were used to longitudinally quantify ScO2, total hemoglobin concentration (THC) and cerebral blood flow daily from birth through surgery (n=50) and through post-operative recovery (n=34) in term CHD neonates (37-42 weeks gestation). Linear mixed-effects models including subject-specific random effects were used to predict mean cerebral hemodynamics as a function of time-after-birth and time-after-surgery.

Results: Pre-operatively, time-after-birth is a significant predictor of ScO2 and oxygen extraction fraction (OEF, p<0.0001) and the effect of time-after-birth on cerebral metabolic rate of oxygen (CMRO2,i) trends significantly (p=0.09). The use of deep hypothermic circulatory arrest (DHCA), reflective of aortic arch obstruction, significantly predicts pre-operative ScO2 (p<0.01), OEF (0.03), and CMRO2,i (p<0.0001). In the post-operative period, time-after-surgery significantly predicts ScO2 (p=0.04), and DHCA is a significant predictor of CMRO2,i (p=0.0065) and THC (p=0.01), and trends significantly with ScO2 (p=0.05).

Conclusions: As cerebral oxygen utilization increases with maturation, these results suggest that timely surgical intervention is crucial to mitigating the accelerated pre-operative decline of cerebral oxygen saturation.

Keywords: Neonatal neurology, Neuroimaging

212. Severe Retinopathy of Prematurity Predicts Delay in Posterior White Matter and Optic Radiation Myelination with Poor Neurodevelopmental Outcomes

Objective: Severe retinopathy of prematurity (ROP) is a disorder of abnormal retinal vascular growth in preterm infants that, when severe, is treated with photocoagulation laser therapy. We addressed the hypotheses that ROP requiring laser therapy predicts (1) adverse white matter maturation in vision and visual-association regions, and (2) worse neurodevelopmental outcomes at 18 months corrected age (CA) relative to neonates without ROP.

Methods: 105 very preterm newborns (24-28 weeks gestational age [GA]) assessed for retinopathy of prematurity were prospectively studied with MRI near birth and at term-equivalent age. Using diffusion tensor imaging, white matter maturation was assessed using mean fractional anisotropy (FA) in 7 predefined regions of interest and with tract-based spatial statistics (TBSS). 90/105 (86%) children were assessed at 18 months CA using the Bayley-III: motor, cognitive, and language composite scores. Associations were examined using Fisher exact test, Kruskall-Wallis and multivariate regression to adjust for GA.

Results: 20/105 (19%) infants had ROP treated with laser therapy. ROP was associated with greater likelihood of bronchopulmonary dysplasia, longer duration of invasive ventilation, hypotension and culture positive infection. ROP had measurable decreases in brain maturation in the optic radiations on TBSS, as well as lower mean FA in the posterior white matter region (p=0.03). Bayley-III cognition and motor scores were significantly lower in ROP, even when adjusted for GA and white matter injury.

Conclusions: ROP is associated with maturational delay in the optic radiations and posterior white matter, the primary visual pathways. ROP predicts poorer cognitive and motor outcomes, independent of GA.

Keywords: Neonatal neurology, Neuroimaging, Cognitive/Behavioral Disorders

INFECTIONS/NEUROIMMUNOLOGY

213. Isolated Neurological Phenotype in Congenital CMV: An Under Recognized and Characterized Cohort

Objective: Congenital CMV (cCMV) is the most common congenital infection in this country and it is a major cause of sensory and neurodevelopmental disabilities in our children. There are known treatments that have shown to improve the neurodevelopmental outcomes if initiated early in the course of the infection. Yet we still have much to learn about its protein manifestations, the best tools for diagnosis and evaluation for the extent of neurological disease, predictors of neurodevelopmental outcome, and the optimal management.

Methods: We performed a retrospective review of a referred cohort of 151 patients with CMV and analyzed the outcomes.

Results: The study showed that 24 patients with cCMV had isolated CNS phenotype without systemic features. 17/24 were confirmed either at birth or retrospectively with PCR of dried blood spot. The reasons for CMV testing included delayed vision, hearing loss, microcephaly and abnormal neuroimaging. Many of the patients had not only focal epilepsy but also myoclonic seizures with electrographic changes with photic stimulation.

Conclusions: Early identification and treatment of cCMV in the mother or infant has shown to improve neurological and developmental outcomes. It is important to recognize this cohort of children who present without the classical features that prompt CMV testing. Advancements
214. Long-Term Functional Outcomes in Anti-NMDA Receptor (Anti-NMDAR) Encephalitis

Yeshokumar A (Baltimore, MD), Gordon-Lipkin E, Arenivas A, Probasco J

Objective: Anti-NMDAR encephalitis is a common cause of autoimmune encephalitis in children. Patients are typically thought to have favorable response to therapy despite dramatic presentation; however, long-term outcomes studies are limited, particularly in children. This study compares adaptive function outcomes in children and adults at least one year following initial diagnosis and treatment.

Methods: Retrospective chart review of inpatient records at Johns Hopkins Hospital identified eleven patients with anti-NMDAR encephalitis diagnosed over a ten year period. Patients and their families were asked to participate in a telephone survey regarding overall health and functional status. The ABAS-III, a validated measure of adaptive function, was also administered.

Results: Eight subjects were enrolled, of whom four were children younger than 18 years. Median duration since diagnosis was 2.90 years (IQR 2.20). Two children and two adults reported difficulty with fatigue, short-term memory, following directions, and/or concentration. On the ABAS-III, although overall adaptive function appeared intact for adults (general adaptive composite: median 100.50, IQR 12.25), the median score for children qualified as “below average” (general adaptive composite: median 82.00, IQR 10.00). Conceptual and practical skill areas were most affected, while social skill areas remain preserved.

Conclusions: Children, more so than adults, affected with anti-NMDAR encephalitis may have deficits in adaptive function, specifically in areas of conceptual and practical skills. These deficits may persist years after initial diagnosis and treatment. Further studies are warranted to quantify common complaints of memory and concentration deficits. These results may have implications for the clinical management, anticipatory guidance, and therapy needs of patients.

Keywords: Infections/Neuroimmunology, Neonatal neurology, Neuroimaging

215. Application of the Latest Proposed Criteria for Diagnosis of Pediatric Autoimmune Encephalitis (AIE)

Basit A (St. Louis, MO), Mar S

Objective: To describe the recently evaluated cases of suspected AIE (2) Utilize the latest proposed algorithm as a diagnostic tool.

Methods: The medical record database at St. Louis Children's Hospital was searched to find patients with autoimmune encephalopathy antibody panel (Mayo) and/or independent anti-NMDA receptor antibody testing sent between 2013 to present. 60 patients were identified and each chart reviewed for neurological presentation, work up and treatment undertaken. These were subsequently analyzed using the diagnostic criteria for AIE published in Lancet Neurology in February 2016.

Results: Mean age of presentation was 10.5 years (2-17 years). Presenting symptoms included altered mental status (70%), memory deficits (9%), psychiatric symptoms (72%), all with subacute onset. 60% had clinical or subclinical seizures. 48% patients had pleocytosis on spinal fluid analysis. Brain MRI findings suggestive of possible immune etiology were present in 30% of patients. 70% fulfilled criteria for Possible AIE and were treated with IV steroids followed by oral taper, IVIG, plasma exchange, rituximab or a combination there-of. Those that did not fulfill criteria were diagnosed with other conditions such as primary psychiatric disorder. Three patients met criteria for Probable Anti-NMDA-receptor encephalitis with subsequent antibody confirmation. One met criteria for definite AI limbic encephalitis but did not have positive antibodies. Two had neuronal K-channel antibody confirmed limbic encephalitis.

Conclusions: Our results add to the existing clinical experience with AIE to help improve approach to management. Early recognition of AIE in children can be accomplished using the latest diagnostic criteria, speeding initiation of immunotherapy and potentially improving outcomes.

Keywords: Infections/Neuroimmunology, Cognitive/Behavioral Disorders

216. Stiff-Person Syndrome, A Diagnostic Challenge

Nagesh D (Kansas City, MO), Pannoor M

Objective: To present a case of Stiff-Person Syndrome, discuss diagnostic challenges and review the literature.

Methods: Chart review of a patient with Stiff-Person Syndrome, followed in our neuromuscular clinic was performed. Patient is a 7-year old girl with type 1 diabetes mellitus, who initially presented with difficulty walking, stiffness in both lower extremities. She had stiffness, external rotation of the right leg while walking and was diagnosed with equino-varus deformity of her right foot. She also had significant psychiatric issues. Since she continued to have worsening difficulty walking with muscle spasms despite orthotic support, developed inability to navigate stairs and incontinence of bladder, she underwent an extensive evaluation for spinal anomalies, which was negative. She was later evaluated by neurologist and on further evaluation found to be positive for antibodies specific to the 65-kDa isofrom of glutamic acid decarboxylase (GAD65-IgG) as well as glycine receptor z1 subunit (GlyRz1)-IgG. She was diagnosed with Stiff-Person Syndrome and treated with intravenous immunoglobulin initially and later, plasmapheresis.

Results: Based on a thorough review of literature, there is a noticeable trend in misdiagnosis of Stiff-Person Syndrome. Symptoms are typically attributed to other diagnoses such as dystonia or thought to be psychogenic in nature1. We propose that there may be a few missed cases due to symptoms determined to be orthopedic in etiology.
Conclusions: Stiff-Person Syndrome is usually a diagnostic challenge and should be considered in the differential of children who present with severe stiffness and spasms. Early identification and serological testing would help in better management of these patients.

Keywords: Infections/Neuroimmunology, Neuromuscular disorders

217. The Role Of T-Cells in Congenital Lymphocytic Choriomeningitis Virus (LCMV) Infection
Klein H (Iowa City, IA), Karacay B, Rabe G, Bonthius D

Objective: LCMV infection during pregnancy injures the human fetal brain. Neonatal rats inoculated with LCMV are an excellent model of congenital LCMV infection, as they develop neuropathology, including cerebellar injuries, similar to those in humans. Our objective was to evaluate the role of T-lymphocytes in LCMV-induced cerebellar pathology.

Methods: LCMV was injected into neonatal congenitally athymic rats, deficient in T-lymphocytes, and into their immunocompetent heterozygote siblings. Viral titers were measured, cellular targets of infection were determined by immunohistochemistry, cytokine/chemokine levels were measured by rtPCR, and pathologic changes were assessed histologically.

Results: Peak viral titers and cellular targets of infection were similar in both strains, but viral infection, particularly from astrocytes, was impaired in the athymic rats. Cytokines and chemokines rose to higher levels and for a greater duration in the euthymic rats than in the athymic rats. The euthymic rats developed an intense lymphocytic infiltration, accompanied by destructive lesions of the cerebellum and a neuronal migration defect, due to T-cell-mediated alteration of Bergmann glia structure. These pathologic changes were absent in the athymic rats, but were restored when the athymic rats received lymphocytes by adoptive transfer. Athymic rats were not free of pathology, however, as the virus induced cerebellar hypoplasia.

Conclusions: T-lymphocytes play key roles in clearance of LCMV from the developing brain, in cytokine/chemokine responses, and in the pathogenesis of destructive lesions and neuronal migration disturbances. However, not all pathology is T-lymphocyte dependent. Cerebellar hypoplasia from LCMV occurs even in the absence of T-lymphocytes and is likely due to the viral infection itself.

Keywords: Infections/Neuroimmunology, Neonatal neurology

218. Bickerstaff’s Brainstem Encephalitis in Pediatrics
Santoro J (Palo Alto, CA), Lazzarechi D, Dunn J

Objective: Bickerstaff Brainstem Encephalitis (BBE) is characterized by acutely progressive ophthalmoplegia, ataxia, and impaired levels of consciousness with a monophasic course and overall good recovery. While this constellation of symptoms is considered to be on a spectrum of post-infectious immune disorders with GBS and Miller Fisher Syndrome, impairments in consciousness differentiate this condition. Prior studies have analyzed the disease course, diagnostic studies, response to treatments, and overall prognosis in adults, although there have been no studies examining differences in these factors in pediatric populations.

Methods: Our study reviewed published reports of BBE in patients less than 18 years of age and compare these findings to previously published studies in adults. A systematic review of utilizing Pubmed and SCOPUS databases was performed in both English and Spanish in order to obtain previously reported cases of BBE in patients less than 18 years of age.

Results: In total 27 studies and 34 individual cases were reviewed in addition to the addition of 2 unreported cases reviewed a Lucile Packard Children’s Hospital over the past 20 years. In review of the data, a higher percentage of patients were noted to be GQ1b Ab positive (78%) and there seemed to be no benefit to therapy with IVIG or steroids with regards to overall prognosis of time to symptom improvement. Nearly all cases were associated with a preceding illness occurring on average 8.4 days prior to development of symptoms.

Conclusions: BBE appears to be a unique entity in pediatric populations with a notable lack of efficacy in interventional therapeutics.

Keywords: Infections/Neuroimmunology, Demyelinating Disorders

219. Nationwide Survey of Childhood Guillain-Barre Syndrome, Fisher syndrome, and Bickerstaff Brainstem Encephalitis in Japan
Fujii K (Chiba, Japan), Mizuochi H, Shiobama T, Uchikawa H, Shimojo N

Objective: Guillain-Barre syndrome (GS), Fisher syndrome (FS), and Bickerstaff brainstem encephalitis (BE) are immunological peripheral nerve disorders, characterized by progressive paresis of extremities, ophthalmoplegia, and consciousness disturbance, respectively. Although many reports have been published, epidemiology of children has not fully been elucidated. We aimed to elucidate the recent epidemiology of GS, FS, and BE in children.

Methods: We sent 1066 questionnaire to specialists for child neurology in Japan, to know the recent incidence, laboratory data, therapy, and outcome of GS, FS, and BE. We also investigated the number of these patients during recent 20 years to know whether the incidence has been increasing in Chiba prefecture.

Results: We obtained clinical data from 450 pediatric neurology specialist (45%). The number of patients with Guillain-Barré syndrome, Fisher syndrome, and Bickerstaff brainstem encephalitis in Japan during 2014, were 33, 3, and 2, respectively, indicating that the incidence rates according to the pediatric population of Japan were 0.2 to 100,000, 0.012 to 100,000 and 0.01 100,0000, respectively. The disease course was variable, but prognosis was generally favorable, except for only two children who remained gait disturbance. The incidence of GS, FS, BE is significantly decreased during recent 10 years, compared to that of previous 10 years (p<0.01).

Conclusions: This is the first nationwide surveillance of childhood GBS, FS, and BE in Japan. The incidence rate of
GBS was lower than those from previous reports. We also confirmed the decreased incidence of GBS in recent 10 years in Japan, suggesting that improved circumstances might contribute recent GBS epidemiology.

Keywords: Infections/Neuroimmunology, Demyelinating Disorders, Movement Disorders

220. Diagnostic Challenges in Angiogram Negative Primary CNS Vasculitis (PCNSV) in Children
Shah N (Memphis, TN), Mudigoudar B, Zhang J, Choudhri A, Dayyat E

Objective: Angiogram negative small vessel CNS vasculitis is frequently missed or misdiagnosed. We present 4 children with PCNSV diagnosed by brain biopsy.

Methods: Retrospective chart review.

Results: Case 1: 16 year old boy presented with recurrent partial seizures and left hemiparesis. Angiography was negative and vWF (von Willebrand factor) level was normal. Brain biopsy was consistent with PCNSV. He responded well to immunosuppressive therapy. Case 2: 16 year old girl presented with visual hallucinations and multifocal neurological deficits which did not respond to intravenous steroids. MRI showed multifocal signal changes with enhancement. MRA and vessel wall imaging were unremarkable, vWF level was elevated. Brain biopsy demonstrated PCNSV. Neurological deficits resolved with immunosuppressive therapy. Case 3: 10 year old girl presented with recurrent headaches and left visual field deficit. Initial diagnosis was complicated migraine. MRI showed focal signal changes with enhancement. vWF level was elevated. Final diagnosis of PCNSV was made by brain biopsy. She responded to immunosuppressive therapy. Case 4: 11 year old boy presented with fever, headache and seizures. He was treated for presumed viral encephalitis. Neuroimaging showed progressive signal changes and calcification in the temporal lobe. vWF level was elevated and brain biopsy confirmed PCNSV. He improved with immunosuppressive treatment.

Conclusions: PCNSV should be in the differential diagnosis of new onset epilepsy and acquired neurological deficits in children. Elevated vWF levels and early brain biopsy are important in angiogram negative PCNSV before initiating immunosuppressive treatment. High index of suspicion and rapid diagnostic evaluation will improve outcome.

Keywords: Infections/Neuroimmunology, Neuroimaging, Epilepsy

221. Involvement of Cerebellum in Leigh Syndrome
Chourasia N (Houston, TX), Koenig M, Patel R

Objective: To describe involvement of cerebellum in Leigh Syndrome and consider it as a differential diagnosis for cerebellitis.

FIGURE 1: (A,B) show stable T2 FLAIR hyperintensity involving the caudate nuclei, putamen bilaterally with associated volume loss consistent with patient’s known Leigh syndrome. (C,D) shows interval development of multifocal T2 hyperintensity involving the both cerebellar hemispheres with associated edema (Abstract 221)
Methods: A known case of Leigh syndrome was evaluated with recurrent episodes of cerebellar inflammation.

Results: A 6 year old male with Leigh syndrome developed recurrent cerebellar inflammation. The patient was diagnosed with Leigh syndrome at 2 years with bilateral basal ganglia lesions on brain MRI. Genetic testing confirmed the diagnosis secondary to a homoplasmic mitochondrial DNA mutation (m.9176T>C). The patient experienced three acute regressive episodes (3, 5, and 6 years). All regressive episodes had a similar presentation with worsening of baseline ataxia and dysarthria. The second episode mimicked infectious cerebellitis, with elevated CSF protein and white blood cell count. No organisms were isolated from the CSF/blood during any of the regressive episodes. Brain MRI consistently showed cerebellar inflammation, however cerebellar spectroscopy during the third episode found an elevated lactate peak, decrease of the N-acetylaspartate peak, and elevation of the choline peak consistent with an acute exacerbation of Leigh syndrome as opposed to infectious cerebellitis.

Conclusions: Our patient with Leigh syndrome demonstrated a predominantly cerebellar phenotype consisting of progressively worsening ataxia and dysarthria. All three regressive episodes have been associated with worsening cerebellar signs in the setting of febrile illnesses. MRS found a cerebellar lactate peak during the third regressive episode suggesting a metabolic etiology for the inflammation. We therefore hypothesize that, although rare, Leigh syndrome can present with primarily involvement of the cerebellum and Leigh syndrome should be considered in the differential for acute cerebellitis.

Keywords: Infections/Neuroimmunology, Genetics, Neuroimaging
222. Serum Concentrations of Visinin-Like Protein-1 in Children with Acute Encephalopathy with Biphasic Seizures and Late Reduced Diffusion (AESD) and Those with Prolonged Febrile Seizures

Ichiyama T (Kume, Japan) Hasegawa S, Matsuhiige T, Sugio Y

Objective: Visinin-like protein-1 (VILIP-1) is a neuronal calcium-sensor protein and is found in all CNS locations. It is known that VILIP-1 has a potential utility as a marker of neuronal injury. Acute encephalopathy/encephalitis in childhood is a life-threatening disease that can result in the development of neurological sequelae. Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is one type of acute encephalopathy. It is difficult to distinguish AESD from prolonged febrile seizures (PFS) during the initial stage. We investigated the neuronal damage by using VILIP-1 in children with AESD or PFS, and analyzed whether VILIP-1 could be diagnostic markers in AESD during the early stage.

Methods: The study participants included in 15 children with AESD and 25 with PFS. The serum concentrations of VILIP-1 were quantified using an enzyme-linked immunosorbent assay (ELISA) kit.

Results: Serum VILIP-1 levels in children with AESD were significantly higher than those in PFS and the controls (p = 0.014, and p < 0.001, respectively). A deceased patients with AESD had markedly elevated serum levels of VILIP-1 (>3,000 ng/mL). Serum VILIP-1 levels in children with AESD were significantly higher than those in the controls (p = 0.004).

Conclusions: Our results suggest that serum VILIP-1 levels could be diagnostic and prognostic markers in early AESD, and PFS could lead to some degree of neuronal damage even in the absence of abnormal clinical neurological findings during the short-term follow up period.

Keywords: Infections/Neuroimmunology, Epilepsy, Neuroimaging

223. Drugs Indicated for Mitochondrial Dysfunction as Treatments for Acute Encephalopathy with Onset of Febrile Convulsive Status Epilepticus


Objective: Acute encephalopathy with onset of febrile convulsive status epilepticus can be difficult to distinguish from febrile convulsive status epilepticus and often results in severe neurological dysfunction. One significant etiology of acute encephalopathy is depletion of energy due to decreased mitochondrial function. In mitochondrial diseases, various vitamins and coenzymes have been used. This study aimed to examine the efficacy of combination of vitamin B1, C, E, biotin, coenzyme Q10, and L-carnitine as ”mitochondrial drug cocktail” in the treatment of acute encephalopathy.

Methods: We studied the efficacy of mitochondrial drug cocktail in the treatment of 21 patients with acute encephalopathy with onset of febrile convulsive status epilepticus. Among them, 11 patients had been treated with a mitochondrial drug cocktail and 10 patients were not. We retrospectively reviewed age, trigger, clinical form, treatment start time, and sequelae. Sequelae were classified as (A) no sequelae group or (B) sequelae group, and differences in the interval between diagnosis and treatment (within 24 h and others) were also evaluated.

Results: There was no significant difference in sequelae (A vs B) between the mitochondrial drug cocktail prescription and non-prescription groups among the 21 patients. However, the sequelae were significantly better in the group administered the mitochondrial drug cocktail within 24 h (P = 0.035).

Conclusions: We concluded that speedy administration of mitochondrial drug cocktails is worthwhile in cases of acute encephalopathy because of the potential to prevent the development of sequelae or the onset of acute encephalopathy.

Keywords: Infections/Neuroimmunology, Epilepsy, Cognitive/Behavioral Disorders

224. A 6 Year Retrospective Study of Inflammatory and Autoimmune Disorders of the Central Nervous System in Children at a Tertiary Academic Medical Center

Vargas W (New York, NY), Beck E, Curcio A, Bain J

Objective: To describe our experience with pediatric immune-mediated disorders of the central nervous system over a six year period.

Methods: Neurological disorders in which auto-immune mechanisms play a key role have been increasingly recognized in children. The expanding number of such cases suggests that child neurologists are likely to encounter these disorders. Here we describe childhood neuro-immunological disorders as seen in our institution from 2010 to 2016. Using retrospective chart review, we identified 80 cases of neuroimmunological disorders with pediatric onset.

Results: The following diagnoses were made: multiple sclerosis (MS) in 16, acute cerebellar ataxia in 14, acute demyelinating encephalomyelitis (ADEM) in 13, anti
n-methyl-D-aspartate receptor encephalitis (NMDA-RE) in 13, opsoclonus myoclonus ataxia syndrome in 4, neuromyelitis optica in 4, idiopathic acute transverse myelitis in 4, presumed inflammatory encephalitis of unspecified cause in 4, Rasmussen’s encephalitis in 3, primary CNS vasculitis in 3, and clinical-isolated syndrome in 2. MS tended to present in teenage years whereas all other disorders tended to present earlier (Figure 1). Seizures were common in ADEM and anti NMDA-RE patients (Figure 2). Oligoclonal bands in the CSF tended to be present across disorders, with the exception of ADEM. Imaging was often abnormal, except in cases of acute cerebellitis (Figure 3). Immunotherapies used included steroids, intravenous immunoglobulin (IVIG), plasma exchange, Rituximab and Cyclophosphamide (Figure 4). Many patients did recover neurologic function after treatment. The poorest outcomes were observed in children with NMDA-RE.

Conclusions: Neuroimmunological disorders occur not infrequently in children. Recognition is important for prompt diagnosis and treatment.

Keywords: Infections/Neuroimmunology, Demyelinating Disorders

TRANSLATIONAL/EXPERIMENTAL THERAPEUTICS

225. Design and Rationale of the Clinical Study Programs for BMN250, A Novel Investigational Enzyme Replacement Therapy for Sanfilippo B Syndrome
Shaywitz A (Novato, CA), Oh M, Kent S

Objective: Sanfilippo B syndrome (mucopolysaccharidosis [MPS] IIIB) is a lysosomal storage disease characterized by rapid and progressive neurological decline, due to deficiency of the human alpha-N-acetylgalcosaminidase (NAGLU) enzyme. Children with severe disease are initially symptom-free but begin to manifest developmental delay between ages 1-4 years, progressing to severe behavioral problems, sleep-wake disturbance, and intellectual decline. Severe decline of all motor functions ensues and death usually occurs in the second or third decade of life. BMN250 is a novel enzyme replacement therapy (ERT) designed to restore functional NAGLU activity to the brain. Development quotient (DQ) has been validated as a cognitive measure in children with MPS III. However, DQ trajectory in young MPS IIIB patients is relatively unknown.

Methods: BMN250-901 (NCT02493998) is an observational study designed to quantify the progression of MPS IIIB over time in children primarily aged 1-5 years and to correlate changes in clinical features of the disease (including DQ) with both MRI and biochemical markers of disease burden. A concurrent treatment study (BMN250-201) is also planned: Part 1 is a dose-escalation period to establish safety; Part 2 is a dose-expansion period. Eligible patients from the BMN250-901 baseline observational study may be able to roll over into Part 2 of BMN250-201.
Results: Efficacy will be assessed by comparing changes in disease progression in the observational study vs. changes observed in Part 2 of BMN250-201.

Conclusions: Data from the BMN250 Study Program will provide valuable information on both the natural history of untreated MPS IIIB patients and the efficacy and safety of BMN250.

Keywords: Translational/experimental therapeutics, Cognitive/Behavioral Disorders

226. Sensitivity of the KiTAP Executive Function Battery and an Eye Tracking Paradigm to Effects of AFQ056 in Fragile X Syndrome

Objective: To determine if the KiTAP executive battery and eye tracking, objective performance-based measures of fragile X syndrome (FXS) core phenotypes, are responsive to treatment with AFQ056 (Novartis), an mGluR5 negative allosteric modulator.

Methods: Adolescents/adults (age 12–45) with FXS (N=57) enrolled in randomized, double-blind, placebo-controlled clinical trials of AFQ056 at Rush or UC Davis completed the KiTAP and social eye-gaze tracking paradigm at baseline and after three months of treatment. KiTAP data was analyzed using LSM differences controlling for baseline performance. Measures of gaze to the eye region were analyzed using a mixed-effects model.

Results: There was a significant increase in correct answers (p=0.03) and decrease in omissions (p=0.03) on the Go/NoGo task from the KiTAP, and a trend toward more correct answers on Flexibility (p=0.059) for the AFQ056 group (N=32) relative to placebo (N=13). There was a significant increase in the proportion of time looking to the eye region (β=0.02, p=0.02) and a trend toward more fixations to the eye region (β=0.05, p=0.07) compared to baseline in the AFQ056-treated group (N=39). No change was observed for proportion of time looking (β=0.0006, p=0.96) with significantly less fixations to the eye region (β=-1.09, p=0.02) in the placebo group (N=18).

Conclusions: Direct measurements that interrogate FXS core phenotypic features of gaze aversion and inhibitory control show improvement on AFQ056 and may better demonstrate target engagement than subjective behavior forms, which failed to show benefit in these trials. The KiTAP and eye tracking paradigm appear to be sensitive to change during pharmaceutical intervention.

Keywords: Translational/experimental therapeutics, Cognitive/Behavioral Disorders

227. The Treatment of Fragile X Syndrome with Trofinetide (NNZ-2566)

Objective: The effects of trofinetide (IGF-1 terminal tripeptide analog) treatment on symptoms of Fragile X syndrome (FXS) were examined in a Phase 2, randomized, double-blind, placebo-controlled clinical trial of adolescent and adult males.

Methods: Participants (n=70) received trofinetide, 35 mg/kg (n=24) or 70 mg/kg (n=21) or placebo (n=25) bid. Safety/tolerability were assessed by adverse events, ECGs, physical exams and lab values. Efficacy was evaluated using clinician and caregiver measures of associated behavioral symptoms and FXS symptom severity, with novel syndrome-specific assessments. The group analysis required improvement in at least two of five core measures from two different efficacy domains, with no clinically significant worsening in all other core endpoints. For the individual analysis, a subject-specific efficacy score of the core measures was calculated and mean scores compared between treatment and placebo groups. Potential placebo response was accounted for in the analyses.

Results: Both doses were well-tolerated. There were no time or dose-dependent adverse events, or laboratory abnormalities and no serious adverse events. The higher dose met the pre-specified efficacy criteria in group and subject-level analyses (p=0.045 by permutation testing). Three core measures demonstrated clinical improvement: FXS Syndrome Rating Scale (core FXS symptoms), FXS Domain Specific Concerns (clinician-identified most concerning aspects of FXS), and Aberrant Behavior Checklist (maladaptive behaviors) with no worsening in any core endpoints.

Conclusions: Trofinetide shows promise for treatment of core symptoms of FXS, assessed by both clinician and caregiver-completed assessments. Novel endpoints such as piloted in this study may be critical for showing benefit across multiple symptom domains in targeted treatment of FXS.

Keywords: Translational/experimental therapeutics, Cognitive/Behavioral Disorders, Genetics

228. Intracerebroventricular Cerliponase Alfa (BMN 190) in Children with CLN2 disease: Results from a Phase 1/2, Open-Label, Dose-Escalation Study de los Reyes E (Columbus, OH), Schulz A, Specchio N, Gissen P, Williams R, Cahan H, Slasor P, Jacoby D

Objective: CLN2 disease, a rare, inherited, pediatric-onset, neurodegenerative lysosomal storage disorder caused by TPP1 enzyme deficiency, is characterized by seizures, ataxia, rapid loss of language and motor functions, blindness and early death. Cerliponase alfa (BMN 190) is a recombinant human TPP1 enzyme. This phase 1/2, multi-center, open-label, dose-escalation study evaluated the safety, tolerability and efficacy of every other week intracerebroventricular (ICV) infusions of cerliponase alfa in children with CLN2 aged 3 - 16 years.

Methods: Following a dose escalation period, all patients received 300mg of cerliponase alfa every two weeks by ICV infusion for 48 weeks. Efficacy was evaluated by monitoring
changes in motor and language functions using a CLN2 clinical rating scale.

Results: 24 subjects (9 male, 15 female, mean age 4.3 years [median: 4 years; range: 3-8 years]) enrolled in the study. Almost all subjects (96%) had adverse events assessed as study drug-related, the majority of which were Grade 1-2 and included pyrexia (46%), hypersensitivity (38%), seizure (38%), and epilepsy (17%). Serious adverse events assessed by the investigator as study drug-related were reported in eight (33%) subjects. There were no anaphylaxis/anaphylactoid reactions, study drug discontinuations or deaths due to AEs. The mean (SD)/median rate of decline in CLN2 score for subjects treated 48-91 weeks (n=23) was 0.48 (0.756)/0.00 units/48 weeks, in contrast to 2.09 (0.97)/1.87 units/48 weeks observed in natural history (n=41).

Conclusions: Enzyme replacement therapy with ICV-administered cerliponase alfa is well-tolerated and slows the progression of functional decline in children with CLN2.

Keywords: Translational/experimental therapeutics, Genetics

229. Functional Outcomes after Out-of Hospital Cardiac Arrest in Children
Silverstein F (Ann Arbor, MI), Slomine B, Christensen J, Holubkov R, Page K, Dean J, Moler F, THAPCA Trial Group

Objective: To analyze functional performance measures collected prospectively during the conduct of a clinical trial that enrolled infants and children (up to age 18 years), resuscitated after out-of-hospital cardiac arrest, who were at high risk for poor neurological outcomes.

Methods: 295 children with Glasgow Motor Scales <5, within 6 hours of resuscitation, were enrolled in a multicenter clinical trial that compared two targeted temperature management interventions (targeted temperatures 33.0°C and 36.8°C for hypothermia and normothermia groups respectively; THAPCA-OH, NCT00878644). The primary outcome, 12-month survival with Vineland Adaptive Behavior Scales, second edition (VABS-II) score ≥70, has been reported and did not differ between groups (NEJM 372:1898).

Results: Baseline measures included VABS-II, Pediatric Cerebral Performance Category(PCPC), and Pediatric Overall Performance Category(POPC). PCPC and POPC were rescored at hospital discharges; all three measures were scored at 3 and 12 months. 270/295 cases had baseline VABS-II scores ≥70; 877270 survived one year. In survivors with baseline VABS-II scores ≥70, we evaluated relationships of hospital discharge PCPC with 3 and 12 month scores, and between 3 and 12 month VABS-II scores. Hospital discharge PCPC scores strongly predicted 3 and 12 month PCPC (r=0.82, 0.79; p<0.0001) and VABS-II scores (r=0.81, 0.77; p<0.0001) Three month VABS-II scores strongly predicted 12 month performance (r=0.95, p<0.0001). Hypothermia treatment did not alter any of these relationships.

Conclusions: In comatose infants and children, with Glasgow Motor Scales <5 in the initial hours after out-of-hospital cardiac arrest resuscitation, functional measures obtained at hospital discharge and at 3 months predicted 12-month performance well in the majority of survivors.

Keywords: Translational/experimental therapeutics

230. Interim Results from a Phase 2/3 Study of the Safety and Efficacy of Hematopoietic Stem Cells Transduced Ex Vivo with Lentiviral Vector (Lenti-D) for Cerebral Adrenoleukodystrophy

Objective: To evaluate safety and efficacy of Lenti-D in childhood cerebral adrenoleukodystrophy (CALD). CALD is a neurodegenerative disease caused by deficiency of the ALD protein (ALDP) encoded by ABCD1. Clinical progression can only be halted with allogeneic hematopoietic stem cell (HSC) transplantation, with the best outcomes in patients with an HLA-matched sibling donor (MSD). Lenti-D, an investigational gene therapy, consists of autologous HSCs transduced with a lentiviral vector encoding ABCD1 cDNA.

Methods: ALD-102 is an open-label, single-arm phase 2/3 study. Subjects have CALD with gadolinium enhancement on MRI, Loes score 0.5-9.0, Neurological Function Score (NFS) ≤1, and no MSD. Following HSC harvest and myeloablative conditioning, subjects receive one intravenous dose of Lenti-D. The primary efficacy endpoint is the proportion of subjects without major functional disabilities (MFDs) at 24 months.

Results: Subjects (N=17), 4-13 years old (median 6y) with median Loes score 2, received 6.0-19.4x10^6 CD34+ cells/kg; current follow-up is 9-24 months. All subjects demonstrated successful engraftment and integration site analysis demonstrated polyclonal reconstitution in all subjects without clonal dominance. ALDP expression in leukocytes was observed in all patients at latest follow-up. Adverse events were consistent with myeloablative chemotherapy, including neutropenia, thrombocytopenia, and febrile neutropenia. One SAE, BK virus cystitis, was possibly related to drug product and resolved with conservative measures. Interim efficacy assessments show no MFDs, stable NFS in 16/17, and median Loes score change of 1 (range 0-8.5).

Conclusions: Early results suggest that Lenti-D is well tolerated and may provide clinical benefit to subjects with CALD.

Keywords: Translational/experimental therapeutics, Demyelinating Disorders
231. Eteplirsen, A Phosphorodiamidate Morpholino Oligomer (PMO) for Duchenne Muscular Dystrophy (DMD): Longitudinal Comparison to External Controls on Six-Minute Walk Test (6MWT) and Loss of Ambulation (LOA)

Objective: DMD is a rare, degenerative, X-linked genetic disease that results in progressive muscle loss and premature death. DMD is primarily caused by whole exon deletions resulting in a shift of the dystrophin mRNA reading frame that prevents production of functional dystrophin protein. Eteplirsen, a PMO, is designed to skip exon 51, restore the reading frame, and induce production of internally-shortened dystrophin in patients amenable to exon 51-skiping.

Methods: An analysis of 6MWT performance over 4 years compared boys treated with 30 or 50 mg/kg/wk eteplirsen IV (N=12) versus a group of comparable, untreated external controls (N=13) as defined by age, corticosteroid use, and genotype.

Results: At Year 4, a statistically significant treatment benefit of 162 meters on 6MWT was observed in eteplirsen-treated patients compared with external controls (p<0.0005). Sensitivity analyses of 6MWT with covariates including baseline 6MWT, age and glucocorticoid use all resulted in differences >150 meters between the groups that were statistically significant (p<0.01).

Kaplan-Meier estimates of Loss of Ambulation (LOA) showed that 85% of the external control patients lost ambulation versus 17% of eteplirsen-treated patients at Year 4 (log-rank p=0.011).

Conclusions: Eteplirsen slows progression in DMD as evidenced by a 162 meter advantage on the 6MWT compared to the external control patients (p<0.0005) at Year 4. In addition, there was a reduction in the risk of loss of ambulation in the eteplirsen treated patients (p=0.011).

Keywords: Translational/experimental therapeutics, Neuromuscular disorders, Genetics

232. Outpatient Treatment with Ultra Low Dose Ketamine Infusion for Neuropathic pain in patients with Neurofibromatosis
Acosta M (Washington, DC), Shibuya P, Brown M, Lee J, Alexander S

Objective: Ketamine is an N-methyl-D-aspartate receptor antagonist used as an anesthetic with less respiratory suppression, making it ideal for pediatric populations. Ultra Low Dose Intravenous Ketamine (ULDIK) has been reported effective in patients with neuropathic pain. It may also be associated with reductions in depression, frequently seen in these patients. We aim to collect data from systematic clinical observations about the effects of ULDIK as treatment for chronic pain in patients with Neurofibromatosis (NF).

Methods: Patients with NF and severe chronic pain refractory to other interventions are evaluated at the Multidisciplinary Neurofibromatosis Pain Clinic (PS, SA, MTA) at CNHS. If clinically indicated, patients are prescribed infusions of the ULDIK. In all patients, standardized evaluations pre- and post-treatment are being collected.

Results: We present the preliminary results of a group of 6 patients, 14 - 40 years old with diagnosis of NF and refractory chronic neuropathic pain. All patients have evidence of plexiform neurofibromas or schwannomas and being refractory to other interventions for pain management. One or two day infusions of ULDIK were used dosing parameter of 0.05mg to 0.4mg/kg/hr every 3 to 6 weeks. Clinical improvements have been observed in all patients.

Conclusions: ULDIK may be an alternative option for treatment of severe chronic neuropathic pain in patients with NF. Additional research is necessary to assess this intervention in NF patients. Longitudinal data is being collected in these patients to better understand the impact of ULDIK in pain, mood disorders and quality of life in NF patients.

Keywords: Translational/experimental therapeutics, Brain Tumors/Oncology, Genetics

233. Neurophysiologic Correlates of Motor Response Inhibition
Guthrie M (Cincinnati, OH), Gilbert D, Huddleston D, Mostofsky S, Dirlikov B, Pedapati E, Wu S

Objective: The objective was to develop a reliable, child-friendly response inhibition task suitable for online measurement of primary motor cortex (M1) excitability and inhibition. We chose a stop-signal task (SST) over Go/No-Go task because “automatic inhibition” is less likely to occur in SST and the calculated stop-signal reaction time (SSRT) accounts for both GO and STOP trials.

Methods: At two centers, twenty healthy children and adults (1:1) completed a modified, “race-car Slater-Hammel” (SH) task with concurrent single and paired-pulse Transcranial Magnetic Stimulation (TMS) paradigms. SH is self-paced, with each trial initiating after a button push to move a car across a monitor. GO trials require finger-lift close to but before 800msec. Interspersed are STOP trials (25%) during which the stop-signal (car suddenly stops) prompts subjects to prevent finger-lift. M1 TMS pulses were delivered at 650msec which the stop-signal (car suddenly stops) prompts subjects to prevent finger-lift. M1 TMS pulses were delivered at 650msec during GO and 150msec after stop-signal during STOP trials. Motor-evoked potentials (MEPs) were recorded.

Results: In children, SSRT were longer (p=0.007) and prolonged by TMS (p=0.01). MEPs were larger during SH (p<0.0001). Mixed model analysis showed a significant interaction between age group, trial type, and TMS paradigms (p=0.007) on MEPs. Task reliability was supported by lack of inter-site difference.

Conclusions: Children and adults successfully completed a SH task with online TMS showing cortical activities reflecting different motor conditions. This is the first description of a pediatric TMS-SST paradigm and may be useful to study response inhibition in various neuropsychiatric conditions.

Keywords: Translational/experimental therapeutics, Movement Disorders

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234. The Role of MEK-Inhibitors for the Prevention of Optic Pathway Gliomas in an NFI-Deficient Mouse Model

Bornhorst M (Washington, DC), Jecrois E, Wang Y, Mugayo D, Zhu Y

Objective: Neurofibromatosis 1 (NF1) is a genetic syndrome resulting in increased activation of the Ras/ERK pathway. Up to 20% of NF1 patients are diagnosed with optic pathway gliomas (OPGs) before 7 years of age, suggesting they are formed during development. Previously, our lab has shown that MEK-inhibitors (MEKi) can prevent brain structural abnormalities in the developing corpus callosum and cerebellum of Nf1-deficient mice. Thus, we hypothesize that early postnatal treatment with a MEKi that has good blood brain barrier (BBB) penetration can also prevent OPG formation in mice.

Methods: We first tested the biological activity of four different MEKis (PD0325901, AZD6244, MEK162, GSK1120212) in the brains of young mice. Then, we treated Nf1-deficient mice that develop OPGs around postnatal day 60 (P60) with PD0325901 from P0.5 to P21, using a previously established MEKi-in-milk protocol. We analyzed the nerves at P21 and P60 to look for improvement in glial pathology.

Results: All the MEKis inhibited pERK in the brain, although only PD0325901 had good potency and BBB penetration. Following treatment with PD0325901, Nf1-deficient mice had a significant improvement in optic nerve glial pathology at both P21 and P60.

Conclusions: Early treatment with PD0325901 prevents OPG formation in Nf1-deficient mice both immediately after treatment and long term after removal of the drug. This suggests that a similar treatment strategy could potentially delay or prevent OPG formation in patients with NF1, improving morbidity and overall outcomes. Additional studies are being done to narrow the preventative treatment window, and to assess functional outcome following treatment.

Keywords: Translational/experimental therapeutics, Brain Tumors/Oncology

235. Development of Phosphorodiamidate Morpholino Oligomers (PMOs) for the Treatment of Duchenne Muscular Dystrophy (DMD)

Duda P (Cambridge, MA), Laforet G, Wentworth B, Mendell J

Objective: DMD is a rare, degenerative, X-linked genetic disease resulting in progressive muscle loss and premature death. DMD is commonly caused by whole exon deletions resulting in a shift of the dystrophin mRNA reading frame that prevents production of functional dystrophin protein.

Methods: Phosphorodiamidate morpholino oligomers (PMOs) are synthetic nucleotide analogs that can be designed to sequence-specifically block spliceosomes from binding to dystrophin pre-mRNA, resulting in omission of a deletion-adjacent exon from the transcript and restoration of the disrupted reading frame. This allows for synthesis of internally-shortened dystrophin in patients with mutations amenable to exon skipping.

Results: Eteplirsen, SRP-4045, and SRP-4053 are three PMOs currently under clinical development for the treatment of DMD. As of August 14, 2015, 114 exon 51 skipping amenable patients aged 4-21 have received eteplirsen in 7 clinical trials. Those who received eteplirsen at 30 or 50 mg/kg/wk IV for ≥4 years (N=12) demonstrated increased dystrophin production and a statistically significant clinical benefit in comparison to an untreated external control cohort (N=13) as measured by the 6-minute walk test (p<0.001). No major safety signal was observed in >3,900 infusions.

SRP-4045 and SRP-4053 for patients amenable to exon 45 or 53 skipping, respectively, have received a favorable DSMB review in separate phase 1, ≥12 week dose escalation studies to 30 mg/kg/wk IV. Patients continue to receive these PMOs in open-label studies, which will assess clinical safety and efficacy.

Conclusions: Additional PMOs are in discovery or non-clinical testing phases for dystrophin production in DMD.

Keywords: Translational/experimental therapeutics, Genetics, Neuromuscular disorders

236. An Efficacious Therapy for Treating Children with CASK Mutations: Combining Lessons from an Animal Model to a Clinical Setting

DeLuca S (Roanoke, VA), Wallace D, Trucks M, Mukherjee K

Objective: Mutations in CASK are associated with mental retardation and microcephaly with pontine and cerebellar hypoplasia (MICPCH; OMIM#300749). Phenotypic manifestations include global developmental delay with substantial neuromotor and cognitive impairment. CASK has long been believed to be a synaptic molecule. A recent animal model suggests that MICPCH may not be a purely a neuronal disorder and that the animals affected were responsive to learning.

Methods: Animal findings led us to apply an intensive therapy protocol on two children with CASK mutations. The treatment protocol was based on a scientifically validated treatment approach used to increase functional skills of children with varied neuromotor diagnoses. In this case-series the treatment targeted visual-motor coordination and social interaction as key areas for improvement and was administered over two weeks for four hours each weekday. Assessments of motor and functional skills were performed via treatment documentation and the Peabody Developmental Motor Scales (PDMS 2).

Results: Treatment documentation indicated improvements in both children in speech production and...
responsiveness, as well as, in object identification and manipulation. Improved motor skills via the PDMS 2 included pre-to post developmental changes across all domains. Two subtests with the largest changes are presented in figure 1.

**Conclusions:** Because the phenotypic spectrum of CASK mutations is varied, little is known about the prognosis of children affected, and there are no known efficacious treatment protocols. This case-series based on findings from animal models suggests that efficacious therapeutic protocols can be developed and could serve as a model for developing treatments for other genetic disorders.

**Keywords:** Translational/experimental therapeutics, Genetics

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**HISTORY/TEACHING OF CHILD NEUROLOGY**

237. **Expression of Neuroanatomy in the Art of Michelangelo**

**Tripathy A (Des Moines, IA), Mishra L**

**Objective:** To show that Michelangelo painted neuroanatomy in the Sistine Chapel ceiling.

**Methods:** Meticulous search of Michelangelo’s work with special references to brain illustrations.

**Results:** Michelangelo painted human figures in the “Creation of Man” in the ceiling of Sistine Chapel. When he painted in 1512, he never gave names to the various panels. Dr. Frank Meshberger in 1990 described the “creation” panel contains an image of brain in cross section which was misunderstood for 500 years. Michelangelo was a world renowned artist and held deep religious beliefs and used to dissect cadavers to study human form for his art. Between the years 1508 and 1512 he painted the ceiling of Sistine Chapel in Rome. Michelangelo surrounded God with a shroud, representing the human brain to suggest that God was endowing Adam not only with life but also with supreme human intelligence. He did the sulci in inner and outer surface of brain, brain stem, basilar artery eyes, pituitary gland, optic chiasma, optic nerve and spinal cord. God is superimposed over the limbic system of brain which is the anatomical counterpart of human soul. God’s right hand extends to the prefrontal cortex, the most creative region of brain. God’s hand does not touch Adam, yet Adam is already alive as if there is a spark of life being transmitted through the synaptic cleft.

**Conclusions:** This report will at least stimulate further scientific and scholarly contributions to this fascinating topic, as the study of these works of art is essential for understanding the history of Neuroanatomy.

**Keywords:** History/Teaching of Child Neurology

238. **Initiating a Career Development Curriculum for Child Neurology Residents**

**Ellett C (Boston, MA), Guerriero R, Peters J, Waugh J, Urion D**

**Objective:** The United States is in dire need of more physician-scientists to translate basic science and clinical research innovations into improved care for children. Trainees and junior faculty in child neurology encounter significant hurdles when embarking on an academic career. Success requires a core skill set often acquired by “on the job training”. We piloted annual career development retreats to teach critical skills and provide a roadmap for academic success.

**Methods:** Two full day retreats were organized with participants divided into beginner and advanced groups based on publication history. Sessions included morning didactic talks, a mentoring panel during lunch, and afternoon “hands-on” software and NIH Biosketch breakout groups. Pre and post assessment by rating survey quantified the educational impact.

**Results:** 94% of our child neurology (n=14) and neurodevelopmental disabilities residents (n=2) participated. A pre-retreat survey demonstrated that 25% had a career development plan, 44% had a mentor, 19% understood academic promotion, 31% could turn cases into abstracts/publications, 25% were confident presenting posters/talks, 25% could network effectively at national meetings, 19% had a NIH Biosketch, 31% could find funding sources, 38% had an efficient system for organizing references and making figures, and 63% were comfortable evaluating articles in Pubmed. A post-retreat survey showed significant improvements in understanding academic promotion, turning cases into abstracts/publications, having a NIH biosketch, finding funding sources, and having an efficient system for references/figures (P<0.05, Mann-Whitney U test).

**Conclusions:** Child neurology trainees are deficient in many domains necessary for success in academic medicine. Formal career development retreats can be an effective intervention.

**Keywords:** History/Teaching of Child Neurology

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239. **A Resident-Medical Student Mentoring Program Increases Medical Student Interest in Child Neurology and Neurodevelopmental Disabilities**

**Harrar D (Boston, MA), Urion D**

**Objective:** To provide first year medical students with exposure to Child Neurology and Neurodevelopmental Disabilities (NDD) with the goal of promoting greater interest in these fields.

**Methods:** First year students at Harvard Medical School were paired with a Child Neurology or NDD resident at Boston Children’s Hospital (BCH). Medical students and residents were recruited via e-mail and paired based on their interests within Child Neurology/NDD. Students shadowed their resident mentor in the Neurology Clinic and/or on one of the inpatient Neurology services at BCH. Students were surveyed regarding their experience in the program.

**Results:** 12 students met with their mentor at least once. All of the students responding to the survey (n=9) stated that the program increased the likelihood of their considering residency training in Child Neurology/NDD and that the program increased their interest in Child Neurology/NDD. Strengths of the program included ‘flexibility’, ‘customizability’, and establishing ‘a longer term relationship with a resident’. The majority of students stated that they
would have preferred to meet with their mentor a greater number of times.

**Conclusions:** Recruitment of medical students to the fields of Child Neurology/NDD is challenging given the lack of exposure to these fields early in training. It has been suggested that early clinical exposure attracts students to subspecialties (1) and that resident mentoring of medical students positively impacts clerkship experiences and possibly career choice (2, 3, 4). Our results suggest that providing first year medical students with exposure to Child Neurology/NDD may enhance recruitment to these fields.

**Keywords:** History/Teaching of Child Neurology

240. **Interprofessional Education: A Practitioner’s Perspective**

*DiMario F (Hartford, CT), Jongbloed W*

**Objective:** Graduate medical education often occurs in environments among similarly trained peers. This mode of learning hinders an appreciation of the competencies held by other health professionals (HP). We studied the perspectives of hospital-based nurse practitioners (APRN) concerning interprofessional education (IPE) using a mixed methods approach.

**Methods:** After IRB exemption, we undertook a prospective anonymous survey of APRN using a 5-point Likert scale about: professional identity, interprofessional teamwork, mutual respect, scholarship with subsequent interviews. Results were compiled and analysed.

**Results:** An email invitation was accepted by 20/70 (28%) hospital based APRN (19 females) of whom 4 were interviewed. They had a median of 10 years experience; 70% had participated in scholarship/research and 90% had some prior IPE. Participants agreed that other HP did not understand APRN roles and responsibilities (mean 2.85, SD 1.04) and that APRN understood the roles and responsibilities of non-APRN HP (mean 4.15, SD 0.37). Participants agreed that learning with other HP enhanced their professional identity (mean 3.5, SD 0.8), felt confident sharing their opinions in a team setting (mean 4.10, SD 0.55), supported working in interprofessional groups (mean 4.45, SD 0.51) and that IPE would promote scholarship (mean 4.15, SD 0.55). Our results suggest that providing first year medical students with exposure to Child Neurology/NDD may enhance recruitment to these fields.

**Keywords:** History/Teaching of Child Neurology

241. **Rett Syndrome Turns 50: Medical Perspectives and the Human Face of RTT**

*Ronen G (Hamilton, Ontario, Canada) Rosenbaum P*

**Objective:** Fifty years ago, Andreas Rett first described in great detail what came to be known as ‘Rett syndrome’ (RTT, MIM 312750). The story of RTT parallels and perhaps illuminates many of the advances in our understanding of biological processes relating to brain development and epigenetic phenomena; the value of tracking and charting the lifelong trajectory of people with evolving chronic conditions; the importance of patient/parent reported outcomes and their active engagement in care; family-centred and multidisciplinary care; contemporary health concepts such as ‘quality of life’ and ‘disability’; societal health perception, rights and advocacy; and the integration of clinical and laboratory research.

**Methods:** N/A

**Results:** For the reasons above the history of the recognition, description and clarification of RTT provides an interesting illustration of developments in contemporary medicine, insofar as it reflects many aspects in the progress of our thinking over the past half-century about an evolving chronic and complex neurodevelopmental encephalopathy. Understanding personal stories of people with this syndrome and their families, as portrayed in a vignette, helped in many ways to revolutionize modern neurodevelopmental medicine. For some people the identification of the genetic underpinning of the syndrome and the ongoing biological research into this condition represented the peak of the scientific accomplishments in RTT. For others it was development in clinical research methodologies that were especially important.

**Conclusions:** Above all, the patient- and family-oriented empathetic and collaborative approach to care by professionals collaborating with families has led to immense achievements, both scientific and humanistic.

**Keywords:** History/Teaching of Child Neurology, Genetics, Cognitive/Behavioral Disorders

242. **Program Coordinator Barriers Impact Accreditation Requirements**

*Feist T (Cincinnati, OH), Campbell J, LaBare J, Gilbert D*

**Objective:** The ACGME Next Accreditation System (NAS) has created substantial administrative challenges. As a means of promoting solutions to implementation barriers in NAS, a survey was sent to Child Neurology (CN) and Neurodevelopmental Disabilities (NDD) Program Coordinators (PCs).

**Methods:** The authors created a survey distributed via SurveyMonkey to all 74 CNN/NDD PCs prior to the 2015 Child Neurology Society conference. It addressed workforce characteristics and NAS implementation. Responses were characterized with descriptive statistics. Relationships between workforce and successful implementation of NAS were evaluated using regression.

**Results:** Response rate was 68%. Most PCs had limited experience: 67% < 5 years. While 73% work full-time, 80% work overtime regularly, including 57% of hourly PCs working overtime unpaid. Most manage multiple programs. Structural administrative challenges were reported, including supervision by individuals without GME knowledge, inconsistent titles and expectations, no career paths, and overwhelming workload. Knowledge barriers included limited faculty awareness and uncertainty among PCs regarding NAS self-study expectations. Programs’ average score for successful NAS implementation (out of 14) was 7.5 (SD 2.5). Using multivariate regression, more complete
implementation of NAS requirements was significantly linked to three PC-related factors: reporting to educational/academic individuals (p = .007); increased GME experience (p = .03); and managing one program (p = .04).

Conclusions: This survey identified substantial workforce and educational challenges which pose multiple barriers to PCs. These have slowed NAS implementation and could affect program accreditation. Changes are needed at institutional and national levels to reduce turnover and frustration and improve the GME learning environment.

Keywords: History/Teaching of Child Neurology

Association of Child Neurology Nurses (ACNN)

Pezzuto T (Wilmington, DE), Chugani D, Xie I

Objective: Pediatric migraine occurs in approximately ten percent of the pediatric/adolescent population. Nemours Neurology Headache Program has been managing pediatric migraine patients with a multifaceted, evidence based practice since it began in 2009. The same goal is set for each of our patients: No more than two headaches a month, no side effects on the medication and the headache is to be gone within one hour of taking their abortive. As suggested in the literature we provide an individualized, multidisciplinary approach for each patient. Yet, commonly asked questions amongst parents remain a mystery. Is there a difference in the average response time to pediatric migraine prevalence depending on the diagnosis, the type of preventative medication used? Does lifestyle management influence this response rate? And, what is our overall response rate to treatment? Response rate is defined as reaching our goal. There is a paucity of literature in reference to pediatric migraine preventative medication management response rates but the most commonly used preventative are topiramate, Depakote, amitriptyline, cyproheptadine, and propranolol.

Methods: We look to answer these questions through a retrospective chart analysis of approximately 4000 patients in our practice from February 2009-March 2016. Internal Review Board permission has been obtained and a data analysis through our electronic medical record will be completed.

Results: To determine response rate by diagnosis and response rate by preventative medication choice gives knowledge to providers for guidance in practice. Conclusion: Answers to these questions in its simplest statistical analysis will answer questions of response rate to preventative treatment for pediatric migraine which will guide practice of the future. But it also looks at the differences between diagnosis and the response rates. Pediatric Migraine management literature is developing but this could help direct the focus of research.

Keywords: ACNN

244. Advanced Practice Provider Use in a Neurofibromatosis Clinic: Development of a Neurology Neurofibromatosis Type I Clinic to Compliment a Multidisciplinary Program at a Larger Tertiary Care Center
Shea S (Aurora, CO), Ndahayo K, Haus T

Objective: Children’s Hospital Colorado (CHCO) has held a quarterly Neurofibromatosis Type 1 (NF1) Multidisciplinary Clinic (MDC) since 2010. If the fall of 2012, the NF1 MDC grew significantly to a monthly clinic with the assistance of a nurse coordinator position. The MDC combines neurology, oncology, neuropsychology, genetics, rehabilitation, and ophthalmology. Patients in the clinic require at least three of the specialties. As the NF1 multidisciplinary program at CHCO has grown, this has resulted in a significant increase in appropriate referrals to the clinic. As a result, two additional patient populations within NF1 were identified. The first population is one with mild to moderate NF1 who did not require evaluation with enough of the specialties in MDC. This population extended the waitlist for the MDC. The second population is a medically complex patient who was unable to wait the length of time to be seen and required triaging to specialties more rapidly.

Methods: A monthly Neurology NF1 Clinic was established with a trained Neurology Advanced Practice Provider (APP) and the nurse coordinator allowing for more appropriate care and rapid access of these subpopulations of NF1 patients. The APP provides a medical assessment, recommends testing, and is able to make referrals to appropriate specialties. The nurse coordinator facilitates education and ensures the recommendations are followed through. The infrastructure in place in this program has provided enhanced coordinated care for these subpopulations.

Results: The waitlist has already reflected improvement as the Neurology NF1 clinic can get a patient seen in 1-2 months. Further progress is needed to monitor appropriateness and improve clinic flow.

Conclusions: This clinic role is crucial in improving and developing a NF1 multidisciplinary program with in a large tertiary care center.

Keywords: ACNN

245. EMU: A Year in Review
Yau I (Toronto, Ontario, Canada), Bradbury L

Objective: Epilepsy is one of the most common neurological conditions affecting the paediatric population. Prolonged inpatient video EEG (vEEG) monitoring (epilepsy monitoring unit [EMU]) is a known and widely used modality in the diagnostic and pre-surgical evaluation of children with seizures. The purpose of this project was to evaluate the outcome of patients referred to a Regional Epilepsy Surgery Centre of Excellence, in Ontario, Canada where our resources are limited to a 5 day admission stay.

Methods: We retrospectively reviewed the data from a consecutive cohort of pediatric patients admitted to the EMU of our center (Sickkids Hospital) over a 1 year period from Jan 1 – Dec 31 2015. Patients were excluded if their admission was intended for < 24 hrs or if intended for
invasive vEEG monitoring. Preadmission diagnosis, reason for referral and outcome were reviewed and compared to management at the time of discharge.

**Results:** In total, 208 patients were admitted to the EMU for prolonged VEEG monitoring in 2015. 115 (55%) of patients were male. 88 (41.83%) patients were referred by either community neurologists, other tertiary or international centers. 99 (47.5%) were referred to characterize paroxysmal events or seizures, 84 (40.3%) for presurgical evaluation and 7 (3.36%) for suspected continuous spike and wave in sleep (CSWS) and high dose diazepam therapy. At discharge from EMU, 82 (39%) were identified as surgical candidates. The diagnosis and management were altered after EMU in 72 (35%) patients.

**Conclusions:** The results of this study demonstrate a high yield of change in diagnosis and management, at time of discharge. Further, a large percentage of patients were referred for surgical candidacy.

**Keywords:** ACNN

### 246. Successful Integration of Subspecialty Services Using Lean Principles

**Hartmann A (Washington, DC), Favor C, Albert J**

**Objective:** Our project utilized lean methodologies to facilitate the clinical integration of two large medical divisions in a major Children's hospital.

**Methods:** Our team was organized to develop a maximally integrated clinic space and function. Team members consisted of physician directors, Nurse Practitioners and Nursing leadership all trained in Lean principles. Initial integration efforts focused on developing an understanding of the needs of each division, including patient characteristics, equipment and personnel requirements. Team members identified challenges to joint space utilization using the 5 Whys and 5S, and worked to determine the best practice to maximally accommodate the needs of clinicians.

**Results:** Initial integration of CNHS Neurology and Physical Medicine & Rehabilitation divisions has been successful. Lean methodologies drove this change, and during this work, participants recognized that many activities and roles were duplicated, producing waste and delay.

**Conclusions:** We found that our front line management and nursing staff were most adept at developing process change, and when given the freedom to implement tests of change, positive outcomes resulted. Further institutional implementation of these principles is recommended.

**Keywords:** ACNN

### 247. Impact of Identifying ADNP Mutations in a Persistently Unsolved Individual with Autism Spectrum Disorder

**Rhee J (Washington, DC), Ulrick N, Hamoud S**

**Introduction:** A 4-year-old male presented with developmental delay, hypotonia, speech apraxia and multi focal white matter abnormalities on MRI remained undiagnosed over a period of 2 years. In an effort to identify the genetic origin of these symptoms, whole genome sequencing (WGS) was completed in a CLIA-certified laboratory through an Illumina Inc. philanthropic program, iHOPE.

**Objective:** Utilize whole genome sequence analysis to obtain precision diagnosis in a patient with nonspecific findings to reduce the financial and emotional burden of a family's diagnostic journey.

**Methods:** MRI imaging and medical records were reviewed and health care charges of diagnostic testing were tabulated. Whole Genome Sequencing (WGS) was performed in a CLIA-certified lab. Pediatric quality of life surveys (PedsQL) were used to assess family stress and quality of life.

**Results:** Prior to WGS, extensive diagnostic testing beginning at 22 months of age included a chromosomal microarray, fragile x analysis, a mucopolysaccaridosis panel, and a basic metabolic panel, all of which were unrevealing. MRI features were non specific and not diagnostic. WGS identified a single pathogenic de novo truncating variant in ADNP at c.1102C>T (p.Gln368Ter). The ADNP gene is thought to play a role in the development of myelin and is associated with Helsmoortel-van der Aa syndrome, a rare syndrome characterized by autism spectrum disorders, dysmorphic faces, and developmental delay. Other features include motor delays, seizures, and neuropsychiatric features. Abnormalities on MRI are also seen, which can include white matter abnormalities.

**Conclusions:** The clinical and radiologic features in this child were non-specific leading to prolonged diagnostic testing before WGS. It is unlikely that this gene would have been identified through serial candidate gene testing. This case supports a next generation sequencing approach early in the diagnostic plan to minimize time to diagnosis, and the financial and emotional burden of a diagnostic odyssey.

**Keywords:** ACNN

### 248. Transitional Care Nurse Practitioner

**Nickolau D (Seattle, WA)**

**Objective:** The Affordable Care Act identifies the transition from the inpatient setting to the outpatient setting as a vulnerable time for patients and their families. There are a number of studies and programs that demonstrate the effectiveness of focused interventions to improve this form of transition of care for adults. However, there is little information about interventions that improve the transition of care in pediatrics. The goal of this project is to identify whether transition of care interventions by a nurse practitioner will improve the readmission rate, the return to the emergency room rate and patient and family satisfaction scores for pediatric Neurology patients.

**Methods:** The Division of Neurology at Seattle Children’s Hospital is implementing a new model of care. A nurse practitioner on the inpatient Neurology service will focus on the transition of care for this pediatric patient population. Interventions will include patient and family education, medication reconciliation, collaborative development of the discharge plan of care (including a seizure action plan), and ensuring the patient has appropriate follow up appointments. The nurse practitioner will assess the readmission...
rates, return to the emergency room rates, and patient and family satisfaction scores prior to the implementation of this new model of care. After six months, the nurse practitioner will reassess this data.

Results: The literature about transition of care for adults demonstrates a reduction in readmission rates, return to the emergency room rates and improved patient and family satisfaction based on focused interventions. The data and results for this project are in process.

Conclusions: Focused interventions for improving transition of care are successful in adults. This project intends to demonstrate the same impact on pediatric Neurology patients.

Keywords: ACNN

249. Headache Plan of Care: Will it Save Time in the Neurology Clinic? Nickolaus D (Seattle, WA), Katowa M, Lasmarías V

Objective: Almost fifty percent of the referrals to the Division of Neurology are related to pediatric headaches. School related paperwork for these patients consumes much of the nurse and provider time in the clinic as well as with each new school year. The objective of this project is to demonstrate that the time required to complete paperwork for those patients with headaches is decreased when a standard electronic headache plan of care is implemented.

Methods: Baseline data related to the time commitment for completing headache care plans will be obtained. A standardized electronic headache plan will be developed which can be customized to each patient. The time commitment for completing this initially and then at follow up visits will be captured. A comparison of the data will be completed.

Results: Data collection is planned, but has not been implemented. The anticipated results are a possible longer time to initiate the headache care plan, but time savings will be recognized with subsequent updates.

Conclusions: Headache care plans that are electronic and customized to a patient will save time for providers and nurses while communicating the plan of care and accommodations that are needed for pediatric patients with headaches.

Keywords: ACNN

250. Applying Family Experience Responses in a Child Neurology Ambulatory Setting: Opportunities for Improvement Kiel S (Seattle, WA), Nickolaus D

Objective: The objective of this project is to determine how family experience scores can be used to improve the care of children in an outpatient child neurology setting.

Methods: The Affordable Care Act has established a pay-for-performance system that ties reimbursement for healthcare services to the consumer’s experience and satisfaction. Family experience surveys have been implemented to obtain feedback directly from the consumers. These surveys use Likert scale scores to indicate the family’s perception of the quality of care received during the clinical encounter. In pediatrics, the consumer is comprised of the pediatric patient and their family or caregivers, and needs of both parties must be considered. We reviewed 6 months of family experience scores for a nurse practitioner (NP) and physician assistant (PA) cohort in an academic ambulatory child neurology setting. Collaborating with our institution’s Family Experience Team, we aim to identify 3 focus points that we predict will have a positive correlation with improved scores. Surveys from the subsequent 6 months will be reviewed, and scores for the same NP/PA cohort will be compared to those prior to the interventions.

Results: Data collection is planned but has not yet been implemented. It is anticipated that identifying and addressing key focus points will result in improved understanding by the NP/PA cohort of the expectations and needs of families. Satisfying these key points will yield improved family experience scores.

Conclusions: Family experience scores help translate the expectations and needs of families seen in our child neurology clinic. Improving these scores will result in a more meaningful clinical encounter for the patient, the family and the provider.

Keywords: ACNN

LATE BREAKING ABSTRACTS


Objective: Evaluate relationship between seizure frequency and developmental outcomes in TSC.

Methods: Analysis of 130 patients ages 0-36 months with TSC participating in the TSC Autism Center of Excellence Network, a large multicenter, prospective observational study evaluating biomarkers predictive of autism spectrum disorder. Infants were evaluated longitudinally at ages 3, 6, 9, 12, 18, 24 and 36 months with standardized evaluations, using cognitive and adaptive measures, and autism-specific testing at later time points. Seizure history was collected throughout the study. EEGs were performed at each visit.

Results: Data was analyzed through 24 months of age. Patients without a history of seizures performed better on all developmental assessments at all time points. Patients with a history of infantile spasms performed worse on all developmental assessments at 12 and 24 months. Patients with a history of any seizure type during infancy performed worse on testing at 24 months. Higher seizure frequency correlated with worse outcomes on developmental testing at all time points, particularly at 12 months and beyond. A logistic model looking at the individual impact of infantile spasms, seizure frequency, and age of seizure onset as predictors of developmental delay revealed age of seizure onset as most important factor in determining developmental outcome.

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FIGURE 1: IMPACT OF SEIZURES ON DEVELOPMENT AND AUTISM RISK (Abstract 251)

TABLE 1. Structural brain abnormalities and neurodevelopmental outcome (N = 83)

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* p<0.01  **p<0.001
Conclusions: Results further define the relationship between seizures and developmental outcomes in young children with TSC. Early seizure onset in infants with TSC negatively impacts early neurodevelopment, which persists through 24 months of age.

Keywords: Epilepsy, Cognitive/Behavioral Disorders
Abbreviations: ECSS- Early Learning Composite Standard Score, ABCS- Adaptive Behavior Composite Score, TLSS- Total Language Standard Score

252. Youth with Epilepsy Identify their Quality of Life Trajectories and Predictors: A 28-month Longitudinal National Study
Ferro M (Hamilton, Ontario, Canada), Avery L, Ronen G, QQALITÉ Research Group

Objective: Some youth with epilepsy report living satisfactory lives while others do not. To understand this perceived experience, we studied longitudinal trajectories and quantified determinants of self-reported quality of life (QoL) of these youth.

Methods: Youth with active epilepsy ages 8-14 years and measured verbal intelligence >70 were recruited from 6 Canadian tertiary centres and assessed every 7 months for 28 months. Trajectories of QoL were derived from the validated CHEQOL-25 instrument total score using latent class mixture models. Multinomial regression was used to predict class membership in these trajectories. Potential predictors included: personal and social demographics, seizure and AED variables, intelligence, child’s mood, parental mood and social support from parents, peers and classmates.

Results: 486 youth were recruited and 354 completed visit 5. The self-reported QoL was fitted best by a 6 class model, with 3 trajectory classes above and 3 below average. Trajectories remained either stable or improved over 28 months. 62% of the young people rated their QoL as high or moderately high. Greater family, classmates and peer social support, better child and parent mood, and higher intelligence were identified as the strongest predictors of better QoL (all p<0.001).

Conclusions: The majority of youth with epilepsy reported themselves as doing well in this first self-reported QoL trajectory study. These findings confirm the heterogeneous QoL outcomes for youth with epilepsy and the primary importance of psychosocial factors over seizure- and AEDs-specific factors in determining QoL trajectory class. These potentially amenable predictors should now be the focus of specific intervention studies.

Keywords: Epilepsy

253. Motor and Cognitive Outcomes in Preterm Newborns with Mild White Matter Injury
Bach A (San Francisco, CA), Ferriero D, Barkovich A, Rogers E, Johnon B, Gano D

Objective: To evaluate the association of mild white matter injury (WMI) on magnetic resonance imaging (MRI) in premature newborns with motor and cognitive outcomes at 4-6y.

Methods: We performed a cross-sectional analysis of neurodevelopment at 4-6y in a cohort of preterm newborns <33 weeks gestation imaged with MRI soon after birth. WMI was scored according to our published criteria by a blinded pediatric neuroradiologist. Newborns with moderate/severe WMI and severe IVH (Papile grades 3/4) were excluded. Motor outcome was cerebral palsy (CP). Cognitive outcome was verbal and performance IQ on the Wechsler Preschool and Primary Scale of Intelligence-III, classified as ≤85 or >85. Descriptive statistics and multivariable logistic regression were used to evaluate the association of mild WMI with outcome.

Results: Among 119 newborns of mean gestational age 27.9 ± 2.3wks, mild WMI was present in 31(26%). Children with mild WMI more commonly had CP (17.2% vs. 7.2%, P=0.1) and performance IQ ≤85 (34.6% vs. 22.1%, P=0.2), but this was not significant. Verbal IQ <85 was similar in both groups (25.9% vs. 26.2%, P=0.98). Adjusting for gestational age, birthweight and gender, mild WMI was not statistically associated with CP (OR 2.6, 95% CI 0.73-9.45, P=0.14), performance IQ ≤85 (OR 2.0, 95% CI 0.68-5.97, P=0.2), or verbal IQ ≤85 (OR 0.97, 95% CI 0.34-2.79, P=0.96).

Conclusions: Adverse motor and cognitive outcomes are common in preterm newborns at school-age, but are not independently associated with mild WMI in this cohort. Quantitative MRI may help identify which newborns with absent/mild WMI develop motor or cognitive deficits.

Keywords: Neonatal neurology

254. The Role of the Electronic Medical Record and Admission Medication Reconciliation in Neurology-Related Medication Errors in Pediatric Inpatients
Messer R (Aurora, CO), Coffman J

Objective: Errors in neurology-related medications can cause significant iatrogenic harm in pediatric inpatients, yet the sources of these errors are poorly understood. We created a multidisciplinary task force to investigate inpatient neurology-related medication errors at a free-standing, tertiary care pediatric hospital. The inpatient electronic medical record (EMR) includes an optional medication reconciliation component which accesses the outpatient EMR. We hypothesized that the integrity of the outpatient EMR medication list would primarily impact admission medication reconciliation.

Methods: Utilizing the hospital’s voluntary incident reporting database from 2013-2015, all errors involving neurology-related medications (anticonvulsants, baclofen, dihydroergotamine, and corticosteroids) were classified by type. Each reconciliation error was further analyzed to determine the source.

Results: From 2013-2015, 203 inpatient neurology-related medication errors were reported. Medication reconciliation errors comprised 16% of total errors (28/203) and 20% of severe errors (intervention was required). More than 20% of the reconciliation errors were attributable to inaccuracies in the outpatient medication list. However, in almost one-third of reconciliation errors, the admission medication
reconciliation process was performed incompletely or bypassed altogether. Surprisingly, another 18% of reconciliation errors were due to transposing milliliters (mL) with milligrams (mg), often as a result of inaccurate history-taking.

**Conclusions:** The primary sources of inpatient neurology-related medication reconciliation errors were inadequate history-taking, underutilization of the EMR’s admission medication reconciliation process, and inaccuracies in the outpatient EMR medication list. Improvements in outpatient medication list management, resident education regarding medication history-taking and common mistakes, and involvement of the neurology consult team in medication reconciliation could reduce inpatient neurology-related medication errors.

**Keywords:** Epilepsy, Headache/Migraine, History/Teaching of Child Neurology
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