FORTY-FOURTH NATIONAL MEETING OF THE CHILD NEUROLOGY SOCIETY

PLANNING COMMITTEE

Child Neurology Society Executive Board

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Kenneth Mack, President-elect
Harvey Singer, Secretary-Treasurer
Bruce Cohen, Councillor
Kevin Ess, Councillor
Kara Lewis, Councillor
Roger Packer, Councillor

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Rochester, MN
Baltimore, MD
Akron, OH
Nashville, TN
Phoenix, AZ
Washington, DC

CNS Scientific Selection and Program Planning Committee

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Nigel Bamford
Josh Bonkowsky
Keith Coffman
Anne Comi
Ed Gilmore
Howard Goodkin
Adam Hartman
Rebecca Ichord
Neel Kamal
Yasmin Khakoo
Sookyoung Koh
Rebecca Lehman
Daniel Licht

Rochester, NY
Seattle, WA
Salt Lake City, UT
Kansas City, MO
Baltimore, MD
Cleveland, OH
Charlottesville, VA
Baltimore, MD
Philadelphia, PA
London, UK
New York, NY
Chicago, IL
Charleston, SC
Philadelphia, PA

Laura Ment
John Mytinger
Marc Patterson
Steven Pavlakis
Toni Pearson
Gerald Raymond
Teri Shreiner
Renee Shellhaas
Elliott Sherr
Lily Tran
Peter Tsai
Yvonne Wu
Andrew Zimmerman

New Haven, CT
Columbus, OH
Rochester, MN
Brooklyn, NY
New York, NY
Minneapolis, MN
Aurora, CO
Ann Arbor, MI
San Francisco, CA
Orange, CA
Dallas, TX
San Francisco, CA
Lexington, MA

National Office
Roger Larson, Executive Director
Sue Hussman, Associate Director
Kathy Pavel, Office Administrator
Emily McConnell, Administrative Assistant

Presented at Gaylord National Resort & Convention Center
National Harbor, MD
October 7-10, 2015

ACCREDITATION

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

MMA designates this educational activity for a maximum of 26.25 AMA PRA Category 1 Credits™. Physicians should only claim 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 10, 2015

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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 (1999-2001)
- Donna Ferriero (2009-2011)
- E. Steve Roach (2011-2013)

#### Councillor
- Isabelle Rapin (1972-73)
- Manuel Gomez (1972-73)
- John Menkes (1972-74)
- James Schwartz (1972-74)
- Karin Nelson (1973-74)
- Raymond Chun (1973-75)
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- Peggy Coppel (Ferry) (1976-78)
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- Francis Wright (1977-79)
- Mary Anne Guggenheim (1978-80)
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- Marvin Weil (1980-82)
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- Roy Elterman (2002-04)
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- Douglas Nordli (2003-05)
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- Wendy Mitchell (2008-10)
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- Gary Clark (2010-12)
- Sidney Gospe (2010-12)
- Barry Kosofsky (2011-13)
- Suresh Kotagal (2011-13)
- Vinod Narayan (2012-14)
- Jayne Ness (2012-14)
- Bruce Cohen (2013-15)
- Roger Packer (2013-15)
- Kevin Ess (2014-)
- Kara Lewis (2014-)

#### Secretary-Treasurer
- Richard Allen (1972-75)
- Raymond Chun (1975-78)
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- Lawrence Lockman (1981-84)
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- Nina F. Schor (2004-2010)
- Harvey Singer (2010-2015)
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### CNS LIFETIME ACHIEVEMENT AWARDS

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<td>Raymond Chun</td>
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### ARNOLD P. GOLD FOUNDATION HUMANISM IN MEDICINE AWARD AT THE CHILD NEUROLOGY SOCIETY

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BERNARD D'SOUZA
INTERNATIONAL FELLOWSHIP AWARD
RECIPIENTS

1989  Meral Ozmen
      Istanbul, Turkey

1990  Najoua Miladi
      Tunis, Tunisia

1991  Sergio A. Antoniuk
      Curitiba, Brazil

1992  Qin Jiong
      Beijing, China

1993  Anu Soot
      Tartu, Estonia

1994  Lai Choo Ong
      Kuala Lumpur, Malaysia

1995  Nina Barisic
      Zagreb, Croatia

1996  Shan Wei Song
      Beijing, China

1997  Aleksandra Djukic
      Belgrade, Yugoslavia

1998  Ana Keleme
      Novi Sad, Yugoslavia

1999  Magda L. Nunes
      Porto Alegre, Brazil

2000  Brahim Tabarki-Melaiki
      Brussels, Belgium

2001  Dimitrios Zafeiriou
      Thessalonikki, Greece

2002  Vedrana Milic Rasic
      Belgrade, Serbia

2003  David Chkhartishvili
      Tbilisi, Georgia

2004  Natalia A. Yermolenko
      Voronezh, Russia

2005  Lusine Kirakosyan
      Yerevan, Armenia

2006  Gia Melikoshvili
      Tbilisi, Georgia

2007  David E. Kombo
      Dars Es Salaam, Tanzania

2008  Ikeolu Lagunju
      Ibadan, Nigeria

2009  Uduak Mayen Offiong
      Abuja, Nigeria

2010  Parayil S. Bindu
      Bangalore, India

2011  Kyaw Linn
      Myanmar

2012  Inga Talvik
      Tartu, Estonia

2013  Samson Gwer
      Nairobi, Kenya

2014  Jithangi Wanigasinghe
      Dehiwela, Sri Lanka

2015  Edward Kija
      Tanzania
### OUTSTANDING JUNIOR MEMBER AWARD RECIPIENTS

**1996**
- **Gyula Acsadi**  
  Children’s Hospital of Detroit
- **Joseph Gleeson**  
  Boston Children’s Hospital
- **Andrea Gropman**  
  Children’s National Medical Center
- **Mary Sutton**  
  Boston Children’s Hospital

**1997**
- **Gyula Acsadi**  
  Children’s Hospital of Detroit
- **Ann Bergin**  
  Johns Hopkins University
- **Edwin Demeritte**  
  Children’s Hospital of Detroit
- **Sanford Shu**  
  Loma Linda University

**1998**
- **June Caruso**  
  Rhode Island Children’s Hospital
- **Andrea Gropman**  
  Children’s National Medical Center
- **Alyssa Reddy**  
  Children’s Hospital of Alabama
- **Janet Soul**  
  Boston Children’s Hospital

**1999**
- **June Caruso**  
  Rhode Island Children’s Hospital
- **Debra Holder**  
  Texas Children’s Hospital
- **Caroline Menache**  
  Boston Children’s Hospital

**2000**
- **Sucheta Joshi**  
  Stanford University Medical Center
- **Lauren Plawner**  
  Stanford University Medical Center
- **Monique Ryan**  
  Boston Children’s Hospital
- **Mustafa Sahin**  
  Boston Children’s Hospital

**2001**
- **Marie Acosta**  
  Children’s National Medical Center
- **Randa Jarrar**  
  Mayo Clinic
- **Steven Miller**  
  UC San Francisco
- **Jane Ness**  
  Children’s Hospital of Alabama

**2002**
- **Tauen Chang**  
  Children’s National Medical Center
- **Mirjana Maletic-Savatic**  
  SUNY Stony Brook
- **Lauren Plawner**  
  Stanford University Medical Center
- **Michael Seyffert**  
  University of Washington Med Ctr

**2003**
- **Tauen Chang**  
  Children’s National Medical Center
- **Yoshimi Sogawa**  
  Schneider Children’s Hospital
- **Ignacio Valencia**  
  St. Christopher’s Hospital
- **Adeline Vanderver**  
  Children’s National Medical Center

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2004
Ignacio Valencia
St. Christopher’s Hospital
Brannon Morris
Mayo Clinic
Haim Bassan
Boston Children’s Hospital
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 Commonwealth 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

AAP SECTION ON NEUROLOGY TRAINEE TRAVEL AWARD

2015
Jennifer Jaskiewicz
Walter Reed National Military Medical Center
BHUWAN GARG HIGH SCHOOL STUDENT NEUROSCIENCE PRIZE

1998
Karla Malloy
Richmond, VA

1999
Nihar Gupta
New York, NY

2000
Rishikesh Dalal
Lenexa, KS

2001
Melanie Napier
Laurelton, NY

2002
Corinna Zygourakis
Houston, TX

2003
Henry Marr
Alhambra, CA

2004
Debashish Zircar
Bronx, NY

2005
Max Christie
Briarcliff Manor, NY

2006
Shoshana Tell
Coral Springs, FL

2007
David Shiovitz
Briarcliff Manor, NY

2008
Lauren Lisann
Dix Hills, NY

2009
Inar Zhang
Mercer island, WA

2010
Pragya Kakani
Jericho, NY

2011
Spencer Chan
Forest Hills, NY

2012
Vincent Shieh
Bronx, NY

2013
Anna Thomas
San Jose, CA

2014
Laura Mariah Herman
Ft. Lauderdale, FL

2015
Amrita Mohanty
Woodbury, MN
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
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

ASSOCIATION OF CHILD NEUROLOGY NURSES
NURSE PRACTITIONER EXCELLENCE AWARD

2015
Regina Laine
Boston, MA
THE CHILD NEUROLOGY SOCIETY GRATEFULLY ACKNOWLEDGES THE FINANCIAL SUPPORT OF

- Akron Children’s Hospital
- Arnold P. Gold Foundation
- Biogen
- BioMarin Pharmaceutical, Inc.
- Child Neurology Foundation
- Children’s National Health System
- Crosby’s Fund
- Eisai, Inc.
- Mallinckrodt, Inc.
- PTC Therapeutics
- Sarepta Therapeutics
- Texas Children’s Hospital
PROGRAM

Wednesday, October 7

7:30 AM - 5:00 PM
Symposium I: Neurobiology of Disease in Children: Epileptic Encephalopathy
Organizer: Bernard L. Maria, MD, MBA, Goryeb Children's Hospital, Morristown, NJ
Co-Organizers: Tallie Z. Baram; MD, PhD; University of California Irvine, Irvine, CA
Shlomo Shinnar, MD, PhD; Albert Einstein College of Medicine, Bronx, NY

Supported by the National Institutes of Health (NIH grant 5R13NS040925-09), the Child Neurology Society, American Epilepsy Society, and Epilepsy Foundation of America

7:30 AM - 7:40 AM
Opening Comments/Introduction
Bernard L. Maria, MD, MBA

7:40 AM - 9:40 AM
SESSION I: CLINICAL ASPECTS
Co-Director and Moderator: Shlomo Shinnar, MD, PhD; Albert Einstein College of Medicine, Bronx, NY

7:40 AM - 8:05 AM
Infantile Spasms
Susan P. Koh, MD; Children's Hospital Colorado, Aurora, CO

8:05 AM - 8:30 AM
Lennox-Gastaut Syndrome
James W. Wheless, MD; University of Tennessee Health Sciences Center, Memphis, TN

8:30 AM - 9:20 AM
ESES/LKS (Electrographic Status Epilepticus in Sleep/Landau Kleffner Syndrome)
Edouard Hirsch, MD; University of Strasbourg, Strasbourg, France

9:20 AM - 9:40 AM
Question and Answer Session

9:40 AM - 10:00 AM
Coffee Break

10:00 AM - 11:30 AM
SESSION II: NEUROBIOLOGY AND PATHOGENESIS
Moderator: Gregory Holmes, MD; University of Vermont School of Medicine, Burlington, VT
Moderator: Amy Brooks-Kayal, MD; Children's Hospital Colorado, Aurora, CO

10:00 AM - 10:30 AM
Vulnerability of the Developing Brain
Gregory Holmes, MD

10:30 AM - 10:55 AM
Neuroinflammation
Sookyong Koh, MD, PhD; Northwestern University, Chicago, IL

10:55 AM - 11:20 AM
From Developmental Neurobiology to Therapeutic Strategy
Tallie Z. Baram, MD, PhD

11:20 AM - 11:30 AM
Question and Answer Session

11:30 AM - 1:00 PM
Lunch & Presentation by American Epilepsy Society
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Presenters</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:00 PM-3:00 PM</td>
<td>SESSION III: THERAPEUTIC TARGETS AND TRANSLATIONAL OPPORTUNITIES</td>
<td>Moderator: Tallie Z. Baram, MD, PhD</td>
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<tr>
<td>1:00 PM-1:25 PM</td>
<td>Current State of the Art</td>
<td>Shlomo Shinnar, MD, PhD</td>
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<tr>
<td>1:25 PM-1:50 PM</td>
<td>Targeting mTOR Pathways</td>
<td>Mike Wong, MD, PhD; Washington University, St. Louis, MO</td>
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<tr>
<td>1:50 PM-2:15 PM</td>
<td>Cannabinoids</td>
<td>Amy Brooks-Kayal, MD</td>
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<tr>
<td>2:15 PM-2:40 PM</td>
<td>Engineering Stem Cells</td>
<td>Jack M. Parent, MD; University of Michigan, Ann Arbor, MI</td>
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<tr>
<td>2:40 PM-3:00 PM</td>
<td>Question and Answer Session</td>
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<tr>
<td>3:00 PM-3:15 PM</td>
<td>Coffee Break</td>
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<tr>
<td>3:15 PM-3:45 PM</td>
<td>EXECUTIVE SUMMARY OF THE DAY</td>
<td>Co-Director and Moderator: Brandy Fureman, MD; NIH, Bethesda, MD</td>
</tr>
<tr>
<td>3:45 PM-4:45 PM</td>
<td>SESSION IV: FUTURE DIRECTIONS PANEL DISCUSSION</td>
<td>Moderator: Brandy Fureman, MD</td>
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<tr>
<td>4:45 PM-5:00 PM</td>
<td>Closing Comments and Thanks</td>
<td>Bernard L. Maria, MD, MBA</td>
</tr>
<tr>
<td>6:00 PM-8:00 PM</td>
<td>WELCOME RECEPTION</td>
<td>Gaylord National Resort &amp; Convention Center (Exhibit Hall A)</td>
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<tr>
<td>8:00 PM-10:00 PM</td>
<td>SIG Meetings</td>
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Thursday, October 8

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Presenters</th>
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<tbody>
<tr>
<td>6:30 AM-7:00 AM</td>
<td>CONTINENTAL BREAKFAST</td>
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<tr>
<td>7:00 AM-8:15 AM</td>
<td>SEMINARS</td>
<td></td>
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<tr>
<td></td>
<td>Breakfast Seminar 1: The 2014 EV-D68 Associated Flaccid Myelitis Epidemic: what have we learned?</td>
<td>Organizer: J.B. Le Pichon, MD, PhD; Children's Mercy Hospital, Kansas City, MO</td>
</tr>
<tr>
<td></td>
<td>Breakfast Seminar 2: Sleep in Special Needs Children: “My Child Doesn’t Sleep and Neither Do I”</td>
<td>Organizer: Michael J. Strunc, MD; CHKD, Norfolk, VA</td>
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<tr>
<td></td>
<td>Breakfast Seminar 3: Neuro-Ophthalmology Primer: Nystagmus, Ptosis, Pupils and Diplopia</td>
<td>Organizer: Robert Avery, DO, MSCE; Center for Neuroscience and Behavior, Washington, DC</td>
</tr>
</tbody>
</table>

© 2015 American Neurological Association
Pupils and Ptosis  
Robert Avery, DO, MSCE

Diplopia  
Steven Stasheff, MD, PhD; National Eye Institute, Bethesda, MD

8:15 AM-8:45 AM  
Coffee Break

8:45 AM-9:15 AM  
Association of Child Neurology Nurses Claire Chee Award for Excellence  
Nancy Elling, RN, BSN, CPN, CNRN; Children's National Medical Center, Washington, DC

9:15 AM-12:00 PM  
Symposium II: Presidential Symposium: The 'Neuro' of Neuroblastoma  
Organizer: Jonathan Mink, MD, PhD; University of Rochester Medical Center; Rochester, NY  
Supported by an unrestricted educational grant from Crosby's Fund

Developmental Biology of the Neural Crest: Lessons from Neurofibromatosis and Neuroblastoma  
Nancy Ratner, PhD; Cincinnati Children's Hospital, Cincinnati, OH

Understanding the Phenomenon of Spontaneous Regression in Neuroblastoma  
Garrett M. Brodeur, MD; The Children's Hospital of Philadelphia, Philadelphia, PA

Opsoclonus-Myoclonus and the Neuroimmunology of Neuroblastoma  
Russell Dale, MBChB, MRCPCH, MSc, PhD; University of Sydney Medical School, Sydney, Australia

Targeted Therapy for Neuroblastoma: A Developmental Neurobiological Approach  
Nina F. Schor, MD, PhD; CNS President; University of Rochester Golisano Children's Hospital, Rochester, NY

12:00 PM-12:30 PM  
CNS Business Meeting

12:30 PM-1:45 PM  
Lunch

12:30 PM-1:45 PM  
Exhibit & Poster Viewing

12:30 PM-1:30 PM  
CNS Humanism in Medicine Workshop 2015: Using Humanism to Improve Patient Care in Child Neurology  
Supported by a grant from the Arnold P. Gold Foundation

1:45 PM-4:00 PM  
Symposium III: Pediatric Epilepsy Surgery: Current State of the Art  
Co-Organizer: Cigdem I Akman, MD; Columbia University Medical Center, New York, NY  
Co-Organizer: Ajay Gupta, MD; Cleveland Clinic Lerner College of Medicine, Cleveland, OH

Epilepsy Surgery in Children: Why, When and How?  
Cigdem I Akman, MD

Who Needs what Imaging, and When? And, Who is Not a Candidate for Surgery?  
William Gaillard, MD; Children's National Medical Center, Washington, DC

What is Pediatric Epilepsy Surgery? Surgical Techniques and Safety Data in 2015  
William Bingaman, MD; Cleveland Clinic Lerner College of Medicine, Cleveland, OH

Long-term Outcomes of Epilepsy Surgery in Children: Discussing Odds with the Family Before Surgery?  
Ajay Gupta, MD

4:00 PM-6:00 PM  
CHILD NEURO NEWS BREAK: POSTER REVIEW  
Wine & Cheese Reception  
Exhibit Viewing  
SIG Meetings

7:00 AM-8:15 AM  
CONTINENTAL BREAKFAST AND POSTER SESSION (Exhibit Hall A)  
Sponsored by Texas Children's Hospital, Houston, TX

EXHIBIT VIEWING

8:30 AM-10:15 AM  
PLATFORM SESSIONS 1 & 2  
PLATFORM SESSION 1:
PL1-1 Wu YW et al
Incidence of Dravet Syndrome in a U.S. Population

PL1-2 Grinspan ZM et al
The Pediatric Epilepsy Emergency Risk Score (PEER) — Predicting Frequent ED Use With Data from an Electronic Health Record System

PL 1-3 Marafie DN et al
SCN1A as a Candidate Gene Modifier Influencing the Severity of Epilepsy in Autosomal Dominant GRIN2A Mutation

PL1-4 Mezgebe M and Akhtar-Danesh G et al
Quality of Life in Childhood Epilepsy: A Comparison with Typical Children and Children with Cerebral Palsy

PL1-5 Postels DG et al
Admission EEG Findings in African Children with Cerebral Malaria are Associated with Mortality, Morbidity, and Malarial Retinopathy

PL 1-6 Sarnat HB et al
Subcortical Synaptic Networks in Focal Cortical Dysplasias

PL1-6 Postels on behalf of Moxon C et al
Lumbar Puncture Does Not Increase the Risk of Death in Comatose Malawian Children

PL 2-1 Ciechanski P et al
Enhancement of Motor Learning with Transcranial Direct Current Stimulation in Healthy Children

PL 2-2 Franz DN et al
Everolimus for Subependymal Giant Cell Astrocytoma Associated with Tuberous Sclerosis Complex: Final Long-Term Results from Approximately 4 Years of Treatment in EXIST-1

PL 2-3 Kirton A et al
Transcranial Direct Current Stimulation for Perinatal Stroke Hemiparesis: interim analysis of a randomized, controlled clinical trial

PL 2-4 Maski KP et al
Sleep Dependent Memory Consolidation in Children with Autism Spectrum Disorders

PL 2-5 Sparagana S et al
Everolimus Exposure and Overall Tolerability in Patients Treated for Subependymal Giant Cell Astrocytoma Associated with Tuberous Sclerosis Complex: results from the 4-year final analysis of EXIST-1

9:45 AM
PL 2-6 Postels on behalf of Moxon C et al
Lumbar Puncture Does Not Increase the Risk of Death in Comatose Malawian Children

10:00 AM
PL 2-7 Yu YW et al
A Phase II Randomized Controlled Trial of Erythropoietin and Hypothermia for Neonatal Neuroprotection in HIE—Feasibility and Preliminary Data

10:30 AM
AAP Section on Neurology Trainee Travel Award
• Jennifer Jaskiewicz, DO; Walter Reed National Military Medical Center, Bethesda, MD

10:45 AM
CNS Outstanding Junior Member Awards
• Robert Blake, MD; Cincinnati Children’s Hospital, Cincinnati, OH
• Dana Marafie, MD; Texas Children’s Hospital, Houston, TX
• Davut Pehlivan, MD; Texas Children’s Hospital, Houston, TX
• Siddharth Srivastava, MD; Kennedy Krieger Institute, Baltimore, MD

11:00 AM
M. Richard Koenigsberger Scholarship Award
• Vincent Carson, MD; Children’s Hospital of Pittsburgh, Pittsburgh, PA

11:45 AM
CNS/PCN Blue Bird Circle Training Program Director Awards: TBA

12:00 PM
Arnold P. Gold Humanism in Medicine Award:
• Robert Zeller, MD; Texas Children’s Hospital, Houston, TX

12:30 PM
Child Neurology Foundation Scientific Awards Announcements

11:00 AM
Philip R. Dodge Young Investigator Award Lecture: Dissection of the molecular, neuronal and circuit abnormalities of the newly delineated SHANK3 duplication syndrome
• Jimmy Holder, MD; Texas Children’s Hospital, Houston, TX

11:30 AM
Bernard Sachs Lecture: Molecular Brain Imaging in Children: Where are we?
• Harry Chugani, MD; Children’s Hospital of Michigan, Detroit, MI

12:30 PM
Lunch & Poster/Exhibit Walkaround
12:30 PM - 2:15 PM  
Committee & SIG Meetings

1:00 PM - 2:15 PM  
Junior Member Seminar: Meet the Editors:  
How to get your Manuscript Published

2:30 PM - 4:45 PM  
Symposium IV: Current Status and Challenges of Drug Development for Rare Diseases  
Organizer: Erika Augustine, MD, MS; University of Rochester, Rochester, NY  
Experimental Therapeutics for Rare Diseases-Progress and Future Directions  
Erika Augustine, MD, MS  
Mechanism-Based Combination Therapies for the CNS Disease Associated with Lysosomal Storage Disorders  
Mark Sands, PhD; Washington University School of Medicine, St. Louis, MO  
Therapeutic Development in Friedreich Ataxia  
David Lynch, MD, PhD; Children’s Hospital of Philadelphia, Philadelphia, PA  
FDA Evaluation and Approval of Drugs for Rare Diseases  
Frank Sasinowski, MS, MPH, JD; Hyman, Phelps, & McNamara, Washington, DC

5:00 PM - 6:00 PM  
JUNIOR MEMBER SEMINARS  
1. Med Students: Finding a Residency  
2. Residents: Finding a Fellowship  
3. Residents & Fellows: Getting Your First Job

5:00 PM - 7:00 PM  
SIG Meetings

7:00 PM - 10:00 PM  
GALA RECEPTION  
(outdoors, overlooking Potomac River)

Saturday, October 10

7:00 AM - 7:30 AM  
CONTINENTAL BREAKFAST

7:30 AM - 8:45 AM  
SEMINARS  
Breakfast Seminar 4: Patient Powered Research Networks for Rare Diseases  
Organizer: Florian Eichler, MD; Harvard Medical School, Boston, MA  
The Duchenne Connect Patient-Report Registry Infrastructure Project  
Holly Peay, PhD, CGC; Parent Project  
Muscular Dystrophy, Hackensack, NJ  
ALD Connect, an All-Inclusive Consortium for X-linked Adrenoleukodystrophy  
Florian Eichler, MD  
The Rare Epilepsy Network (REN)  
Barbara Kroner, MPH, PhD; RTI International, ResearchTriangle Park, NC

9:00 AM – 10:00 AM  
Hower Award Lecture: Tuberous Sclerosis: Toward Molecular-Based Therapy  
E. Steve Roach, MD; Nationwide Children’s Hospital, Columbus, OH

10:00 am – 12:15 pm  
Symposium V: Optimizing Epilepsy and Developmental Outcomes in Pediatric Genetic Disorders: TSC as a Model for Early Diagnosis and Intervention During Infancy  
Organizer: E. Martina Bebin, MD, MPA; University of Alabama at Birmingham, Birmingham, AL  
TSC Diagnostic Criteria and role of genetic testing in TSC
Hope Northrup, MD; University of Texas Medical School at Houston MSB, Houston, TX

*Early Recognition of TSC, the Risk of Epilepsy in the First 2 Years of Life, and Role of EEG as a Biomarker for Epilepsy*
E. Martina Bebin, MD, MPA

*Early Signs of ASD in TSC Infants and the Role of Early Developmental Services*
Darcy Krueger, MD, PhD; Cincinnati Children's Hospital Medical Center, Cincinnati, OH

*How can Early Diagnosis and Treatment of TSC be Applied in Pediatric Genetic Disorders with High Risk of Epilepsy and/or ASD?*
Mustafa Sahin, MD, PhD; Children's Hospital of Boston, Boston, MA

**12:45 pm – 4:00 pm**

**Symposium VI: Child Neurology**
**Foundation Symposium: State of Infantile Spasms: From Research to Bedside to the Community**

Organizer: Donald Shields, MD; President of Child Neurology Foundation, UCLA, Los Angeles, CA

*State of Infantile Spasms*
James Wheless, MD; St. Jude Children's Research Hospital; Memphis, TN

*What I Wish I Would have Known from My Child Neurologist about IS and TSC*
Danielle Boyce, MPH; Johns Hopkins University, Baltimore, MD

*Looking at the Future – Preventative Trials*
E. Martina Bebin, MD MPA

*Living Beyond the Child Neurologist's Clinic – What Resources are Available to Help Support Children Living with IS and TSC?*
Kari Luther Rosbeck, Tuberous Sclerosis Alliance, Silver Spring, MD

Amy Brin Miller, MSN, MA, PCNS-BC, ACHPN, Executive Director (acting) - Child Neurology Foundation, Minneapolis, MN
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>Tuesday, October 6</td>
<td>7:00 pm – 9:00 pm ACNN Welcome Reception (Nurses Only)</td>
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<td>Wednesday, October 7</td>
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<tr>
<td>7:00 am – 8:00 am</td>
<td>Registration and Continental Breakfast</td>
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<tr>
<td>8:00 am – 8:15 am</td>
<td>Welcome and Introduction</td>
</tr>
<tr>
<td>8:15 am – 9:00 am</td>
<td>Janet Bruckner Keynote Speaker <em>Pain Management in the Pediatric Neurology Patient</em> Nancy Santilli, PNP, MN, FAAN</td>
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<tr>
<td>9:00 am – 9:45 am</td>
<td>Concussion in the Pediatric Population Elaine Philipson, MS, PPCNP-BC</td>
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<tr>
<td>9:45 am – 10:00 am</td>
<td>Break</td>
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<tr>
<td>10:00 am – 10:45 am</td>
<td>Understanding the Ketogenic Diet in the Treatment of Epilepsy Elaine Philipson, MS, PPCNP-BC</td>
</tr>
<tr>
<td>10:45 am – 11:30 am</td>
<td>ESES (Electrical Status Epilepticus of Slow-wave Sleep) - Beyond Landau-Kleffner Syndrome Rhonda Werner, MS, RN, APNP, PCNS-BC</td>
</tr>
<tr>
<td>11:30 am – 12:00 pm</td>
<td>Awards Presentation and Annual Business Meeting</td>
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<td>12:00 pm – 1:00 pm</td>
<td>Lunch</td>
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<tr>
<td>1:00 pm – 1:30 pm</td>
<td>2015 Clinical Practice Award - Nemours Neurology Headache Program Tara Pezzuto, APRN, MSN, PCNS</td>
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<tr>
<td>1:30 pm – 2:30 pm</td>
<td>I Feel Dizzy; A Clinical Approach to Evaluation Mona Jacobson, MSN, CPNP-PC</td>
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<tr>
<td>2:30 pm – 2:45 pm</td>
<td>Break</td>
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<td>2:45 pm – 3:30 pm Utilizing Patient Engagement to Improve Decision Making in Pediatric Onset Multiple Sclerosis Lisa Duffy, PhD, RN, CPNP, CNRN, MSCN</td>
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<tr>
<td></td>
<td>3:30 pm – 4:15 pm X-linked Creatine Transporter Disorder-A Tale of 3 Brothers Carolyn Zook Lewis, RN, MSN, CPNP-DC, PMHS</td>
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<tr>
<td>Thursday, October 8</td>
<td>12:00 pm – 12:45 pm Lunch</td>
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<tr>
<td></td>
<td>12:45 pm – 1:15 pm Febrile Seizures...To Treat Or Not To Treat, That Is The Question Lauren Siebrase, MSN, FNP-C</td>
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<tr>
<td></td>
<td>1:15 pm – 1:45 pm You Never Told Me She Would GO BALD!” Addressing the anxieties and fears of parents, patients, and providers when encountering medication related hair thinning/hair loss with commonly used pediatric neurology drugs Bethany Hutchinson, MSN, RN, CPNP, PPCNP-BC</td>
</tr>
<tr>
<td></td>
<td>1:45 pm – 2:15 pm Evaluation and Treatment Management of Childhood Epilepsy Syndromes Lauren Siebrase, MSN, FNP-C Lai Brooks, DNP, FNP-BC</td>
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<tr>
<td>Friday, October 9</td>
<td>12:00 pm – 12:45 pm Lunch</td>
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<td>12:45 pm – 1:30 pm SIG and Table Discussions</td>
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<tr>
<td></td>
<td>1:30 pm – 2:30 pm Up in Smoke: Cannabis for Pediatric Epilepsy Maureen Sheehan, RN MS CPNP</td>
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<tr>
<td></td>
<td>1:30 pm – 2:00 pm Fetal Surgery for Myelomeningocele: The UNC Experience Gretchen Delametter, RN, MSN, CPNP-AC, CNS</td>
</tr>
</tbody>
</table>
PL1-1. Incidence of Dravet Syndrome in a U.S. Population

Wu YW (San Francisco, CA), McDaniel SS, Sullivan J, Meisler MH, Walsh EM, Li S, Kuzniecik MW Xu S

Objective: De novo mutations of the sodium channel gene SCN1A are the major cause of Dravet Syndrome (DS), an infantile epileptic encephalopathy. U.S. incidence of DS has been estimated at 1 in 40,000, but no U.S. epidemiologic studies have been performed since the advent of genetic testing.

Methods: In a retrospective population-based cohort of all infants born at Kaiser Permanente Northern California between January 1, 2007 and June 30, 2010, we electronically identified all patients who received ≥2 diagnoses of seizure before age 12 months, and who were receiving anticonvulsants at 24 months. A child neurologist reviewed records to determine which infants met 4 of 5 criteria for clinical DS: normal development before seizure onset; ≥2 seizures before age 12 months; myoclonic, hemi or generalized tonic-clonic seizures; ≥2 seizures lasting > 10 minutes; and refractory seizures after 2 years of age. SCN1A gene sequencing was performed as part of routine clinical care.

Results: Eight infants met study criteria for clinical DS, yielding an incidence of 1 per 15,700. Six of these infants (1 per 20,900) had a de novo SCN1A mutation likely to be pathogenic, while 1 had an inherited variant of unknown significance. All 8 had febrile seizures by 7 months of age. None had seizures induced by hot water.

Conclusions: Dravet Syndrome due to SCN1A mutation is twice as common in the U.S. as previously suspected. A high index of suspicion is needed to make an early diagnosis in infants with recurrent prolonged febrile seizures.

Keywords: Epilepsy, Genetics

PL1-2. The Pediatric Epilepsy Emergency Risk Score (PEER): Predicting Frequent ED Use with Data from an Electronic Health Record System

Grinspan ZM (New York), Hafeez B, Haridas B, Patel AD

Objective: Frequent ED use by children with epilepsy indicates poor access to care or poor seizure control. Although several disease-related and socioeconomic factors associate with frequent ED use, accurate predictions of future ED use are understudied. We aimed to identify ~200 high risk patients for enrollment in care management.

Methods: We performed a retrospective cohort study on children receiving epilepsy care in 2013-14. We assembled 100+ variables from EHR data in 2013. We employed regression variants and machine learning techniques to predict ED visits in 2014. In 100 trials, we fit each algorithm on half the data then used the other half to evaluate predictive accuracy. We selected the algorithm that, on average, identified ~200 patients with the largest number of ED visits in 2014.

Results: We studied 2063 children. Bivariate analyses found multiple potential predictors of ED use: younger age, male, Medicaid, frequent use of health services, medical complexity, several comorbidities and AEDs, and home zip code characteristics. The best predictive algorithm included two variables with similar coefficients. We combined these into the Pediatric Epilepsy Emergency Risk Score (PEER Score): count of ED visits plus count of head CTs in one year.

In 2013, 181 children had a PEER Score ≥ 3. In 2014, 138 (76%) visited the ED; 53 (29%) visited four or more times. As a group, they generated 515 ED visits, including 192 unscheduled hospital admissions.

Conclusions: The PEER Score predicts frequent ED use in children with epilepsy, with similar performance to machine learning techniques.

Keywords: Epilepsy

PL1-3. SCN1A as a Candidate Gene Modifier Influencing the Severity of Epilepsy in Autosomal Dominant GRIN2A Mutation

Marafie DN (Houston, TX), Emrick LT, Coorg RK, Proud MB, Zeller RS, Clark GD

Objective: GRIN2A has been recently implicated as a monogenic cause in the pathogenesis of idiopathic focal epilepsy with rolandic spikes spectrum. We describe a four-generation family in which three members affected by severe childhood-onset epilepsy syndromes were found to have a pathogenic variant in GRIN2A with a concomitant variant of unknown significance (VUS) in SCN1A.

Methods: Whole Exome Sequencing of a 6 year-old female with acquired epileptic aphasia identified a heterozygous c.594G>A (p.W198X) pathogenic variant in GRIN2 and a heterozygous c.1961T>C (p.V54A) VUS in SCN1A. A four-generation pedigree was obtained. Sanger sequencing for the two variants was performed in four family members.

Results: A four-generation pedigree identified 12 maternal family members affected by variable degrees of unspecified and focal epilepsy, acquired epileptic aphasia, speech dyspraxia, and neurodevelopmental disabilities. The proband’s mother had an unspecified severe childhood-onset epilepsy and learning disability while a maternal cousin was similarly affected with acquired epileptic aphasia. Maternal half-sister has a well-controlled focal epilepsy, dyslexia and ADHD. Sanger sequencing of both variants was performed on the asymptomatic father and the symptomatic mother, maternal half-sister, and maternal cousin. Both variants were identified in the mother and the maternal cousin affected by severe childhood-onset epilepsy. The GRIN2A variant but not the SCN1A variant was identified in the maternal half-sister with well-controlled focal epilepsy. Father was negative for both.

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Conclusion: The genetic analysis in this family suggest that the SCN1A gene may play a role as a gene modifier influencing the severity of epilepsy in patients with GRIN2A mutations.

Keywords: Epilepsy, Genetics

PL1-4. Quality of Life in Childhood Epilepsy: a comparison with typical children and children with cerebral palsy
Mezgebe M (Hamilton, Ontario, Canada), Akhtar-Danesh G, Streiner DL, Fayed N, Rosenbaum PL, Ronen GM

Little is known about how the quality of life (QOL) of children with epilepsy compares to that of children with other neurological impairments or typically developing children.

Objective: To compare the QOL of children with epilepsy to children with cerebral palsy (CP) and children from the general population.

Methods: We measured self- and proxy-reported QOL of children with epilepsy, and contrasted that with data for CP and the general population from the SPARCLE group and European KIDSCREEN project, respectively. Participants: Children ages 8-12 years with epilepsy were recruited from 6 sites across Canada (N=345). Same-aged children with CP (N=489) came from 6 European countries, while typical children aged 8-11 (N=5950) came from 13 European countries. All participants completed the self- and proxy KIDSCREEN-52 questionnaire.

Results: There were no clinically important differences (>0.5 standard deviation) between self-reported quality of life in children with epilepsy compared to children with CP or children from the general population. In contrast, proxy-reported QOL revealed clinically important differences among the three groups in five of ten KIDSCREEN-52 domains: parents of children with epilepsy reported better QOL in (1) physical wellbeing, (2) autonomy and (3) social support, but poorer QOL in the domains of (4) bullying and (5) mood and emotions (all at p <0.001).

Conclusions: Families should find comfort in the results of this study as they indicate that children with epilepsy do not perceive any important differences in QOL in comparison to their typical peers.

Keywords: Cognitive/Behavioral Disorders

PL1-5. Admission EEG Findings in African Children with Cerebral Malaria are Associated with Mortality, Morbidity, and Malarial Retinopathy
Postels DG (East Lansing, MI), Wu X, Li C, Seydel KB, Kaplan P, Taylor TE, Opoka R, Birbeck GL, John CH, Kousa Y

Objective: The spectrum and implication of electroencephalographic (EEG) findings in children with cerebral malaria (CM) has been described in small case series, but to date there has been no study assessing these findings in children in more than one site or comparing findings in children with and without malaria retinopathy. We characterized and compared admission EEG findings in Malawian and Ugandan children with CM, identified EEG factors associated with mortality or adverse neurological outcome, and compared EEG findings in patients of differing malarial retinopathy status.

Methods: We reviewed admission EEG tracings from 281 hospitalized children with clinical CM, 122 from Uganda and 159 from Malawi, admitted between 2008 and 2012. Tracings were interpreted by neurologists blinded to the patient’s outcome and retinopathy status.

Results: Admission EEG factors associated with mortality included a slower frequency, lower average voltage, focal slowing, and lack of EEG reactivity. A generalized voltage attenuation to painful stimulation decreased the odds of death compared to those with no EEG reaction to stimulation (OR= 0.33, 95%CI: 0.12, 0.92). The presence of electrographic seizures was not associated with mortality but was associated with an increased odds of a neurologic deficit in survivors (OR= 12.5, 95% CI: 2.8, 56.2). Malarial retinopathy status did not modify these associations. There were few differences in admission EEGs in children with retinopathy positive vs. negative CM.

Conclusions: Specific EEG factors associated with mortality included a slower frequency, lower average voltage, focal slowing, and lack of EEG reactivity. A generalized voltage attenuation to painful stimulation decreased the odds of death compared to those with no EEG reaction to stimulation (OR= 0.33, 95%CI: 0.12, 0.92). The presence of electrographic seizures was not associated with mortality but was associated with an increased odds of a neurologic deficit in survivors (OR= 12.5, 95% CI: 2.8, 56.2). Malarial retinopathy status did not modify these associations. There were few differences in admission EEGs in children with retinopathy positive vs. negative CM.

Keywords: Infections, Neuroimmunology
PL1-6. Subcortical Synaptic Networks in Focal Cortical Dysplasias
Sarnat HB (Calgary, Alberta, Canada), Flores-Sarnat L, Hader W, Bello-Espinosa L

Objective: Scattered subcortical white matter neurons occur in normal brains. White matter neurons are more numerous (>20/HPF) beneath epileptogenic focal cortical dysplasias (FCD). These subcortical neurons cause blurring of the grey/white boundary in MRI. Their contribution to epileptic circuitry is uncertain. Synaptophysin, a structural glycoprotein of all synaptic vesicle membranes, demonstrates sequences of fetal synaptogenesis and identifies synapses in mature brain. It also displays axoplasm of immature neurons and of subcortical mature neurons. This study addresses synaptic connections of subcortical neurons in FCD.

Methods: We examined 54 cortical epilepsy resections from 44 patients, ages 2mos to 18yrs. Synaptophysin immunoreactivity was examined for subcortical synaptic networks of FCD I (20 cases), II (7), IIIb (6), IIIId (2), TSC (6), HME (3). Controls were adjacent normal cortex and 10 age-matched brains without dysplasia.

Results: An elaborate synaptic network of increased white matter neurons was demonstrated in FCD, regardless of age, with axonal projections between each other and to overlying cortex. This network extended more deeply than normal (>500um beneath cortex) in types I, II, III, TSC, HME. Axonal orientation often was perpendicular to cortex; axons of normal white matter neurons lie parallel.

Conclusions: Subcortical white matter neurons are an integral component of FCD and can participate in epileptic circuitry. Neuropathological examination of brain resections for epilepsy should include synaptophysin immunoreactivity for white matter networks.

Keywords: Neonatal Neurology, Translational, Experimental Therapeutics


Objective: During a 3-week period in August 2012, the California Department of Public Health (CDPH) received 3 reports of acute flaccid myelitis (AFM), a rare syndrome in North America since regional elimination of wild poliovirus in 1991. We investigated to identify and characterize additional cases, estimate incidence, and determine possible etiologies.

Methods: A case was defined as AFM affecting >/=1 limb and electromyography or magnetic resonance imaging (MRI) indicating damaged spinal motor neurons among California patients with illness onset during June 2012–December 2014. Confirmed cases of botulism, Guillain-Barré syndrome, West Nile virus disease, myasthenia gravis, or stroke were excluded. We requested that healthcare providers and local health department report AFM. We abstracted medical records and requested CSF, serum, respiratory, and stool specimens from reporting physicians for laboratory testing to identify infectious agents, including enteroviruses, arboviruses, parechoviruses, and respiratory viruses.

Results: Among 58 cases identified, 53 (91%) had a respiratory or gastrointestinal prodrome, 46 (79%) fever, and 42 (72%) CSF pleocytosis. The median age was 9 years (range: 5 months–72 years), and California incidence was 0.06 cases per 100,000 individuals/year during June 2012–December 2014. Of patients with follow-up information, 26 of 27 (96%) experienced persistent flaccid weakness 60 days after onset, and 12 of 15 (80%) had weakness persisting >1 year. Of specimens tested from 41 cases, the most frequently detected virus in respiratory specimens was Enterovirus D68 (n = 9). No pathogens were detected in CSF.

Conclusions: In California, AFM remains rare. No common etiology for these cases was confirmed. The significance of identifying Enterovirus D68 in respiratory specimens is unclear, and investigation of the potential for Enterovirus D68 to cause neurologic illness is warranted.

Keywords: Infections, Neuroimmunology

Platform Session 2
Friday, October 9
(8:30 am - 10:15 am)

PL2-1. Enhancement of Motor Learning with Transcranial Direct Current Stimulation in Healthy Children
Ciechanski P (Calgary, AB, Canada), Zevdie E, Kirton A

Objective: Transcranial direct-current stimulation (tDCS) can enhance motor learning in normal and hemiparetic adults but is untested in children. We aimed to determine the effects, safety, tolerability and neurophysiology of tDCS on motor learning in the developing brain.

Methods: Nineteen healthy right-handed children (8-17 years old) practiced a dexterity-based motor task (Purdue Peg-Board, PPT) with their left hand over 3 consecutive days. Participants were randomized to 4 primary motor cortex tDCS groups: 1mA contralateral anodal, 1mA ipsilateral cathodal, 2mA ipsilateral cathodal, or sham. Primary outcome was change in PPT score. Additional outcomes included safety and tolerability, pre/post-motor measures, online/offline learning, and TMS measures of neurophysiology.

Results: Procedures were well-tolerated with no adverse events (mild itching in 52%). All tDCS groups improved PPT scores 2 to 3-fold more than sham (p=0.01). Cathodal-tDCS also improved untrained hand performance. Learning effects were predominantly online. Untrained motor skills also improved with tDCS (Jebsen-Taylor Test). Anodal-tDCS decreased reaction time in an implicit learning-reaction test. tDCS effects on TMS neurophysiology were complex. Cathodal-tDCS decreased stimulated M1 excitability and motor evoked potential latency. Gains in function

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correlated with decreases in right M1 short-interval intracortical inhibition (SICI).

**Conclusions:** Neuromodulation with tDCS appears feasible, safe, and well-tolerated in children. Both contralateral anodal and ipsilateral cathodal-tDCS enhance motor learning with large effect sizes in short training times. Effects appear to extend to other motor tasks and the untrained hand. The neurophysiological mechanisms underlying such plasticity are measurable with TMS but require further study.

**Keywords:** Stroke

**PL2-2. Everolimus for Subependymal Giant Cell Astrocytoma Associated with Tuberous Sclerosis Complex: Final Long-Term Results from Approximately 4 Years of Treatment in EXIST-1**


**Objective:** To analyze the long-term efficacy and safety results of everolimus in treating subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) from the conclusion of the EXIST-1 study (NCT00789828).

**Methods:** Patients with new or growing TSC-associated SEGA were randomly assigned to receive everolimus 4.5 mg/m²/day (target trough 5–15 ng/mL) or placebo. Upon achieving positive results for the primary endpoint (SEGA response rate) during the core phase (cutoff March 2, 2011), all remaining patients were offered open-label everolimus in an extension phase.

**Results:** In total, 111 patients (median age 9.5 years) received ≥1 dose of everolimus. Median duration of everolimus exposure was 47.1 months (last patient last treatment, October 2, 2014). SEGA response rate (proportion of patients with ≥50% reduction in sum volume of target SEGA versus baseline) increased from 34.6% in the core phase to 57.7% (95% confidence interval [CI]: 47.9-67.0). SEGA progressions were observed in 13 patients (11.7%) Estimated progression-free survival rate at 3 years was 88.8% (95% CI: 80.6%-93.6%). Incidences of adverse events (AEs) were comparable to previous reports and generally decreased over time. Most common AEs (≥20%) were stomatitis (44.1%), convulsion (36.9%), nasopharyngitis (35.1%), mouth ulceration (34.2%), pyrexia (28.8%), vomiting and cough (26.1% each), pneumonia and upper respiratory tract infection (25.2% each), and diarrhea (24.3%). Eleven patients (9.9%) experienced an AE that led to study discontinuation.

**Conclusions:** Everolimus showed increased efficacy and safety results of everolimus in treating subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) from the conclusion of the EXIST-1 study (NCT00789828).

**Keywords:** Stroke

**PL2-3. Transcranial Direct Current Stimulation for Perinatal Stroke Hemiparesis: interim analysis of a randomized, controlled clinical trial**

Kirton A (Calgary, AB, Canada), Ciechanski P, Zewdie E, Andersen J, Herrero M, Quigley J, Carolos L, Hill MD

**Objective:** Perinatal stroke causes hemiparetic cerebral palsy and lifelong disability. Non-invasive brain stimulation may enhance motor recovery in adult stroke with emerging evidence in children. Transcranial direct current stimulation (tDCS) carries unique advantages but is untested in hemiparetic children.

**Methods:** Double blind, randomized, controlled trial of tDCS in perinatal stroke hemiparesis (www.clinicaltrials.gov/NCT02170285). Children 6-18 years participate in a 2 week, goal-directed, peer-supported, motor learning camp. Participants are randomized to daily cathodal, 1mA tDCS over contralesional primary motor cortex during the first 20 minutes of therapy. A predefined interim safety analysis was planned after 12 participants. Primary safety outcome was decrease in function of either upper extremity (Melbourne Assessment, box-and-blocks, grip and pinch strength) at 1 week and 2 months. A pediatric brain stimulation tolerability measure was applied daily. Efficacy outcomes are the Assisting Hand Assessment (AHA) and Canadian Occupational Performance Measure (COPM).

**Results:** All twelve subjects (median 11 years, 6 males) completed all outcomes. No decrease in paretic or unaffected upper extremity function was observed at 1 week or 2 months. There were no serious adverse events and favourable tolerability scores. Mild, transient scalp itching was common. Mean change in AHA was positive and possibly larger in tDCS versus sham (p=0.09). Change in COPM at 2 months was greater in those receiving tDCS (p=0.01).

**Conclusions:** Trials combining intensive therapy with tDCS appear feasible and safe in children with perinatal stroke and hemiparesis. Evidence of efficacy requires completion of this phase 2 trial and additional study.

**Keywords:** Stroke

**PL2-4. Sleep Dependent Memory Consolidation in Children with Autism Spectrum Disorders**

Maski KP (Boston, MA), Holbrook H, Manoach D, Hanson E, Kapur K, Stickgold R

**Objective:** Overwhelming evidence shows that sleep is important for the consolidation of newly acquired memories. While sleep disturbances among children with ASDs are a major clinical concern, it is unclear how these sleep disturbances affect their memory consolidation. In this study, we determine if sleep disturbances in children with ASD result in failure of overnight sleep dependent memory consolidation.

**Methods:** 22 children with ASDs (mean age 11.4 years (+/-2.1) and 20 control subjects (mean age 12.3 years (+/-2.2) participated. Subjects were trained and tested on a 2D object location task. Retesting occurred 10 hours later over a period of wake and sleep with condition counterbalanced. Memory consolidation was determined by the relative difference in performance at retetesting minus the performance at the last trial at learning. Overnight sleep architecture data were collected using home
polysonmography. Analyses were adjusted for age, gender and NVIQ.

Results: Children with ASDs had poorer sleep efficiency (p<0.001) but there was no significant difference in sleep architecture between groups. ASD subjects demonstrated poorer overall memory consolidation compared to controls (p=0.02). Interestingly, both groups demonstrated better memory consolidation across the sleep interval compared to the wake interval (p<0.05). No group x condition interaction was detected.

Conclusions: This is the first report showing that despite their more disturbed sleep quality, children with ASD still demonstrate more stable memory consolidation across sleep than in wake conditions. Our results suggest that improving sleep quality in children with ASD could have direct benefits to improving their overall cognitive functioning.

Keywords: Cognitive, Behavioral Disorders

PL2-5. Lumbar Puncture Does Not Increase the Risk of Death in Comatose Malawian Children

Moxon C (Liverpool, United Kingdom), Zhao L, Li C, Seydel KB, Diggle P, MacCormick I, Taylor TE, Postels DG

Objective: Coma is a common presentation for critically ill children in sub-Saharan Africa. Differential diagnoses include cerebral malaria, encephalitis, and bacterial or tuberculous meningitis. Lumbar puncture (LP) is crucial to optimizing treatment. However, clinicians may be hesitant to perform an LP due to concerns of precipitating herniation and death, particularly as neuroimaging is rarely available. This concern may be compounded by the findings of a recent study demonstrating that brain swelling in children in sub-Saharan Africa. Differential diagnoses include cerebral malaria, encephalitis, and bacterial or tuberculous meningitis. Lumbar puncture (LP) is crucial to optimizing treatment. However, clinicians may be hesitant to perform an LP due to concerns of precipitating herniation and death, particularly as neuroimaging is rarely available. This concern may be compounded by the findings of a recent study demonstrating that brain swelling in children with cerebral malaria is strongly associated with fatal outcome.

Methods: We performed a retrospective cohort study in comatose Malawian pediatric inpatients recruited from 1997-2013. We assessed whether performing an LP changed the odds of mortality within the twelve hours after the procedure or during hospitalization. As assignment to having an LP was non-random, we used propensity score-based analyses to estimate the independent effect of LP on outcome.

Results: 966 children had data on all key covariates, 746 (77%) had an LP and 191 (23%) did not. Following matching, all baseline characteristics were balanced between LP and non-LP pairs. In all analyses, LP was associated with either no change or a reduction in mortality risk: average risk reduction 4.70% at 12 hours (95% confidence interval 0.9% to 8.4%, p=0.02) and 1.3% during hospital admission (95% confidence interval −4.6% to 7.3%, p=0.56). Similar results were observed when data were examined by propensity score based logistic regression, stratification, and inverse probability weighting.

Conclusions: In our study population of comatose African children, performing a diagnostic LP in the absence of prior neuroimaging was not associated with increased mortality risk.

Keywords: Infections, Neuroimmunology

PL2-6. Everolimus Exposure and Overall Tolerability in Patients Treated for Subependymal Giant Cell Astrocytoma Associated with Tuberous Sclerosis Complex: results from the 4-year final analysis of EXIST-1

Sparagna S (Dallas, TX), Flamini JR, Wu YJ, Kuperman R, Berkowitz N, Niolet J, Franz DN

Objective: To assess everolimus exposure and overall tolerability during the long-term EXIST-1 study (NCT00789828) in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC).

Methods: Patients were initially randomly assigned (2:1) to everolimus or placebo. After positive results for the primary endpoint (SEGA response rate; data cutoff March 2, 2011), all patients could continue on open-label everolimus for up to 4 years after the last patient was randomized. Everolimus starting dose was 4.5 mg/m²/day, which was titrated to a target trough level of 5-15 ng/mL based on tolerability. Everolimus blood trough concentrations were measured throughout the study. Safety assessments included adverse event (AE) reporting and laboratory monitoring.

Results: In total, 111 patients (median age 9.5 [range, 1.1-27.4] years) received ≥1 dose of everolimus. Median duration of everolimus exposure was 47.1 (range, 1.9-58.3) months at study conclusion (October 2, 2014), and median daily dose intensity was 5.89 (range, 1.0-13.8) mg/m². Median everolimus trough concentrations over the study course were generally between 5-7 ng/mL. Eighty patients (72%) required a dose reduction or interruption due to an AE; 8 patients (7.2%) discontinued the study due to a drug-related AE. One accidental death occurred (not related to study drug). The most common AEs suspected to be treatment-related were stomatitis (43.2%) and mouth ulceration (32.4%). The incidence of newly emergent AEs generally decreased over time. Clinically significant laboratory abnormalities were mainly grade 1 or 2 and resolved spontaneously.

Conclusions: Exposure to everolimus over 4 years showed no new safety concerns in patients with TSC-associated SEGA.

Keywords: Brain Tumors, Oncology, Genetics

PL2-7. A Phase II Randomized Controlled Trial of Erythropoietin and Hypothermia for Neonatal Neuroprotection in HIE—Feasibility and Preliminary Data

Wu YW (San Francisco, CA), Mathur AM, Chang T, Mulkey SB, Mayock DE, Van Meurs KP, McKinstry RC, Rogers EE, Massaro AN, Gonzalez FF, Dong L, Comstock BA, Heagerty PJ, Ballard RA, Juul SE

Objective: To describe feasibility of a phase II RCT testing erythropoietin with hypothermia in term newborns with hypoxic-ischemic encephalopathy (HIE).

Methods: In a double-blind placebo-controlled trial, we enrolled 50 newborns with moderate (N=43) or severe (N=7) HIE. All patients had encephalopathy; perinatal depression (10-minute Apgar ≤5, pH <7.00 or base deficit ≥15, or need for resuscitation at 10 minutes); and received

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hypothermia therapy. We randomized newborns to receive erythropoietin 1000 U/kg IV or placebo at 1, 2, 3, 5 and 7 days. Two independent observers determined MRI brain injury severity using the Washington University scoring system. Plasma biomarker, 6- and 12-month outcome evaluations are in process. We present feasibility data and correlate MRI injury score with 6-month developmental outcomes assessed by Warner Initial Developmental Evaluation (WIDEA) questionnaire.

Results: Of 154 newborns with HIE at 7 hospitals, 81 (53%) met study eligibility over 10 months, and 50 were enrolled (consent rate =74%). Mean consent age was 12.6 (SD 7.2) hours. Mean age at 1st study drug was 16.5 (SD 5.9) hours. In hospital mortality was 14%. Median brain injury score was 6 (IQR 0-14, range 0-58). Mean 6-month WIDEA score among 77% of survivors was 73.0 (SD 10.0, range 0-93). A higher brain injury score correlated with a lower 6-month developmental WIDEA score (P=0.05).

Conclusions: A randomized trial testing high doses of erythropoietin starting at <24 hours of age is feasible. A large efficacy trial is needed to determine whether erythropoietin further improves outcomes in infants undergoing hypothermia for HIE.

Keywords: Neonatal Neurology

POSTER PRESENTATIONS

Brain Tumors/Oncology

1. Severe Neurotoxicity Following Nelarabine Administration in a Pediatric Patient

Hainlen MH (Houston, TX), Chao H, Agarwal S, Lee JC, Wolf VL.

Objective: This case report focuses on grade 4 peripheral and central neurotoxicity attributed to nelarabine in an 8-year old male with refractory T-ALL. This description contributes to the understanding of treatment-limiting side effects of nelarabine.

Methods: We report an 8-year-old male with T-cell acute lymphoblastic leukemia (T-ALL) with CNS 1 disease who failed induction therapy on AALL0434 regimen D, then received a five day course of post-induction chemotherapy with nelarabine. On day 5 of nelarabine treatment the patient experienced generalized pain and hyperesthesias. This progressed rapidly to agitation, confusion, altered mental status, seizures and ultimately coma with minimal brainstem responses.

Results: Workup included an EEG with diffuse background slowing, an EMG with severe axonal sensorimotor peripheral polyneuropathy, and MRI with multifocal T2 prolongation suggestive of chemotherapy related neurotoxicity. Treatment with B12, thiamine, and intravenous immunoglobulin did not result in improvement. Nine months following receipt of nelarabine the patient remains in a persistent vegetative state; his T-ALL remains in remission. Neurotoxicity with nelarabine is typically limited to somnolence, malaise, and fatigue that resolve after cessation of nelarabine. A pediatric patient during phase 1 testing experienced seizures, myoclonic jerks, ascending paralysis, and coma without resolution of neurotoxicity prior to death three months later (Kurtzberg, et al, 2005).

Conclusions: Our patient experienced severe peripheral and central neurotoxicity after nelarabine administration and his prolonged survival has allowed continued observation of this neurotoxicity. The occurrence of similar symptoms in another patient further supports nelarabine as the causative agent.

Keywords: Brain Tumors/Oncology

2. Large Vessel Arteriopathy After Cranial Radiation Therapy in Pediatric Brain Tumor Survivors

Nordstrom M (San Francisco, CA), Sear K, Tamrazi B, Torkildson J, Gauvain K, Haar-Kogan DA, Chen J, Del Buono B, Banerjee A, Samuel D, Fullerton HJ, Mueller S.

Objective: Among childhood cancer survivors, increased stroke risk after cranial radiation therapy (CRT) is thought to be caused by a radiation-induced arteriopathy. Limited data exist to support this hypothesis. To assess the timing and presence of cerebral arteriopathy identified by magnetic resonance angiography (MRA) after CRT in childhood brain tumor survivors.

Methods: In a prospective cohort of 106 brain tumor patients who received CRT between 1987 – 2014 at age <21 years, we performed chart abstraction and prospective annual follow up at 3 medical centers to assess large vessel cerebral arteriopathy by brain MRA. All images were reviewed by a board-certified neuroradiologist. We used survival analysis techniques to determine the cumulative incidence of arteriopathy after CRT.

Results: The median follow up time post CRT was 6.1 years (interquartile range (IQR) 4.6-9.3). We identified 10 patients with arteriopathy. The median age at onset of CRT was 6.3 years (IQR 4.5-8.5 years) and median time to detection of arteriopathy following CRT was 4.8 years (IQR 2.3-7.8 years). The cumulative incidence of arteriopathy at 5 years after CRT was 5.7% (CI 2.4-13%) and at 10 years was 19% (CI 9.3-46%). One patient with arteriopathy had a confirmed arterial ischemic stroke that occurred 1.4 years from CRT in the distribution of the stenotic artery.

Conclusions: Radiation-induced arteriopathy can develop relatively early following CRT. In an ongoing study we are following this cohort prospectively to define the long-term cumulative incidence and risk factors of arteriopathy, and the temporal relationship between CRT, arteriopathy and stroke.

Keywords: Brain Tumors/Oncology, Neuroimaging, Stroke

3. Cellular and Behavioral Effects of Molecularly Targeted Anti-Cancer Agents on the Developing White Matter

Ritter J (Washington, DC), Edwards JB, Gallo V, Scafidi J.

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Objective: To test the effects of molecularly targeted anti-cancer therapy on the developing brain.

Background: Pediatric brain tumors are the second most common form of childhood cancer. Histological examination of many of these tumors demonstrate aberrant signaling in: i) epidermal growth factor receptor (EGFR); ii) vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) receptor; and/or iii) altered mTOR signaling. Inhibition of these pathways with molecularly targeted therapeutics has come to the forefront of pediatric neuro-oncology. However, these pathways are crucial for normal brain development and the result of inhibiting these pathways is unknown.

Methods: We administered Gefitinib (EGFR antagonist), Sunitinib (PDGFR and VEGFR inhibitor) and Rapamycin (mTOR inhibitor) from postnatal day 12 (P12) to P17 – Paradigm #1 or from P17 to P22 – Paradigm #2. We performed a white matter (WM) specific behavioral assay in addition to cellular analysis in the sub-cortical WM and sub-ventricular zone (SVZ).

Results: We demonstrate that after administration of each agent, the inclined-beam walking test at P30 and P60 was impaired in both paradigms. However, those treated earlier in development had more pronounced deficits compared to those treated later in development. Cellular analysis of the subcortical WM demonstrated decreased: i) immature and mature oligodendrocytes; ii) oligodendrogenesis; and iii) oligodendrogial proliferation, with all cell numbers normalizing by P60. In the SVZ, these agents also caused significant decreases in proliferation and neural progenitors.

Conclusions: Inhibition of specific molecular pathways in the developing brain has long-term functional consequences, with greater deficits observed with earlier treatment.

Keywords: Brain Tumors/Oncology, Translational/experimental therapeutics

5. Convergent Excitability Defects in the Prefrontal Corticothalamic Circuit Unite Diverse Mouse Models of Autism

Brumback AC (San Francisco, CA), Sohal VS

Objective: Autism is one of the most heritable neurodevelopmental disorders, and though many genes have been linked to the condition, how these genetic changes translate into deficits in social interactions is largely unknown. Recent work suggests that defects in diverse genes and signaling pathways associated with autism converge upon the deep projection layers (L5/6) of medial prefrontal cortex (mPFC). L5/6 of mPFC is comprised at least two distinct circuits of pyramidal neurons projecting either subcortically (corticothalamic – CT cells) or to the contralateral mPFC (corticocallosal – CC cells).

Methods: We studied the physiology of these two subpopulations of mPFC L5/6 pyramidal neurons in three distinct mouse models of autism: prenatal exposure to valproate (VPA, a commonly used anticonvulsant and histone deacetylase inhibitor), knockout of the Fragile X gene (FMR1, an mRNA binding protein), and knockout of the Contactin Associated Protein-Like 2 gene (CNTNAP2, a cell adhesion molecule).

Results: We found that these three autism models are united by a common circuit-level deficit in prefrontal CT cell excitability. In the autism models, mPFC L5/6 CT cells had depolarized resting membrane potentials, decreased input resistance, and fired fewer action potentials in response to depolarizing current steps. These changes were not seen in CC neurons. CT (but not CC) cells also showed decreased responses to long-range excitatory synaptic inputs. Finally, acute optogenetic inhibition of mPFC CT cells increased social exploration in the VPA autism model.

Conclusions: Together, these results demonstrate a specific circuit-level defect in the mPFC associated with multiple etiologically distinct forms of autism.
Keywords: Cognitive/Behavioral Disorders, Translational/experimental therapeutics

6. Feasibility of a Mobile Cognitive Intervention in Children with Childhood Absence Epilepsy
Glynn P (Chicago, IL), Eom S, Zelko F, Koh S

Objective: Childhood absence epilepsy (CAE) accounts for 10% of all childhood epilepsy1 and is associated with academic struggles and deficits of problem solving, language, and in particular, attention.2-6 The present study sought to evaluate the feasibility of a tablet-based cognitive intervention to address these comorbidities. A secondary goal was to collect preliminary data regarding the potential neurocognitive benefit of the intervention. The therapy application studied, Constant Therapy, has been demonstrated to be efficacious in the post-stroke rehabilitation setting.7

Methods: Eight children with CAE were asked to use Constant Therapy for 80 minutes per week over a four-week period. They were evaluated before and after the intervention using the Cognitive Domain of the NIH Toolbox.8 Their parents completed the Behavioral Rating Inventory of Executive Function (BRIEF) at both time points.9 Parents and children also completed a satisfaction survey upon study conclusion.

Results: The children used the application for an average of 77.5 minutes/week. All eight reported that they enjoyed using it, with six stating they would use it “just for fun”. Parents rated their average satisfaction as 4.4/5, with 5 being “very satisfied”. Parents universally said their child enjoyed using the application. Potential neurocognitive benefit was suggested by significant improvements on Toolbox tasks of processing speed (p=0.018) and fluid intelligence (p=0.018), though practice effects must be considered.

Conclusions: A tablet-based cognitive intervention is feasible in children with CAE. A randomized controlled trial is underway to vigorously evaluate the efficacy of the application in a larger cohort of children with epilepsy.

Keywords: Cognitive/Behavioral Disorders

7. Electrophysiological and Behavioral Profiles of Children with Dup15q Syndrome
Jeste SS (Los Angeles, CA), Frohlich J, Bhatt R, DiStefano C

Figure 1: Social communication and cognitive function in Dup15q vs. ASD

Figure 2: Absolute beta power, frequency variance (measure of complexity) and peak beta frequency in Dup15q vs. ASD vs TD
Objective: Duplications of chromosome 15q11.2-13.1 (Dup15q syndrome) are highly penetrant for autism spectrum disorder (ASD) and Intellectual Disability (ID), with heterogeneity in symptom severity. Resting state EEG represents a promising biomarker of this syndrome, with case reports of excessive beta band activity that relates to GABA_A receptor upregulation. In partnership with the Dup15q Alliance, we are characterizing EEG and behavior in children with Dup15q syndrome, with the goal of identifying distinctive features that may define this syndrome.

Methods: Three cohorts are studied: Children with Dup15q syndrome, Age and IQ matched non-syndromic ASD, Age matched typically developing (TD) children. Measures target cognition, motor skills, social communication skills, and adaptive function. High density baseline EEG is recorded per previously published protocols. EEG analysis focuses on resting state power, peak frequency, and signal complexity.

Results: The average age was 64 months (SD 39 months), with developmental quotients (DQ) ranging from 20 to 110. Children with Dup15q showed greater gross and fine motor impairment and less impairment in certain social communication skills (social smile and facial expressions; fig.1). DQ andADOS scores were highly correlated in Dup15q (R^2=-0.78, p<0.01 vs. ASD group R^2=-0.48, p=0.16), suggesting that social communication impairment may be secondary to cognitive impairment. Children with Dup15q showed significantly higher absolute beta power and peak beta frequency across scalp regions. Peak beta frequency significantly correlated with NVIQ (R^2=-0.59, p=0.030; fig.2).

Conclusions: A distinctive electrophysiological and behavioral profile is emerging that will facilitate the design of targeted interventions and outcome measures in this high risk syndrome.

Keywords: Cognitive/Behavioral Disorders, Genetics

8. Children with Autism Spectrum Disorders Show Timing-Related Changes During Praxis Execution

Johnson TL (Baltimore, MD), Pillai A, McAliffe D, Mostofsky S, Ewen J

Objective: Impaired execution of learned, skilled movement—praxis—is known to be deficient in children with Autism Spectrum Disorders (ASD). Praxis impairments are correlated with social and communicative symptoms. Praxis therefore functions as a model on which we can examine altered brain physiology, particularly related to the left central and parietal regions of the praxis network. Several hypotheses about the neurobiological basis of praxis suggest the presence of altered timing. We therefore aimed to examine timing differences in brain activation during a praxis execution task.

Methods: 20 children with ASD and 28 typically developing (TD) controls, right-handed and aged 8-12 years, performed a praxis task, panтомимing the use of common tools, while EEG was recorded. We assessed event-related potentials (ERPs) in left central and parietal channels, time-locked to the “Go” stimulus.

Results: During praxis execution, latency (calculated as time to reach 25% of the total rectified area within the 0-1 second time window) in the left parietal channel did not differ between groups. However, activation latency of the left central channel was 77msec slower in the ASD subjects when compared with the TD subjects (p=0.03).

Conclusions: In ASD, delayed activation in left central regions during a praxis task could be due to delayed transmission from parietal regions, consistent with the connectivity hypothesis of ASD; due to slowed dendritic computation within the central region itself; or due (based on the nature of ERP measurements) to temporal dispersion over multiple trials, consistent with altered putative synchrony in ASD. Further work may separate out these possibilities.

Keywords: Cognitive/Behavioral Disorders, Movement Disorders

9. Prevalence of Autism Spectrum Disorder in Extremely Low Gestational Age Newborns (ELGANs) at Age 10 Years

Joseph R (Boston, MA), Kuban KCK, O'Shea TM, Heeren T, Hirtz D, Allred EN, Levin A

Objective: Preterm birth is associated with increased risk of ASD compared to general population prevalence estimates of about 1.5%. Prevalence estimates of ASD among ELGANs vary widely, and whether ASD among ELGANs is predominantly associated with global intellectual disability remains unclear. In a prospective study of 887 ELGANs born before 28 weeks gestation, we assessed the prevalence of ASD at age 10 years in relation to intellectual ability.

Methods: The ELGAN cohort was screened for ASD with the Social Communication Questionnaire (SCQ). Children meeting SCQ criteria were assessed with the Autism Diagnostic Interview – Revised (ADI-R), a semi-structured, parent interview. Those meeting ADI-R criteria for ASD were assessed with the Autism Diagnostic Observation Schedule (ADOS-2), a structured, interactive assessment between child and examiner. Only children meeting ADOS-2 diagnostic criteria were classified as having ASD. Intellectual disability (IQ < 70) was identified with the Differential Ability Scales - II.

Results: Of 873 children assessed with the SCQ, 15% (128 children) met SCQ screening criteria and 11% (93 children) met ADI-R criteria for ASD. Of these children, 64 (7.3% of the cohort; 95% CI 5.7% - 9.3%) met ADOS-2 criteria for ASD. Among the 64 children meeting diagnostic criteria for ASD, 36 (56%) had IQ in the intellectually disabled range, whereas 28 (44%) scored within normal limits.

Conclusions: In the ELGAN sample, the prevalence of ASD (7.3%) was approximately 5-fold above general population estimates, and in at least 44% of the children, an autism diagnosis was not better attributed to intellectual disability.

Keywords: Cognitive/Behavioral Disorders
10. Clinical Diagnosis in Rett Syndrome at Cincinnati Children's Hospital Medical Center

Knight VM (Cincinnati, OH), Horn P, Standridge S

Objective: Rett Syndrome is a common genetic cause of intellectual disability in girls and is caused by a mutation in MECP2 gene. The diagnosis is based on clinical criteria. The aim of this study was to compare the frequencies of the clinical criteria in patients with the mutation compared to gene negative patients.

Methods: A retrospective review was conducted at Cincinnati Children's Hospital from 2008 to 2013 who had MECP2 testing. Logistic regression was performed to determine which criteria were most predictive of MECP2 status.

Results: 139 patients were reviewed. 36 patients (33%) were MECP2 gene positive. Loss of language skills (MECP2+: 100%; MECP2-: 84.9%) was the most common finding amongst both groups (p = .045). The other main criteria were more common in MECP2+: gait abnormalities (90% vs 33.4%; p < .0001); stereotypic hand movements (85.3% vs. 18.4%; p < .0001); loss of hand skills (75.8% vs 7.7%; p < .0001). Logistic regression analysis demonstrated that loss of language was not predictive of MECP2 status (p = NS), while odds of MECP2 positive results were higher for all other factors; (loss of hand skills OR 9.4 (CI 2. to 44.2); gait abnormalities OR 12.8 (CI 2.1 to 78.4); and stereotypic hand movements OR 20.0 (CI 4.1 to 98.5).

Conclusions: Odds of a positive test were highest in patients with stereotypic hand movements. Many patients who have language delays had gene testing; however, this is the least specific of the major criteria. These findings have implications for which patients should have gene testing performed.

Keywords: Cognitive/Behavioral Disorders, Genetics, Movement Disorders

11. Duration of Institutionalization is Associated with Functional Neural Outcomes in Children with Histories of Early Deprivation

Kumar A (Detroit, MI), Behen ME, Pilli V, Jeong WJ, Muzik O, Chugani HT

Objective: Studies investigating the effects of institutional rearing have revealed that duration of deprivation is a consistent predictor of neurocognitive/behavioral outcomes; additionally there is some evidence that there may be sensitive periods for healthy/pathological outcomes. There has been less investigation of the relationship between length of deprivation and functional-neural outcomes. We investigated the degree and shape of relationship(s) between duration of institutionalization and regional brain glucose metabolism in children with histories of early deprivation.

Methods: Thirty children (mean age=11.3 ± 2.4 years; range=8.0-15.0; 14 females) raised from birth in international orphanages and later adopted in the USA, underwent neuropsychological evaluations and F-18-Fluoro-deoxy-glucose (FDG) PET scans. Images were spatially normalized and FDG uptake values were obtained for 29 cortical and 20 sub-cortical regions. Partial correlations, controlling for age, between duration in the orphanage and FDG PET regional values were calculated, after adjusting alpha to p<0.01.

Results: Duration in the orphanage was negatively correlated with right caudate nucleus (p=0.008), left inferior frontal (p=0.007), left parahippocampal gyrus (p=0.003), and bilateral temporal pole (left, p=0.004; right, p=0.002), and positively correlated with bilateral posterior cingulate (left, p=0.004; right, p=0.002) FDG uptake. Examination of the nature of the relationship indicated significant non-linear associations between duration of deprivation and FDG uptake for several of these regions.

Conclusions: These findings indicate that duration of deprivation is also associated with functional neural outcomes. Further, the above-mentioned nonlinearity also may be consistent with the presence of sensitive periods for duration for functional neural outcomes.

Keywords: Cognitive/Behavioral Disorders, Neuroimaging


Levin AR (Boston, MA), O’Leary H, Varicin KJ, Crossman M, Tager-Flusberg H, Nelson CA

Objective: Tierney et al. demonstrated that the trajectory of EEG gamma power development during infancy differed in infants with an older sibling with autism spectrum disorder (ASD) compared to infants with a typically developing (TD) older sibling. Here we evaluate the developmental trajectory of EEG gamma power in infants who go on to meet criteria for ASD, compared to those that do not.

Methods: We collected serial high-density EEGs on infants 3-36 months of age. At 36 months, diagnosis of ASD was determined via ADOS and confirmed by clinical impression. We calculated frontal gamma power in EEGs from 3 groups of subjects: Low risk controls (LRC-, n=80), who have a TD older sibling and do not develop ASD; high risk subjects who have an older sibling with ASD (and thus a 20-fold increased risk of ASD) but do not develop ASD themselves (HRA-, n=64); and high risk subjects who do develop ASD (HRA+, n=23). We used hierarchical linear modeling to assess change over time in frontal gamma power for subjects in each of the 3 groups.

Results: Children who subsequently developed ASD showed an altered trajectory of frontal gamma power during the first 36 months of life, compared to children who did not develop ASD (p<.05). This effect persists even when HRA+ subjects are compared only to HRA- subjects.

Conclusions: The developmental trajectory of frontal gamma power is altered in infants who later develop ASD. This finding may serve as a step toward identifying a predictive biomarker for ASD.

Keywords: Cognitive/Behavioral Disorders

13. Shared Decision Making (SDM) and the Treatment of Autism Spectrum Disorders (ASDs)

Levy SE (Philadelphia, PA), Frasso R, Colantonio S, Reed H, Stein G, Mandell DS, Fisk A
Objective: To describe influences on shared decision making (SDM) between primary care pediatricians and parents of young children with autism spectrum disorder (ASD).

Methods: We conducted a qualitative study using semi-structured interviews from May, 2011 through March, 2012. Twenty pediatricians from 10 primary care practices and 20 English speaking parents of children (2-5 years) with a parent reported diagnosis of ASD were recruited through purposive sampling. Interviews were conducted in person or by telephone, audio taped, transcribed verbatim and analyzed using modified grounded theory. Differences in coding were resolved by consensus.

Results: Three primary themes emerged: 1) pediatricians and parents report knowledge gaps by pediatricians about ASD treatments and available resources; 2) there is little communication between parents and pediatricians about treatment choices and families may seek support and advice outside of the biomedical community; 3) use of CAM treatments creates conflict between pediatricians and parents and as a result, parents may independently pursue treatments, without benefit of discussing safety and efficacy with pediatricians.

Conclusions: Much work is needed to effectively foster SDM in the context of ASD treatment decisions in primary care, including enhancing clinician knowledge about evidence based and novel treatments and resources for referral for community treatment. New processes for care in the medical home and clinical guidelines about management of children with ASD should address barriers to SDM and ensuring that primary care pediatricians have sufficient resources to support families.

Keywords: Cognitive/Behavioral Disorders

15. Mechanisms of Circadian Dysfunction in Models of Tuberous Sclerosis Complex

Lipton JO (Boston, MA), Boyle LM, Yuan ED, Nathan A, Lecch J, Goldman S, Tsai PT, Sahin M

Objective: Sleep and circadian rhythms are commonly abnormal in developmental disorders such as autism. Tuberous Sclerosis Complex (TSC) is a neurogenetic developmental syndrome caused by mutations in either the Tsc1 or Tsc2 genes and variably causes epilepsy, autism, and sleep dysfunction and represents a genetically tractable, well-characterized model for developmental disorders of brain function. The proteins encoded by Tsc1 and Tsc2 form a complex that primarily serves to inhibit the function of the mammalian target of rapamycin (mTOR), a conserved and critical regulator of protein synthesis. The role of the circadian clock mechanisms in TSC remains poorly understood.

Methods: Here we use a combination of animal behavior, cell biology, biochemistry, to examine circadian rhythms abnormalities in mouse models of TSC.

Results: We show that Tsc2 heterozygote mice demonstrate a shortened free-running circadian period. Neuron-specific homozygous loss of Tsc1 causes a more severe period defect with some animals demonstrating arrythmicity. We find that the key circadian protein BMAL1 is translationally regulated by the mTOR pathway and is thereby elevated in Tsc2 knockout cells. BMAL1's nuclear localization is elevated in Tsc2 cells and in vivo in brain. The expression and subcellular localization of BMAL1 in Tsc2 mutant cells correlates with massive increases in the BMAL1 transcriptional targets Per1 and Per2 and subsequent period shifts in their circadian rhythmicity.

Conclusions: The Tsc complex regulates the circadian clock through translational control of BMAL1. These results may underlie circadian and sleep-related disorders in patients with TSC and represent a novel avenue for therapeutic intervention.

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

16. Postictal Phenomena Affect Return to Normal Activity in Children with Epilepsy

MacEachern SJ (Calgary, Alberta, Canada), Thornton N, Buchhalter JR

Objective: Following a seizure, patients with epilepsy have reported diverse symptoms in the postictal period, from headache to psychosis, with varying degrees of frequency, duration, and severity. However, these phenomena are not well characterized, and their impact on patient well-being is not understood. The aim of this study is to characterize postictal symptoms in a population of children with epilepsy.

Methods: We propose that in a subset of epilepsy patients, postictal symptoms will affect their ability to return to normal childhood behavior. To test this hypothesis, we used a questionnaire-based approach to characterize postictal symptoms, including type, frequency, and duration, in a
population of children with epilepsy and we evaluated the impact these symptoms had on the ability of these children to perform their regular activities.

**Results:** Preliminary data was analyzed from 32 respondents seen in the outpatient Neurology clinic at the Alberta Children's Hospital (average age: 8.25 [1-16]; 41% F, 59% M). Initial results found that 94% (30/32) of respondents experienced postictal symptoms, with the most common symptom being fatigue (93%; 28/30; Fig 1) and the most bothersome being vision changes, which prevented 100% (1/30) of respondents from returning to normal activities of childhood.

**Conclusions:** With this preliminary study, we hope to further our understanding of symptoms experienced in the postictal period and gain a better understanding of how these symptoms impact children with epilepsy. To the best of our knowledge, this is the first prospective study of this type in the pediatric population.

**Keywords:** Cognitive/Behavioral Disorders

17. **Children and Adolescents Experience Long-Term Morbidity with Cumulative Concussions**

Oyegbile TO (Washington, DC), Zecavati N, Santos C

**Objective:** There is increasing evidence of long-term adverse effects of cumulative concussions in the adult literature. However, it is unclear if there are any long-lasting effects of repeated concussions in children and adolescents. This aim of this study is to determine if cumulative concussions result in long-term neurologic morbidity in the children and adolescents.

**Methods:** Forty children and adolescents (ages 9-19) with a history of concussion were evaluated retrospectively through IMPACT testing and questionnaires. The data obtained included presence or absence of headaches, headache treatment, and cognitive testing – visual and verbal memory scores, visual motor speed testing, and reaction times. Furthermore, loss of consciousness (LOC), memory loss, and/or confusion around the time of sustaining the concussions were evaluated.

**Results:** Participants with a history of cumulative concussions have long-term chronic headaches often requiring medication treatment compared to participants with fewer past concussions (F(1,30)=5.052, p=0.034). Furthermore, participants with history of repeated concussions performed worse on visual motor speed testing compared to those with a history of fewer concussions (r = 0.387, p=0.046, N=31).

Finally, participants with a greater number of concussions were more likely to have experienced LOC (r=0.583, p=0.001, N=30), memory loss (r=0.593, p=0.001, N=30), and confusion (r=0.523, p=0.001, N=30).

**Conclusions:** Cumulative concussions may indeed have prolonged adverse effects on recovery and cognition in children and adolescents with concussion. Our results indicate that chronic headaches and cognitive dysfunction occur in youth with repeated concussions. Further investigation with a larger sample size is warranted.

**Keywords:** Cognitive/Behavioral Disorders, Headache/Migraine

18. **Methylphenidate Extended-Release Oral Suspension (MEROS) Improves ADHD-Rating Scale and Permanent Product Measure of Performance Scores in Children With ADHD**

Palumbo DR (New York, NY), Belden HW, Berry SA

**Objective:** This study evaluated the efficacy and performance effect of Methylphenidate Extended-Release Oral Suspension (MEROS; Quillivant XR [methylphenidate HCl]), a long-acting liquid for the treatment of children with ADHD.

**Methods:** This randomized, double-blind (DB), placebo-controlled, crossover study enrolled 45 patients 6–12 years of age with ADHD. Following an open-label (OL) dose-optimization phase, patients were randomly assigned to 1 week of MEROS treatment followed by 1 week of placebo (or the opposite) during the DB phase. Each week of DB treatment was followed by a laboratory classroom session during which PERMP scores were measured predose and 0.75, 2, 4, 8, 10 and 12 hours postdose. ADHD Rating Scale (ADHD-RS) scores were assessed at screening, baseline, and all visits during the OL period. Treatment response was defined as a ≥50% improvement in ADHD-RS score from baseline. Safety was assessed using adverse events (AEs).

**Results:** A total of 45 patients were enrolled. MEROS treatment resulted in improvements in ADHD-RS scores (total and subscales) at weeks 1–4 compared with baseline. At week 4, 87.2% of children who received MEROS had achieved treatment response. PERMP scores (number of problems attempted and number correct) were significantly higher with MEROS versus placebo as early as 45 minutes (P<0.0001) and at each time point through 12 hours postdose (P<0.002). The most commonly reported AEs were decreased appetite, upper abdominal pain, affect lability, insomnia, insomnia, and headache.

**Conclusions:** These findings suggest MEROS is safe and effective in improving ADHD-RS and PERMP scores in children with ADHD.

**Keywords:** Cognitive/Behavioral Disorders
19. Regional Cortical Thickness is Associated with Deprivation-specific Neurocognitive/Behavioral Symptoms in Children with Histories of Institutional-rearing

Pilli V (Detroit, MI), Desai T, Kumar A, Jeong JW, Chugani HT, Behen ME

Objective: Previous studies have shown altered cortical thickness in fronto-temporal brain regions in children with histories of early deprivation (ED) as compared to typically developing non-adopted children. In the present study we investigated whether regional cortical thickness was associated with deprivation-specific behavioral symptoms/phenotypes in ED children.

Methods: Seventy-one ED children (mean age: 10.0 months ± 2.5; 31 males) underwent MR-SPGR and detailed neuropsychological evaluation. All ED children were raised from birth in European/Asian orphanages, and subsequently adopted in USA. Exclusionary criteria included pre- or perinatal problems, prematurity, focal neurological abnormality, medical problems. Participants were subcategorized into following groups: within normal limits, global cognitive impairment, inattentive/overactive, and atypical. Cortical thickness was determined for thirty-three cortical regions via a surface-based approach using FreeSurfer software. Discriminant function analysis was used, with cortical thickness for independent variables, and subgroup as the dependent variable.

Results: Results revealed significant overall discriminant function based on above mentioned regions (p<0.001); nearly 95% of cases were correctly classified into one of the four groups. Specifically, global cognitive impairment was associated with reduced thickness in left prefrontal, bilateral postero-lateral temporal and superior parietal regions; atypicality with reduced thickness in left middle posterior cingulate and bilateral inferior orbital frontal cortices; and inattentive/overactivity problems with reduced left precentral and superior temporal cortical thickness, and increased right posterior cingulate and precentral gyr cortical thickness.

Conclusions: Different deprivation-specific phenotypic symptoms have distinct patterns of cortical thickness abnormalities, which suggest differential treatment protocols dependent on behavioral phenotype.

Keywords: Cognitive/Behavioral Disorders

20. Effects of Lovastatin on Neurobehavioral Function in Neurofibromatosis I

Roser T (Los Angeles, CA), Pacheco L, Hellemann G, Montojo C, Enrique N, Silva A, Bearden CE

Objective: The HMG-CoA reductase inhibitor Lovastatin can reverse the biochemical, electrophysiological and cognitive deficits observed in the NF1 mouse model. We explored the efficacy of Lovastatin on cognitive dysfunction in individuals with Neurofibromatosis Type 1 (NF1).

Methods: A prospective, double-blind, placebo-controlled, randomized 14-week clinical trial was conducted in children and adults with NF1 between January 2010 and February 2013. Neuropsychological/behavioral testing and fMRI studies were performed on 44 individuals with NF1. Outcome measures were assessed at baseline and after 14 weeks of treatment. The primary outcome measures evaluated visual-spatial memory and attention. An fMRI spatial capacity working memory (SCAP) task investigated pre-post treatment neural activity in 10 regions of interest (ROIs).

Results: There was a significant difference in trajectories over time between the two treatment groups for the Hopkins Verbal Learning Task (HVLT; F(1,33)=6.37, p=.02) and Letter-Number Sequencing (LNS; F(1,30)=20.93, p<.01), in both cases with differential improvement in the statin-treated group. For the CBCL Young Adult Self Report the Internalizing score showed greater improvement in the statin group (F(1,19)=5.09, p=.03). On fMRI, changes in the HVLT were significantly associated with changes in neural activity in the left parietal ROI (r=.51, p=.04), while changes in LNS performance were associated with changes in neural activity in the left frontal eye fields (r=-.61, p=.01) and right Brodmann Area 10 (r=-.59, p=.02).

Conclusions: Compared to the placebo group, NF1 subjects taking Lovastatin showed improvement in verbal learning, working memory and attention tasks which mirror findings seen in the NF1 mouse model.

Keywords: Cognitive/Behavioral Disorders, Neuroimaging, Translational/experimental therapeutics
This profile suggests an intact global semantic knowledge system in ASD, with differential impairments in verbal and nonverbal semantic tasks resulting from modality-specific (e.g., language) abnormalities in the semantic network.

**Keywords:** Cognitive/Behavioral Disorders

### 22. Abnormalities in Large-Scale Brain Network Architecture in Autism

Zielinski BA (Salt Lake City, UT), Prigge MDB, Alexander AL, Bigler ED, Lange N, Lainhart JE, Gerig G

**Objective:** Autism is a complex neurological condition characterized by childhood onset of dysfunction in socioemotional regulation, speech and language, and processing of internally- versus externally-directed stimuli. Accumulating evidence suggests that autism is a network-based disease. However, abnormalities in large-scale brain network structure are not yet fully characterized. Using structural covariance MRI (scMRI), we sought to determine whether specific abnormalities in large-scale brain network organization are associated with autism, and whether network-level abnormalities in brain architecture can be detected with standard clinical MRI.

**Methods:** We used scMRI to interrogate network-level differences in gray matter structure within eight large-scale ‘intrinsic connectivity networks’ (ICNs), in 49 autistic subjects and age-, gender-, and IQ-matched controls (mean age 13.4 yrs, all male). T1-weighted anatomical MRI scans were

### TABLE 1. Abstract 21

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<thead>
<tr>
<th>Demographics</th>
<th>TYP (n=20)</th>
<th>ASD (n=20)</th>
<th>TYP vs ASD, two-sample t-test p-value</th>
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<td>Age, years (mean±SD)</td>
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<td>Male</td>
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<td>PIQ (mean±SD)</td>
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<th>% Incorrect</th>
<th>TYP (n=20)</th>
<th>ASD (n=20)</th>
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<th>Mean Latency to Correct Responses, mean ± SD</th>
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<th>ASD (n=20)</th>
<th>TYP vs ASD, two-sample t-test p-value</th>
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<th>Difference in % Incorrect between NV and V Tasks (negative numbers indicate higher % incorrect for V task)</th>
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<th>ASD (n=20)</th>
<th>TYP vs ASD, two-sample t-test p-value</th>
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<td>SemA (NV) - Nam (V)</td>
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<td>-8 [&lt;0.001]</td>
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<td>SemA (NV) - Comp (V)</td>
<td>1612 [&lt;0.001]</td>
<td>1755 [&lt;0.001]</td>
<td>0.7</td>
</tr>
<tr>
<td>SP (NV) - WP (V)</td>
<td>877 [&lt;0.001]</td>
<td>445 [0.04]</td>
<td>0.1</td>
</tr>
</tbody>
</table>

**TYP=typicals; ASD=autism spectrum disorder; NV=Nonverbal; V=Verbal; Nam=Naming, Comp=Comprehension, SemA=Semantic Association, WP=Word-Picture Matching, SP=Sound-Picture Matching**

**No latency comparison with Naming since it uses a different response modality (speech, not computer mouse)
obtained, and seed regions-of-interest (ROIs) were identified within core ICN hubs. Extracted mean ROI gray matter intensities provided covariates-of-interest for whole brain condition(diagnosis)-by-covariate analyses, and direct between-group comparisons were performed.

Results: scMRI revealed specific abnormalities in brain network architecture, consistent with phenotypic manifestations of autism. The salience network, involved in socio-emotional regulation, is markedly underdeveloped in autism. In contrast, the default mode network (DMN) is larger in autism, but demonstrates 'posteriorization'. Moreover, discrete nodes outside of canonical DMN boundaries are present in the autism group, including many regions historically associated with autism. Other networks demonstrate concurrent over- and under-development, regional decoupling, or remain unaffected.

Conclusions: Selective vulnerabilities in large-scale brain network structure underlie autism. Structural brain network abnormalities in autism are quantifiable using standard clinical MRI.

Keywords: Cognitive/Behavioral Disorders, Neuroimaging

23. Connectome Biomarkers of Pure Speech Delay and Global Developmental Delay in Young Children
Jeong JW (Detroit, MI), Sundaram S, Beben ME, Chugani HT

Objective: Pure speech delay (SD) is a common developmental disorder which, according to some estimates, affects 5-8% of the population. SD may be not only an isolated condition but can be part of a broader condition such as global developmental delay (GD). The present study investigates whether DWI-tractography based-connectome can provide a biomarker to differentiate GD from SD in young children.

Methods: 8 children with pure SD (age: 34.5 ± 13.5, 8 boys), 12 children with GD (age: 36.8 ± 14.1 months, 12 boys) and 5 children with typical development (TD, age: 38.5 ± 20.5 months, 4 boys) underwent 3T diffusion weighted MRI. For each subject, whole brain connectome analysis was performed using 116 cortical regions of interest. The following network metrics were measured at individual region: strength (number of the shortest paths), efficiency (measures of global and local integration), cluster coefficient (measure of local aggregation), and betweenness (measure of centrality).

Results: Compared with TD, global and local efficiency were significantly reduced in both GD and SD (p-value<0.0001). The nodal strength of cognitive network is significantly reduced in GD whereas the nodal strength of language network is significantly reduced in SD, which resulted in high accuracy of > 0.9 to differentiate GD and SD from each other and from TD.

Conclusions: The network abnormalities identified in the present study may be effective biomarkers underlying the neurocognitive and behavioral consequences commonly identified in children with GD and SD. Further validation studies in larger samples are required.

Keywords: Cognitive/Behavioral Disorders, Neuroimaging

24. Prediction of Hand and Leg Motor Weakness
Using Novel Diffusion Tensor MRI Tractography in Children with Central Motor Dysfunction
Jeong JW (Detroit, MI), Lee J, Kamson DO, Juhász C, Chugani HT

Objective: To examine whether an objective segmentation of corticospinal tract (CST) associated with hand and leg movements can be used to predict central motor weakness in the corresponding extremities in a pediatric population.

Methods: 25 children with central paresis affecting at least one limb (age: 1.5-16.5 years, mean age: 9.0 ± 4.2 years, 15 boys) and 42 control subjects (age: 1.8-19.0 years, mean age: 9.0 ± 5.5 years, 21 boys) underwent 3 Tesla diffusion tensor imaging (DTI). The DTI-maximum a posteriori (DTI-MAP) classification was applied to objectively identify the two segments of CST streamlines associated with primary motor pathways of the hand and leg. The resulting CST volumes were divided by total supratentorial white matter volume to obtain the normalized streamline volume ratio (NSVR), a marker that quantifies the degree of axonal loss in separate CST pathways associated with leg and hand motor function.

Results: Paretic children showed significant decreases of the NSVR values in hand and leg CST of the affected hemisphere corresponding to motor weakness of hand and leg in the opposite side as compared to normal controls. The subsequent ROC analyses found high accuracy to detect motor weakness (i.e., 0.84/0.82/0.78/0.79 for right hand, left hand, right leg and left leg, respectively).

Conclusions: Our study demonstrates that DTI-MAP classification may provide a critical translational step to the development of a novel imaging marker that selectively quantifies axonal loss in children with central motor dysfunction. This technique may be useful to facilitate evidence-based treatment and rehabilitation of paretic children.

Keywords: Movement Disorders, Neuroimaging

25. Agenesis of the Corpus Callosum Diagnosed by Fetal MRI: Medical and Developmental Outcomes
Blake RB (Cincinnati, OH), Thomas CW, Merhar S, Kline-Fath BM, Hopkin RJ, Bierbrauer KS, Oldham MS

Objective: Agenesis of the Corpus Callosum (ACC) is a brain malformation readily diagnosed on fetal MRI. However, there is paucity of evidence on the medical and neurodevelopmental outcomes of patients prenatally diagnosed with ACC, leading to difficulties in counseling these families in the prenatal period.

Methods: Chart review of 35 consecutive cases where agenesis or dysgenesis of the corpus callosum was diagnosed by fetal MRI between September 2009 and March 2015. Medical outcomes of fetuses were determined: termination, spontaneous intrauterine fetal demise, demise after live birth, or still living. Developmental outcomes were
determined by administering the Ages and Stages Questionnaire, third edition (ASQ-3), a validated developmental screen.

**Results**: Medical outcomes: 19/35 (54%) living; 6/35 (17%) died after live birth; 4/35 (12%) spontaneous intrauterine fetal demise; and 6/35 (17%) of the pregnancies terminated. Fetal MRI of children still living had on average 1.2 (range 0-4) additional CNS abnormalities and 0.7 (range 0-5) non-CNS abnormalities, compared to 2.4 (range 0-4) additional CNS abnormalities and 2.6 (range 0-5) non-CNS abnormalities in those no longer living. Developmental outcomes: 8/11 (73%) were in the normal range for all 5 developmental domains tested; 2/11 (18%) were delayed in the gross motor domain only; 1/11 (9%) was delayed in fine motor domain only.

**Conclusions**: Fetuses diagnosed prenatally with agenesis of the corpus callosum prenatally have a wide variety of outcomes. Children still living had fewer additional CNS and non-CNS abnormalities on fetal MRI than those no longer living. Most survivors had no identified early developmental impairments.

**Keywords**: Neuroimaging

26. Metabolic and Structural Imaging at 7T After Mild Traumatic Brain Injury (mTBI) in Immature Rats

*Fidan E (Pittsburgh, PA), Foley L, New LA, Kochanek PM, Hitchens TK, Bayir H*

**Objective**: mTBI in children is a common and serious public health problem. Traditional neuroimaging findings are often normal in children who sustain mTBI putting them at risk for repeated mTBI (rmTBI). There is a need for more sensitive imaging techniques capable of detecting subtle alterations in neurophysiology after injury. In a pre-clinical model, we examined neurochemical and white matter changes in immature brain resulting from mTBI and rmTBI using proton magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI).

**Methods**: Eighteen day old male rats received Sham, mTBI, or rmTBI (three impacts 24h apart). MRS if the hippocampi and DTI of whole brain were examined at 7 Tesla at 7d post-injury.

**Results**: After mTBI and rmTBI, N-acetylaspartate/creatinine ratio (NAA/Cr) was reduced ($p=0.03$, $p<0.0001$, respectively), and the myo-inositol/creatinine ratio (Ins/Cr) increased ($p=0.017$, $p=0.01$, respectively) vs sham. rmTBI exacerbated the reduction in NAA/Cr ($p=0.01$ vs mTBI). The choline/creatine (Cho/Cr) and lipid/creatine (Lip/Cr) ratios were also decreased ($p=0.04$, $p=0.02$, respectively) after rmTBI vs sham. There were significant increases in axial diffusivity, radial diffusivity and significant decreases in fractional anisotropy primarily in ipsilateral corpus callosum, external capsule, hippocampus and cortex after rmTBI vs sham.

**Conclusions**: NAA and Ins are altered after mTBI and rmTBI likely reflecting neuro-axonal cell damage and glial proliferation, respectively. The decrease in Cho and Lip after rmTBI along with the DTI findings may reflect damage to axonal membrane. These findings may be relevant to understanding the extent of disability following mTBI and rmTBI in the immature brain. Support: NS061817, NS076511, S10 OD010755

**Keywords**: Neuroimaging

27. Neuroimaging Utilization in a Cohort of Youth with Concussion

*Heyer GE (Columbus, OH), Schaffer CE, Rose SC, Young JA, McNally KA, Fischer AN, Clemson SC*

**Objective**: An estimated 1.6-3.8 million sport-related traumatic brain injuries (TBIs) occur in the United States each year. The majority of these injuries represent concussions. Little is known about the utilization of neuroimaging when concussions occur. The aim of the present study is to determine the utilization and results of neuroimaging from a pediatric concussion cohort.

**Methods**: All concussion-related CT and MRI dates and results were analyzed from a retrospective cohort of 1,953 patients, aged 10-19 years, who presented to a concussion clinic within 30 days of injury. Survival analyses using the log rank (Mantel-Cox) test compared neuroimaging utilization and concussion duration.
Results: The mean patient age was 14.1 years; 63% were male. Acute imaging with CT was common, 141 (86%) of the 164 scans performed were within 72 hours of injury, while only 3.1% of 129 MRIs were performed acutely. The majority of MRIs were done to evaluate persistent postconcussion symptoms. Patients with acute CT scans had no differences in concussion durations compared to those without acute CTs (median 18 days versus 19 days, p=.72), yet symptom durations did differ among patients with MRI compared to those without MRI (median 52 days versus 18 days, p<.001). Neuroimaging abnormalities were not detected by CT or MRI performed after two weeks from the concussion date.

Conclusions: Neuroimaging has a very low clinical yield when done for the sole indication of persistent postconcussion symptoms. CT scans are commonly used for acute assessments, while the majority of MRI studies are used in patients with protracted recovery.

Keywords: Neuroimaging

28. Brain Tubers in Tuberous Sclerosis Complex (TSC): MRI and Alpha-[11C]-methyl-L-tryptophan (AMT) positron emission tomography (PET) correlations

Patel R (Detroit, MI), Luat AF, Altinok D, Kumar A, Chugani HT

Background: In TSC, MRI shows variable appearances of tubers. However, their exact functional/biochemical significance is unclear. We previously demonstrated increased AMT-uptake in epileptogenic tubers, suggesting altered serotonin or kynurenine metabolism.

Objective: We evaluated the AMT-uptake pattern of various tuber types, as seen on MRI, to assess their biochemical nature.

Methods: Thirty TSC subjects, who underwent dynamic brain AMT PET and MRIs with T1/T2/T2*/FLAIR and contrast enhancement, were included. Each patient’s AMT-PET was normalized and coregistered with his/her own MRI, and each tuber was evaluated. Subsequently, an AMT-uptake ratio was determined for each tuber by calculating the ratio for tuber to non-tuberous normal homotopic cortex AMT-uptake. An AMT-uptake ratio of >1.0 was considered increased based on previously validated studies.

Results: The mean age at MRI was 6.5 years (range: 7 months to 19 years). A total of 527 (17.6 ± 9; range: 1-37) tubers with a mean largest diameter of 3.4 ± 1.3 cm (1.1-7.2) were analyzed; 33 (6.3%) tubers showed increased AMT-uptake ratio. On MRI, 8 tubers were T2 dark/T1 bright; 6/8 showed increased AMT-uptake. Twenty-seven tubers enhanced, and two had increased AMT-uptake. Of the 14 calcified tubers, only 1 showed increased AMT-uptake. Three cystic tubers were noted and none showed increased AMT-uptake.

Conclusions: Contrast enhancement, suggesting breakdown of blood brain barrier, calcification or cystic changes do not typically show increased AMT uptake. Dark T2/bright T1 tubers, indicative of underlying melanin, iron or microcalcification deposition, were associated with increased AMT-uptake and may be an MRI biomarker for epileptogenicity.

Keywords: Neuroimaging

29. Three-Dimensional (3D) Motion-Corrected Super-Resolution MRI of the Fetal Posterior Fossa

Pier DB (Boston, MA), Gholipour A, Velasco-Annis C, Clancy S, Kapur K, Estroff JA, Warfield SK

Objective: Current diagnosis of fetal posterior fossa anomalies by sonography and conventional MRI is limited by fetal position, motion, and by 2D, rather than 3D representation. In this study, we aimed to validate the use of motion-corrected super-resolution 3D MRI to image the fetal posterior fossa.

Methods: Using a database of pregnant women with fetal MRIs performed at our institution from 2013-2014, images of 49 normal fetal brains between 19 and 38 weeks gestation were reconstructed using our 3D reconstruction technique (Figure 1). Measurements of the cerebellum, vermis, and pons were obtained for all cases on conventional 2D and reconstructed 3D images in axial, coronal, and sagittal planes, and the concordance between methods was determined using concordance correlation coefficients. As a secondary analysis, concordance of axial and coronal measurements of the transcerebellar diameter was compared.

Results: The concordance of measurements within the same structure was high (p < 0.001) for all structures measured in both conventional 2D and reconstructed 3D images. Between axial and coronal measurements of the

FIGURE 1: Conventional 2D MRI versus motion-corrected super-resolution 3D MRI. Three planar views of (a) an original 2D fetal MRI scan acquired in the sagittal plane with spatial resolution 1.2x1.2x2 mm$^3$, and (b) the reconstructed motion-corrected super-resolution 3D MRI with an isotropic spatial resolution of 1x1x1 mm$^3$. The out-of-plane views in image (a) are disrupted by interslice fetal motion and limit resolution. The cerebellum and cerebral tissue are visualized with coherent anatomic boundaries in (b).
transcerebellar diameter, the concordance was superior, with 3D reconstructed images surpassing conventional 2D images ($p < 0.001$).

**Conclusions:** This comparison study validates the use of motion-corrected super-resolution 3D MRI for imaging the fetal posterior fossa. Measurements of the transcerebellar diameter within a 3D reconstruction are more concordant between imaging planes, because they correct for fetal motion and orthogonal slice acquisition. This technique will facilitate further study of fetal posterior fossa anomalies.

**Keywords:** Neonatal neurology, Neuroimaging

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**Epilepsy**

30. **Surgical Treatment for Refractory Infantile Spasms: The Detroit Series**

*Chugani HT* (Detroit, MI), *Ilyas M, Kumar A, Juhász C, Kapisky WJ, Sood S, Astano E*

**Objective:** We reviewed our experience of surgery for infantile (epileptic) spasms (ES) to determine ideal surgical candidates.

**Methods:** Data from 65 (33 males) ES patients who underwent surgery between 1993-2014 at our institution were reviewed; palliative cases were excluded.

**Results:** Mean age at surgery was 5.1 (0.2-19) years, with mean post-surgical follow-up of 43.3 (6-120) months. Mean number of anticonvulsants used pre-operatively was 4.2 (2-8) which declined to 1.15 (0-4) post-operatively ($p<0.0001$). Total hemispherectomy was the most commonly performed surgery (n=20), followed by subtotal hemispherectomy (n=17), multilobar resection (n=13), lobectomy (n=7), tuberculum (n=6) and lobectomy + tuberculum (n=2), with ILAE class-I outcome in 20, 10, 7, 6, 3 and 0 patients, respectively (total=46/65 (71%); 22 off medication). Surgical outcome was ILAE class-III, IV and V in 8, 9, and 2 patients, respectively. Among 47 patients with lesional MRI, 37 (79%) had class-I outcome, whereas 9/18 with normal MRI had class-I outcome (50%). PET scan was abnormal in almost all patients (61/63 (97%) with lateralization/localization in 56/61 (92%) patients, thus helping in surgical decision-making and guiding sub-dural grid placements, particularly in patients with non-lesional MRI. Of 34 patients operated ≤3 years of seizure onset, 30 (88%) achieved class-I outcome. Seventeen had some post-operative complications, mostly minor.

**Conclusions:** Curative epilepsy surgery in ES patients is best accomplished at an early age and in those with lesional abnormalities on MRI with EEG concordance. However, good outcomes can be achieved even when there is no MRI lesion but positive PET localization.

**Keywords:** Epilepsy, Neuroimaging

32. **Reversible Retinopathy and Systemic Manifestations in P5P Dependent Epilepsy: a case series**

*Guerriero RM* (Boston, MA), *Patel AA, Baumer FM, Peters JM, Rodan LH, Shah AS, Pearl PL, Takeoka M*

**Objective:** Pyridoxine is converted to its biologically active form, pyridoxal-5-phosphate (P5P) by the enzyme pyridox(amine) oxidase (PNPO), and serves as a cofactor in nearly 200 CNS reactions. PNPO deficiency leads to P5P dependence, and post-operative seizures in children with neurological disorders was sepsis (OR 1.7, 95%CI 1.2-2.4), and in children without CNS disorders was bone marrow transplant (OR 2.6, 95%CI 1.3-5.0).

**Conclusions:** This study demonstrates that post-operative seizures occur in almost 25% of children with pre-existent CNS conditions and rarely in children without. This data allows planning to improve management particularly in the first week after surgery in order to reduce seizure burden and post-operative complications especially in children with CNS disorders.

**Keywords:** Epilepsy

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**Introduction:** Seizures in the postoperative period are understudied, particularly in patients without pre-existent neurological conditions. We sought to investigate the incidence of post-operative seizures in patients with and without pre-existent neurological disorders.

**Methods:** American College of Surgeons NSQIP database was queried for the years 2012-2013. NSQIP is the most comprehensive multi-specialty pediatric surgical database in the US and it studies the occurrence of multiple outcomes within 30 days after surgery. The surgical population was stratified between children with pre-existent CNS (central neurological system) conditions and without. Rates were calculated for the most common procedures associated with post-operative seizures and logistic regression analysis was performed to identify pre-operative factors associated with seizures.

**Results:** A total of 114,395 patients were analyzed of which 5,348 (4.7%) had postoperative seizures. There were 18,397 (16.1%) that had pre-existent CNS conditions and 4,105 had a seizure for a seizure rate of 22.3%. For children without CNS conditions, seizure rate was 1.3%. 51.8% of seizures occurred within five days of surgery. The most strongly associated pre-operative risk factor for post-operative seizures in children with neurological disorders was sepsis (OR 1.7, 95%CI 1.2-2.4), and in children without CNS disorders was bone marrow transplant (OR 2.6, 95%CI 1.3-5.0).

**Conclusions:** This study demonstrates that post-operative seizures occur in almost 25% of children with pre-existent CNS conditions and rarely in children without. This data allows planning to improve management particularly in the first week after surgery in order to reduce seizure burden and post-operative complications especially in children with CNS disorders.

**Keywords:** Epilepsy
All patients had neonatal onset epilepsy and were on a continuum of developmental delay to encephalopathy.

**Conclusions**: PNPO deficiency causes P5P dependent epilepsy and associated encephalopathy but also a range of systemic manifestations. The degree of encephalopathy appeared to correlate with the degree of systemic illness. The retinopathy may be considered analogous to gyrate atrophy associated with mutations in B6-dependent ornithine aminotransferase (OAT) deficiency. OAT requires P5P as a cofactor, therefore its absence may provide a mechanism for improvement of the retinopathy following P5P administration. The retinopathy and these systemic symptoms add to the broadening clinical spectrum of P5P dependent epilepsy.

**Keywords**: Epilepsy, Genetics, Neonatal neurology

### 33. Attenuation of Seizure Frequency and Resolution of Hypsarrhythmia in Response to Vigabatrin Treatment in Pediatric Epilepsy

**Jackson M** (Boston, MA), **Klehm J**, **Thome-Souza S**, **Jafarpoor S**, **Loddenkemper T**

**Objective**: Vigabatrin has recently been FDA approved to treat infantile spasms and refractory complex partial seizures in the US. We evaluated the efficacy and safety of vigabatrin in pediatric epilepsy. Efficacy and side effect considerations continue to be a concern.

**Methods**: We retrospectively reviewed patients with epilepsy who used vigabatrin at a pediatric tertiary center from 1/2013 to 2/2014. Five patients who underwent epilepsy surgery were excluded from seizure reduction calculations.

**Results**: Of 103 patients, median epilepsy onset age was 0.3 years (IQR: 0.1-0.6; 55 (53.4%) female), epilepsy duration was 0.3 years (IQR: 0.1-0.7)), vigabatrin initiation age was 0.7 years (IQR: 0.4-1.3), vigabatrin treatment duration was 1.1 years (IQR: 0.4-1.9). Etiology was structural/metabolic in 50 (48.5%), unknown in 28 (27.2%) and genetic in 25 (24.3%). 91.3% had epileptic spasms and were treated with median of one concomitant AED. 68.9% (71/103) discontinued vigabatrin due to controlled seizures in 20/27 (n=79 w/EEG before&after treatment, McNemar’s, p<0.001) and during treatment in 20/27 (n=79 w/EEG before&after treatment, McNemar’s, p=0.009). Median seizure reduction from baseline to first follow-up was 83.3% with a 1.6 month follow-up median duration (IQR: 0.9-2.5). Seizure freedom during both treatment and following discontinuation was observed in 24/62, while 4/62 relapsed.

**Conclusions**: Vigabatrin improved seizure control and resolved hypsarrhythmia with few side effects and mild visual field effects in patients.

**Keywords**: Epilepsy, Neonatal neurology, Translational/experimental therapeutics

### 34. Quantifying Risks of Seizure Types in Autism


**Objective**: Children with autism are known to have increased rates of epilepsy. Prevalence rates vary widely. Past studies aimed to quantify these rates are small. This study aims to determine whether and how much more likely children with autism are to be diagnosed with a specific seizure problem including status epilepticus, infantile spasms and petit mal (absence) seizures.

**Methods**: A retrospective matched case cohort study was performed. We identified pediatric patients 0-18 years of age in the Military Health System database between 2000-2013. Children with ASD were matched 1:5 to children without ASD by birthdate, gender, and enrollment time. ICD9 diagnosis codes were used to identify patients. Conditional logistic regression was used to calculate the odds of varied seizure types.

**Results**: 48,762 ASD patients were identified and matched to 243,810 controls. For autistic children, the odds ratio (OR) of having some kind of seizure or seizure disorder was 6.03 (95% CI; 5.84-6.22). This represented 19% of the patients with autism. In a subgroup analysis of patients with status epilepticus the OR was 8.00 (CI 7.11-8.99). The OR of patients of absence seizures was 9.54 (CI 8.76-10.38). The OR of patients with infantile spasms was 7.30 (CI 5.74-9.28). Although the OR of febrile seizures was significant, it was far less so (OR 2.19 (CI 2.05-2.33).

**Conclusions**: This study helps to quantify the percentage of autistic patients with seizures, and different seizure types. Rates of epilepsy in children with autism are vastly increased in a wide variety of seizure types, known to have different etiologies, genetic and otherwise.

**Keywords**: Cognitive/Behavioral Disorders

### 35. Juvenile Myoclonic Epilepsy and Narcolepsy: A Series of Three Cases

**Joshi PA** (Manhattan, NY), **Poduri A**, **Kothare SV**

**Objective**: We set out to demonstrate the coexistence of juvenile myoclonic epilepsy (JME) and narcolepsy, and raise the possibility of a shared genetic predisposition to both conditions.

**Methods**: The electronic medical records (EMRs) were searched for a su s e dt oc a l c u l a t et h eo d d so fv a r i e ds e i z u r et y p e s .

**Results**: We identified three young adult women, diagnosed with JME in their teenage years, with myoclonic, generalized tonic-clonic and absence seizure semiology, along with psychiatric co-morbidity, well managed on lamotrigine and/or levetiracetam. Our patients were also found to have disturbed sleep preceding the diagnosis of JME by many years, including excessive daytime sleepiness (EDS), fragmented nocturnal sleep, hypnagogic vivid hallucinations and REM behavior disorder along with daytime cataplexy. They were ultimately diagnosed with co-existing narcolepsy, confirmed by sleep studies and multiple sleep latency testing, along with positive genetic testing for HLA-DQB1*0602 in all three patients. Stimulants, selective serotonin receptor
inhibitors and/or sodium oxybate were used to successfully treat their narcolepsy.

Conclusions: The coexistence between JME and narcolepsy has not been well recognized and may be clinically relevant. In addition, it raises the possibility of a shared genetic predisposition to both conditions.

Keywords: Genetics, History/Teaching of Child Neurology

36. QI project: The Yield of Head CTs Performed in the Evaluation of Status Epilepticus among Children with Epilepsy

Jülich K (Boston, MA), Nguyen JT, Jayakar A, Benitez V, Winden KD, Jafarpour S, Maski KP

Objective: Status epilepticus (SE) is a common complication in childhood epilepsy. Current practice parameters show insufficient evidence to support or refute routine brain imaging in SE. Our goal was to evaluate frequency and yield of head CTs (HCT) used in the diagnostic assessment of SE in children with a prior history of epilepsy.

Methods: We performed a retrospective study based on chart analysis of 96 children (0-17 years), who presented to our institution between 2005-2009 with an episode of SE (seizure greater than 30 minutes), and had a history of epilepsy. We compared demographic characteristics, HCT findings, seizure triggers, duration, focality, and interventions based on HCT findings.

Results: In this cohort, 24 patients (25%) had HCTs. Of those, 11 (46%) were normal, and 9 (38%) showed chronic abnormalities. 4 HCTs (16%) were obtained in children with VP-shunt. None of the patients had an acute hemorrhage, ischemic stroke or tumor, and no acute interventions were performed as a result of HCT findings. There were no differences between the groups with and without HCT regarding age, triggers such as fever or missed medication, duration, focality, or whether they had undergone prior MRI imaging.

Conclusions: Children with epilepsy are at increased risk for SE, and frequently undergo HCT imaging when presenting with SE. The yield of acute abnormalities diagnosed by HCT in patients with epilepsy without a history of shunt placement was low in our study. Thus, the risk of radiation exposure should be taken into consideration in this cohort.

Keywords: Epilepsy, Neuroimaging

37. Diurnal and Nocturnal Patterns of Autonomic Neurophysiological Measurements are Related to Timing of Seizures

Kim B (Boston, MA), Nogueira AB, Thome-Souza S, Kapur K, Klehm J, Jackson M, St. Louis L, Papadelis C, Doshi C, Loddenkemper T

Objective: Autonomic nervous system dysfunction may play a role in sudden death in pediatric epilepsy patients. Our goal was to evaluate the relationship between seizure occurrence and diurnal and nocturnal changes of temperature and electrodermal activity (EDA) in pediatric patients with epilepsy.

Methods: We retrospectively studied data from children monitored by video-EEG, skin surface temperature, actigraphy and EDA recordings during an inpatient stay.

Results: Mean temperature (Celsius) and EDA (μS) during wakefulness and sleep of the first wake-sleep cycle (Tw, Ts, EDA and EDAw) and Ts/Tw and EDAs/EDAaw for each case were correlated with seizure occurrence over the
following days. Video-EEG was performed on average for a duration of 3.17 ± 2.28 days in 24 children (mean age 8.62 ± 6.45 years). Seventeen children displayed seizures after the first wake-sleep cycle. The results for children with and without seizures were respectively Ts = 33.93 ± 1.49 and 34.97 ± 1.76, Tw = 33.02 ± 1.38 and 31.75 ± 1.26, Ts/Tw = 1.03 ± 0.04 and 1.10 ± 0.04, EDAs = 1.86 ± 1.38 and 2.02 ± 2.36, EDAs/EDAw = 1.66 ± 2.35 and 0.63 ± 0.45, and EDAs/EDAw = 1.95 ± 1.56 and 4.55 ± 3.69. The most prominent differences were observed for Ts/Tw (p = 0.002), Tw (p = 0.045), and EDAs/EDAw (p = 0.061).

Conclusions: The ratio of mean temperature (and possibly EDA) during sleep and the preceding wake period and the mean temperature during wake may be related to seizures over the following days in children with epilepsy. Analyses of additional confounding factors in larger numbers are in progress. These findings may have potential implications for seizure prediction algorithms, for the management of children with refractory epilepsy, and the understanding of SUDEP-pathophysiology.

Keywords: Epilepsy, History/Teaching of Child Neurology, Translational/experimental therapeutics

38. Genetic Causes of Neonatal Seizures: Potential Predictive Factors and Outcome Spectrum
Mohammed A (Montreal, Quebec, CA), Garfinkle J, Shevell M

Objective: To identify predictive factors of genetic and metabolic causes of neonatal seizures and to compare their outcomes to patients with other causes.

Methods: Retrospective case series of patients referred to neonatal neurology clinic with a diagnosis of neonatal seizures over a 12-year period. The two comparison groups were defined as (a) metabolic and confirmed genetic syndromes (n=6), and (b) other confirmed etiologies (n=168).

Results: The metabolic/genetic group demonstrated: (a) significantly raised mean Apgar scores at 5 minutes (p = 0.01); (b) significantly increased frequency of dysmorphic features (p = 0.03), cerebral malformations (p = 0.02), and acute treatment with multiple antiepileptic drugs (p = 0.05); and (c) significantly reduced frequency of case room resuscitation efforts (p = 0.01), cesareans (p = 0.02), fetal distress (p = 0.01), and meconium staining (p = 0.02). The metabolic/genetic group was also associated with an increased frequency of global developmental delay (p = 0.03), epilepsy (p = 0.02), the use of two or more maintenance antiepileptic drugs, and epilepsy surgery (p = 0.01) and a reduced frequency of cerebral palsy (p = 0.04) compared to the group with other etiologies.

Conclusions: Our results demonstrated some clinical features, including the relative absence of fetal and neonatal distress, which can be used to emphasize clinical efforts to find genetic or metabolic etiologies for neonatal seizures. In addition, those with genetic or metabolic etiologies had more global developmental delay and epilepsy but less cerebral palsy, perhaps reflecting the topography of their injury.

Keywords: Genetics, Neonatal neurology

39. Onset of Infantile Spasms (IS) in Children with Perinatal Hypoxic-Ischemic Encephalopathy (HIE)
Muskan Govindan R (Detroit, MI), Kumar A, Marandi E, Chugani HT

Objective: Apart from the potential brain injury associated with HIE, significant neurological dysfunction may result further from seizures, including infantile spasms (IS). The objective was to analyze the onset of IS and its relationship to various clinical factors in children with HIE.

Methods: We reviewed the clinical records of 11 children (6 boys and 5 girls) who developed IS following perinatal HIE, particularly the onset of IS, the EEG findings and clinical progression.

Results: All 11 children had spastic, dystonic or mixed types of cerebral palsy and seizures. The mean age of IS onset was 5.1 ± 1.8 months (see Table 1). In children with EEG abnormalities predominantly in the anterior (frontal or fronto-temporal) regions, the mean age of IS onset was 6.7 ± 1.4 months, whereas for children with abnormalities in the posterior (parieto-occipital) regions, the mean age of onset was earlier at 4 ± 1.1 months (p = 0.009). The mean time-intervals between the onset of the first focal seizure (mostly neonatal) and IS between the two groups were 111 ± 46 and 197 ± 47 days, respectively (p = 0.014). Eight children had hyspsarrhythmia on EEG. All 3 children tried on ketogenic diet responded. Five children continued to have seizures following cessation of spasms.

| TABLE 1. Gestational period, onset of focal seizure, onset of infantile spasms and electrographic findings (focus of frequent spike-wave activity, F-frontal, P-parietal, O-occipital, T-temporal and C-central) (Abstract 39). |
|-------------------------------|-----------|-----------|-----------|-----------|-----------|
| Patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| Gestation (full-term/weeks) | 31 | term | term | term | term | 36 | term | 37 | term | 37 |
| Focal Seizure onset (days) | 0 | 0 | 0 | 0 | 15 | 120 | 10 | 7 | 3 | 0 | 0 |
| Onset age of IS (months) | 6 | 3 | 5 | 3 | 5 | 5 | 6 | 7 | 3 | 9 |

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Conclusions: The latency period from the onset of brain injury to the development of clinical spasms in HIE is around 5 months. The age of onset of IS is later in children with frontal EEG abnormalities as compared to those with parieto-occipital abnormalities. Ketogenic diet should be considered early in children with HIE who develop IS.

Keywords: Epilepsy

40. Epilepsy or a Seizure Disorder? Caregiver Understanding and Misconceptions

Nagan MR (Boston, MA), Caffarelli M, Donatelli SL, Chen N, Roman NP

Objective: To determine primary caregiver’s understanding of the term epilepsy.

Methods: We performed a cross-sectional telephone survey. Participants were primary caregivers of children who were diagnosed with epilepsy at our institution after July 1, 2012. Epilepsy was defined as, “having two or more unprovoked seizures.” Caregivers rated their own understanding of the term epilepsy using a 5-point scale. We then assessed caregiver understanding using three measures: (1) identifying if their child had a seizure disorder, epilepsy, or both; (2) providing an open-ended definition of epilepsy; and (3) selecting from multiple-choice definitions of epilepsy. Caregivers answering all three measures correctly were assigned the highest level of understanding.

Results: Of forty surveys, 22/40 caregivers (55%) said their child had both “a seizure disorder and epilepsy,” 4/40 (10%) provided correct open-ended definitions of epilepsy, and 12/40 (30%) selected correctly from multiple-choice definitions. Fifteen caregivers (37.5%) answered one measure correctly, 7/40 (17.5%) answered two, and 3/40 (7.5%) answered all three measures correctly.

There was no significant relationship between a caregiver’s perceived and actual level of understanding of the term epilepsy. Having a child neurologist as the first person to discuss the diagnosis with the caregiver was the only statistically significant predictor of better caregiver understanding (p=0.0074). Education level, primary language and insurance type were not predictive.

Conclusions: Among caregivers of children with epilepsy, the term epilepsy is poorly understood. With changing definitions, it will be most important for healthcare practitioners to educate patients and families about the meaning of the terms we use.

Keywords: Epilepsy

41. Vagus Nerve Stimulation for Drug-Resistant Epilepsy: A long-term study up to 24 months in 347 children

Orosz I (Los Angeles, CA), Alexis A, Lieven L

Objective: To gain insight into the long-term impact of vagus nerve stimulation in children with drugresistant epilepsy, we conducted the largest retrospective multicenter study to date over a follow-up period of up to 24 months.

Methods: The primary objective was to assess change in seizure frequency of the predominant seizure type (defined as the most disabling seizure) following VNS device implantation. Treating physicians collected data from patient records from baseline to 6, 12, and 24 months of follow-up.

Results: The analysis population included 347 children (aged 6 months to 17.9 years at the time of implant). At 6, 12, and 24 months after implantation, 32.5%, 37.6%, and 43.8%, respectively, of patients had >50% reduction in baseline seizure frequency of the predominant seizure type. The responder rate was higher 46.2% (79/171) at 12 months follow-up in a subgroup of patients who had no change in antiepileptic drugs (AEDs) during the study. Favorable results were also evident for seizure severity and quality of life. Post hoc analyses demonstrated a statistically significant correlation between VNS total charge delivered per day and an increase in response rate. Children under the age of 12 years and with predominantly generalized seizures from genetic and structural epilepsies could also benefit from VNS Therapy. No new safety issues were identified.

Conclusions: The results demonstrate that children with drug-resistant epilepsy benefit from VNS Therapy and it is well tolerated over a 2-year follow-up period. A post hoc analysis revealed a dose–response correlation for VNS in patients with epilepsy.

Keywords: Epilepsy

42. A Potential Pitfall of FDG-PET/MRI Coregistration in the Presurgical Evaluation for Focal Cortical Dysplasia in Pediatric Epilepsy Patients

Orosz I (Los Angeles, CA), Trinh V, Harris R, Qiao J, Salehi B, Geannette C, Salamon N

Objective: Focal Cortical Dysplasia (FCD) is the most common etiology found in surgical series of pediatric epilepsies. Incorporating FDG-PET/MRI coregistration in the presurgical evaluation improved the detection of FCDs. However, there is a subtype of FCD Type IIA/B, which is subtle on MRI and difficult to detect on FDG-PET.

Methods: We retrospectively reviewed 22 patients (mean age 14.5y, sd=3.1) with histopathology proven FCD Type IIA/B in the frontal lobe. Two neuroradiology fellows, who were blinded to the known locations of FCDs evaluated pre-operative FDG-PET/MRI coregistration images to identify the zone of hypometabolism. Locations of FCDs were subdivided into three groups: 1, Lateral/Opercular Frontal, 2, Superomedial Frontal; and 3, Orbital Frontal. The degree of FDG-PET hypometabolism was separately measured using the lesion’s median standard uptake value (SUV) related to the basal ganglia (SUV ratio), which was used as a reference.

Results: Raters were able to identify 80% of lateral frontal (n=10) and 80% of orbital frontal (n=5) FCDs. For superomedial frontal FCD (n=7) only 28.6% was detected. The lesions in the superomedial frontal lobe had a significantly less hypometabolism (SUV ratio >0.56). Raters were able to identify the FCDs only when SUV ratio was lower than 0.56.

Conclusions: Subtle FCD Type IIA/B located in the superomedial frontal lobe and with SUV ratio over 0.56 showed false negative results on FDG-PET/MRI coregistration. Understanding this pitfall will be important for presurgical epilepsy evaluation and will require a different approach.
approach using other modalities in these pediatric epilepsy patients such as SPECT or MEG.

**Keywords:** Epilepsy, Neuroimaging

43. Skin Integrity During Prolonged EEG Recording in Hospitalized Neonatal and Pediatric Patients

Pasupuleti A (Washington, DC), Amling J, Tsuichida T, Scafidi J, Chang T

**Objective:** To identify the incidence of and potential risk factors contributing to skin injury during continuous EEG (cEEG) recordings.

**Methods:** This is a retrospective study of all patients admitted to Children’s National with skin breakdown while undergoing cEEG monitoring over a 2 year interval. Patients were identified from a patient log prospectively maintained by our Wound Care Team. Clinical variables examined included age, hospital location, length of cEEG, nutritional status, concurrent therapeutic hypothermia, coagulopathies, allergies, and skin issues.

**Results:** 7144 patients received cEEG: NICU (N=863), PICU (N=1098), CICU (N=201), Non-ICU (N=4982). Median cumulative duration of cEEG was 1 day (range 4 hours to 29 days). Skin injury, ranging from scalp excoriation to deep tissue injury (DTI) to Stage 2 pressure ulcers (PU), occurred in 7 patients (0.1%). NICU had one skin excoriation and two Stage 2 PU; PICU had one Stage 2 PU; CICU had a DTI and Stage 2 PU; non-ICU had two Stage 2 PU. ICU patients had a higher incidence of skin injury compared to non-ICU patients (0.23% vs 0.04%, p=0.018). In 6 out of 7 patients, the following risk factors were present: i) febrile or sepsis; ii) NPO at time of cEEG placement; iii) coagulopathies with INR > 1.35; iv) >3 days of cEEG recording. In all 3 neonatal cases, wound was noted after 4 days of cEEG.

**Conclusions:** Skin injury due to cEEG is a rare occurrence at our institution. Critical illness and prolonged cEEG recordings are common in patients with skin injury.

**Keywords:** Epilepsy, Neonatal neurology

44. Novel Intervention in GABA-Transaminase Deficiency

Pearl PL (Boston, MA), Koenig MK, Riviello J, Christie M, Bain J, Averill K, Chung WK, Chiriboga CA, Hodgeman R, Parviz M, Gibson KM

**Objective:** GABA-transaminase (GABA-T) deficiency has been reported previously in only three patients from two families, with the first two children (siblings) having had neonatal onset epileptic encephalopathy, macrosomia, and early mortality. We describe the only three known living patients including a novel therapeutic approach.

**Methods:** Two new patients, identified by whole exome sequencing, are reported, with 5-year follow-up provided on the only other reported surviving case. Clinical features, MRI, EEG, genotype, and CSF GABA are reported, followed by a trial of benzodiazepine-receptor antagonist intervention in the newest diagnosed patient.

**Results:** Patient ages are 21 months and 7 years; clinical features are developmental impairment, GTCS, choreoathetosis, and myoclonus. WES revealed ABAT compound heterozygosity (case 1): c.454C>T (p.P152S), c.1393G>C (p.G465R), and homozygous c.1129C>T (p.R377W) mutations (case 2). In case 1, CSF [GABA] was elevated: free 0.25 μmol/L (ref range 0.02-0.07) and total 33.4 μmol/L (4.2-13.4). Metabolites showed increased plasma 2-pyrrolidinone, a GABA ketone reported in the first published family. EEG showed high-voltage polymorphic delta and multifocal and generalized spike-wave. Treatment (case 1) was implemented with flumazenil infusion and the patient tolerated 0.5 mg/kg/hr with clinical and EEG improvement. The other surviving case, reported at 28 months

**TABLE 1. Characteristics from all five known patients with GABA transaminase deficiency (Abstract 44)**

<table>
<thead>
<tr>
<th>Subject</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at last follow-up</td>
<td>22 months</td>
<td>7 years</td>
<td>7 yr. 10 mo.</td>
<td>Deceased at 25 mo.</td>
<td>Deceased at 12 mo.</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
<td>Male (sibling of patient 4, dx’ed posthumously)</td>
</tr>
<tr>
<td>Age of Onset (mo.)</td>
<td>6</td>
<td>5</td>
<td>7</td>
<td>Neonatorum</td>
<td>Neonatorum</td>
</tr>
<tr>
<td>Developmental Status</td>
<td>Holds head up, rolls over</td>
<td>Profound impairment</td>
<td>Profound impairment</td>
<td>Newborn level</td>
<td>Newborn level</td>
</tr>
<tr>
<td>High pitched Cry</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Increased head size</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Seizures</td>
<td>Myoclonic</td>
<td>GTCS</td>
<td>GTCS</td>
<td>GTCS</td>
<td>GTCS</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Lethargy</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

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of age and now 7 years 10 months, has profound developmental impairment without mobility or language.

Conclusions: GABA-transaminase deficiency is likely to be detected in more individuals with increased clinical use of advanced generation sequencing. Of five patients now reported, three have survived infancy and intervention with flumazenil appears to be associated with improved short-term outcome.

Keywords: Epilepsy, Translational/experimental therapeutics

45. Electrical Source Imaging and Epilepsy Surgical Outcome in Tuberous Sclerosis Complex

Peters JM (Boston, MA), Hyde D, Prohl AK, Erem B, Boom MS, Chu-Shore CJ, Sahin M, Warfield SK

Objective: To assess the utility of electrical source imaging for epilepsy surgery in children with tuberous sclerosis complex (TSC) with respect to surgical outcome.

Methods: Retrospective study of all patients with TSC who underwent epilepsy surgery from 2002-2014 with available pre- and post-operative magnetic resonance imaging (MRI), pre-operative EEG data, and follow-up for ≥12 months. Ictal and interictal waveforms were marked by a neurophysiologist blinded to surgical outcome, but not to pre-operative clinical data. Electrical source imaging (ESI) was based on a patient-specific head model and low resolution brain electromagnetic tomography (LORETA). Sensitivity was defined as the ESI solution falling in the resection cavity upon visual review, in patients with good outcome (Engel I-II), and specificity as the ESI solution falling outside of the resected area, in patients with a poor outcome (Engel III-IV).

Results: 19 patients underwent pre-surgical evaluation, 10 were operated (mean age 5.8 year, range 1.0 – 13.8), 7 with a good outcome (70%). One patient had no post-operative imaging available but underwent lobar resection, one had no ictal EEG data, and three patients required a generic head model. Sensitivity of ictal and interictal ESI was 83.3%, and 100% respectively. Specificity was 66.7% for both ictal and interictal ESI. The probability of a good outcome with resection of the source focus was 83.3% and 87.5% for ictal and interictal data, respectively.

Conclusions: In this small study, ESI of routine clinical EEG data provides valuable information in pre-surgical epilepsy evaluation in Tuberous Sclerosis Complex. Prospective validation of this tool is needed.

Keywords: Epilepsy, Neuroimaging

46. Pyridoxine-Dependent Epilepsy: not just for neonates

Svoboda MD (San Antonio, TX), Ahmad S, Ng YT

Pyridoxine-Dependent Epilepsy (PDE) is rare, and often not considered as an etiology of refractory epilepsy outside of the neonatal period. We report 2 cases of older children with PDE presenting within the same week to our institution. The first is a 2 year, 6 month old girl admitted for supra-refractory status epilepticus requiring a phenobarbital coma, ketogenic diet, and 4 other anti-epileptics for over 2 years. The second is a 11 year old boy referred for seizures associated with hypotonia and delayed development. Flumazenil and ketogenic diet were used for refractory seizures, with resolution of seizures and improvement in motor function.
weeks. She had a history of seizures beginning on her first day of life and a sister who died of “Alpers” in early childhood. MRI revealed a very thin corpus callosum and hydrocephalus. She was given pyridoxine trial and had complete seizure cessation after the third 100mg intravenous bolus. The second is an 11 month old boy also admitted for refractory status epilepticus. His seizures were partially responsive to anti-epileptic medications but he had recurrent episodes of status during his admission requiring midazolam drip with subsequent intubation four times in 10 days. He developed his first seizure at 2 months old. 100mg of pyridoxine was given early in his course with obvious improvement. He later had a dramatic resolution to his status epilepticus with administration of 3 boluses of pyridoxine. Both were positive for the ALDH7A1 gene indicating PDE. Both are now off all seizure medications and maintained on pyridoxine without further seizures. PDE should be considered, even in older children, with refractory epilepsy- even if brain MRI is abnormal and there is some response to anti-epileptics. Higher doses for the trial are often required.

**Keywords:** Epilepsy, Genetics

47. **Sleep-Wakefulness Ratio as a Measure to Quantify Interictal Epileptiform Discharges in Patients with Electrical Status Epilepticus in Sleep (ESES)**

**Tantriranir A** (Boston, MA), **Fernandez IS**, **Kapur K**, **Jackson M**, **St. Louis L**, **Loddkenemper T**

**Objective:** Interictal epileptiform activity in Electrical Status Epilepticus in Sleep (ESES) has been quantified with spike wave index (SWI) and spike frequency (SF). We describe a quantification tool, sleep wakefulness ratio (SWR), and evaluate its utility.

**Methods:** Retrospective descriptive study of consecutive patients with abnormal overnight EEG during 2009-2014 for clinical suspicion of ESES. SWI was defined as percentage of one-second bins containing at least one spike. SF was defined as spike number. SWR was defined as sleep-SF divided by wakefulness-SF. Measures were calculated during a random 5 minute period awake and asleep. We compared patients with SWI of <and> 50%.

**Results:** 47/106 (44%); 70 males; median age 10.15 years, 25-73-13.6 years) had a SWI of 50% or greater. 93 patients had seizures, 33 had global developmental delay, 26 had learning disability and 10 had attention deficit disorder. Patients with seizures had more frequent spikes (SF130; SWI44%) than patients without seizures (SF17; SWI6%). Patients with attention deficit disorder presented with more frequent spiking (SF252; 85% vs SF111; SWI36%). Learning disability was seen in patients with overall more frequent spiking (SF189; SWI63 vs SF84; SWI28%). SWR and SWI correlated during sleep (Spearman R=0.245; p<0.05) and wakefulness (R=0.490; p<0.01). SWR and SF were correlated during sleep (R=0.246; p<0.05) and wakefulness (R=0.493; p<0.01). SWI and SF were correlated during sleep (R=0.996; p<0.01) wakefulness (R=0.994; p<0.01). SF and SWI discriminated better among these diagnoses than SWR.

**Conclusions:** Patients with more frequent spiking were more likely to present with seizures, ADHD and learning disability. SWR, correlated with SWI and SF, but SF and SWI discriminated better among clinical diagnoses than SWR.

**Keywords:** Epilepsy

48. **Epilepsy in Infancy-onset Hydrocephalus**

**Tally HM** (Seattle, WA), **Mueller BA**, **Kikull WA**, **Dobyns WB**

**Objective:** Children with hydrocephalus are at risk for epilepsy due to both their underlying condition and as a consequence of surgical treatment. We sought to characterize epilepsy among children with acquired and developmental (non-acquired, often genetically-based) hydrocephalus and to examine the interplay between hydrocephalus-associated and surgery-related factors.

**Methods:** Retrospective review of medical records of a cohort of children with infancy-onset hydrocephalus. Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for associations.

**Results:** Among 378 children with hydrocephalus, 85 (22%) had epilepsy, almost one fifth of whom had a history of infantile spasms. At most recent follow-up, seizures were well-controlled in 44 (55%), not controlled but not meeting criteria for medical intractability in 20 (25%), and medically intractable in 16 (20%). Children with acquired hydrocephalus were almost twice as likely to have epilepsy as those with developmental hydrocephalus (OR: 1.9; 95% CI: 1.2-3.1). Epilepsy was not dependent upon subtype in acquired hydrocephalus, but was significantly associated with subtype among children with developmental hydrocephalus, and was most common in children with aqueductal stenosis and with cysts. Overall, each additional surgical procedure was associated with a 20% higher risk of epilepsy (OR: 1.2; 95% CI 1.1-1.4). However, this may have been mediated by shunt infection, which greatly increased the risk of epilepsy (OR: 3.5; 95% CI: 1.6, 7.4).

**Conclusions:** Epilepsy – infantile spasms in particular – is common among children with hydrocephalus, particularly among those with acquired hydrocephalus and certain subtypes of developmental hydrocephalus. Shunt infection further increases the risk of epilepsy.

**Keywords:** Epilepsy, Genetics

49. **The Burden of Seizure Clusters on Children with Epilepsy and Caregivers**

**Whaleb JW** (Memphis, TN), **Penovich PE**, **Louenberg K**, **Steinberg K**, **Sirven JI**

**Objective:** To characterize the burden of seizure clusters (SC; ≥2 seizures within 24 hours and outside the typical pattern experienced in the past 12 months) on children and caregivers.

**Methods:** The SC Burden of Illness US survey was conducted online by Harris Poll on behalf of The Epilepsy Foundation (unrestricted grant sponsorship from Upsher-Smith Laboratories) from September 2-30, 2014. Over 800 participants were surveyed to evaluate SC impact on emotional wellbeing, functionality, and productivity. Subset analyses pertaining to children ages 0-17 (103 caregivers of children; 139 pediatric clinicians [neurologists, n=78; epileptologists, n=61]) are presented here. Raw data were weighted as needed to achieve representativeness within the respective respondent populations.

**Keywords:** Epilepsy

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Results: Overall, 63% of caregivers reported the child experienced SC within the past month. Most caregivers (61%) and clinicians (81%) felt that SC have a major/moderate negative impact on patient quality of life, particularly on school attendance/performance and extracurricular activity participation. Moreover, 58% of caregivers said SC have a major/moderate negative impact on caregiver quality of life, with 25% reducing work and 17% stopping work altogether. Many caregivers and clinicians reported that SC made the child feel scared, stressed, and helpless. Similarly, caregivers felt scared, stressed, helpless, anxious, and overwhelmed when the child experienced SC.

Conclusions: The effects of SC on emotional wellbeing and daily living for children and caregivers include feelings of fear/helplessness and negative impact on productivity (school/jobs). These data suggest the need for increased education on managing SC and new rescue therapies to potentially reduce burden of illness.

Keywords: Epilepsy

50. Efficacy, Adverse Effects, and Additional Benefits of Epidiolex® in Children and Young Adults with Treatment Resistant Epilepsy

Wilson CA (Salt Lake City, UT), Spigarelli M, Sweeney M, Van Orman C, Alger F, Merrill S, Skidmore J, Filloux F

Objective: Epidiolex is an investigational drug containing pure Cannabidiol (CBD), a substance shown to have anticonvulsant properties. We describe the efficacy, adverse effects, and other beneficial effects of Epidiolex in an open-label trial approved by the FDA and DEA for children and young adults with treatment resistant epilepsy.

Methods: 25 subjects received Epidiolex 2 to 25 mg/kg/day. Eligibility criteria included drug resistant epilepsy, stable medication doses, and not taking another cannabis product. Patient demographics, CBC, CMP, and adverse or beneficial effects reported. Seizure burden (type/frequency/severity) recorded daily by caregivers. Data at 3 months of Epidiolex use were compared with baseline.

Results: Outcome data are reported in Table. Total number of seizures were reduced by a median of 38% at 3 months. Eighteen patients (72% of participants) experienced fewer seizures with an average frequency reduction of 50%. While many patients experienced adverse effects, the vast majority were mild and transient. Seven serious adverse events were reported, none deemed to be directly related to study medication. Seven patients reduced dose due to side effects; one discontinued due to diarrhea and lack of efficacy, another for persistent nausea/vomiting. The additional beneficial effects reported (12%) were more sustained throughout treatment.

Conclusions: Caretakers reported decreased seizures in the majority of patients treated with Epidiolex. Common side effects included fatigue and diarrhea, but the drug was generally well tolerated. Caretakers reported several other benefits during treatment. The results support future controlled trials of Epidiolex (CBD) in various pediatric epilepsies.

Keywords: Epilepsy

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td></td>
</tr>
<tr>
<td>&gt;30% reduction</td>
<td>14 (56%)</td>
</tr>
<tr>
<td>&gt;50% reduction</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>Seizure free</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Abnormal Laboratory</td>
<td></td>
</tr>
<tr>
<td>Leukocytopenia</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>Low RBC/Hematocrit</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Other Benefits</td>
<td></td>
</tr>
<tr>
<td>More alert</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>Better social interaction</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>Less irritable</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>Happier</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Improved Appetite</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Improved Cognition</td>
<td>3 (12%)</td>
</tr>
</tbody>
</table>

Acknowledgments:
We thank our participating families and patients. Study medication and administrative/regulatory advice graciously provided by GW pharmaceuticals.

51. Prognosis of Psychogenic Non-Epileptic Seizures (PNES) in a Cohort of Children Seen at a Tertiary Care Children’s Hospital

Yadav AK (Cleveland, OH), Agarwal RL, Park J

Objective: To determine the outcome of psychogenic non-epileptic seizures (PNES) in children.

Methods: We retrospectively analyzed 90 cognitively intact patients ≤18 years of age (58 females; mean age 14.03 ± 3.3 years), who were diagnosed with PNES in the Epilepsy Monitoring Unit between January 2008 to December 2012 (out of 2097 total evaluations), and in whom a 2-year follow-up data was available. Remission of events at 6, 12 and 24 months after diagnosis was noted. Patient and disease variables affecting outcome were studied.

Results: Thirty-two patients (35%) achieved remission before first follow-up and continued to manifest event-
freedom throughout the 2-year study period (“favorable outcome”). Thirty patients (33%) did not achieve remission at any point during the 2-year follow-up (“unfavorable outcome”). The third group of 28 patients (32%) were categorized as “indeterminate outcome” and excluded from subsequent analysis determining predictors for prognosis. Factors associated with unfavorable outcome (vs. favorable outcome) included presence of co-morbid epilepsy (12/30 vs. 0/32; p<0.0001) and prolonged duration of symptoms before diagnosis (452 ± 476 days vs. 74 ± 72 days; p<0.0001). Age, gender, frequency of events, presence of major psychosocial stressor, co-morbid psychiatric conditions and outpatient psychiatry treatment did not significantly impact disease outcome.

Conclusions: About one-third of the children with PNES achieve early and sustained remission of symptoms for at least 2 years after diagnosis. Presence of co-morbid epilepsy and prolonged duration of undiagnosed PNES may be associated with poor remission rates. Early suspicion and diagnosis of PNES, especially in patients with epilepsy, may improve outcome.

Keywords: Cognitive/Behavioral Disorders, Epilepsy

52. High Incidence of Mitochondrial Respiratory Chain Complex Deficits in Children with Infantile Spasms


Objective: Several series of children with epilepsy and mitochondrial (mt) respiratory chain complex deficits (RCCD) found Infantile Spasms (IS) in a mean of 15%. Vice versa, isolated IS case reports have demonstrated the presence of underlying mt RCCD. However, no research has systematically investigated mt RCC function in patients with IS. The objective of this study was to evaluate the incidence of mt RCCD in a group of children with IS.

Methods: The following clinical data were gathered: age at onset, etiology, developmental delay or cognitive deficit, presence of refractory epilepsy and antiepileptic drugs (AEDs) used. In buccal swabs we determined RC-I activity by immunocapture and RC-IV and citrate synthase (CS) activities using microspectrophotometry. RCC activity was normalized relative to CS activity, and expressed as ratios (I/CS and IV/CS)

Results: A total of 26 children with IS (17 males, 8 females) were studied. Mean age at diagnosis was 6 months. Fifty percent patients had an identified etiology. Ninety percent had developmental delay/cognitive deficit, and 60% had refractory epilepsy. An average of 5 AEDs per patient was used. RCCD (<2 SD from controls’ mean) were found in 10/26 (38%) children: 2 complex I, 7 complex IV, and 1 both.

Conclusions: Children with IS have a high incidence of mt RCCD. It is unclear whether they are primary or secondary to their disease or treatment. It could be hypothesized that a bidirectional pathogenic relationship between IS and mt function exist. Alternative therapies for IS supporting mt function should be considered in further prospective studies.

Keywords: Epilepsy, Genetics

Neonatal Neurology

53. Epilepsy and Leukoencephalopathy in a Child with MFN2 Mutation Associated with Charcot-Marie-Tooth 2A Disease

Mehta P (Philadelphia, PA), Marks HG, Poletto E, Legido A, Khurana DS

Mutations of the mitochondrial fusion protein mitofusin 2 gene, MFN2, cause Charcot-Marie-Tooth type 2A (CMT2A), the most common type of autosomal dominant axonal Charcot-Marie-Tooth disease. In addition to sensorimotor polyneuropathy, other clinical features described with this mutation include visual, hearing and cognitive impairment, vocal cord palsy, pyramidal signs and proximal weakness. MRI white matter abnormalities with involvement of basal ganglia, thalami, cerebellum and pons were recently described in up to 39% of patients. Seizures have not been previously reported.

We present a patient with CMT2A with leukoencephalopathy and partial onset epilepsy. Initial signs and symptoms at age 3 years were left foot drop, distal leg weakness and areflexia. EMG/NCV showed axonal sensorimotor peripheral neuropathy and genetic testing showed a MFN2 mutation consistent with CMT2 disease.

At age 11 yrs she started having stereotypic episodes of nausea, unresponsiveness and chewing automatisms with post-ictal lethargy. Episodes increased from 2-3/month to daily. An EEG showed right hemisphere slowing. An MRI found white matter T2 hyperintensities in right temporal, parietal and frontal lobes and changes suggestive of encephalomalacia in right thalamus and basal ganglia.

She was started on oxcarbazepine with complete resolution of epileptic events.

This case further emphasizes that MRI changes of both gray and white matter are seen in patients with MFN2 mutations, and adds epilepsy to the neurological complications of this disease. Being aware that seizures occur in children with MFN2 mutations, especially in those with MRI changes would be helpful in early identification and treatment of epilepsy.

Keywords: Genetics, Neuroimaging

54. Clinical and EEG Characteristics of Preterm Neonates Undergoing Continuous Electroencephalography in the NICU

Buraniqi E (Boston, MA), Sansevere AJ, Klehm J, Fernandez IS, Pearl PL, Loddenkemper T

Objective: To describe the clinical and EEG characteristics of preterm neonates undergoing continuous electroencephalography (cEEG) in the neonatal intensive care unit (NICU).

Methods: Retrospective descriptive study of preterm neonates (<37 weeks gestation) who underwent clinically indicated cEEG (>3 hrs) in the NICU at Boston Children’s Hospital from 2011-2013.

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Results: Fifty-two patients were studied with a median gestational age of 35 weeks (Table 1). Acute intracranial structural lesions were present in 58% (N=30). Main indications for monitoring were to characterize clinical events (N=39) followed by concern for non-convulsive seizures (N=19) (Figure 1). Electrographic seizures were detected in 12/52 (23%) of patients, in whom 4 (33%) were electrographic only (Figure 2). The typical seizure duration was 1 to 5 minutes (66.7%). One patient met criteria for status epilepticus, defined as seizure lasting greater than 30 minutes or totaling greater than 50% of a one hour epoch. The median time to first seizure was thirty minutes (p25-p75) with seizures captured in all 12 patients by 7.3 hours (Figure 3). In-hospital mortality was 25% (N=13) for the entire group. Of the patients that died, 38% (N=5) had electrographic seizures (Table 2).

Conclusions: Patients born preterm are at high risk for seizures. The majority of these seizures would go undetected without the use of cEEG given the high percentage of electrographic only seizures. In-hospital mortality is high in premature infants selected for monitoring. Next steps include further characterization of this cohort with regard to the effect of seizure burden and therapeutic intervention on outcome.

Keywords: Epilepsy, Neonatal neurology

<table>
<thead>
<tr>
<th>TABLE 1. Demographics (Abstract 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong> = 52</td>
</tr>
<tr>
<td><strong>Gestational age (weeks)</strong></td>
</tr>
<tr>
<td>Median (p25-p75)</td>
</tr>
<tr>
<td>35 (29-36.14)</td>
</tr>
<tr>
<td>Mean (SD) Minimum - Maximum</td>
</tr>
<tr>
<td>32.82 (4.17) 24.14-36.86</td>
</tr>
<tr>
<td>Prematurity (weeks of gestational age)</td>
</tr>
<tr>
<td>&lt;28 9 (17.3%)</td>
</tr>
<tr>
<td>28-&lt;32 9 (17.3%)</td>
</tr>
<tr>
<td>32-&lt;37 34 (65.4%)</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Male 24 (46.15%)</td>
</tr>
<tr>
<td>Female 28 (53.85%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 2. Mortality</th>
<th>Alive</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (25%)</td>
<td>39</td>
<td>13</td>
</tr>
<tr>
<td>Mortality if seizures (42%)</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Mortality if no seizures (20%)</td>
<td>32</td>
<td>8</td>
</tr>
</tbody>
</table>
55. A Pilot Cohort Study of Cerebral Autoregulation and 2-Year Neurodevelopmental Outcomes in Neonates with Hypoxic-Ischemic Encephalopathy who Received Therapeutic Hypothermia


**Objective**: Neurodevelopmental disabilities persist following neonatal hypoxic-ischemic encephalopathy (HIE) despite treatment with therapeutic hypothermia. Our objective was to determine the relationship between cerebrovascular autoregulation, which maintains cerebral perfusion across changes in blood pressure, and neurodevelopmental outcomes.

**Methods**: We measured cerebral autoregulatory vasoreactivity with the NIRS-derived hemoglobin volume index (HVx) during therapeutic hypothermia, rewarming, and normothermia in 28 neonates with HIE. The optimal mean arterial blood pressure (MAPOPT) at which autoregulatory vasoreactivity was greatest was identified. Nineteen of these children participated in neurodevelopmental evaluations at 2 years. MAPOPT blood pressure in relation to MAPOPT, blood pressure below the gestational age + 5 (ga+5), and the regional cerebral oxygen saturation (rSO2) were compared to the neurodevelopmental outcomes.

**Results**: The children’s performance was in the average range on cognitive and motor evaluations, although the mean performance was lower than that of published normative samples. Eight (42%) had below-average cognitive performance or inability to walk unassisted. Children with impairments had higher MAPOPT values (p=0.023), spent more time with blood pressure below their MAPOPT (p=0.048), and had greater blood pressure deviation below MAPOPT (p=0.019) during rewarming than those without impairments. No association was observed between rSO2 or blood pressure below ga+5 (p>0.10) and outcomes.

**Conclusions**: Motor and cognitive impairments at 2 years were associated with greater blood pressure deviation below MAPOPT during neonatal rewarming but not with rSO2 or blood pressure below ga+5, suggesting that identifying individual MAPOPT is superior to using hemodynamic goals based on gestational age or rSO2 in the acute management of neonatal HIE.

**Keywords**: Neonatal neurology

56. Etiology of Neonatal Hypoxic-Ischemic Encephalopathy—Value of Placental Pathology in a Prospective Cohort

Chang T (Washington, DC), Malkey SB, Glass HC, Harris KN, Massaro AN, Mathur AM, Maycock DE, Van Meurs KP, Bonifacio SL, Gonzalez FF, Dong L, Rogers EE, Comstock BA, Heagerty PJ, Jaul SE, Wu YW

**Objective**: To describe the potential placental etiologies of hypoxic ischemic encephalopathy (HIE) in a cohort of infants enrolled in a phase II randomized control trial of erythropoietin.

**Methods**: In a double-blind placebo-controlled trial, we enrolled 50 newborns with moderate (N=41) or severe (N=9) HIE. All patients had encephalopathy, perinatal depression, and received hypothermia therapy. We excluded infants with IUGR or congenital anomalies. Clinical history for maternal infection/inflammation (maternal fever or infection during or after labor) and sentinel events (tough nuchal cord, prolapsed cord, placental abruption, shoulder dystocia, uterine rupture, maternal arrest/trauma/demise) were prospectively collected. Placental pathology clinical reports were obtained from the birth hospital and/or tertiary cooling center.

**Results**: Of 50 infants enrolled at 7 hospitals, placental pathology was available in 35 (70%), 25 (71%) were abnormal, with findings of vascular abnormalities (N=20); inflammatory abnormalities (N=13); or both (N=8). Pathologic processes were acute (N=8), chronic (N=8) or acute-on-chronic (N=7). 20 births (40%) had at least one sentinel event (9 placental abruption, 7 tight nuchal cord, 4 shoulder dystocia, 2 uterine rupture, 2 maternal arrest/trauma/demise). 11 births (22%) were complicated by maternal infection/inflammation (10 clinical chorioamnionitis; 1 endometritis). Of the 21 cases with no sentinel event or maternal infection, 16 had placental pathology available, of which 11 (69%) were abnormal: vascular lesions (N=9), inflammation (N=5), or both (N=3), representing acute (N=8) and/or chronic (N=7) abnormalities.

**Conclusions**: The causes of HIE are varied and multifactorial. Placental pathology may provide key insights into etiology in cases of unexplained HIE.

**Keywords**: Neonatal neurology

57. Prevalence and Characteristics of Seizures and Epilepsy in the First 10 Years of Life in Children Born Before 28 Weeks Gestation (Extremely Low Gestational Age Newborns - ELGANs)

Douglas LM (Boston, MA), Kabat KCK, Hereen T, Allred EN, DeBassio W, Stafstrom CE, O’Shea M, Hirtz D, Rollins J, Leviton A

**Objective**: To evaluate whether the prevalence of seizures and epilepsy in the first decade of life among ELGANs exceeds the general population prevalence.

**Methods**: In a prospective, multicenter observational study of 966 eligible survivors, 838 (87%) were evaluated at age 10 for occurrence of post-neonatal seizures by a pediatric epileptologist using a 2-stage structured interview. A 2nd pediatric epileptologist established an independent diagnosis based on the recorded responses of the structured interview. When the first 2 evaluators disagreed, a third independent epileptologist (3% of cases) determined the final diagnosis.

**Results**: 271 cohort members were positive on an 11-item screen, and 223 of these underwent the full 42-item structured interview. 87 (10.4% of the cohort, 95% CI 8.4–12.4%) of those screened were diagnosed to have had at least one seizure. Among these, 55 (6.5%, 95% CI 5.0–8.5) were diagnosed as having had epilepsy, 22 (2.6%) had purely febrile seizures, and 10 (1.1%) had a single, unprovoked seizure. Seizures occurred in 14% of those born at 23-24 weeks.
gestational age (GA), 11% born at 25-26 weeks, and 8% born at 27 weeks. Seizures were not associated with small for GA status, and seizures risk was comparable in males and females. Our evaluation diagnosed epilepsy for the first time in one-third of those with epilepsy.

Conclusions: In the first decade, 10.4% of ELGANs have seizures. 6.5% have epilepsy, an approximate 6-12-fold increase above the .5% in the pediatric population.

Keywords: Neonatal neurology

58. EEG Spectral Power Analysis and Cerebral Tissue Oxygen Extraction in Very Low Birth Weight Infants

Objective: Fractional cerebral tissue oxygen extraction (FTOE) can be continuously monitored by simultaneous near infra-red spectroscopy (NIRS) and pulse oximetry. The objective of this study is to test the hypothesis that, in very low birth weight (VLBW) infants, the more mature EEG activity is, the less variable FTOE is.

Methods: A prospective study was conducted on VLBW infants (<1500 grams and ≤34 weeks gestation) without significant brain injury. Simultaneous continuous 2-channel EEG, NIRS and pulse oximetry were recorded for at least 12 hours sessions. Absolute and relative powers of delta, theta, alpha, beta and total bands have been calculated. FTOE variability was measured on 2 scales: short scales (3-20 seconds) and long scales (20-150 seconds). FTOE variability was examined against changes in relative spectral power of different EEG bands.

Results: We evaluated 67 studies performed on 48 VLBW infants. Relative power of delta band positively correlated with FTOE short and long scale variability (r=0.45, p<0.001, r=0.44, p<0.001 respectively). Relative power of alpha bands negatively correlated with FTOE short and long scale variability (r=−0.38, p=0.002, r=−0.42, p=0.001 respectively). (Figure 1) Relative power of beta bands negatively correlated with FTOE short scale variability (r=0.29,
Conclusions: Increased maturation of EEG activity is associated with decreased variability in cerebral oxygen extraction. The implications of increased variability in FTOE on brain injury in extremely immature infants need further exploration.

Keywords: Neonatal neurology

59. Therapeutic Hypothermia Reduces Long Term Risk of Seizures in Neonatal Hypoxic Ischemic Encephalopathy
Ghosh S (Gainesville, FL), Tran L, Zapanc ML

Objective: Hypoxic ischemic encephalopathy (HIE) is a major cause of seizures in infancy. Therapeutic hypothermia for the treatment of moderate to severe HIE has shown to reduce death or disability. Our hypothesis is therapeutic hypothermia reduces long term seizure burden.

Methods: This retrospective chart review evaluated the risk of seizures after therapeutic hypothermia in neonates with HIE. 56 neonates with HIE who met criteria for selective brain cooling were admitted to the Neonatal Intensive Care Unit at the Children's Hospital of Orange County from 1/1/2007 through 9/1/2013. 41 patients received selective head cooling, 15 patients were admitted prior to the availability of head cooling and received supportive care. A total of 42 patients had outpatient neurology follow-up visits.

Results: Seizures developed in 24 patients (59%) from the hypothermia group and 12 (80%) from the control group. All 36 patients with seizures were initially treated with phenobarbital. 36 patients from the hypothermia group and 14 from the control group received either routine or continuous video EEG after head cooling. Of the patients seen in clinic who received hypothermia, 11% of these patients continued to have seizures at 2-12 months compared to 67% of untreated patients. Long term risk of seizures at 2-12 months was reduced in patients who received selective head cooling to a relative risk of 0.17 (Confidence Interval 0.05 to 0.51, p= 0.0018).

Conclusions: This study suggests that therapeutic hypothermia may reduce long term risk of seizures from hypoxic ischemic encephalopathy.

Keywords: Neonatal neurology

60. Contemporary Profile of Neonatal Seizures: A Prospective Cohort Study of the Neonatal Seizure Registry
Glass HC (San Francisco, CA), Chang T, Shellhaas RA, Wusthoff CJ, Abend NS, Bonifacio SL, Tsuchida T, Chu CJ, Massey S, Silverstein FS, Cilio MR, Soul JS

Objective: To examine the etiology, burden, management and short-term outcomes of seizures in neonates monitored with continuous, video-electroencephalogram (cEEG) per American Clinical Neurophysiology Society (ACNS) guidelines at 8 tertiary U.S. sites.

Methods: Prospective study of consecutive neonates ≤44 weeks postmenstrual age with clinical events suspicious for seizure and/or confirmed electrographic seizures. Data were obtained using pre-determined definitions from medical records.

Results: 420 subjects (55% male/87% term) were enrolled from 1/2013-4/2015 (Table). Electrographic seizures without clinical correlate were present in 60%; 58% had frequent seizures (≥7) or status epilepticus. Phenobarbital was the most common loading (88%) and discharge

<table>
<thead>
<tr>
<th>TABLE 1. Data are presented as N(%) and median(interquartile range) (Abstract 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=420</td>
</tr>
<tr>
<td><strong>Indication for cEEG monitoring</strong></td>
</tr>
<tr>
<td>- Clinical event suspicious for seizure 256 (61%)</td>
</tr>
<tr>
<td>- Encephalopathy 74 (18%)</td>
</tr>
<tr>
<td>- Clinical event and encephalopathy 60 (14%)</td>
</tr>
<tr>
<td><strong>Duration of monitoring (initial EEG), hrs</strong></td>
</tr>
<tr>
<td>57 (29, 83)</td>
</tr>
<tr>
<td><strong>Seizure Type (subjects can have more than one type)</strong></td>
</tr>
<tr>
<td>- Electrographic seizures without clinical correlate 252 (60%)</td>
</tr>
<tr>
<td>- Electroclinical seizures 196 (47%)</td>
</tr>
<tr>
<td>- Clinical events suspicious for seizures occurring prior to EEG recording 130 (31%)</td>
</tr>
<tr>
<td>- Clinical events suspicious for seizures without EEG correlate 76 (18%)</td>
</tr>
<tr>
<td>- Electrographic seizures recorded at outside hospital 31 (7%)</td>
</tr>
<tr>
<td><strong>Anticonvulsant medications administered during the admission</strong></td>
</tr>
<tr>
<td>- Phenobarbital 387 (92%)</td>
</tr>
<tr>
<td>- Levetiracetam 130 (31%)</td>
</tr>
<tr>
<td>- Fosphenytoin 116 (27%)</td>
</tr>
<tr>
<td>- Benzodazepine 81 (19%)</td>
</tr>
<tr>
<td>- Benzodiazepine infusion 34 (8%)</td>
</tr>
<tr>
<td>- Vitamin(s) (pyridoxine, folic acid, pyridoxal 5 phosphate) 32 (8%)</td>
</tr>
<tr>
<td>- Topiramate 17 (4%)</td>
</tr>
<tr>
<td>- Other 18 (4%)</td>
</tr>
<tr>
<td><strong>Number of anticonvulsants administered</strong></td>
</tr>
<tr>
<td>- 0 10 (2%)</td>
</tr>
<tr>
<td>- 1 194 (46%)</td>
</tr>
<tr>
<td>- 2 97 (23%)</td>
</tr>
<tr>
<td>- ≥3 119 (28%)</td>
</tr>
<tr>
<td><strong>Anticonvulsants at discharge</strong></td>
</tr>
<tr>
<td>None 114 (27%)</td>
</tr>
<tr>
<td>Phenobarbital 253 (60%)</td>
</tr>
<tr>
<td>Levetiracetam 96 (23%)</td>
</tr>
</tbody>
</table>

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61. A Resuscitation Scale for Predicting the Need for Therapeutic Hypothermia

Harbert MJ (San Diego, CA), Brown MK, Lazarus DV, Steen SJ, Wozniak M, Poeltler DM, Rasmussen MR

Objective: Therapeutic hypothermia (cooling) is a proven treatment for neonatal encephalopathy. Identifying candidates for cooling is challenging; the Apgar and Sarnat scores depend upon the assessing clinician, who is usually not a child neurologist. We tested a simple resuscitation scale within a cohort of newborns with perinatal acidosis to assess the utility of the scale in detecting cooling candidates.

Methods: All neonates ≥36 weeks gestation and with a cord gas pH of ≤7.1 or base deficit ≥12 were evaluated over an 18-month period at a single center with a consistent screening protocol for cooling candidates. Data collected for all subjects included cord gas pH, treatment with hypothermia and extent of resuscitation. Extent of resuscitation was gauged by a scale from 0 to 8 (Table 1).

Results: 166 subjects with perinatal acidosis were identified, of whom 24 were treated with cooling. A logistic regression was performed to ascertain the effects of acidosis and resuscitation score on the likelihood of qualifying for therapeutic hypothermia. The logistic regression model was statistically significant, \( \chi^2(2)=47.818, P<0.0001 \). The model correctly classified 89.1% of cases. The resuscitation score was predictive of the need for hypothermia (p < 0.0001), more so than cord gas pH (p = 0.01).

Conclusions: In this cohort of newborns with perinatal acidosis, the extent of resuscitation at birth was highly predictive of the need for therapeutic hypothermia. The resuscitation score is an objective measure that may be a useful tool for educating labor-and-delivery clinicians in screening newborns for therapeutic hypothermia.

Keywords: Neonatal neurology

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<table>
<thead>
<tr>
<th>Score</th>
<th>Resuscitation Measure Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Drying and stimulation</td>
</tr>
<tr>
<td>1</td>
<td>Blow-by oxygen</td>
</tr>
<tr>
<td>2</td>
<td>Continuous positive airway pressure</td>
</tr>
<tr>
<td>3</td>
<td>Intubation and suction for meconium</td>
</tr>
<tr>
<td>4</td>
<td>Positive pressure ventilation</td>
</tr>
<tr>
<td>5</td>
<td>Intubation with positive pressure ventilation</td>
</tr>
<tr>
<td>6</td>
<td>Chest compressions for bradycardia (&lt;60 bpm)</td>
</tr>
<tr>
<td>7</td>
<td>Chest compressions for asystole</td>
</tr>
</tbody>
</table>

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62. Factors Associated with Mortality in the Era of Therapeutic Hypothermia for Neonatal Encephalopathy

Harbert MJ (San Diego, CA), Brown MK, Lazarus DV, Poeltler DM, Rasmussen MR

Objective: Therapeutic hypothermia improves developmental outcomes in survivors of neonatal encephalopathy. However, there is limited data enabling prediction of which newborns die despite therapeutic hypothermia. We assessed a cohort of newborns treated with therapeutic hypothermia to identify which perinatal factors were associated with in-hospital mortality.

Methods: We performed a retrospective analysis of all newborns receiving therapeutic hypothermia at a single referral center from January 2008-September 2014. Data collected included demographics, Apgar scores, cord gas values, means of birth resuscitation, time-to-target temperature (<34°C), and significant injury on neuroimaging (MRI), defined as diffusion-weighted hyper-intensity in two or more of the following regions: deep gray nuclei, white matter or cortex.

Results: Of the 86 newborns treated with therapeutic hypothermia, nine (10.5%) died during the hospital stay. Delivery room factors associated with mortality included receipt of bicarbonate (p=0.01) and epinephrine (p=0.03); chest compressions for asystole were trending towards significance (p=0.06.) Association between 5-minute Apgar and mortality was approaching significance (median Apgar 2 in the mortality group, IQR 0-5, p=0.053.) Having two or more injured brain regions on MRI was tightly associated with mortality (p<0.0001.)

Conclusions: Identifying newborns at a substantial risk of dying despite therapeutic hypothermia is very important for accurate prognostication and counseling of parents. For our cohort, these risk factors included needing extensive resuscitation and at least two areas of brain injury on neuroimaging. Further studies are needed to fully understand which population of newborns is least likely to benefit from therapeutic hypothermia.

Keywords: Neonatal neurology
63. Severity of Medical Issues is Associated with Poor Neurobehavioral Performance in Newborns with Hypoxic-Ischemic Encephalopathy (HIE) Treated with Therapeutic Hypothermia (TH)

**Objective:** To determine whether severe medical co-morbidities (i.e. cardiovascular instability, significant respiratory morbidity, and glucose instability) are risk factors for poor neurobehavioral performance in newborns with HIE following TH.

**Methods:** Term newborns with HIE were enrolled in an observational study evaluating neurobehavioral status following TH. Neurobehavioral performance was evaluated using the NICU Network Neurobehavioral Scale (NNNS) at approximately two weeks of age. Data regarding the presence of cardiovascular (severe bradycardia or hypotension), respiratory (pulmonary hypertension, extracorporeal membrane oxygenation, or prolonged ventilation >4 days), and glucose (hyper- or hypoglycemia) instability during TH were prospectively collected. T-tests were used to assess the association between the medical co-morbidities and neurobehavioral performance.

**Results:** Eighty-seven newborns with moderate (n=72) or severe (n=15) HIE were assessed with the NNNS at median age 13 days (range 5-22). Mean ± SD birthweight was 3.3 ± 0.6 Kg, gestational age 38.8 ± 1.8 wks, and 55% were male. Cardiovascular (p=0.034) and respiratory (p=0.036) morbidities were associated with increased stress behaviors. Glucose instability was associated with impaired higher order functions of self-regulation (p=0.048) and orientation (p=0.032).

**Conclusions:** In newborns with HIE, medical co-morbidities are associated with poorer neurobehavioral performance after TH. The NNNS can identify functional evidence of brain injury related to severity of medical issues during the NICU course. Further research will examine the impact of medical co-morbidities on long-term developmental outcomes in this cohort.

**Keywords:** Neonatal neurology

64. Arsenic is Associated with Reduced Effect of Folic Acid in Myelomeningocele Prevention: A Case-Control Study in Bangladesh

**Hibne Haian OS (Dhaka, Bangladesh), Hamid R, Valeri L, Rodrigues ES, Quarmnuzzaman Q, Rahman M, Christiani DC, Mazumdar M**

**Objective:** Arsenic induces neural tube defects in animal models, but its potential to cause neural tube defects in humans is unknown. Our objective was to investigate the associations between maternal arsenic exposure, periconceptional folic acid supplementation and risk of posterior neural tube defect (myelomeningocele) among a highly exposed population in Bangladesh.

**Methods:** We performed a case-control study that recruited physician-confirmed cases from health clinics served by Dhaka Community Hospital in Bangladesh. Controls were selected from pregnancy registries in the same areas. Maternal arsenic exposure was estimated from drinking water samples taken from wells used during the first trimester of pregnancy. Periconceptional folic acid use was ascertained by self-report, and maternal plasma folate levels were measured at the time of the study visit.

**Results:** Fifty-seven cases of myelomeningocele were identified along with 55 controls. A significant interaction was observed between drinking water arsenic concentrations and folic acid use. As drinking water arsenic concentrations increased from 1 to 25 micrograms/liter, the estimated protective effect of folic acid use declined (OR 0.22 to 1.03), and was not protective at higher concentrations of arsenic.

**Conclusions:** Results suggest that environmental arsenic exposure reduces the effectiveness of folic acid supplementation in preventing myelomeningocele.

**Keywords:** Neonatal neurology, Translational/experimental therapeutics

65. Among Children Born Before 28 Weeks Gestation (Extremely Low Gestational Age Newborns- ELGANs), Girls Have a Lower Risk of Adverse Neurocognitive and Academic Outcomes at Age 10 Years

**Kaban KCK (Boston, MA), Joseph R, O'Shea TM, Allred EN, Heeren T, Hirtz D, Leviton A**

**Objective:** To evaluate the hypothesis that rates of neuro-cognitive and academic deficits among ELGANs do not differ between girls and boys at age 10 years.

**Methods:** In a prospective, multicenter observational study of 966 eligible survivors, 895 (93%) were evaluated at age 10 years with measures of IQ, executive function, and academic achievement.

**Results:** 20% of males vs 11% of females had IQ values ≤70 for verbal abilities (OR=2.0, 95% CI: 1.4-3.0) and 17% vs 10% for nonverbal abilities (OR=1.8, 1.2 – 2.7). 39% of males and 30% of females and had a verbal IQ ≤ 85 (OR=1.5; 1.1 – 2.0), and 43% of males and 33% of females had a nonverbal IQ ≤85 (OR=1.5; 1.2 – 2.0). 15 to 33% of males scored more than 2 SD below the population mean on 8 executive function (EF) tasks, compared
with 10 to 29% of females (expectation: 2.3%). Half of males and females scored ≤1 SD on 6 EF tasks (expectation: 16%). On academic achievement tests, 16% of males scored less than 2 SD below the population mean on reading-related tasks, compared with 10% of females. 20% of males scored less than 2 SD below the population mean on numeric operations, compared to 13% in females.

**Conclusions:** Neuropsychological and academic deficits are evident at age 10 years, and more prevalent among boys than girls. Compared to normative samples, the distribution of neuropsychological scores on all assessments was shifted downward, and a much larger number of children than expected had very low scores.

**Keywords:** Cognitive/Behavioral Disorders, Neonatal neurology

### 66. Hyperperfusion on MRI ASL Sequences Localizes the Seizure Focus in Newborns

**Mabray PD** (Washington, DC), **Whitehead MT**, **Chang T**, **Gaillard WD**, **Tischida T**

**Objective:** Increased perfusion in ictal SPECT studies is more localizing for seizure onset than interictal decreased perfusion. Arterial spin labeling (ASL) magnetic resonance imaging (MRI) can demonstrate increased perfusion without using radiolabeled tracer. MRI ASL has recently been shown to be potentially useful in adults for identifying seizure foci in epileptic patients or following strokes. There are no reports on the utility of MRI ASL in neonates.

**Methods:** We report three newborns with focal seizures localized on continuous video EEG, anatomical brain MR imaging and ASL images. All brain MR exams were performed on a 3T magnet (Signa HDxt Optima; GE Healthcare, Milwaukee, WI). Each patient underwent pseudocontinuous ASL (pcASL) with segmented 3D fast spin-echo (FSE) readout.

**Results:** Case #1 is a term male infant presenting with clinical seizures from an idiopathic large left intraventricular hemorrhage. cEEG had left temporal status epilepticus then improved the prognosis in neonates with hypoxic ischemic encephalopathy. Seizures and seizure-like events are common in these cases. We evaluated the possibility of a shortened continuous long-term video EEG monitoring (cVEEG), thereby reducing health costs and resource utilization.

**Methods:** This was a single-institution retrospective study of neonates undergoing TH and cVEEG monitoring between 2008 to 2014. Included were patients that underwent cVEEG monitoring throughout the 72 hours of hypothermia and 8 hours of rewarming phases. cVEEG studies were reviewed for occurrence of seizures, seizure-like/push button events and their timings.

**Results:** Twenty-four cases were reviewed. Thirteen patients (54%) did not have push button events or seizures. 9/10 (90%) patients with push button events or seizures began within the first 24 hours of cooling. Of the 21 total push button events in these 9 patients, only 1 (4.8%) episode correlated with seizure activity. Three patients (12%) had definite seizures of which two had electroclinical and subclinical seizures that started within 24 hours. One patient had a single brief subclinical seizure on day 2 of cooling. None had seizures or seizure-like events during the rewarming phase.

**Conclusions:** Our experience with TH is that the maximum utility of continuous long-term video EEG monitoring is in the first 24 hours when there is the highest incidence of seizure-like events and seizures. Conversely, patients who have not had such events in the first 24 hours may not necessarily need 80 hours of monitoring.

**Keywords:** Epilepsy, Neonatal neurology

### 68. The Importance of Functional Ability on Perceived Quality of Life in Adolescents with Congenital Heart Disease

**Majnemer A** (Montreal, Quebec, Canada), **Rohlicek C**, **Dahan-Oliel N**, **Riley P**, **Hatzigeorgiou S**, **Mazer B**, **Maltais D**, **Schmitz N**

**Objective:** This study describes intrinsic factors associated with perceived quality of life in adolescents with congenital heart defects (CHD).

**Methods:** Eighty-six adolescents (15.8 ± 1.71 years; 51.2% male) with CHD who required infant open-heart surgery and their parents completed self and proxy-report questionnaires of health-related quality of life (PedsQL; physical/psychosocial). The adolescents were evaluated using standardized measures of intelligence (Leiter-IQ), motor ability (Movement-ABC) and behavior (SDQ=Strengths and Difficulties Questionnaire). Activity limitations (communication, socialization, daily living skills, adaptive behavior) were assessed by parent interview (Vineland Adaptive Behavior Scale).

**Results:** Behavioral, cognitive and motor deficits were common (23%-38% of youth). A third of youth had low physical (31.3%) and psychosocial (35.0%) well-being scores. Physical well-being correlated with Leiter-IQ (r=-.27, p=.017), SDQ score (r=-.48, p<.001), and activity limitations, particularly socialization (r=.39, p=.002), adaptive
behavior (r=-.42, p<.001) and communication (r=-.47, p<.001). Similarly, Letter IQ (r=.25, p=.026), SDQ (r=.56, p<.001), socialization, adaptive behavior (both r=.39, p=.001) and communication (r=.44, p<.001) difficulties also correlated with psychosocial well-being. Mastery motivation was also associated with quality of life (r=-.33, p=.03). Similar relationships were found when quality of life was reported by their parents. Higher parenting stress was correlated with lower well-being of these youth.

Conclusions: Brain-based sequelae are common in youth with CHD. These persisting behavioral and cognitive impairments and limitations in communication and socialization negatively impact their physical and psychosocial well-being. Findings highlight the importance of addressing long-term developmental and functional challenges to promote the health of youth with CHD in this critical stage of development. (Acknowledgements: Study funded by the Canadian Institutes of Health Research MOP-102720)

Keywords: Cognitive/Behavioral Disorders, Neonatal neurology

69. Early Brain Injury Pattern and Brain Volume at Age 1 year in Newborns with Hypoxic-Ischemic Encephalopathy
Mulkey SB (Little Rock, AR), Ramakrishnaniah RH, Bai S, Luo C, Chowdhury N, Bland C, Schaefer GB

Objective: To determine effects of early clinical factors and brain injury pattern on brain volumes at age 1 year in newborns with hypoxic-ischemic encephalopathy (HIE)

Methods: We performed a retrospective study of infants with HIE treated with therapeutic hypothermia from 2012-2014. Included infants had brain MRI at <7 days of age with MRS and clinical brain MRI at 1 year of age. The initial MRI injury pattern was classified as predominantly diffuse global injury, deep gray matter, or cortex/white matter injury. The total intracranial volume (TICV), whole brain (WB), and corpus callosum (CC) volumes were measured on the follow-up brain MRI. The data from individual slices was compiled using a customized algorithm to render a final volumetric estimate for each structure.

Results: Nineteen infants with a gestational age of 37.9 ± 2.72 weeks, 5-minute Apgar 3.4 ± 2.0, and initial blood pH 6.966 ± 0.171 were included. Sixteen infants had an abnormal MRI and 9 had an abnormal MRS at 4.8 ± 1.3 days of age. Seven infants had a diffuse injury pattern, 3 had deep gray matter injury, and 6 had injury of the cortex/white matter. Follow-up brain MRI was at 360.8 ± 76.7 days of age. Initial pH and base excess were associated with CC volume (P<0.05). Infants with diffuse injury had smaller TICV and WB compared to infants with cortex/white matter injury (P<0.05). Abnormal MRSs was associated with reduced head circumference, TICV, and WB (P<0.05).

Conclusions: Clinical factors and brain injury pattern on initial MRI correlate with brain volumes at age 1 year in infants with HIE.

Keywords: Neonatal neurology, Neuroimaging

70. Neurocognitive Impairments at 10 Years of Age in the Extremely Low Gestational Age Newborn (ELGAN) Cohort
O'Shea TM (Winston-Salem, NC), Kahan KCK, Joseph R, Alfold EN, Hooten T, Hirtz D, Levition A

Objective: Children born extremely preterm frequently exhibit neurocognitive impairments. We studied the prevalence of such impairments at 10 years of age, and their relationship to gestational age (GA) at birth, in a large cohort of children born before 28 weeks of gestation (the ELGAN Study cohort).

Methods: In 887 ELGAN Study members, we evaluated general cognitive ability with the Differential Ability Scales–II (DAS-II) Verbal and Nonverbal Reasoning scales. Attention and executive function were assessed with two DAS-II Working Memory subtests and five subtests from the NEPSY-II. For each of the 8 tests, a severe impairment was defined as a score more than two standard deviations below the general population mean. (The normative expectation for scores this low is 2.3%.) We used multinomial logistic regression to analyze associations between GA and severe impairment, adjusting for maternal IQ, insurance status, and child's sex.

Results: The risk of severe impairment on the 8 neurocognitive tests examined ranged from 14% to 31%. Risk was increased 1.6- to 3.2-fold among children born at 23-24 weeks (p<0.05 for all 8 tests), and 1.6- to 2.2-fold among those born at 25-26 weeks (p<0.05 for 4 tests), as compared to children born at 27 weeks.

Conclusions: In a large sample of ELGANs, the frequencies of severe impairment, across a range of neurocognitive tests, is 6- to 13-fold higher than in the general population. Even within the narrow range of 23-27 weeks of gestation, the risk of severe impairment decreases with increasing GA.

Keywords: Cognitive/Behavioral Disorders, Neonatal neurology

71. Effect of Hypoxic-Ischemic Injury on Resting State fMRI Maps in Term Neonates: preliminary data on a small cohort of subjects
Pergami P (Morgantown, WV), From C, Regier M

Objective: The relation between structural lesions and neurologic deficit is not absolute, particularly in the developing brain. Hence, traditional MRI is frequently insufficient to accurately predict functional outcome in neonates with moderate, but clinically significant ischemic lesions. The objective of this study was to evaluate differences in resting state functional connectivity obtained 4-7 days after the ischemic event between neonates with Hypoxic Ischemic Encephalopathy (HIE) and healthy controls.

Methods: Brain MRI was obtained during natural sleep in 5 healthy neonates and three HIE subjects on a 3T Verio Scanner including high-resolution T1-weighted images (MP-RAGE) and Echo-Planar-Images (EPI) sensitized to bold signal changes (TR 2800ms,TE 28ms, voxel size 2.4X2.4X2.4; FOV 150mm; 200 frames). All analysis was performed using AFNI (Cox, 1996). Differences in connectivity maps for selected Regions of Interest (ROI) - motor,
prefrontal, thalamus, occipital cortex- were obtained and significant differences were determined using t-test statistics.

Results: Comparison of connectivity maps obtained from controls and neonates with HIE demonstrated significant differences (p <0.05) in all selected regions (medial prefrontal, motor cortex, thalamus) except for occipital ROI.

Conclusions: The study is ongoing; correlation between aberrant connectivity and clinical outcome remains to be investigated. Obtaining rs-fcMRI in neonates with HIE in the sub-acute phase is feasible and could contribute to more accurate quantification of brain damage in this population, and possibly support prediction of clinical outcome.

Keywords: Neonatal neurology, Neuroimaging

72. Neutrophil and Lymphocyte Counts in Neonatal Hypoxic Ischemic Encephalopathy and Acute Ischemic Stroke: A Possible Role for Immunity in Ischemic Brain Injury
Pergami P (Morgantown, WV), Povrozni J, Nanavati T, Engler-Chiurazzi E

Objective: Neutrophil/lymphocyte ratio (NLR) is predictive of clinical outcome in adults with thromboembolic stroke, but no such evidence exists in neonates with ischemic brain injury. The objectives of this study are to identify differences in absolute neutrophil and lymphocyte counts and/or neutrophil/lymphocyte ratio between neonates with two forms of ischemic brain injury, hypoxic ischemic encephalopathy (HIE) and acute ischemic stroke (AIS), and controls, and to determine if a specific NLR pattern is associated with long-term neurological outcome.

Methods: Retrospective chart review of neonates with HIE, AIS, and full- and late pre-term neonates with Transient Neonatal Tachypnea (TTTN) -control group- was conducted. The HIE group included neonates who did or did not receive total-body cooling. Absolute neutrophil and lymphocyte counts at 12-hour intervals (birth-to-60 hours) were collected, and NLR was calculated. Neurological outcome was based on a 5-point clinical scale of progressive severity.

Results: A marginal trend in the omnibus ANOVA (p<0.06) suggested differences in absolute lymphocyte counts among the groups at the 12-36 hour time frame. When we probed this treatment main effect, we found that HIE neonates who had received cooling had lower absolute lymphocyte counts than did controls (p<0.05), AIS neonates (p<0.08), and HIE neonates who did not receive cooling (p<0.05).

Conclusions: Immune suppression following stroke is described in adults and possibly prevents excessive tissue destruction from activation of the inflammatory cascade. The reduction of circulating absolute lymphocyte among the HIE neonates who received cooling suggest that cooling treatment could enhance outcome via a beneficial immunosuppressive effect.

Keywords: Infections/Neuroimmunology, Neonatal neurology, Stroke

73. Effect of Administration of Normal Saline Bolus on Intraventricular Hemorrhage in Preterm Neonates
Sankaran J (Camden, NJ), Brandsma E, Kushnir A

Objective: To evaluate if normal saline (NS) bolus administration on the first day of life increases the risk of Intraventricular hemorrhage (IVH) in preterm infants.

IVH causes long-term neurological disability in preterm infants. There is little evidence that acute elevation of blood pressure improves perfusion and organ blood flow. However, circulatory management in neonatal intensive care unit (NICU) often focuses on normalization of blood pressure (BP) by giving normal saline boluses. As changes in BP are associated with IVH (1, 2), we wanted to evaluate this association.

Methods: This is an IRB approved retrospective study of NICU admissions of preterm infants less than 32 weeks gestation between 1/1/10 and 5/1/14. Primary outcome was the presence and grade of IVH following NS bolus in the first 24 hours of life. Secondary outcome analyzed included the CRIB (Clinical risk index for babies) score.

Results: Of the 110 preterm infants ≤32 weeks gestation who qualified for the study, 40 (36.4%) received fluid bolus. NS bolus on the first day of life increased the rate of IVH from 17% to 30% and increased the relative risk of developing IVH (relative risk =1.755). Risk of IVH significantly increased on receiving more than 1 (10 ml/kg) bolus (p=0.02). Even after adjusting for CRIB score, there was a higher rate of IVH following NS bolus (p =0.04).

Conclusions: Normal saline bolus administration in the first 24 hours of life in preterm neonates may increase the chances of developing IVH, proportionately to increased volume of fluids administered.

Keywords: Neonatal neurology

74. Impairment of White Matter Microstructural Integrity Based on Diffusion Tensor Imaging in Neonates with Hypoxic-Ischemic Encephalopathy and Seizures
Schapiro MB (Cincinnati, OH), Zorn E, Merhar S, Horn P, Rajagopal A, Yuan W

Objective: Seizures are common in neonates with hypoxic-ischemic encephalopathy (HIE). We hypothesized that neonates with HIE and seizures (HIESz+) may have abnormalities on diffusion tensor imaging (DTI) compared to those without seizures (HIESz-).

Methods: EPIC medical record was reviewed for all neonates with HIE between the years 2008 and 2013 at our institution. Seventeen subjects with DTI were included in the final analysis: HIESz+ (n=10); HIESz- (n=7). Charts were reviewed for demographic variables, and neonatal resuscitation and seizure severity scores were calculated (Miller 2002). DTI images were analyzed using DTI Studio (Johns Hopkins University). Regions of interest were drawn over the genu and splenium of corpus callosum, and the anterior (ALIC) and posterior (PLIC) limbs of the internal capsule. Fractional anisotropy (FA) values were calculated and groups were compared using Student’s t-tests, analysis-of-covariance, and Pearson correlations.
**Results:** There were no significant differences in gestational age, birth weight, sex, age at MRI scan, or percentage of neonates receiving therapeutic hypothermia. HIESz+ required more resuscitation at birth ($p=0.045$). HIESz+ had lower FA values in PLIC ($p=0.034$) and splenium ($p=0.059$), but not ALIC ($p>0.100$) or genu ($p>0.100$) versus HIESz-. After adjustment for resuscitation score, gestational age, and hypothermia, this effect of seizure on FA remained in the PLIC ($p=0.023$) and splenium ($p=0.053$). Lastly, we found that PLIC and splenium had a statistically significant negative correlation with composite seizure score ($p=0.005$ and $0.066$, respectively).

**Conclusions:** After adjustment for potential confounding variables, HIESz+ have more disrupted white matter integrity as compared to HIESz-.

**Keywords:** Neonatal neurology, Neuroimaging, Neuromuscular disorder

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**75.** *Quantitative MRI of Extremely Low Gestational Age Newborn (ELGAN) Children at Nine-to-Eleven Years Of Age: Brain Volumetry*

Zhou Q (Boston, MA), Aakil A, Alshamrani K, Jara H, Norbash AM, Sakai O, Kuhin KCK, Leiton A, Hirtz D, Heeren T, O'Shea TM, Allred EN

**Objective:** Whole-brain volumetry was evaluated at 9-to-11 years in a cohort of extremely low gestational age newborns (ELGANs), infants born before the 28th week gestation, using quantitative magnetic resonance imaging (qMRI) methodologies.

**Methods:** Children underwent MRI scans at twelve ELGAN participating sites: 11 used 3T scanners (GE, Philips and Siemens), and one used a 1.5T (GE) machine. The dual-echo turbo spin echo (DE-TSE) MR images of ninety-eight subjects (38 males and 60 females) were qMRI processed resulting in three-dimensional proton density and transverse relaxation time maps covering the whole-head. All tissues contained in the intracranium (intracranial matter (ICM) = gray matter plus white matter plus meninges and cerebrospinal fluid) were segmented using a dual-clustering algorithm programmed in Mathcad. Additionally, normal brain MRI volumes of age-matched full term (FT) children was obtained from published data from NIH (Cerebral Cortex May 25, 2011, Table 4).

**Results:** Histogram of total brain volume shows that ELGAN subjects have wider distribution compared to control full term children. Quantitative tissue-specific volumetry further reveals that the mean total brain matter (gray plus white matter) of ELGAN children is larger than FT children (ELGAN: 1350 ± 191 cm$^3$ vs. FT: 1265 ± 115 cm$^3$) and have disproportionately higher GM (ELGAN:982 ± 181 cm$^3$ vs. FT:794 ± 82 cm$^3$) and lower WM (ELGAN:366 ± 94 cm$^3$ vs. FT:458 ± 64 cm$^3$) mean volumes.

**Conclusions:** In a sample of ninety-eight ELGAN children born at the onset of myelination, qMRI volumetry reveals patterns of abnormality in terms of GM vs. WM proportions relative to age matched full term children.

**Keywords:** Neonatal neurology, Neuroimaging

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**Demyelinating Disorders**

**76.** *Brown-Vialetto-Van Laere Syndrome Mistaken for Neuroimmune Disorders: three cases from the clinic and review of the literature*

Allison TJ (Kansas City, MO), Forsyth R, Coffman KA, LePichon JB

**Objective:** Illustrate the potential for confusion with neuroimmune disorders when assessing patients with riboflavin transporter deficiencies.

**Methods:** We present three patients identified at two different institutions with Brown-Vialetto-Van Laere syndrome (BVVL). Each patient was initially diagnosed with a
neuroimmune disorder for a period of a few weeks to a few months. The first patient was initially diagnosed as an acute axonal motor neuropathy based on neurophysiological and CSF findings. The second patient's CSF was returned as positive for anti-LGL1 antibodies, suggesting autoimmune encephalitis. The third patient's clinical picture, including anti-GM-1 antibodies suggested CIDP.

Results: In each case genetic analysis revealed mutations in one of the riboflavlin transporters, confirming Brown-Vialetto-Van Laere syndrome: Index case 1 is clinically confirmed, with elevated acylcarnitine profile, hearing loss, hyporeflexia and respiratory failure. She is heterozygous for point mutations in SLC52A2 and A3, the deletion analysis confirming heterozygosity is still pending. The other two cases are homozygous or compound heterozygous for BVVL.

Conclusions: It is likely that Brown-Vialetto-Van Laere is a syndrome more common than previously reported and may be misdiagnosed as a neuroimmune disorder. It shares many features with diseases such as chronic inflammatory demyelinating neuropathy, may present with positive CSF antibody titers and may transiently respond to IVIG. We emphasize the importance of correctly diagnosing the disease, as its treatment is relatively benign and will stop progression of the disease and may even reverse it.

Keywords: Demyelinating Disorders, Genetics, Neuromuscular disorders

77. Natural History of Metachromatic Leukodystrophy
Carson VJ (Pittsburgh, PA), Poe MD, Escolar ML

Objective: Metachromatic leukodystrophy (MLD) is a rare inherited lysosomal storage disease caused by the deficiency of Arylsulfatase A, the enzyme responsible for degradation of 3’O-sulphogalactosylceramide. A better understanding of the natural history of MLD is necessary in order to select patients likely to benefit from current and future therapies.

Methods: We performed a retrospective review of patients with MLD who were evaluated longitudinally between 2002 and 2015, at the same site and using a standardized evaluation. Assessments included growth parameters, standardized evaluations of adaptive and cognitive behavior, motor function, and speech/language skills. MRI of the brain, nerve conduction studies, visual evoked potentials and brainstem auditory evoked responses were also obtained.

Results: 90 patients were evaluated: 3 adults, 29 juveniles and 58 late infantile patients. The average time to diagnosis was 9 months. The course of the disease in the late infantile patients varied with most children deteriorating rapidly within 6 months of diagnosis. The initial symptoms in late infantile were mostly related to changes in gait while in the older forms it was associated with changes in cognitive and behavioral function. Peripheral neuropathy and brain auditory evoked responses abnormalities started early in the disease process.

Conclusions: To date, this is the only longitudinal study of MLD that spans over 13 years in a single site using the same evaluation protocol. The longitudinal trajectory of the disease and the range of variability are extremely important in assessing the efficacy of new therapies such as hematopoietic stem cell transplantation, gene therapy, and enzyme replacement.

Keywords: Demyelinating Disorders, Genetics

78. TUBB4A Mutations Cause Diverse Neurologic Phenotypes Related to Differences in Microtubule Dynamics

Objective: Mutations in the gene encoding Tubba4a, a tubulin highly expressed in brain tissue, results in diverse neurologic phenotypes including the leukodystrophy hypomyelination with atrophy of basal ganglia and cerebellum (H-ABC), isolated hypomyelination without basal ganglia involvement and the familial movement disorder whisker dystonia (DYT4). We hypothesize differences in clinical phenotypes may result from differing effects of the distinct mutations on microtubule dynamics. We examined microtubule polymerization to correlate tubulin function with the clinical presentation in 5 distinct causative mutations in the gene Tubba4a.

Methods: HEK cells were transfected with plasmids for expression of WT Tubba4a and Tubba4a bearing mutations causative for distinct clinical phenotypes. Cell lysates were harvested in BRB80-buffer, treated with GTP and Taxol to promote polymerization, and subjected to ultracentrifugation to separate polymerized from unpolymerized tubulin. Ratios of tubulin polymerization (pellet contains polymerized and supernatant contains unpolymerized) were assayed using Western Blot analysis.

Results: Mutations R2G, D249N, and N414K have normal microtubule polymerization. Mutations R282P and V255I have decreased polymerization in HEK cells when compared to WT Tubba4a.

Conclusions: Mutations R282P and V255I, leading to isolated hypomyelination, are biochemically distinct from mutations leading to disorders with primary neuronal dysfunction or degeneration such as H-ABC or DYT4. Mutations leading to isolated hypomyelination may be dominant negative mutations causing reduced microtubule polymerization, affecting glial cells predominantly. Additional work is needed to explain mechanisms of Tubba4amutations resulting in primary neuronal dysfunction. We highlight how a single gene defect can result in distinct biochemical defects and variable, cell specific, phenotypes.

Keywords: Demyelinating Disorders

79. Brain Endothelial Dysfunction in Cerebral Adrenoleukodystrophy
Musolino P (Boston, MA), Gang Y, Snyder JMT, Jimenez S, Lok J, Lo E, Moser AB, Grabowski EF, Frosch MP, Eichler FS

Objectives: Cerebral X-linked adrenoleukodystrophy (CALD) is a progressive inflammatory demyelinating disease caused by mutations in the ABCD1 gene. A prominent perivascular infiltrate a the leading edge suggests that blood
brain barrier (BBB) disruption plays an important role in lesion progression. The purpose of this study is to assess the effects of ABCD1 deficiency upon brain endothelium and its role in the pathogenesis of CALD.

Methods: We examined brain endothelial markers involved in endothelial-leukocyte interactions and BBB permeability in brain autopsy specimens of 21 ALD, 6 relapsing remitting MS, and 11 controls using IHC and IF. To determine the effect of ABCD1 in brain endothelium, primary human brain microvascular endothelial cells (HBMEC) ABCD1 was silenced via siRNA. Molecular characterization was performed using RT-PCR arrays, western blot, CL-CTMS and adhesion and transmigration assays used to assess monocyte-endothelial cells interactions.

Results: We found that progressive inflammatory demyelination in CALD coincides with BBB disruption, increased MMP-9 expression, and changes in endothelial tight junction proteins as well as adhesion molecules. Silencing of ABCD1 in HBMEC caused upregulation of adhesion molecules and decrease in tight junction proteins and resulted in greater adhesion and transmigration of monocytes across the endothelium. After ABCD1 silencing HBMEC revealed down regulation of the transcription factor c-MYC and c-MYC silencing mimicked the effects of ABCD1 silencing without decreasing the levels of ABCD1 protein itself.

Conclusions: Our data suggests that ABCD1 deficiency induces significant alterations in brain endothelium via c-MYC and may thereby contribute to the increased trafficking of leukocytes across the BBB as seen in CALD.

Keywords: Demyelinating Disorders, Genetics

80. A Unique Co-existence of Myotonic Dystrophy Type-I (DM-I) and Multiple Sclerosis (MS)
Rashid S (Detroit, MI), Sivaswamy L, Tasos D

Objective: We report the co-occurrence of DM-I and MS for the first time in literature.

Methods: DM-I is a trinucleotide expansion disorder.[1] MS is widely understood as an auto reactive lymphocyte mediated inflammatory autoimmune disorder in the initial phases with subsequent microglial activation and chronic neurodegeneration [2-4]. Co-occurrence of DM-II and MS has been reported before. [5]

Results: 15 years old female presented with a 7-day history of ataxia, diplopia and incontinence. Physical examination was noticeable for bilateral atrophy of the temporalis muscles, elongated face, hypophonia, bilateral intranuclear ophthalmoplegia, left sided limited vertical gaze, symmetric weakness in the muscles of facial expression and decreased palatal elevation on the right side. The patient had difficulty in releasing the handgrip with weakness of intrinsic muscles of both hands. The rest of the examination was unremarkable. There was family history of MS on maternal side and patient's brother had similar pattern of hand weakness.

Magnetic resonance imaging revealed numerous supra and infratentorial T2 hyperintensities with demyelinating configuration, satisfying the revised 2010 McDonald criteria for MS. Work up for other infectious and autoimmune diseases were unremarkable. Electromyography revealed findings of myotonia. Genetic testing showed 520 CTG repeats (normal 5-34) confirming the diagnosis of DM-I.

Conclusions: MS and DM-I are two seemingly unrelated diseases with different pathophysiological mechanisms, clinical courses and treatment options. The fact that autoimmune diseases are 10 times more frequent with DM-II as compared to DM-I, imparts uniqueness to this combination of an inflammatory autoimmune disorder with a purely genetic disease. [6]

Keywords: Demyelinating Disorders, Genetics

81. Oxidative Stress Profiles Show Phenotypic Specific Differences in Adenoleukodystrophy Patient Plasma and Fibroblasts
Turk BR (Baltimore, MD), Tiffany CW, Jones RO, Moser AB, Fatemi S

Objective: X-linked adrenoleukodystrophy (ALD) is an inherited peroxisomal disorder whereby mutation of the ALD protein leads to accumulation of unbranched very long chain fatty acids, promotes oxidative stress and may lead to cell death in manifold cell populations. Phenotypic variance in ALD presents most commonly as either slow progressive spinal adrenomyeloneuropathy (AMN), or central white matter demyelination, cerebral ALD (CALD) in either early childhood or spontaneously later in life. We aim to assess oxidative stress and inflammatory parameters for cALD, AMN and heterozygote female patients.

Methods: Oxidative stress parameters in patient blood plasma and fibroblast cell culture were assessed. Total antioxidant content (TRAP), glutathione (GLT) and superoxide

![Plasma SOD in ALD phenotypes](image-url)

FIGURE 1: Plasma levels of Superoxide Dimutase (SOD) levels in cerebral adrenoleukodystrophy (CALD) (n=8) (p<0.0003), adrenomyeloneuropathy (AMN) (n=15), heterozygote female carriers of the adrenoleukodystrophy (ALD) mutation (n=10) and age and sex matched controls (n=9), with all assays repeated 3 times (Abstract 81).

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dismutase (SOD) were assessed in plasma and prostaglandin E2 (PGE2) in cell culture.

**Results:** CALD patients (n=8) showed significantly lower (p<0.0003) plasma SOD levels than AMN patients (n=15), who in turn showed a lower tendency than both female heterozygote carriers (n=10) and age matched control subjects (n=9) [Figure 1]. No significant difference in glutathione levels were shown. Cell culture media showed significantly higher PGE2 in cALD patients (n=6) compared to AMN patients (n=6), who in turn had lower levels than in controls and female heterozygotes.

**Conclusions:** Extracellular SOD 1 and intracytoplasmic mitochondrial SOD 2 are anterior antioxidant barriers to the superoxide anion radical in the brain. These decreased levels in plasma and increased prostaglandin levels in culture media of CALD patients may reflect higher levels of oxidative stress and/or inflammation, supporting biomarker development for measuring oxidative stress parameters in future clinical trials.

**Keywords:** Demyelinating Disorders, Genetics

### 82. Pediatric Anti-Myelin Oligodendrocyte Glycoprotein Syndrome: case series of a newly recognized central nervous system inflammatory disease

Venkateswaran S (Ottawa, ON, Canada), Thulasirajah S, Pohl D, Rostasy K, Davila J

**Objective:** Under the umbrella of pediatric acquired demyelinating syndromes (ADS), there is a multitude of disorders including monofocal and polyfocal demyelinating events, optic neuritis, transverse myelitis, multiple sclerosis, acute disseminated encephalomyelitis (ADEM), and neuromyelitis optica spectrum disorders (NMOSD). Due to overlapping clinical and MRI features, it can be challenging to provide an accurate diagnosis. Recent studies of myelin oligodendrocyte glycoprotein (MOG) identify MOG as a promising target for antibody mediated demyelination.

**Methods:** This was a retrospective chart review on a consecutive series of patients who presented with a CNS demyelinating syndrome and tested MOG-Ab positive.

**Results:** We described the clinical and MRI presentation of four children presenting with an acute, severe central nervous system (CNS) inflammatory disease with involvement of the brain and spinal cord, all of whom were positive for MOG IgG antibody. Encephalopathy was uncommon at presentation and all had quick resolution of symptoms with intravenous steroid and intravenous immunoglobulin (IVIg) treatment.

**Conclusions:** We propose that anti-MOG positive CNS inflammatory disease appears to be unique in its clinical presentation, resolution and MRI findings. In the short-term, it appears that children with anti-MOG antibody syndrome may have more favourable outcomes when compared to other CNS relapsing inflammatory conditions with rapid resolution of both clinical and imaging findings following steroid and IVIg therapy.

**Keywords:** Demyelinating Disorders

### 83. Pediatric Multiple Sclerosis Incidence and Healthcare Costs

Wright MA (Salt Lake City, UT), Bonkowsky JL, Korgenski EK, Candee MS

**Objectives:** Pediatric patients account for approximately 5% of multiple sclerosis (MS) cases. Pediatric MS has distinct differences compared to adult-onset MS, and overall incidence, disease progression, relapse rates, costs, treatment, and prognosis are poorly understood. Our goal was to establish a population-based cohort of pediatric MS, to determine the incidence of pediatric MS, and to evaluate the burden of healthcare costs associated with the disease.

**Methods:** A retrospective analysis of all patients with MS 18 years of age or younger who were diagnosed or treated between 2002-2012, as identified by ICD-9 codes using the Intermountain Healthcare (IH) electronic database and confirmed by manual chart review. Demographics and healthcare costs were extracted from the IH Enterprise Data Warehouse.

**Results:** Thirty-nine pediatric patients with multiple sclerosis were identified. This included twenty males and nineteen females. The race distribution was as follows: twenty-nine Caucasian, one Asian, four Hispanic, and five not specified. The incidence of MS in our population was calculated to be 1/15,026 live births. Total hospital costs for this cohort totaled $269,220 over a 10-year period with an average of $6,900 per patient. Costs were organized by Therapeutics; Room/Supplies; and Diagnostics. The biggest source of cost for the cohort was Diagnostics, totaling $162,321.

**Conclusions:** We found a substantially higher rate of pediatric MS than previously reported. The cost of healthcare for pediatric patients with MS is significant. Diagnostic expenses were the highest source of cost. More efficient means of identifying pediatric MS is a potential area for healthcare cost reduction.

**Keywords:** Demyelinating Disorders

### 84. Strength and Balance Show Measurable Change Over Time in Adrenomyeloneuropathy

Srivastava S (Baltimore, MD), Keller J, Bezman L, Raymond GV, Fatemi A, Zackowski K

**Objective:** Adrenomyeloneuropathy (AMN) is a variant of X-linked adrenoleukodystrophy that presents with spinal cord dysfunction, with/without cerebral involvement, resulting in impairments in strength, sensation, balance, and gait. Evaluating AMN treatments is often limited by slow disease progression before clinical changes manifest. Thus, it is essential to establish markers of disease progression in AMN.

**Methods:** In 74 adults with AMN over 3 years (0, 12, 24, 36 months), we evaluated: lower extremity strength (hand-held dynamometry); great toe vibratory sensation (Vibratron II); sway amplitude (Kistler 9281 force plate); and timed up and go (TUG). Data was collected from a placebo controlled trial of oral glyceryl trioleate-glycerol tri-erucate in AMN (NCT00545597); our analysis was restricted to patients receiving placebo. We used a
generalized least squares regression model, accounting for age, Kurtzke Expanded Disability Status Scale score, and years of symptoms at baseline.

Results: At baseline there were 30 males and 44 females (mean age 43.0 ± 11.5 and 47.7 ± 11.9 years, respectively). Hip flexion strength decreased over time in the women (p<0.0001) and men (p=0.036). Vibratory sensation worsened over time for the women (p=0.001) but not for men. Sway amplitude in the eyes closed feet apart (ECFA) position worsened over time in the women (p<0.0001) and men (p=0.042). There was no statistically significant change in TUG for men or women.

Conclusions: Hip flexion and sway amplitude with ECFA show significant changes over time in AMN. These measures may serve as markers of disease progression in AMN, opening the door for their use as therapeutic markers in intervention trials.

Keywords: Demyelinating Disorders, Genetics, Translational/experimental therapeutics

Genetics

85. Expanding the Phenotype of BRAT1 Mutations: Ataxia and Beyond

Srivastava S (Baltimore, MD), Cohen JS, Gupta S, Davis BT, Shahrizadi L, Naidu S

Objective: Ataxia is a genetically heterogeneous condition, with the number of identified genes rapidly increasing. We report on two sisters, aged 9 and 5 years, with ataxia and cerebellar atrophy on brain MRI who were discovered via whole exome sequencing (WES) to have compound heterozygous mutations in BRAT1, encoding BRCA1-associated ATM activator 1. BRAT1 mutations have previously been reported in patients with a severe phenotype referred to as lethal neonatal rigidity and multifocal seizure syndrome (RMFSFL). The sisters’ presentation is notable for intellectual disability, disruptive behaviors, subtle dysmorphisms, pendular nystagmus, hypotonia, and ataxia manifesting as dysmetria, truncal titubation, and wide-based gait. Extensive prior genetic and metabolic workup was unremarkable.

Methods: WES was performed as a trio including the affected sisters and their mother, and co-segregation analysis by Sanger sequencing was performed in their father and affected sisters and their mother, and co-segregation analysis worsened over time in the women (p<0.0001) and men (p=0.036). Vibratory sensation worsened over time for the women (p=0.001) but not for men. Sway amplitude in the eyes closed feet apart (ECFA) position worsened over time in the women (p<0.0001) and men (p=0.042). There was no statistically significant change in TUG for men or women.

Conclusions: Hip flexion and sway amplitude with ECFA show significant changes over time in AMN. These measures may serve as markers of disease progression in AMN, opening the door for their use as therapeutic markers in intervention trials.

Keywords: Demyelinating Disorders, Genetics, Translational/experimental therapeutics

86. Mitochondrial Membrane Protein-Associated Neurodegeneration Mimicking Juvenile ALS

Acsadi G (Farmington, CT), Lonita CM, Darras B

Objective: Mitochondrial Membrane Protein-Associated Neurodegeneration (MPAN) is a slowly progressive subtype of Neurodegeneration with Brain Iron Accumulation (NBIA) caused by mutations in C19orf12 gene. We report a young patient with initial clinical features of both upper and lower motor neuron disease.

Methods: We reviewed the relevant retrospective clinical history, neurological examination, electrophysiological (EMG) and neuroimaging tests. The genetic analysis was carried out by targeted next generation exome sequencing of known NBIA genes.

Results: The patient appeared healthy until she started falling at three years of age. Her initial clinical findings included mild proximal weakness in legs, spasticity, hyperreflexia and Babinski sign raising a suspicion of spastic paraparesis. Her EMG test showed wide-spread denervation suggestive a diffuse process affecting the anterior horn cells and/or motor axons. Her muscle biopsy showed mild neurogenic atrophy and a sural nerve biopsy was not contributory. Her gradual clinical progression over the next five years has led to dysarthria, dysphagia, loss of ambulation, dyskinesia and diminished reflexes. Now, she is non-verbal and encephalopathic with pseudo-bulbar affect. Her brain MRI at five years was normal but at nine years showed iron accumulation in the globus pallidus and substantia. Extensive metabolic testing was normal. Initial gene sequencing of ALS2 and SETX genes for juvenile ALS were non-informative. Targeted exome sequencing of NBIA genes showed a novel compound heterozygous mutation in the C19orf12 gene.

Conclusions: MPAN and C19orf12 gene mutation should be considered in young children with clinical signs of upper and lower motor neuron disease or spastic paraplegia.

Keywords: Genetics, Movement Disorders, Neuromuscular disorders

87. Neuronal Ceroid Lipofuscinosis-2 (CLN2) Disorder, a Type of Batten Disease Caused by TPP1 Enzyme Deficiency: current knowledge of the natural history from international experts


Objective: The neuronal ceroid lipofuscinoses (NCLs) are the most common group of neurodegenerative disorders in children and adolescents. CLN2, a type of NCL caused by
TPP1 enzyme deficiency, is characterized by seizures, rapid deterioration of language, cognition, motor skills and vision, and premature death. Our aim is to describe expert knowledge of CLN2 disease.

Methods: 18 international NCL experts answered a survey on CLN2 natural history.

Results: Clinical suspicion for CLN2 is low due to its rarity and non-specific presenting symptoms. A 1-4 year delay was reported between first onset of symptoms and diagnosis. Speech delay/decline, developmental delay/regression and seizures/epilepsy were identified as initial presenting symptoms. Symptom onset typically occurs between 1.5-5 years of age, but may occur later (9-12 years). Myoclonic epilepsy was the most commonly reported seizure type. Notably, seizures are refractory oftentimes requiring polytherapy. Cardiac rhythm anomalies, not previously associated with CLN2, were also identified.

Conclusions: CLN2 is a severe, progressive, pediatric-onset neurodegenerative disorder. Disease awareness is low, causing delays in diagnosis. Seizures in concert with a regression of language and/or motor milestones should raise suspicion for CLN2. Knowledge of CLN2 is paramount to ensure timely diagnosis and to enable early initiation of future therapies.

Keywords: Cognitive/Behavioral Disorders, Genetics, Movement Disorders

88. Real-world Experience in the Diagnosis of Neuronal Ceroid Lipofuscinosis Type 2 (CLN2): Report from an International Collaboration of Experts


Background: CLN2 disorder is a lysosomal storage disorder resulting from TPP1 enzyme deficiency that causes progressive neurological degeneration and early mortality. CLN2 disorder is rare and often unsuspected, leading to delays in diagnosis.

Methods: In late 2014, 18 international CLN2 experts (clinicians, academic researchers, and laboratory directors) answered a comprehensive survey on CLN2 disorder and a subset met to discuss experiences, current practices and shortcomings in diagnosis of CLN2.

Results: 70% of laboratory experts considered the standard for CLN2 diagnosis to be a demonstrated decrease in TPP1 enzyme activity, with the remaining experts favoring molecular detection of pathogenic CLN2/TPP1 mutations. Delays in the diagnosis of CLN2 were identified as a crucial concern: 82% of the group responded that patient referral to a specialist can typically take longer than one year. Laboratory experts identified the challenge in reaching a suspicion of CLN2 (50%) and lack of awareness of available tests (83%) as common reasons for delays.

DISCUSSION: Experts agreed that reliable techniques exist for CLN2 diagnosis and identified timely referral as a key challenge. An upcoming CLN2 expert meeting will define laboratory-based screening and diagnostic guidelines in order to establish best practices for use of biochemical genetics testing in CLN2 diagnosis.

Keywords: Genetics

89. Parental Opinion About Pediatric Biospecimen Permission

DiMario FJ (Hartford, CT), Vresilovic J

Objective: Parental opinions about permission for pediatric biobank research has had limited study.

Methods: After IRB exemption, a prospective parental survey of current patients using 18 multiple choice and Likert scale questions was completed. Results were compiled and analyzed.

Results: A convenience sample of 147 English comprehending parents volunteered. Parents wanted to know who (79%), what (76%), where (73%), and how (74%) the sample was processed and to whom their child's medical history would be provided (84%). Sixty-five percent of parents would provide broad permission for research on a blood sample, 43% for other tissue types, 35% for genetic-based research and 28% would permit stem cell research. Only 50% of those surveyed would allow unrestricted future research. Whites compared to non-whites were more likely to allow research (82% vs. 45%, p < 0.05) similar to parents who had previously given consent compared to those who had not (81% vs. 59%, p < 0.05). Parent gender had no effect on results.

Conclusions: The majority of surveyed parents would allow their child's blood samples to be banked for research. Parents surveyed preferred detail of; what would be studied, who would perform the research, where it would be done, and for how long the sample would be used, biased by race and prior experience.

Keywords: Genetics

90. Identification of Early Clinical Markers Associated with Neurologic Involvement in Patients with Hunter Syndrome: Data from the Hunter Outcome Survey (HOS)

Escolar ML (Pittsburgh, PA), Morin I, Amartino H, Scarpa M

Objective: All children with Hunter syndrome present with somatic disease manifestations, and the most severely affected patients also display progressive neurologic involvement leading to cognitive impairment. This analysis investigated early clinical markers that may be associated with the development of neurologic disease.

Methods: As of January 2014, data on disease manifestations reported before 2 years of age were available for 435 patients followed prospectively in the Hunter Outcome Survey (a Shire-sponsored, multinational, observational registry). Patients aged 5 years or older were categorized into severe and non-severe disease groups based on their most recent functional classification by clinical impression. Disease manifestations in the two groups were compared.

Results: The median ages at onset of signs or symptoms in the severe (n=205) and non-severe (n=230) groups were 1.3 and 2.4 years, respectively. A larger proportion of...
patients with severe disease experienced regression in developmental milestones, and the prevalence of some somatic and neurologic manifestations reported before 2 years of age was higher in the severe than in the non-severe group. In addition to cognitive problems (33% versus 4%, respectively), the greatest differences (≥10 percentage points) were in hyperactivity (18%, 2%), behavioral problems (17%, 2%), upper airway infections (32%, 20%), nasal obstruction (19%, 8%), rhinorrhea (24%, 13%), and coarse facial features (50%, 39%).

Conclusions: This analysis identified some early clinical markers that were frequently reported in children with Hunter syndrome who later developed neurologic disease, and may, with the support of additional investigations, indicate patients likely to progress to severe neurologic involvement.

Keywords: Genetics

91. Unique Presentation of 4-Aminobutyric Acid Transaminase Deficiency Diagnosed Through Whole Exome Sequencing and Metabolomic Analyses
Friederich KE (Houston, TX), Cardon MW, Donti T, Elsea SH, Bonnen PE, Emrick LT

Introduction: GABA-transaminase deficiency (OMIM 613163) is a rare disorder of GABA metabolism caused by recessive mutations in the gene 4-aminobutyric acid transaminase (ABAT). To date, only a few patients have been reported worldwide. Their clinical presentation has been remarkably consistent, with primary features of severe psychomotor retardation, hypotonia, hypertonia, and infantile-onset refractory epilepsy. We present a case of GABA-T deficiency that marks an important departure from previous clinical findings and significantly expands the phenotype of GABA-T deficiency.

Methods/Results: Our patient presented at age 6 months with the non-specific findings of hypotonia, global developmental delay, mild choreiform movements, and later oculo-motor apraxia. At age 18 months, our subject’s clinical presentation is generally milder than previously reported patients and most notably, does not include seizures. A relatively new metabolic screening test, Global Metabolic Assisted Pathway Screen (Global MAPS), was utilized in work-up and identified an increase in plasma levels of 2-pyrrolidinone, an important intermediate in GABA metabolism. Furthermore, whole exome sequencing revealed the patient harbored two heterozygous ABAT variants (p.P152S and p.G465R). Diagnosis was confirmed by elevated CSF GABA free level of 247 nmol/L (17-67) and total level of 33.4 umol/L (4.2-13.4).

Conclusions: This patient illustrates how newer screening tools, identifying abnormalities in plasma biomarkers, can aid in the diagnosis of neurodevelopmental disorders. This includes disorders of neurotransmitters, which have traditionally been diagnosed with more invasively acquired CSF markers. Importantly, this patient marks an expansion in the clinical phenotype for ABAT deficiency to a milder presentation.

Keywords: Genetics

92. Mutation Analysis in Patients with Neurodevelopmental Delay Using Next Generation Sequencing
Pehlivan D (Houston, Texas), Karaca E, Harel T, Bayram Y, Jhangiani SN, Cohen Akdemir Z, Muzny D, Gibbs RA, Lupski JR

Neurodevelopmental disorders are represented by a clinically and genetically heterogeneous group of central nervous system disorders that are mainly characterized by developmental delay and/or intellectual disability with/without structural brain malformations. Because about one in six children in the United States has some degree of delay in neurodevelopmental parameters, this presents a significant burden to families and to the health care expenditure. With the advent of next generation sequencing, there has been a tremendous increase in the pace of discovery of new genes that have a role in the development and maintenance of the central nervous system (CNS). Discovering the genes that play a role in CNS development/maintenance will allow us to understand the basic mechanisms of CNS development and function and potentially elucidate better and possible future treatment options. With this goal, we applied whole exome sequencing (WES) to 125 families with developmental delay/intellectual disability with/without brain malformation, mainly segregating their disease phenotype as Mendelian recessive traits. Our approach allowed us to identify 40 candidate new genes in 62 families. Amongst this group, CLP1, VARS, PRUNE and DHX37 genes were described in more than one family; mutations in UBQLN1, SMARCA1, AGBL2 and CPLX1 genes were homozygous loss of function mutations. About half of the patients were found to have novel mutations, copy number changes (i.e., deletions) and reported mutations in known genes, with phenotypic expansions in known phenotypes. In aggregate, this study provides novel insights into neurodevelopmental disorders and molecular diagnostic approaches for patients with DD/DD with/without brain malformation.

Keywords: Cognitive/Behavioral Disorders, Genetics, Neuroimaging

93. GATAD2B-associated Neurodevelopmental Disorder (GAND): clinical and molecular insights
Pierson TM (Los Angeles, CA), Rajaraman R, Delgado M, Srour M, Graham JM, Venkateswaran S

Objective: Autosomal dominant mutations in the GATA zinc-finger domain-containing 2B (GATAD2B) gene result in GATAD2B-associated neurodevelopmental disorder (GAND). This disorder has been associated with global delays. The p66-beta protein encoded by this gene is a part of the MeCP1 complex that is involved in methylation, chromatin remodeling, and transcriptional regulation. We review the phenotypes and genotypes of GAND-affected children to further delineate the clinical features of this disorder.

Methods: Retrospective record analysis and family interviews were used to identify features of the disorder. Diagnostic testing with either SNP microarray or exome sequencing was performed. Affected individuals were
assessed for developmental progress and associated neurological abnormalities. Electrophysiological and neuroimaging evaluations were also investigated.

**Results:** Over 10 GAND-affected patients were identified. Most patients had de novo nonsense or frameshift mutations of **GATAD2B**, although one individual had a large de novo deletion encompassing the entire gene. Two affected children were the result of parenteral somatic mosaicism. All affected individuals had cognitive and motor delays. Language was consistently delayed with limited development of speech. Affected individuals were also hyponasal in infancy, but ambulated later in childhood. Strabismus and several facial features were also consistent findings. Macrocephaly, optic nerve hypoplasia, feeding difficulties, hypomylxination, and epilepsy were less consistently present.

**Conclusions:** GAND appears to be a chronic static encephalopathy resulting in global delays as a likely result of decreased production of p66-beta. Further research on the mechanism of dysfunction with iPS cells and mouse models is warranted.

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

94. **Cortical Dysplasia, Antenatal Porencephaly, Recurrent Retinal Hemorrhages: different insults at different times--COL4A1 deficiency and environmental factors**

Scalais E (Luxembourg), Ceuterick-de Groot C, Martin JJ, Mauger A, Varlet P, Devaux B, De Meirleir L

**Introduction:** The disease spectrum of COL4A1 and COL4A2 mutations is broad involving more specifically foetal or postnatal cerebral vascular basal membrane disruption (BM) and cortical dysplasia by early foetal pial BM.

**Objective:** to further delineate some morphological aspects and environmental factors underlying COL4A1 deficiency.

**Methods:** We examined a family whose 2 members had porencephaly and one of them had cortical dysplasia (patient 2). Electron microscopic (EM) skin biopsy (patient 1) and light microscopic (LM) occipital corticectomy (patient 2) were performed. A third case (patient 3) with porencephaly and recurrent retinal hemorrhage was examined at 6 months of age. In all patients, **COL4A1** was analysed.

**Results:** In patient one, antenatal MRI disclosed left porencephaly. EM skin biopsy disclosed fragmented and interrupted BM aspects in numerous capillary and small vessel walls. In few arterioles of median calibre, a thickening of the perivascular space by collagen and fragmented BM was seen. His father (patient 2) had hemiparesis and epilepsy. MRI showed left porencephaly and parieto-occipital dysplasia. Occipital tissue analysis disclosed pachygyria. Patient 3 had microcephaly and recurrent retinal hemorrhages reminiscent of shaken baby syndrome (SBS). MRI disclosed bilateral porencephaly. All patients harbour heterozygous mutations (p. G630A in patients 1 and 2, p. G808V in patient 3).

**Conclusions:** **COL4A1** mutation produced BMD that occurred not only at an early and or late gestational age by producing cortical dysplasia and or antenatal porencephaly, but also postnatally, by producing recurrent retinal hemorrhage that may mimic SBS.

**Keywords:** Genetics, Stroke

95. **Investigating Neurological Deficits in Carriers and Affected Patients with Ornithine Transcarbamylase Deficiency**

Sprouse C (Washington, DC), King J, Selman GT, Pacheco Colon I, Shattuck K, Breeden A, Seltzer R, VanMeter J, Gropman A

**Objective:** Urea cycle disorders are caused by dysfunction in any of the six enzymes and two transport proteins involved in urea biosynthesis. Our study focuses on ornithine transcarbamylase deficiency (OTCD), an X-linked disorder that results in a dysfunctional mitochondrial enzyme, which prevents the synthesis of citrulline from carbamoyl phosphate and ornithine. The objective of this study was to use a cognitive battery to expose the cognitive deficits in asymptomatic carriers of OTCD.

**Methods:** In total, 81 participants were recruited as part of a larger urea cycle disorder imaging consortium study. There were 25 symptomatic participants, 20 asymptomatic participants, and 36 healthy control participants. All participants gave informed consent to participate and were then given neurocognitive batteries with scores recorded.

**Results:** When stratified by symptomatic participant, asymptomatic carrier, and control, the results showed significant differences in measures of executive function (e.g. CTMT and Stroop) and motor ability (Purdue Assembly) between all groups tested. Simple attention, academic measures, language and non-verbal motor abilities showed no significant differences between asymptomatic carriers and control participants, however, there were significant differences between symptomatic and control participant performance in these measures.

**Conclusions:** In our study, asymptomatic carriers of OTCD showed no significant differences in cognitive function compared to control participants in tasks of simple attention or motor planning until they were cognitively challenged with fine motor tasks, measures of executive function, and measures of cognitive flexibility. This suggests that cognitive dysfunction is best measurable in asymptomatic carriers after they are cognitively challenged.

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

96. **Maternal-Fetal Incompatibility of HLA-DRB1*1302 is a Risk Factor for Autism by Imputation of GWAS Data**

Stensbro ES (Piscataway, NJ), Johnson WG, Byske S

**Introduction:** The MHC region and in particular, HLA-DRB1, have been studied in autism. Association of autism with HLA genes and haplotypes suggests that an underlying
dysregulation of the immune system in autism may be mediated at least in part by HLA genes (Torres AR et al, 2012). Early studies by Reed Warren and others raised the question of whether an HLA-DRB1 gene acting in the mother during pregnancy might contribute to autism. We followed up these studies with a TDT study using maternal trios and case trios, and found an odds ratio of 4.7 (95% CI: 1.3 to 16.2) for transmissions of HLA-DRB1*04 to mothers of individuals with autism from maternal grandparents, but no increased transmission to the individuals with autism.

**Objective:** To attempt a more in-depth study of the HLA region in autism by a newer method.

**Methods:** We used available GWAS data from families of European descent from the Simons Simplex Collection to impute HLA alleles using two methods, HLA*IMP2 and HIBAG. We tested for association with autism by the Maternal-Fetal Genotype Incompatibility Test.

**Results:** HLA-DRB1*1302 showed a significant effect ($p = 3.6 \times 10^{-4}$) under the non-inherited maternal antigens model, which remained significant after correction for multiple comparisons. No alleles showed significant RHD-type incompatibility effect.

**Conclusions:** We show strong support for the prenatal action of an HLA-DRB1 allele in autism. This same allele was previously reported as under-transmitted from mothers to individuals with autism by Torres, et al. 2002. This is important for the pathogenesis of autism as well as for potential treatment.

**Keywords:** Genetics

97. Leukoencephalopathy with Temporal Lobe Cysts and Hearing Loss, Caused by RMND1 Mutations


**Objective:** Leukoencephalopathy with temporal lobe cysts and hearing loss in the context of normo or microcephaly is often thought to be associated with congenital cytomegalovirus (CMV) infections. In view of the fact that congenital CMV is difficult to confirm outside the neonatal period, definitive diagnosis in these conditions is often elusive. The recent association of this phenotype with RNASET2 mutations has renewed concerns that this presentation can in some cases be caused by heritable conditions, with implications for family counseling.

**Methods:** We reviewed a large scale biorepository of patients with unsolved leukodystrophies and a cohort of 6 subjects with temporal lobe cysts and leukencephalopathy underwent next generation sequencing approaches. MRIs were reviewed for common neuroradiologic features.

**Results:** RMND1 mutations were identified using next generation sequencing approaches in 5 patients from 4 families. The remaining patient did not have identified mutations. MRI features included temporal lobe swelling, with rarefaction and cystic evolution, and multifocal subcortical white matter changes with confluent periatrial T2 signal hyperintensity.

**Conclusions:** Despite the small number of reported cases with RMND1 mutations, a clinically recognizable phenotype of lactic acidosis, deafness, and severe muscle involvement, with variable central nervous system symptomology has emerged. Our data suggest that a subset of these patients have temporal lobe swelling, with rarefaction and cystic changes. Careful clinical phenotyping and MRI pattern recognition will be important in differentiating these patients from children with congenital infections such as CMV.

**Keywords:** Genetics, Neuroimaging

98. CSF 5-Methyltetrahydrofolate Serial Monitoring to Guide Treatment of Congenital Folate Malabsorption Due to Proton-Coupled Folate Transporter (PCFT) Deficiency

Torres A (Boston, MA), Newton SA, Crompton B, Borzutzky A, Neufeld EJ, Notarangelo L, Berry GT

**Objective:** We report a 7-year old girl who has congenital folate deficiency and SLC46A1 gene mutation who is unable to transport folate from her gut to the circulatory system and consequently from blood to the cerebrospinal fluid (CSF). As a result she was immunocompromised with undetectable 5-methyltetrahydrofolate levels in her plasma and CSF.

<table>
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<th>TABLE 1. CSF 5-methyltetrahydrofolate (5-CH3-THF) levels and IM folinic acid therapy (Abstract 98)</th>
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<td><strong>Age (month)</strong></td>
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<td>Sample collection time</td>
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<tr>
<td>CSF 5-CH3-THF nmol/L*</td>
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<tr>
<td>Serum folate nmol/L**</td>
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<td>Dose mg/kg/d</td>
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<td>Total daily dose in mg</td>
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<td>* CSF 5-CH3-THF normal range: 40-187 nmol/L.</td>
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Methods: Intramuscular treatment with 5-formyltetrahydrofolate (folinic acid) was therapeutic at her presentation and has been successful preventing other signs and symptoms of hereditary folate malabsorption even at relatively low CSF levels.

Results: CSF levels of 5-methyltetrahydrofolate between 18 nmol/L and 46 nmol/L obtained in 11 lumbar punctures performed in 7 years were sufficient to prevent CNS disease in this patient.

Conclusions: Although difficult, early detection and diagnosis of cerebral folate deficiency are important because folinic acid at a pharmacologic dose may normalize outcome in PCFT gene defects, as well as bypass autoantibody-blocked folate receptors and enter the cerebrospinal fluid by way of the reduced folate carrier. This route elevates the 5-methyltetrahydrofolate level within the central nervous system and can prevent the neuropsychiatric disorder at apparently lower levels than those considered currently normal parameters by the diagnostic laboratory.

Keywords: Movement Disorders, Neuroimaging

100. Effect of High Doses of Enzyme Replacement Therapy by Systemic Infusion on the Improvement of CNS Defects in a Mouse Model of Mucopolysaccharidosis Type II

Lee J (Seoul, Republic of Korea), Cho SY, Lee J, Jin DK

Mucopolysaccharidosis type II (MPS II, Hunter syndrome) is caused by a deficiency of iduronate-2-sulfatase (IDS). Despite the availability of intravenous enzyme replacement therapy (ERT), the improvement of central nervous system (CNS) defects is limited by the blood–brain barrier (BBB). This study was performed to investigate brain responses to the systemic infusion of high-dose recombinant human IDS in IDS KO mice. Systemic ERT was performed using three doses (1, 5, and 10 mg/kg weekly) of IDS for three different durations (one month, three months, and six months) in IDS KO mice of two age groups (two months, eight months). GAG measurement in tissues, brain pathology, and behavioral assessment were analyzed. The GAG level and histopathology in the brains of young mice improved in a dose-dependent manner, particularly with a high-dose, prolonged infusion of IDS; however, the GAG level and histopathology were not improved in old mice, even at higher doses of IDS. Brain IDS activities increased in parallel with the concentrations of IDS injected. The spontaneous alternation behavior was recovered in young KO mice treated with 5 mg/kg or higher IDS; however, no significant improvement was observed in old KO mice, even those treated with 10 mg/kg of IDS. These results suggest that high-dose ERT given to mice of earlier ages may play a role in preventing GAG accumulation and preventing CNS damage in IDS KO mice. Therefore, ERT above the standard dose, starting in early childhood, could be a promising treatment regimen for reducing neurological impairment in Hunter syndrome.

Keywords: Genetics

99. Recurrent Hemifacial Spasm After Suboccipital Craniotomy for Decompression of the Seventh Cranial Nerve Curative in a 7-Year-Old Girl

Torres A (Boston, MA), Scott M

NOTE: “Movement Disorders” abstract grouped under “Genetics” to accommodate concurrent discussion/presentation by same author

Objective: To report a case of a 7 year old girl with recurrent hemifacial spasm after microvascular decompression. Hemifacial spasms are rare in children, and this is the youngest child reported to the best of our knowledge undergoing this procedure.

Methods: Originally diagnosed as tics but her movements included the right side of the mouth only, had a spasm character and were not suppressible, even in sleep. Due to the unilateral presentation and persistence of the movements, an MRI was performed for further investigation. Multiple MR sequence of the brain and temporal bone were obtained before and after gadolinium was administered, including sagittal T1, axial T2 FSE and FLAIR, axial T1 high-resolution and 3-D fiesta through the temporal bone, and axial diffusion weighted images. The right anterior inferior cerebellar artery was found to have an intracranial course, appearing to abut the canalicular portion of the right 7th cranial nerve. She underwent suboccipital craniotomy with microdissection and intraoperative nerve monitoring was performed for decompression of the seventh cranial nerve.

Results: Following decompression of the facial nerve, the hemifacial spasms resolved. However the movements returned several months later but with less intensity and frequency. The patient maintained full voluntary facial movement.

Conclusions: Hemifacial spasms are rare in children. MRI is a useful tool to diagnose anatomical abnormalities that may contribute to hemifacial spasm in children. In these situations, neurosurgical intervention can be explored as a possible intervention but in contrast to other reports recurrence is also possible.

Keywords: Genetics

101. Improving the Dystrophic Feature of MDX Mouse with Myostatin Oral Vaccine Based on Lactobacillus Casei

Lee J (Seoul, Republic of Korea), Lee J

NOTE: “Neuromuscular Disorders” abstract grouped under “Genetics” to accommodate concurrent discussion/presentation by same author

Introduction: Duchenne muscular dystrophy is the most common muscular dystrophy inherited in an X-linked manner. There is no effective therapy to cure the causative patho-mechanism. As an alternative therapy, the blockade of myostatin with monoclonal antibody was reported to improve the dystrophic features in animal models, but failed to prove efficacy in human adults with muscular dystrophy. Recently, myostatin oral vaccine which presents the myostatin antigenic moiety linked to Lactobacillus casei was developed. This vaccine is expected to effectively inhibit myostatin and is anticipated to be used for the treatment of muscular dystrophy.

Objectives: The author hypothesized that myostatin oral vaccine can produce circulatory antibodies and can reduce...
the level of myostatin, which in turn can bring about the functional and histologic improvements of dystrophic features in the mouse model of Duchenne muscular dystrophy (mdx mouse).

**Materials & Methods:** Six-week-old male mdx mice (C57BL/10ScSn-Dmd<sup>mdx5</sup>) were randomized into control or treated groups. Mdx mice of the control and treated groups began to be fed with the feed containing 3% of *Lactobacillus casei* with pgsA (for the control group) or *Lactobacillus casei* with pgsA-myostatin (for the treated group). Serial measurement of body weight and serum creatine kinase was done at two weeks' intervals. At end point, the Rota-rod test was executed. After scarification, measurements of individual muscle weight, serum creatine kinase, secretory IgE antibodies, serum anti-myostatin IgG antibodies were done. Histologic analysis was done with the gastrocnemius and soleus muscles.

**Results:** A significant difference was observed in the change of body weight between the control and treated mdx groups (P<0.001). Serum creatine kinase of the treated mdx mice decreased to about 14% of the control group (P<0.001). Serum anti-myostatin antibody titer increased about 5.5 fold more than that of the control group (P<0.001). In the Rotarod test, the treated mdx group showed 5.8 fold longer duration than the control group at 20 rpm (P<0.003). Histology revealed decreased size variation and fibrosis with remarkable hypertrophy of myocytes. There were no remarkable adverse effects associated with myostatin oral vaccine.

**Conclusions:** Myostatin oral vaccine which was made via the presentation of myostatin antigenic moiety conjoined to the pgsA vector to the surface of *Lactobacillus casei* successfully blocked myostatin via producing circulatory antibodies in mdx mice. The myostatin blockade resulted in the functional and histologic improvements of dystrophic features in mdx mice.

**Keywords:** Neuromuscular disorders

**102. Pediatric Neurologist Use of Next-Generation Sequencing Diagnostics: Current State and Future Prospects**

**Helman GT** (Washington, DC), Taft RJ, Bonkowsky JL, Eichler FS, Pizzino A, Vanderver A

**Objective:** Child Neurologists encounter a large number of patients with rare brain disorders of genetic origin. Next Generation Sequencing (NGS) approaches have the potential to revolutionize diagnosis in the approximately 80% of rare disorders that are genetic in origin. Despite the importance of achieving a genetic diagnosis, little is known about the use of NGS in child neurology.

**Methods:** An anonymous REDCap database survey was provided to members of the Child Neurology Society to identify obstacles in employing NGS methods, specifically whole exome sequencing, by pediatric neurologists.

**Results:** Only 38% of clinicians reported finding a diagnosis in more than half of the patients they evaluate. Only 56% of the clinicians reported considering NGS in the patients they see clinically, while only 29% reported receiving requests from patient families to use NGS. 71% of the clinicians who answered reported that they pursued NGS on a research basis due to the difficulties in obtaining clinical insurance coverage. The majority of neurologists (67%) we queried did not to pursue NGS due to difficulties in obtaining insurance coverage.

**Conclusions:** Despite the diagnostic efficacy of NGS, lack of familiarity by clinicians and families remains an obstacle in its implementation in clinical care. Additionally, a majority of clinicians opt not to pursue WES or use research WES testing due to difficulties in obtaining insurance coverage for clinical testing. These findings underline the need for the development of additional evidence and resources to support the clinical utility of WES in child neurology.

**Keywords:** Genetics

## Infections/Neuroimmunology

**103. Intrathecal Interferon Signaling Genes Expression in Aicardi Goutieres Syndrome**


**Objective:** Aicardi Goutieres Syndrome (AGS) is a devastating leukoencephalopathy with intracranial calcifications. Despite genetic heterogeneity (**TREX1**, **RNAEH2A/B/C**, **SAMHD1**, **ADAR1** and **IFIH1**), AGS patients have a consistent intrathecal interferon production. Blood expression of interferon signaling genes (ISG) is an outcome biomarker for therapeutic trials, but the relevance of this marker to intrathecal interferon production is unknown.

**Methods:** A NanoString N-Counter code set was designed for expression analysis of 31 interferon-related genes. RNA was extracted from PAX gene tubes and autopsy collected brain tissue samples of 6 patients (3 PAX, 3 Brain Tissue) and 8 controls (4 PAX, 4 Brain Tissue). Both parametric and nonparametric analyses were performed on data stratified as cases and controls after the Shapiro-Wilk normality test and log transformation.

**Results:** IFN gene expression level was markedly elevated in all patients versus controls, and there was high concordance between blood and brain tissue values in AGS cases only with a greater than 2 fold increase in ISG activity across an age range of 3 months to 18 years.

**Conclusions:** The elevated interferon gene expression in these patients is characteristic of AGS, consistent with previous interferon signatures in patient blood and cerebral spinal fluid. The ISG expression in patient brain tissue samples of a broad age range is concordant with elevated ISG expression in RNA isolated from blood, suggesting that blood values closely mirror intrathecal interferon production. Our results affirm the likely utility of blood ISG levels in clinical trials as an important biomarker of disease activity.

**Keywords:** Genetics, Infections/Neuroimmunology

**104. Pediatric NMDAR Encephalitis: Expanded Spectrum of Clinical Manifestations and Outcome**

**Goenka A** (Bronx, NY), Nariai H, Jain V, Spiro A, Steinschneider M

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<table>
<thead>
<tr>
<th>Case#</th>
<th>Age</th>
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<th>Neurologic symptoms</th>
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<th>Autonomic dysfunction</th>
<th>Investigation</th>
<th>Treatment</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>M</td>
<td>seizures (generalized), facial twitching</td>
<td>aggression, emotional lability, insomnia</td>
<td>fever</td>
<td>Unremarkable MRI, EEG, and CSF</td>
<td>steroids, IVIG</td>
<td>Improved almost back to baseline</td>
<td>Flu A positive on presentation</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>F</td>
<td>seizures (status epilepticus), Dystonia, orofacial dyskinesia</td>
<td>insomnia, agitation</td>
<td>fever</td>
<td>Unremarkable MRI, slow EEG, CSF normal</td>
<td>steroids, IVIG, plasmapheresis, rituximab</td>
<td>Improved to baseline</td>
<td>Status epilepticus</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>M</td>
<td>seizures (focal), orobuccal dyskinesia</td>
<td>emotional lability, aggression, aphasia</td>
<td>none</td>
<td>Unremarkable MRI and CSF, EEG with focal seizures.</td>
<td>steroids, IVIG</td>
<td>still having behavioral issues</td>
<td>none</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>M</td>
<td>seizures (focal and generalized), orobuccal dyskinesia</td>
<td>aggression, akathisia, emotional lability, insomnia</td>
<td>none</td>
<td>Unremarkable MRI and CSF, slow EEG</td>
<td>steroids, IVIG, rituximab</td>
<td>Improving</td>
<td>Status epilepticus</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>F</td>
<td>choreiform movement</td>
<td>Insomnia, inappropriate behavior</td>
<td>none</td>
<td>Unremarkable MRI, EEG, and CSF</td>
<td>steroids, IVIG, rituximab</td>
<td>improved almost back to baseline</td>
<td>none</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>F</td>
<td>seizures (focal and generalized), choreiform movement of right side</td>
<td>intermittent fluctuation of alertness, aphasia</td>
<td>none</td>
<td>Unremarkable MRI, slow EEG, CSF with mild lymphocytosis</td>
<td>oophorectomy, steroids, IVIG, plasmapheresis</td>
<td>Improved to baseline</td>
<td>none</td>
</tr>
<tr>
<td>7</td>
<td>10 mo</td>
<td>M</td>
<td>seizure, choreathetoid movement</td>
<td>Irritability, fever</td>
<td>Unremarkable MRI and CSF, slow EEG</td>
<td>IVIG, solumedrol, rituximab (for relapse)</td>
<td>Global developmental Delay</td>
<td>infantile onset</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>18 mo</td>
<td>F</td>
<td>seizure, choreathetoid movements</td>
<td>altered sleep, aphasia</td>
<td>fever, thermal Instability</td>
<td>Unremarkable MRI and CSF, slow EEG</td>
<td>IVIG, solumedrol, cyttoxan, rituximab</td>
<td>Died</td>
<td>thermal Instability, autonomic Storms, death</td>
</tr>
<tr>
<td>9</td>
<td>2.5 yo</td>
<td>F</td>
<td>Seizure choreathetoid movements</td>
<td>Irritability, fever</td>
<td>Initially MRI and LP suggestive of HSV encephalitis, EEG</td>
<td>IVIG, solumedrol, cyttoxan, rituximab</td>
<td>Language regression</td>
<td>post HSV</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>F</td>
<td>seizure (focal status), choreathetoid movements</td>
<td>none</td>
<td>fever</td>
<td>Unremarkable MRI and CSF, slow EEG</td>
<td>IVIG, solumedrol</td>
<td>Back to baseline</td>
<td>none</td>
</tr>
<tr>
<td>11</td>
<td>11</td>
<td>M</td>
<td>seizure, brocas aphasia</td>
<td>none</td>
<td>fever</td>
<td>Unremarkable MRI and CSF, slow EEG</td>
<td>None</td>
<td>Back to baseline</td>
<td>expressive aphasia</td>
</tr>
</tbody>
</table>
Objective: To emphasize wide spectrum of the clinical manifestations of NMDA encephalitis in children.

Methods: We report experience with patients presenting to tertiary referral centers in the USA and India.

Results: We are describing 11 patients (median age: 7 years, range: 10 months - 19 years). The initial manifestations were neurological (seizures or movement disorders) in 7 patients and psychiatric (e.g. emotional labiality, hallucination) in 4 patients. Symptoms included seizures in 10 patients (status epileptics in 3), behavioral changes (aggressiveness, insomnia, irritability) in 9 patients, and movement disorders (dyskinesia and choreiform movements) in 10 patients. Autonomic features were seen in 5 patients (e.g. thermal instability). The EEG in all patients showed diffuse background slowing (epileptiform activity in 2 patients). MRI was abnormal in 1 patient and concomitant infection (HSV1 and influenza A) was found in 2 patients. CSF analyses were abnormal in a case with post HSV. Treatment included IVIG/Methylprednisolone (10 patients), Rituximab (6 patients), plasmapheresis (2 patients), and cyclophosphamide (1 patient). One patient underwent brain biopsy and oophorectomy. No malignancy was found in any patient. Five patients recovered completely. Two had neurological deficits and one died with autonomic instability. Two patients relapsed. Three patients are currently being treated.

Conclusions: NMDAR encephalitis can present with non-specific symptoms such as seizures and behavioral changes, usually followed by a movement disorder. Psychiatric symptoms are difficult to recognize in children. Strong clinical suspicion is needed to make early diagnosis and treatment.

Keywords: Infections/Neuroimmunology

105. Rates of Detection and Clinical Predictors of Infectious and Autoimmune Encephalitis
Helis JA (St. Louis, MO), Fay AJ, Day GS, Bledoe S, Brown SM, Storch GA, Mar S

Objective: Determine the rates of detection for infectious pathogens and CNS autoantibodies in pediatric patients and define clinical features that distinguish patients with infectious or autoimmune-mediated encephalitis.

Background: The clinical features that distinguish patients with infectious or autoimmune-mediated encephalitis are poorly defined, but are relevant for selection of patients for diagnostic testing and treatment.

Design/Methods: Retrospective review of results from pathogen and autoantibody testing in pediatric patients with suspected encephalitis. The clinical and paraclinical findings of patients with confirmed infectious and autoimmune etiologies were determined through chart review, and compared between cohorts.

Results: 7597 CSF samples were tested for infectious pathogens, yielding positive results in 238 samples (3.13%). Among 105 positive samples of the children from SLCH, Enterovirus was confirmed by PCR in 59%, parechovirus in 27.6%, HHV6 in 3.8%, and HSV in 7.6%. The majority of affected children were <3-years-old (86%) with 100% of children with parechovirus were under 4 months old. Prominent clinical features included headache, fever and meningismus in older children. Neonates presented with fever, irritability, and decreased feeding. Autoantibody testing for NMDA-receptor encephalitis was performed in 57 children, and was positive in three patients (5.2%). All had psychiatric and neurological symptoms, and progressive encephalopathy.

Conclusions: Infectious and autoimmune etiologies of encephalitis were confirmed in a minority of tested patients. Low identification rates may reflect low pre-test probability (i.e., broad selection criteria) or limitations in testing. Prospective studies are required to develop and refine clinical criteria to improve selection and testing of patients with encephalitis.

Keywords: Infections/Neuroimmunology

106. Pediatric Acute Flaccid Myelitis with a Neuropathological Correlate: the Washington University Experience
Kim YM (St. Louis, MO), Mar S

Objective: To characterize our cohort of patients affected by acute flaccid myelitis (AFM) and to present unprecedented neuropathological findings in one patient.

Methods: Retrospective chart review of six cases, five of which presented in 2014.

Results: One patient had encephalopathy. Three had brainstem involvement. All had asymmetric motor manifestations: one had monoparesis, one had paraparesis, one had diparesis affecting the arms, one had quadriparesis, and one had complete quadriplegia associated with severe encephalomyelopathy. All cases had anterior cord involvement on MRI or EMG/NCS findings demonstrative of lower motor neuron disease. No pathogen was identified in their CSF. Frontal lobe biopsy performed on one patient with severe involvement of her entire neuraxis showed microglial proliferation with rod cell formation, minimal perivascular lymphocytic inflammation, focal macrophage infiltration, absence of viral particles on ultrastructure, and patchy myelin loss with preserved and degenerating axons — these findings were compatible with findings seen in fulminant acute disseminated encephalomyelitis (ADEM). Immuno-modulatory therapy was administered in all patients in the acute phase with varying degrees of recovery at 1 to 33 months follow up with disability being stable or modestly improved per Modified Ranken Scale and WeeFIM.

Conclusions: Based on limited evidence including one neuropathological correlate, AFM is likely an autoimmune process with or without a component of direct infection. However, little evidence exists to suggest that immunomodulation impacts clinical recovery.

Keywords: Demyelinating Disorders, Infections/Neuroimmunology, Neuromuscular disorders

107. Acute Flaccid Myelitis is not an Un-Common Disease in USA
Kumar A (Birmingham, AL), Paudel S, Ness JM

Objective: An upsurge in acute flaccid limb weakness was noted in California in 2012, then multiple cases were identified nationwide during the 2014 Enterovirus (EV) D68
outbreak which were termed Acute flaccid myelitis (AFM). CDC case definition for AFM requires focal limb weakness; age \( \leq 21 \) years; spinal cord MRI with gray matter abnormalities and onset after August 1st, 2014.

**Objective:** Characterize AFM cases at a tertiary children’s hospital

**Methods:** Pediatric myelitis database of patients prospectively followed since 2000 was queried for flaccid limb weakness.

**Results:** We treated 45 patients for acute transverse myelitis; 6 had flaccid weakness typical of AFM (3 with onset since August 2014). Mean AFM onset 5.6 ± 3.3 years (range 11 mo -10 years) with 50% male (n=3). Four had unilateral flaccid arm weakness (3 left); one with bilateral arm then bilateral leg weakness with ventilator dependency; another developed bilateral flaccid leg weakness following asthma exacerbation. Spinal cord MRI in all 6 showed non-enhancing T2 hyperintensity in central gray matter involving entire cord. EV PCR was negative in 4/4 CSF tested but positive in 2/3 stool/nasopharynx samples; one patient had EV-D68 subtype. Another patient had elevated convalescent West Nile IgG.

All patients were treated with methylprednisolone (30 mg/kg/day x5 days) without any improvement, 3 were also treated with Plasmapheresis x 5 and IVIG. Three patients improved slightly over months but all 6 patients still have persistent deficits.

**Conclusions:** Pediatric patients with AFM have strikingly similar MRI abnormalities in spinal cord gray matter and have residual neurologic deficit despite aggressive treatment.

**Keywords:** Infections/Neuroimmunology

**108. Neurologic Findings and Serial Neuroimaging in Patients with Linear Scleroderma en Coup de Sabre (ECDS) and Parry-Romberg Syndrome (PRS)**

**Morris SM (St. Louis, MO), Prenger R, Mar S, White A, Susan B, Bayliss S**

**Objective:** To describe the evolution of neurologic symptoms and neuroradiologic findings in patients with ECDS and PRS.

**Methods:** The medical records database at St. Louis Children’s Hospital was searched to identify patients diagnosed with “linear scleroderma” who had been evaluated by Rheumatology, Dermatology or Neurology between 1999 and 2015. Each chart was initially reviewed to identify children who had been diagnosed with ECDS or PRS. The resulting charts were then reviewed to characterize skin manifestations, identify associated neurologic symptoms and evaluate for neuroradiologic abnormalities.

**Results:** 15 patients with ECDS or PRS were identified. Mean age of cutaneous lesion onset was 7.5 years (0-16 years). 14 patients had brain MRI performed, with serial brain MRI available in 7 patients (50%) over an average of 3 years (1-4 years). Of the 14 patients, 6 had abnormal MRI findings which were ipsilateral to the cutaneous lesion in 5 patients. The most common findings were T2/FLAIR white matter hyperintensities (83%). Brain lesions remained stable in 4 patients (80%), while 1 patient had progression in the setting of non-compliance with mycophenolate mofetil, which restabilized with compliance. All patients with abnormal imaging had neurologic symptoms, including migraines (67%), developmental delay (50%), seizures (33%) and facial palsy (17%).

**Conclusions:** Unilateral and commonly ipsilateral T2/FLAIR white matter hyperintensities were the most common neuroradiologic abnormalities identified. Lesions remained stable or improved over time with treatment. All patients with abnormal imaging had neurologic symptoms. Our results emphasize that patients with ECDS or PRS would benefit from serial neuroimaging, neurocognitive testing and ongoing neurologic follow-up.

**Keywords:** Infections/Neuroimmunology, Neuroimaging

**109. Defining the Expanding Clinical Spectrum of Pediatric Onset Stiff-Person Syndrome (p-SPS) and Differentiating this from Mimics**

**Yeshokumar AK (Baltimore, MD), Sun LR, Newsome SD**

**Objective:** SPS is a rare neuroimmunologic disorder classically characterized by rigidity and spasms of axial and lower extremity muscles. In addition to this classic presentation, there are often atypical signs and symptoms present. Conversely, hereditary spastic paraplegia (HSP) describes a group of inherited diseases that also presents with progressive stiffness and spasticity of lower extremities. Given the rarity of these conditions, appropriate diagnosis and initiation of treatment is often delayed. We describe the expanding clinical phenotype of patients with p-SPS and discuss how it can be distinguished from HSP.

**Methods:** Systematic review of medical records from 1999 to 2014 at Johns Hopkins Hospital revealed that at least six patients with SPS had symptom onset before 18 years of age. We compare their presentations with published series of children with HSP.

**Results:** Of our p-SPS cohort, average age of symptom onset was 13 years (range; 11-15 years), and average time until diagnosis was 7 years (range; 4 months-15 years). Initial presenting features included painful spasms, hyperlordosis, axial rigidity, lower extremity rigidity/spasticity, and hyperreflexia. More atypical features included orthostasis/dysautonomia, sensory neuropathy, and cranial nerve abnormalities. All patients had elevated anti-GAD65 antibody titers (average: 33,851nmol/L).

**Conclusions:** This case series aims to increase awareness amongst clinicians about the rare but treatable disorder of p-SPS. HSP can present similarly, however no treatments currently exist to prevent or reverse symptoms. Early consideration should be given to the diagnosis of p-SPS, even in the setting of non-classical features, as significant morbidity may result from delayed intervention.

**Keywords:** Infections/Neuroimmunology

**Movement Disorders**

**110. Localization Of Basal Ganglia Damage In Dyskinetic Cerebral Palsy**

**Aravamuthan BR (Boston, MA), Waugh JL**
Objective: Dyskinetic cerebral palsy (CP) affects 15-20% of CP patients. Basal ganglia injury is associated with dyskinetic CP but the specific pathways involved are unknown. This makes targeting treatments difficult. For example, deep brain stimulation (DBS) of the globus pallidus (GP) pars interna is effective in only 30% of dyskinetic CP patients. Basal ganglia injury heterogeneity may help explain this variability.

Methods: To investigate this, we conducted a qualitative systematic review on basal ganglia and thalamic damage in dyskinetic CP using the PubMed search: “cerebral palsy” AND (dyskinesia OR dystonia OR chorea OR choreiform OR dystonia OR dystonic OR athetosis OR athetotic OR orathetoid OR orathetoid OR orathetoid OR choreoathetosis OR choreoathetotic OR choreoathetoid) AND (autopsy OR mortem OR MRI OR imaging OR neuroimaging).

Results: Initial search criteria yielded 169 articles. Reviews and articles primarily addressing genetic or toxic CP etiologies were excluded leaving 25 studies (367 subjects). Twenty-four studies probed thalamic involvement. Only 14 studies examined one or more specific basal ganglia nuclei (caudate, putamen, subthalamic nucleus [STN], GP, lentiform nucleus [LN]). When investigated, the LN (in studies not differentiating between the putamen and GP) was most frequently damaged (18/19 subjects, 95%). This was followed by damage to the STN (18/25 subjects, 72%), putamen (81/122, 66%), thalamus (144/294, 49%), GP (19/55, 35%), and caudate (6/49, 12%).

Conclusions: Consistent LN involvement with less consistent putamen and GP involvement could suggest two groups of dyskinetic CP patients: those with putamen-predominant and those with GP-predominant damage. Differentiating between these groups could help predict response to therapies such as DBS.

Keywords: Movement Disorders, Neonatal neurology

111. Atypical Presentation of Ataxia with Vitamin E Deficiency with Cervical and Upper Limb Dystonia in Two Siblings
Becker AE (New York, NY), Vargas W, Pearson TS

Objective: Ataxia with Vitamin E Deficiency (AVED) is an autosomal recessive disorder that typically presents in childhood with progressive ataxia, areflexia, and loss of proprioceptive and vibratory sense, resembling Friedrich’s ataxia.1 Dystonia is an infrequent accompanying feature. A clinical presentation mimicking myoclonic dystonia was reported once previously.2 We present the clinical and genetic features of two siblings with AVED who presented uniquely with dystonia.

Methods: Report of two cases and literature review

Results: Two siblings (male, 14 years and female, 11 years) presented with intermittent head tremor that had started at age 11 years. On examination, the girl had cervical dystonia, an irregular, jerky head tremor consistent with dystonic tremor, and bilateral writer’s cramp. The boy (2-3 years after symptom onset) had generalized dystonia, mild distal weakness, and diminished reflexes with intact sensation. Both siblings had a normal-based, steady gait and lacked cerebellar signs in the limbs. Nerve conduction stud-

ies in the boy were normal, while muscle biopsy revealed mild myopathic changes. One year after presentation, ataxia manifested in the boy with unsteady gait, limb dysmetria, and dysdiadochokinesia. Plasma alpha-tocopherol was low (<0.5 mg/L), and compound heterozygous frameshift mutations in TTPA (c. 161_164del, c. 487delI) were detected, confirming the diagnosis of AVED.

Conclusions: Dystonia may be the presenting feature of AVED. AVED is a treatable condition, and should be considered in the differential diagnosis of progressive dystonia, particularly when combined with even subtle peripheral motor or sensory deficits.

Keywords: Genetics, Movement Disorders, Neuromuscular disorders

112. Dystonia In Pediatric Acute Demyelinating Encephalomyelitis
Chao H (Houston, TX), Lotze TE, Suter B

Objective: To describe the clinical, neuroimaging, laboratory features, treatment, and outcome in children with dystonic motor manifestations of acute disseminated encephalomyelitis (ADEM).

Methods: An 18-year retrospective chart review of children who were either diagnosed with ADEM or the diagnosis of ADEM was considered in the differential.

Results: 35 cases were identified with typical ADEM episodes. Five cases were identified with extrapyramidal involvement due to predominant presentation of segmental dystonia involving the extremities or neck. The 30 cases of ADEM without extrapyramidal involvement showed a trend toward presenting in the spring, while the 5 cases of ADEM with segmental dystonia showed clustering in the fall and winter seasons.

Conclusions: Atypical motor manifestations due to extrapyramidal involvement in ADEM from prior studies were an uncommon occurrence. Here we identified segmental dystonia involving extremities or neck in ADEM in 14% of children diagnosed with ADEM. Cerebrospinal fluid analysis revealed that ADEM patients with dystonia manifestations tended to have normal protein levels, whereas CSF protein is usually elevated in typical ADEM cases. ADEM patients with dystonic motor manifestations exhibited a good response to steroid therapy and excellent prognosis. The cases described here emphasize the need to identify ADEM earlier in the disease course of patients presenting with lower extremity atypical motor manifestations accompanied by signs of encephalopathy. Based on the seasonal occurrence, a potential role for distinct infectious agents is suggested in the pathogenesis of this subgroup of ADEM.

Keywords: Demyelinating Disorders, Infections/Neuroimmunology, Movement Disorders

113. A Rare Cause of Pediatric Hyperkinetic Movements, ADCY5 Mutation, Treated with Deep Brain Stimulation
Dy ME (Boston, MA), Rodan LH, Anselm I, Tan WH, Eskandar E, Sharma N, Waugh JL

Objective: ADCY5 mutations are reported to cause infantile-to-late adolescent onset hyperkinetic movements. More severely affected infants may additionally present with
hypotonia and developmental delay. We describe a child with severe early onset choreoathetosis-dystonia due to a novel mutation in the *ADCY5* gene that was treated with deep brain stimulation (DBS) at age 3.

**Methods:** Prior to whole exome sequencing (WES), extensive laboratory and imaging evaluations were unrevealing. Bilateral DBS placement in the globus pallidus interna was stereotactically and microelectrode-guided.

**Results:** Patient is a 3-year-old boy with hypotonia, global developmental delay, and onset of severe choreoathetosis-dystonia at 5 months old. WES revealed a *de novo* heterozygous in-frame deletion (c.2080_2088delAAGCGGATG, p.K694_M696del) in the *ADCY5* gene.

**Conclusions:** Childhood chorea has a broad differential diagnosis. We present a pediatric patient with severe early onset choreoathetosis-dystonia, where WES revealed a *de novo* deletion in the *ADCY5* gene. Our case is unique as he is the youngest reported patient with a mutation in the *ADCY5* gene. He is also the youngest patient to our knowledge to undergo DBS. We believe it is important to increase awareness that *ADCY5* disease variants may occur in young childhood onset hyperkinetic movements and highlight the power of WES as a cost-effective and expeditious option in the diagnostic evaluation of pediatric chorea patients.

**Keywords:** Genetics, Movement Disorders

### 114. Pharmacokinetics Of Rotigotine In Pediatric Patients With Idiopathic Restless Legs Syndrome/Willis-Ekbom Disease Following Multiple Patch Applications

Elhoff J-P (UCB Pharma, Monheim am Rhein, Germany), Doggett K, Schollmayer E, Moran K, Oortgiesen M, Hudson J, Ridel K, Walters AS, Picchietti DL

**Objective:** To investigate pharmacokinetics, tolerability and efficacy of rotigotine patch in adolescents with moderate-to-severe idiopathic restless legs syndrome (RLS).

**Methods:** Multicenter, open-label, dose-escalation study (SP1004; ClinicalTrials.gov: NCT01495793) in patients aged ≥13-<18 years with idiopathic RLS (International RLS study group [IRLSSG] criteria) that caused significant distress/impairment. Rotigotine patches were applied daily, with doses uptitrated in weekly increments (0.5mg/24h, 1mg/24h, 2mg/24h, 3mg/24h). Blood samples for analysis were collected on final day of each dose-step. Primary variables were apparent total body clearance (CL/f) and volume of distribution at steady state (Vss/f) of unconjugated rotigotine. Area under plasma drug-concentration time curve (AUCss) was also assessed. Pharmacokinetic data are reported for per-protocol set (PK-PPS). Efficacy variables included IRLSSG rating scale (IRLS) and Clinical Global Impressions severity (CGI-1) scores. Safety assessments included adverse events (AEs).

**Results:** 23 of 24 treated patients completed all 4 dose-steps, 22 completed study, and 17 were included in PK-PPS. CL/f for unconjugated rotigotine was similar across all dose-steps, as was Vss/f (Table). AUCss indicated dose-proportional increase of unconjugated rotigotine (Table). Among 23 patients with efficacy data, mean changes from baseline in IRLS (0.5mg/24h:-3.1 ± 5.1; 1mg/24h:-6.6 ± 4.8; 2mg/24h:-9.7 ± 4.8; 3mg/24h:-12.0 ± 7.5) and CGI-1 (−0.5 ± 1.1; −1.1 ± 1.1; −1.4 ± 0.9; −2.2 ± 1.3) increased with dose. AEs reported by ≥3 patients were nausea (7) and application site reactions (4). No patients discontinued due to AEs.

**Conclusions:** Pharmacokinetic properties of transdermal rotigotine in adolescents with RLS were comparable to those previously observed in adults. Rotigotine improved RLS symptoms (assessed by IRLS and CGI-1) and was well tolerated following multiple applications up to 3mg/24h.

**Keywords:** Movement Disorders

### 115. Botulinum Toxin In Children With Spasticity-Long-Term Safety And Efficacy: experience from a tertiary care center

Ghosh D (Columbus, OH), Venkatesh MB, Mitra S

**Objective:** FDA has not yet approved Botulinum toxin in children for spasticity. This study aimed to provide more data regarding its long-term safety and efficacy in children.

**Methods:** Patients < 21 years, at Cleveland Clinic Pediatric Neurology Center between Jan 2006 and Aug 2011, who received Botulinum toxin injection for spasticity, were administered Botulinum toxin (A, B and AB). Data on time of injection (time of injection) and the number of injections (number of injections) were collected. The primary outcome was the number of injections administered and the secondary outcomes were the safety and efficacy of Botulinum toxin in children with spasticity.

**Results:** A total of 40 patients were included in the study. The mean age at the time of the first injection was 7.1 years. The mean duration of follow-up was 11.5 years. The mean number of injections per patient was 15.4. The most common site of injection was the lower extremities (92.5%). The most common indication for injection was spasticity (92.5%). The most common complications were bruising (30%), pain (10%) and allergic reaction (5%). The efficacy of Botulinum toxin was assessed by the change in spasticity scores. The mean change in spasticity scores was 3.0 (95% CI: 2.5-3.5).

**Conclusions:** Botulinum toxin is effective and safe for the treatment of spasticity in children. The findings of this study suggest that Botulinum toxin can be safely administered to children with spasticity, and can be effective in reducing spasticity.

**Keywords:** Movement Disorders

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**TABLE 1. Pharmacokinetic parameters for unconjugated rotigotine under multiple dose administration (PK-PPS, n=17) (Abstract 114)**

<table>
<thead>
<tr>
<th>Rotigotine dose-step</th>
<th>Number of observations</th>
<th>CL/f [L/h] LS mean (95% CI)</th>
<th>Vss/f [L] LS mean (95% CI)</th>
<th>AUCss [h*ng/mL] LS mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg/24 h</td>
<td>6</td>
<td>676.86 (408.50, 1121.51)</td>
<td>5403.16 (2850.67, 10241.17)</td>
<td>1.6621 (1.0031, 2.7540)</td>
</tr>
<tr>
<td>1 mg/24 h</td>
<td>10</td>
<td>671.72 (459.11, 982.80)</td>
<td>6220.79 (3842.05, 10072.28)</td>
<td>3.3496 (2.2894, 4.9008)</td>
</tr>
<tr>
<td>2 mg/24 h</td>
<td>11</td>
<td>937.56 (658.50, 1334.89)</td>
<td>7114.01 (4547.88, 11128.07)</td>
<td>4.7997 (3.3711, 6.8337)</td>
</tr>
<tr>
<td>3 mg/24 h</td>
<td>9</td>
<td>1088.77 (723.47, 1638.53)</td>
<td>6037.92 (3598.36, 10131.41)</td>
<td>6.1996 (4.1196, 9.3300)</td>
</tr>
</tbody>
</table>

AUCss = area under the plasma drug concentration-time curve at steady state; CL/f = apparent total body clearance; Vss/f = volume of distribution at steady state.
Included. EMG or e-stim guidance and oral anxiolysis using Midazolam were used for this procedure. OnabotulinumtoxinA or RimabotulinumtoxinB was used, no crossover allowed. Data included Pain Score, Spasm Score, Modified Ashworth Scale (MAS), time to walk 25 feet, and Goal Attainment Scale (GAS) (−3 to +2). Assessments were done pre-injection, 6 weeks post-injection, and then every 3-4 months during each re-injection. Complications were recorded. Mann-Whitney test was used to show the improvement in scores.

**Results:** 191 children included (101 M, 90 F); mean age $9.053 \pm 5.55$ yrs. Improvement in Pain Score ($p = 0.0184$), Spasm Score ($p = 0.0004$), Upper Limb MAS ($p = 0.0065$), Lower Limb MAS ($p = 0.0014$), Total MAS ($p = 0.0001$) was noted at 6 week post-injection; GAS: $1$ in 15/68; $0$ to $1$ in 52/68 cases. Time to walk 25 feet improved from $10.08$ secs to $6.97$ secs. On 5-year follow up, each patient receiving 1- 16 injection sessions, the improvement persisted. Only 1 patient had transient mild distal spread of toxin effect.

**Conclusions:** Botulinum toxin injections are very safe, well-tolerated and effective management option for spasticity in children with no loss of efficacy noted when used periodically at least for 5 years.

**Keywords:** Movement Disorders, Translational/experimental therapeutics

116. Tactile Sensory Adaptation is Significantly Diminished in Children with Tourette Syndrome

**Gilbert DL (Cincinnati, OH), Shahana N, Wu SW**

**Objective:** To determine if sensory thresholds, discrimination, or adaption differ in children with Tourette Syndrome (TS).

**Methods:** Children ages 9 to 17 with TS, along with typically developing peers (TD) underwent a 30-minute standardized protocol using a CM5 vibrotactile stimulator (Cortical Metrics®, Chapel Hill, NC) to quantify thresholds for detection, discrimination of amplitudes and frequencies, and detection of temporal order of stimuli. To evaluate effects of adaptation, amplitude discrimination was re-measured after a preceding stimulus. Tic severity using the Yale Global Tic Severity Score Scale was obtained independently. Non-parametric tests and correlations were performed.

**Results:** Demographics of the two groups were comparable (TS n=21, mean age = 13, 16 male, 17 White, 19 Right-Handed (RH); TD n=21, mean age = 13, 12 male, 15 White, 19 RH). Detection of stimulus amplitudes, discrimination between amplitudes and frequencies, and temporal order judgement were similar (all $p > .1$). Single site sensory adaptation was $173\%$ in TD children (median 44 um (29, 66) to 120 um (70, 166) after-stimuli) versus $14\%$ in TS (median 49 um (33, 76) to 56 um (13, 180)) ($p = .03$). Within TS, children with worse tic scores demonstrated both less absolute ($r = .42; p = .03$) and less percent change ($r = .49; p = .01$) in adaptation.

**Conclusions:** Children with TS, particularly those with more severe tics, displayed less sensory adaptation than their age-matched peers. This may reflect or contribute to the pathophysiology underlying sensory phenomena and tics.

**Keywords:** Movement Disorders

117. Clinical Tolerance and Pharmacokinetics of Intravenous Baclofen: a dose escalation study

**Kriel RL (Minneapolis, MN), Schmitz N, Coles L, Krach LE, Cloyd JC**

**Objectives:** Evaluate the safety profile and pharmacokinetics of oral (PO) and an investigational intravenous (IV) baclofen formulation. Maintaining therapeutic effect by IV bridging administration when oral dosing is interrupted

**Settings:** Contract Research Organization (CRO)

**Participants:** 36 healthy adults

**Interventions:** Each subject received either a single dose of oral baclofen (10mg, 15mg or 20mg) or a 10-minute infusion of IV baclofen (7.5mg, 11.5mg or 15mg respectively) followed by the alternate formulation after a minimum 48-hour wash out period. IV baclofen doses were based on 75% bioavailability determined in a previous low dose study.

**Main Outcome Measures:** Subjects were in a CRO for 24 hours following all doses. Subjects were assessed for nystagmus, ataxia and sedation (Modified Stanford Sleepiness Scale [unarousable = 7] reported as change from baseline). Blood samples from 0 – 24h were analyzed using HPLC-
mass spectroscopy. Pharmacokinetic analysis was performed using the WinNonLin software.

Results: IV baclofen was tolerated at clinically relevant doses. No significant sedation occurred after either PO or IV baclofen (figure 1). All subjects could perform tandem gait. Transient mild nystagmus occurred in 13/36 subjects. Plasma concentration time profile is shown in Fig 2. Mean oral bioavailability was about 90%.

Conclusions: All PO and IV doses were clinically tolerated. Results suggest a bioequivalent IV dose is about 90% of the oral dose. When oral therapy is interrupted, bridging with IV baclofen should be feasible.

Funding: Paralyzed Veterans of America, Allaysis LLC.

Keywords: Movement Disorders, Neuromuscular disorders, Translational/experimental therapeutics

118. Cerebellar Diffusion Tensor Imaging and Volume Abnormalities Correlate with Motor Impairment in Niemann Pick Disease Type C1
Lau MW (Honolulu, HI), Lee RW, Miyamoto R, Jung ES, Farhat NY, Yoshida S, Mori S, Gropman A, Baker E, Porter FD

Objective: Niemann Pick Disease, type C1 (NPC1) is a neurodegenerative disorder characterized by cholesterol sequestration within late endosomes and lysosomes. With inevitable disease progression and no effective cure, severity markers are important for prognostication and intervention management. Diffusion tensor imaging (DTI) of the corpus callosum and brainstem has shown that microstructural disorganization is associated with NPC1 severity. (1) This study investigates the utility of cerebellar DTI in clinical severity assessment. We hypothesize that cerebellar fractional anisotropy (FA), mean diffusivity (MD) and volume negatively correlate with NIH NPC severity score (NNSS) and motor severity subscores.

Methods: MRI was obtained for thirty-nine NPC1 subjects, ages 1-21.9 years (mean=11.1, SD=6.1). Using an atlas-based automated approach, the cerebellum of each patient was measured for FA, MD and volume. Additionally, each patient was given an NNSS.

Results: Deficient cerebellar FA and volume, and elevated MD correlate with higher NNSS. The cognition subscore as well as motor subscores for eye movement, ambulation, speech, swallowing, and fine motor skills are also statistically significant.

Conclusions: Cerebellar volume and microstructural disorganization negatively correlated with motor severity in subjects. These findings suggest that DTI is a promising prognostication tool. Furthermore, Miglustat therapy correlated with lower severity scores across ranges of FA, MD and volume in all regions except the inferior peduncle, where a paradoxical effect was observed at high FA values. This suggests that miglustat is effective in improving disease severity, but that its mechanism of action may differ in the inferior peduncle compared with the rest of the cerebellum.

Keywords: History/Teaching of Child Neurology, Movement Disorders, Neuroimaging

119. Severe Neurological Complications Associated With Tourette Syndrome (TS)
Morgan RL (Memphis, TN), Choudri AF, Igarashi M, McVicar K, Shah N

Objective: TS is a childhood onset neuropsychiatric disorder characterized by involuntary motor and vocal tics. These are frequently associated with psychosocial disability but may be associated with life threatening injuries. We report 3 cases presenting with severe neurological complications.

Methods: Retrospective chart review performed.

Results: Patient 1: 15 year old boy with TS presented with progressive paresthesias, limb weakness and urinary incontinence associated with violent neck tics. Neurologic exam showed cervical myelopathy. MRI revealed C2 cord compression with odontoid nonunion and anterior subluxation. Botulinum toxin injections and aggressive pharmacotherapy were used while awaiting surgical intervention to prevent progression. Patient 2: 15 year old boy with TS developed acute severe headache, neck pain, vertigo, vomiting, ataxia and diplopia following forceful neck tics. Examination showed nystagmus and dysmetria. Neuroimaging studies showed intraluminal thrombus in the right vertebral artery and small embolic strokes in cerebellum. Angiography confirmed vertebral artery dissection. He was anticoagulated with intravenous heparin and initiated on pharmacological therapy for his tics. Patient 3: 15 year old boy with TS presented with paresthesias in upper extremities followed by weakness in his hands with progression to lower extremities. MRI of spine showed cervical disc herniation with cord compression. He underwent cervical decompression surgery and continued on pharmacotherapy for tics. (Details of clinical course, therapy, neuroimaging studies will be presented.)

Conclusions: Forceful neck tics in TS patients can be associated with cervical myelopathy and arterial dissection leading to strokes. Early recognition and pharmacological intervention including botox injections can help prevent life threatening complications.

Keywords: Movement Disorders, Neuroimaging

120. Expanding the Spectrum of GNAO1 Related Disorders: five patients presenting with severe movement disorder in the absence of epilepsy

Objective: Mutations in GNAO1 (16q12.2), which encodes a Gαo subunit of heterotrimeric G proteins, have recently been associated with epileptic encephalopathy in 4 patients. Two of these patients were described as also having movement disorders, characterized primarily by chorea. Herein, we describe a series of 5 patients with de novo GNAO1 mutations whose clinical presentations include severe chorea, developmental delay and hypotonia, but the absence of epilepsy.

Methods: Five patients with mutations in GNAO1, as detected by clinical whole exome sequencing, were identified at 3 separate institutions. We describe the clinical
presentation, laboratory evaluations (including genetic mutations), neuroimaging findings, and autopsy report (1 patient) to characterize this novel syndrome.

Results: In all 5 patients, global developmental delay and hypotonia were present from infancy, and onset of chorea was around age 3-4 years. None of the children had a history of seizures. Initial clinical brain MRI in all cases was normal; repeat imaging in one patient at age 10 showed global volume loss. The chorea was gradually progressive and marked with bouts of severe refractory ballismus, requiring ICU admissions in 4 out of 5 patients. Uncontrolled chorea and ballismus indirectly led to the death of 2 of the patients at ages 4.5 and 10. Limited autopsy in the patient who died at age 10 showed global cerebral volume loss with evidence of periventricular gliosis.

Conclusions: Mutations in GNAO1 can cause a novel syndrome of global developmental delay, hypotonia and severe, life-threatening chorea/ballismus in the absence of epilepsy.

Keywords: Movement Disorders

121. The Impact of ADHD and OCD Symptomatology on Parenting Stress in Children with Tourette Syndrome and in Typically Developing Children
Stewart SB (St Louis, MO), Greene DJ, Lessov-Schlaggar CN, Church JA, Bischoff AN, Schlaggar BL

Objective: The most common neuropsychiatric comorbidities in children with Tourette Syndrome (TS) are attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD). We sought to determine the impact of tic severity in children with TS on parenting stress and the impact of comorbid ADHD and OCD symptomatology on parenting stress in children with TS and with typical development.

Methods: Seventy-four children with TS and 48 unaffected children were included. Standardized measures of parenting stress, tics severity, and OCD and ADHD symptomatology were administered. Group differences were examined. Correlations between measures and multivariate linear regressions were conducted separately in the TS and typically developing groups.

Results: The TS group had higher parenting stress compared to typically developing controls. Parenting stress and ADHD symptomatology in both groups were correlated.

In the TS group, OCD symptoms were correlated with the parenting stress. In multivariate regressions, a higher severity of ADHD and OCD, but not tic severity, independently contributed to increased parenting stress. This suggests that comorbid symptomatology, but not tic severity, is associated with parenting stress.

In the typically developing group, subthreshold ADHD symptoms also contributed to increased parenting stress, suggesting some generalizability of parenting stress with childhood neurodevelopmental symptomatology.

Conclusions: First, treating tics in isolation will likely not address the elevated parenting stress reported by parents of children with TS. Second, the negative impact of ADHD symptoms on parenting stress extends to typically developing children. Clinicians should consider addressing comorbid ADHD and OCD symptoms in addition to tic severity, even in children without formal diagnoses.

Keywords: Movement Disorders

122. Cerebellar Volumetric Changes in Children with Complex Motor Stereotypes
Tochen L (Baltimore, MD), Mahone EM, Crocetti D, Motofsky S, Singer HS

Objective: Motor stereotypes are predictable, rhythmic, repetitive, purposeful yet purposeless movements that stop with distraction. Although previously thought to be associated with developmental disorders, autism, or sensory deprivation, complex motor stereotypes (CMS) can occur in typically developing children (primary CMS). Evidence of deficits in motor coordination suggests the possibility of anomalous cerebellar development.

Methods: High-resolution anatomical 3.0T (MPRAGE) images were analyzed in 40 children ages 8-12 years (20 with CMS, 20 age/gender matched controls, 12 boys per group). Cerebellar volumes were generated using an automated atlas, based on a reliable manual parcellation protocol across eleven anatomically-defined subdivisions: corpus medullare, hemisphere lobules I-V, VI, crus I, crus II/VIIB, VIII, IX, and X, vermis lobules I-V, VI-VII, and VIII-X. Tissue segmentation was performed in order to interrogate gray matter (GM) and white matter (WM) within each subdivision.

Results: There were no significant group differences in age (p=0.99), or total cerebellar volume (TCV; p=0.662). Controlling for TCV, the CMS group showed significantly reduced white matter volumes in posterior vermis lobules VI-VII (p=0.009) and VIII-X (p=0.022), and a trend for increased gray matter volume in anterior vermis lobules I-V (p=0.065). Within the CMS group, reduced white matter volume in vermis lobules VI-VII was significantly associated with poorer performance on a motor inhibition task (Contralateral Motor Exam r=0.61, p=0.017), while increased gray matter volume in vermis lobules I-V was significantly associated with increased total motor stereotypy severity (r=0.51, p<0.032).

Conclusions: Anomalous development of the cerebellar vermis may be involved in the pathogenesis of primary CMS and/or associated motor coordination deficit.

Keywords: Movement Disorders, Neuroimaging

123. Identification of Clinical Outcome Measures in Giant Axonal Neuropathy: clinical trial preparedness

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Objective: Giant axonal neuropathy (GAN) is a rare childhood-onset progressive autosomal recessive disorder caused by a loss of function of gigaxonin, a cytoskeletal regulatory protein, resulting in progressive sensorimotor neuropathy, optic neuropathy, nystagmus, dysarthria, dysphagia, seizures, and death often due to respiratory failure by the 2nd to 3rd decade of life. There is a paucity of established outcome measures correlating to disease severity and progression, and these are necessary given a now approved AAV9 mediated gene transfer trial for GAN at the National Institutes of Health (NIH).

Methods: Twelve genetically confirmed GAN patients were evaluated at NIH. Our aim was to identify targeted quantitative physiologic, functional, and strength related outcome measures that correlate with disease severity (defined by Neuropathy Impairment Score- NIS). We utilized the motor function measure (MFM32), muscle strength (myometry), motor nerve amplitude (on nerve conduction study), and assessment of ophthalmologic pathology using ocular coherence tomography to evaluate the retinal nerve fiber layer (RNFL) thickness.

Results: We found a significant correlation between: NIS and MFM32, MFM32 and lower extremity myometry, MFM32 and the median motor amplitude, and MFM32 and RNFL thickness. There was no significant correlation between upper extremity myometry and MFM32, likely indicative of the relative sparing of proximal upper extremity function in earlier stages of disease in these patients.

Conclusions: We identify quantitative measures of muscle strength, muscle function, electrophysiologic, and ophthalmologic function correlating with clinical severity that may serve as feasible and clinically meaningful clinical trial endpoints.

Keywords: Neuromuscular disorders, Translational/experimental therapeutics

Conclusions: Here we describe a patient with a deletion in chromosome Xp21.1 encompassing exons 49-51 of Dystrophin. This in-frame deletion would be expected to cause a phenotype of Becker Muscular Dystrophy with elevated serum CK, and perhaps signs on neurologic exam by this age. His normal serum CK levels and normal neurologic exam prompts questions about other genetic modifiers that could influence his phenotype. In the age of genetic testing, it is possible that more asymptomatic patients with changes in the dystrophin gene may be identified. Further studies can be helpful to determine key features in these patients' genetic milieu that result in this benign phenotype.

Keywords: Neuromuscular disorders

125. Height Prediction using Anthropometric Measurements in Children with Neuromuscular Diseases, Treated and not Treated with Glucocorticoids (GC)

Duff I (Cincinnati, OH), Hu S, Horn P, Rybalsky I, Miller L, Morehart P, Wong B

Objective: Estimation of Standing Height (SH) is essential for assessing growth, calculating medication doses, BMI, glomerular function, and PFTs. Accurate estimation of SH is difficult in patients unable to stand or with spinal deformities. In this study we present new equations for prediction of SH in children with neuromuscular disorders (NM) using Sitting Height (SitH), Arm Span (AS), and ulna length, evaluating the accuracy of these equations for potential clinical use.

Methods: This cross sectional study included 40 males with NM on GC therapy (NM-GC) (age=9.94± 2.9y) and 29 males with NM not on GC therapy (NM-notGC) (age=10.6± 4.16y). SH, AS, Segmental Arm Span, SitH, Ulna length by rular (UR) and Unla length by Anthropometer were measured on all children.

Results: In stepwise regressions, SH was well predicted by AS or SitH for NM-nonGC children, SH= 2.211*SitH-29.392, r2=0.981; SH=0.903*AS+14.355, r2=0.985. In NM-GC children, optimal prediction was obtained by including age (DecAge), SH= SitH*1.724 +DecAge*0.981-6.705, r2=0.965; SH= AS*0.692+DecAge*1.146 +27.8, r2=0.957. SitH and AS were better predictors than other anthropometric measures for both groups.

Conclusions: We developed equations for predicting SH from AS, ULna measurements, and SitH both for NM-GC children and NM-notGC children. Prediction equations for NM-notGC have a better precision than similar equations for NM-GC children. Additional studies may further elucidate factors that improve the accuracy of prediction equations in NM-GC children.

Keywords: Neuromuscular disorders

126. The Importance of Clinical Diagnosis: Pompe Disease or Central Core Myopathy

Harper-Shankie MR (Detroit, MI), Rashid S, Jiang H

Objective: 1. To report the co-occurrence of Pompe disease and a new variant of central core myopathy 2. To educate that in cases where clinical findings conflict with the
laboratory diagnosis, a reluctance to explore further may lead to delayed or missed diagnosis of potentially treatable diseases.

**Methods:** Central core disease is a genetic disorder with no available treatment. Pompe Disease is a metabolic disorder that is currently treatable with enzyme replacement infusions. Timely and accurate diagnosis is thus of supreme importance in confounding scenarios.

**Results:** A 17-year-old female presented with diffuse myalgias and elevated creatine kinase levels (1,000 to 2,000 U/L). Magnetic resonance imaging of the thighs showed evidence of myositis. Evaluation for systemic and autoimmune diseases was unremarkable. Muscle biopsy showed type 1 fiber predominance and extensive central core formation consistent with central core myopathy. Mild focal prominence of myofiber glycogen without a definite pathological pattern was also noted on electron microscopy. Genetic testing revealed a previously unreported variant of the ryanodine receptor gene. However, this diagnosis appeared inconsistent with her normal developmental history and physical exam. This paradox prompted a second muscle biopsy that revealed findings consistent with Pompe disease. Reduced acid alpha-glucosidase activity confirmed the diagnosis.

**Conclusions:** Co-existence of these two muscle tissue pathologies has not been reported before. Inconsistent clinical features should alert the physician to conduct further investigations in order to avoid delays in the diagnosis of a potentially treatable disease.

**Keywords:** History/Teaching of Child Neurology, Movement Disorders, Neuromuscular disorders

127. **Recurrent Episodes of Hypoglycemia in Patients with Congenital Muscle Disease**


**Objective:** Congenital disorders of muscle are genetic neuromuscular diseases that present at birth or early childhood and frequently cause muscle loss, weakness, and physical disability. Anecdotal evidence suggests that some patients with congenital muscle disease may also experience frequent episodes of hypoglycemia. We aimed to better characterize this phenomenon in patients with congenital muscular dystrophy or congenital myopathy and evaluate the possible association of this phenomenon with low muscle mass.

**Methods:** We identified patients who experience hypoglycemia through the Congenital Muscle Disease International Registry (CMDIR) and obtained retrospective data through interviews and medical records review.

**Results:** Ten patients with congenital myopathy or muscular dystrophy responded to participate in our study. Most patients report a total of 5-8 episodes of hypoglycemia, with the median onset at 2.5 years of age. The average number of hospitalizations for hypoglycemia was 3.8. These study patients have a lower body mass index compared to peers with congenital muscle disease that do not have problems with glucose regulation.

**Conclusions:** Based on this descriptive study, we conclude that hypoglycemia occurs at clinically significant rates in patients with congenital muscle disease and low muscle mass may be a contributing factor. We speculate that low muscle mass results in a low amino acid substrate pool for gluconeogenesis during fasting and hence patients with muscle disease are more prone to hypoglycemia at an age when liver glycogen storage may still be insufficient. Additional studies are needed to establish a casual link and delineate the mechanism.

**Keywords:** Genetics, Neuromuscular disorders

128. **Abnormal Neuronal Migration Identified by Brain Pathology in Congenital Muscular Dystrophy Type 1A**

_Jayakody HR (St Petersburg, FL), Nguyen H, Mathews KD, Moore SA_

**Objective:** Congenital muscular dystrophy type 1A (MDC1A), or merosin-deficient congenital muscular dystrophy, is caused by recessive mutations in LAMA2 and loss of laminin alpha 2 chain expression. Individuals with MDC1A typically have white matter signal changes on MRI; rarely, structural brain abnormalities are seen. We describe the second published case of autopsy neuropathology in MDC1A.

**Methods:** This male was born at term, hypotonic at birth. He had normal cognitive milestones, sat independently, but never walked. Nocturnal BiPAP was started at 4 years. LAMA2 sequencing identified two frameshift mutations: c.2049_2050delAG, p.R683Sfs*21 and c.8669dupT, p.L2890Ffs*16. Brain MRI at 2 years showed abnormal white matter T2 signal, but was structurally normal. At 17 years, he died of an esophageal hemorrhage. An autopsy was done.

**Results:** Postmortem evaluation revealed a diffuse, bilateral cobblestone appearance of the cerebral cortex including many sites of fusion between adjacent gyri. There were multifocal disruptions of the glia limitans, associated with mildly abnormal cortical lamination. White matter was normal. Subcortical nodular heterotopia and sites of failed cerebellar granule cell migration were seen in the cerebellum. Cobblestone pathology is more commonly associated with dystroglycanopathies; a shared mechanism is likely as alpha-dystroglycan binds to merosin at the glia limitans in the developing brain.

**Conclusions:** Together with the single previously published autopsy in MDC1A, our case suggests that cobblestone neuropathology can be present despite a structurally normal brain MRI, thus is more common than imaging studies demonstrate, and this pathology could account for epilepsy seen in some MDC1A patients.

**Keywords:** Genetics, Neuroimaging, Neuromuscular disorders

129. **Reported Multisystemic Manifestations in Congenital Muscle Disease can Help Guide Diagnosis in the Era of Next Generation Sequencing**

_Leach ME (Washington, DC), Hatchkis L, Donkervoort S, Zukoisky K, Roje DP, Mayer OH, Thompson WR, Auh S_

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Avery R, Bharucha-Goebel DX, Collins J, Foley AR, Bönemann CG

Objective: To determine the reported incidence of multisystemic complications in genetically confirmed CM/CMD subtypes to help guide the interpretation of gene-based diagnostic evaluations. There is an expanding overlap between genotypes and phenotypes in congenital myopathies (CM) and congenital muscular dystrophies (CMD). The expanding use of Next Generation sequencing can lead to diagnostic challenges when interpreting variants in multiple CM/CMD genes. The identification of multisystemic involvement can help narrow the diagnostic possibilities. Establishing genotype-phenotype databases that can pull in information to correlate genetic variants with phenotypic discriminators will help establish genetic diagnoses and initiate proactive clinical management.

Methods: A PubMed search of peer-reviewed literature limited to human case reports, series, and multicenter studies was performed using "congenital myopathy," "congenital muscular dystrophy" and CM/CMD specific genes as search terms. Articles that did not report on multisystemic involvement, patients without genetic confirmation, and patients with neuromuscular symptom onset after 2 years of age were excluded.

Results: Approximately 300 articles met the review criteria, which included over 1,400 patients who had CM/CMD with confirmed mutations in 20 genes. Reported multisystemic symptoms include neonatal joint contractures, joint laxity, spine abnormalities, respiratory insufficiency, cardiac problems, feeding difficulties, seizures, eye abnormalities, and cognitive impairment.

Conclusions: Multisystemic manifestations are common in patients with congenital muscle disease and differ significantly between genetic subtypes. Examples of gene-specific differences that are helpful in correlating gene variants with specific phenotypes are discussed. Implications for the incorporation of non-muscle phenotypic features into genotype-phenotype databases are highlighted.

Keywords: Genetics, Neuromuscular disorders

130. Eteplirsen, a Phosphorodiamidate Morpholino Oligomer (PMO) for Duchenne Muscular Dystrophy (DMD): Clinical Update

Objective: DMD is a rare, degenerative, X-linked recessive genetic disease affecting approximately 1:3500 male births. It is caused by mutations in the DMD gene that result in the inability to produce functional dystrophin, an essential protein for muscle fiber function. Eteplirsen, a PMO designed to enable functional dystrophin production in boys amenable to exon 51 skipping is being evaluated in ongoing clinical trials.

Methods: Twelve boys aged 7-13 years with eligible genotypes were randomized 1:1:1 to weekly IV eteplirsen 30 mg/kg, 50 mg/kg, or placebo for 24-weeks. All patients then transitioned into an ongoing open-label extension trial with 30 or 50 mg/kg eteplirsen. Clinical efficacy endpoints included the 6 Minute Walk Test and Pulmonary Function Testing. Safety assessments included adverse event recording, ECG, ECHO, hematology, blood chemistry, and urinalysis.

Results: A statistically significant treatment benefit of 65.4 meters (p<0.017) on the 6MWT over 168 weeks was observed for patients in the continuous 30 and 50 mg/kg eteplirsen cohorts who were able to perform the 6MWT (n=6) compared with the placebo/delayed-treatment cohort (n=4). PFTs including MIP (+11.1%), MEP (+13.5%), and MIP/MEP %-predicted (−2.4% & −6.3%) were stable from Week 1 through 168 in all 12 subjects.

No deaths, discontinuations due to AEs, treatment-related SAEs, immune activation including infusion reactions, or clinically significant abnormal laboratory findings were reported. Treatment compliance was high with ~99% of all possible doses administered.

Conclusions: Eteplirsen’s long-term tolerability and statistically significant clinical benefit suggest it could be a viable therapy for DMD boys amenable to exon 51 skipping.

Keywords: Genetics, Neuromuscular disorders, Translational/experimental therapeutics

131. Muscle and Cerebral Perfusion Differences During Tilt Table Test in Young Patients with Dysautonomia of Variable Disease Severity
Pabst LM (Houston, TX), Tran YX, Hsihmi SS, Butler IJ, Numan MT

Objective: Patients with autonomic dysfunction (dysautonomia) have abnormal regulation of heart rate, temperature and vascular tone, which can produce varied clinical presentations, symptom burden and severity. This study aimed to explore the differences in muscle and cerebral perfusion trends based on dysautonomia severity using near infrared spectroscopy (NIRS) during head up tilt table testing (HUTT).

Methods: This retrospective study reviewed patients who underwent HUTT between 2009 and 2013 in which NIRS (Nonin® - Minneapolis, MN) was used in each patient to simultaneously measure perfusion of bilateral cerebral hemispheres and two muscle groups: 1) shoulder-leg, 2) back-shoulder, and 3) back-leg. Paired t-tests were utilized to analyze differences between perfusion changes.

Results: 133 patients with dysautonomia between 6 and 22 years were enrolled in the study and assigned to muscle pair groups. There were 47, 46 and 40 patients within groups 1, 2 and 3, respectively. Diagnostic classification by HUTT was 23% mild, 43% moderate and 34% severe. We observed that decrease in cerebral perfusion intensified incrementally by severity by the end of HUTT, while there was no difference observed within muscle group perfusion based on dysautonomia severity.

Conclusions: In young patients with dysautonomia, we observed that decrease in cerebral perfusion is most indicative of disease severity and there is minimal correlation between clinical severity and degree of change in muscle perfusion. With further investigation, these results may
guide clinical management of these patients such as treatment targeting improvement of brain oxygenation.

Keywords: Neuromuscular disorders

132. Chronic Administration of Translarna (Ataluren) is Generally Well Tolerated in Patients with Duchenne Muscular Dystrophy
Reha A (South Plainfield, NJ), Justice N, Northcutt V, Ong T, Spiegel R, Park S, Peltz SW

Objective: Ataluren is a first-in-class nonsense mutation (nm) readthrough medicine approved in Europe for the treatment of Duchenne muscular dystrophy (DMD) resulting from an nm in the dystrophin gene, in ambulatory patients aged 5 years and older. Clinical safety experience to date was reviewed.

Methods: Over 750 human subjects, including healthy volunteers and patients with nm genetic disorders, primarily nmDMD and cystic fibrosis (nmCF), have received >1 dose of ataluren. To date, >200 patients aged 5 years and older with disease status spanning early- to late-stage nmDMD have received ataluren for ≥48 weeks and the longest duration of continuous exposure is >4 years.

Results: In a 48-week placebo-controlled trial of ataluren in patients with nmDMD, the adverse event (AE) profile of ataluren was generally comparable to that of placebo. The most frequent adverse reactions at the recommended dose (40 mg/kg/day) were nausea, vomiting, and headache, which
Stroke

134. Does Prevention of Acute Clot Propagation at Diagnosis Improve Long Term Outcome of Neonatal Cerebral Sinovenous Thrombosis (NCSVT)?

Andrade A (Toronto, ON, Canada), deVeber G, Akalan, MacGregor D, Westmacott R, Yau I, Allen A, Moharir M

Objective: To compare outcomes between newborns with CSVT who had and did not have acute clot propagation.

Methods: A retrospective study of a prospectively enrolled consecutive cohort (1992-2009) of 104 NCSVT cases. Eighty-eight newborns had follow-up brain and venous imaging within 2-weeks of diagnosis. Fifteen [1/41(2%) on anticoagulation (ACT) vs 14/47(30%) off ACT, p=0.007)] of these had CSVT propagation, defined as new thrombosis in sinovenous channels distant/adjacent to initial thrombus with/without new brain lesions. These 88 newborns were further analyzed for this study. Clinical outcome [the validated pediatric stroke outcome measure (PSOM), neuropsychological testing] was pursued by extending follow-up period from 2009 to September 2014. Outcome was considered poor when there was any abnormality on PSOM/neuropsychological testing or epilepsy.

Results: Fifty-three (35 lost to f/u) of 88 newborns had additional outcome data available. There were 35(65%) males. CSVT propagation occurred in 12/53(23%) (1 treated, 11 untreated) and none in 41/53(77%) (17 treated, 24 untreated). Mean follow-up from CSVT diagnosis to most recent assessment was 5.5-y (1-18 y). One patient died (unrelated cause) after one outcome assessment (included in analysis). Clinical outcome (PSOM) in patients with propagation [8/12(66%)] was poorer than those without [22/41(53%)] (p=0.42). Neuropsychological testing, performed in 7/12 patients with propagation was abnormal in 6/7(90%) compared to those without [21/41 tested, abnormal in 18/21(85%)] (p=0.75). Epilepsy occurred in 4/12(33%) patients with propagation and 10/41(24%) patients without [p=0.53].

Conclusions: A slightly higher number of newborns with CSVT who had propagation had poor outcome compared to those who did not. Overall long term outcome from NCSVT remains poor. A prospective clinical trial, to determine the effect of ACT in preventing acute clot propagation and improving long term outcome, is essential.

Keywords: Neonatal neurology, Neuroimaging, Stroke

135. Pediatric Quality of Life in Children with Moyamoya Disease and Stroke

Ball AJ (Stanford, CA), Steinberg GK, Elbers JM

Objective: Moyamoya Disease (MMD) is a chronic, progressive intracranial arteriopathy with a high risk of stroke. The effect of this diagnosis on quality of life beyond physical and cognitive function remains unstudied. We aimed to survey children with MMD and compare quality of life to chronically-ill children and children with stroke, to better understand the impact of this diagnosis.
Methods: All children with MMD between 7-17 years of age from Stanford’s Moyamoya Center were approached for consent. Children with syndromic neurodevelopmental diagnoses were excluded. Patients were surveyed using the Pediatric Quality of Life (PedQL) 4.0 survey, and Pediatric Stroke Outcome Measure or Recovery Recurrence Questionnaire to measure physical/cognitive deficits. PedQL scores were compared to normative data for healthy and chronically-ill children, and children with stroke.

Results: Of 74 children contacted, 30 consented to participate, including 10 males, with median age of 13.5 years (range 7-17 years). Twenty children (67%) had an accompanying stroke, and 24 children had good neurological outcome (80%). Mean PedQL scores in the psychosocial domain were lower than healthy controls (p=0.02) and all scores were comparable to chronically-ill children, and children with stroke. Patients with stroke did not appear to have worse quality of life than those without.

Conclusions: Children diagnosed with MMD have lower psychosocial scores on PedQL compared to healthy controls, and similar quality of life to chronically-ill children and those with stroke. To maximize quality of life, children with MMD may benefit from mental health support beyond what their mild or asymptomatic presentation indicates.

Keywords: Stroke

136. Impact of Epilepsy on Attention, Intellectual and Executive Functioning in Children with Perinatal Arterial Ischemic Stroke
Bosenbark D (Philadelphia, PA), Krivitzky L, Ichord RN, faistraub L, Billinghurst LL

Objective: Children with perinatal arterial ischemic stroke (PAIS) frequently display neurocognitive deficits across multiple domains, yet the added impact of epilepsy is largely unknown. We examined the effect of co-morbid epilepsy on attention, intellectual and executive functioning.

Methods: Forty children born at term (≥37 weeks) ages 3-16 (median age=7.2 years; 58% male) with PAIS underwent comprehensive neuropsychological battery (WPPSI-II, WASI-II, NEPSY-II, TEA-Ch, WMTB-C, TOL-Dx, TMT-A & B). Of these, 10 (25%) had co-morbid epilepsy (≥2 unprovoked seizures) and 4 (10%) had provoked seizures diagnosed prior to testing. Composite scores were calculated from subtests within each neuropsychological domain. Parents completed questionnaires (ADHD-IV, BRIEF) regarding real-world functioning.

Results: Children with epilepsy (n=10, mean FSIQ=78) had significantly lower IQ scores than those without (n=30, mean FSIQ=100) [t(38)=4.70, p<0.001]. They also scored lower in working memory, verbal fluency, inhibition, planning/organization, and processing speed (all p<0.01), though not in attention or flexibility/shifting (p=0.6). Parent report indicated a higher incidence of clinically elevated ADHD symptoms (p<0.05) in the epilepsy group and greater difficulties in all aspects of executive functioning: self-control, flexibility, metacognition, behavior rating inventory, global executive composite (p>0.2).

Conclusions: Children diagnosed with epilepsy after PAIS demonstrate greater weaknesses in IQ and many aspects of attention and executive functioning. They are also at higher risk of ADHD diagnosis. Future research examining other predictors of poor neurocognitive outcomes after PAIS (e.g., epilepsy severity, anticonvulsant use, lesion location and volume) is crucial for early identification of vulnerable children, timely institution of school-based accommodations, and design of therapeutic interventions.

Keywords: Cognitive/Behavioral Disorders, Neonatal neurology, Stroke

137. Multiple Epochs of P-CIMT are of Greater Importance for Children with Greater Impairment
DeLuca SC (Roanoke, VA), Ramey SL, Trucks MR, Wallace DA

Objective: The current study presents findings about receiving multiple epochs of Pediatric Constraint Induced Movement Therapy (P-CIMT) on upper extremity (UE) skills and function for children with asymmetric motor impairment. The P-CIMT protocol implemented has shown efficacy in rigorous clinical trials; and involves full-time constraint of the less impaired UE, high-intensity shaping (and repetitive practice) with the weaker UE (6 hrs/day, 5 days/wk X 4 wks), therapy in natural settings, and a transfer package. A critical question is whether repeated P-CIMT epochs can produce continued benefits; and if so, of what magnitude and for whom?

Methods: Study design is a clinical cohort of children with CP and whose parents sought P-CIMT from a university research clinic: 28 children received two epochs, and 8 had three epochs. Primary assessments included the Emerging Behaviors Scale (EBS) and Pediatric Motor Activity Log (PMAL).

Results: Children gained a μ=13.2 (s.d. 4.2) functional skills on the EBS after the first epoch, and on a group basis maintained many of the gains at start of the second epoch (μ=13.9 mos later) where they gained another μ=7.3 (4.7) skills; and 8 children then gained another μ=6.5 (4.2) skills after epoch 3. PMAL ratings also improved. Individual patterns of improvement varied as a function of children’s classification on the Manual Abilities Classification System and are presented.

Conclusions: Children showed significant improvements after repeated epochs of P-CIMT. The data suggests that repeated epochs may be particularly important for lower functioning children in helping them gain and maintain skills.

Keywords: Movement Disorders, Stroke

138. Younger Age Predicts Acute Seizures and Epilepsy after Pediatric Stroke
Fox CK (San Francisco, CA), Mackay MT, Douling MM, Pergami P, Luigi T, deVeber G, SIPS Investigators

Objective: To determine risk factors for acute seizures and epilepsy after pediatric stroke.

Methods: Seizures in Pediatric Stroke investigators prospectively enrolled neonates (birth - 28 days) and children (29 days - 18 years) with arterial ischemic stroke (AIS).
Acute (≤7 days post-stroke) and remote (>7 days post-stroke) seizures and active epilepsy (≥ one remote seizure and maintenance anti-convulsant treatment at one year post-stroke) were identified by chart review and parental questionnaires. Odds ratio (OR) and 95% confidence intervals (CI) for seizure incidence and predictors were determined by logistic regression and Cox-proportional hazard ratios.

**Results**: Acute seizures occurred in 26 of 28 neonates (93%, CI 83-100%) and 32 of 86 children (37%, CI 27-48%). For each one-year increase in age, acute symptomatic seizures were 20% less likely (OR 0.8, CI 0.7-0.9). At one year, 10% of patients (CI 4-16%) had active epilepsy. Acute seizures (OR 11, CI 1.4-92) and younger age were associated with active epilepsy. For each one-year increase in age after childhood AIS, epilepsy risk decreased by 30% (OR 0.7, CI 0.5-1.0). Children with higher frequency and longer duration acute seizures had higher odds of active epilepsy. For each 10-minute increased duration of the longest acute seizure, the risk of active epilepsy was increased five-fold (OR 4.7, CI 1.7-13). Patients with >10 acute seizures had a 30-fold increased epilepsy risk (OR 30, CI 2.9-305) compared to patients without seizures.

**Conclusions**: Younger children and those with longer and multiple acute seizures have elevated risk of epilepsy one year post-stroke.

**Keywords**: Neonatal neurology, Stroke

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**139. Robotic Quantification of Bilateral Motor Dysfunction in Children with Perinatal Stroke**

Kuczynski A (Calgary, AB, Canada), Dukelow SP, Kirton A

**Objective**: Perinatal stroke causes most hemiplegic cerebral palsy (CP). Clinical measures have limited resolution. Robots can quantify complex sensorimotor function in adult stroke but are untested children. We aimed to define the mechanics of motor deficits in both upper limbs in children with perinatal stroke, hypothesizing unique dysfunction in both extremities.

**Methods**: Prospective case-control study. Alberta Perinatal Stroke Project children had MRI-confirmed unilateral arterial ischemic stroke (AIS) or periventricular venous infarction (PVI) and hemiparesis. An exoskeleton robot (KINARM) tested planar upper limb movements in an augmented reality environment. A visually guided reaching task had subjects move each hand to multiple virtual targets. Twelve movement parameters including initial direction error and maximum speed were compared to clinical assessments including Assist-Hand Assessment (AHA) and stroke type.

**Results**: Forty children with stroke (12.6 ± 3.6 years, 22 AIS, 18 PVI) and 59 controls (12.2 ± 3.7 years) were studied. Paretic limb was impaired in 11/12 and 8/12 parameters for AIS and PVI respectively. Most impaired were increased initial direction errors (AIS:8.70 ± 4.9 degrees; PVI:7.17 ± 3.4; controls: 3.51 ± 1.1; p<0.001) and slower movement times (AIS:1.35 ± 0.2s; PVI:1.20 ± 0.2s; controls: 0.93 ± 0.2s; p<0.001). The “unaffected” limb was impaired on 8/12 (AIS) and 4/12 (PVI) parameters. Both AIS (1.12 ± 0.2s; p<0.001) and PVI (0.99 ± 0.2s; p<0.05) were slower than controls (0.88 ± 0.1s). AHA scores correlated with reaction time (p=0.57, p<0.01), initial direction error (p=0.52, p<0.05) and movement time (p=0.48, p<0.05).

**Conclusions**: Robotics can measure discrete parameters of motor dysfunction in children with perinatal stroke. Unaffected limb function is often impaired and a potential therapeutic target.

**Keywords**: Movement Disorders, Stroke
motor evoked potentials (MEP) determined rest and active thresholds (RMT/AMT), latencies, and stimulus-recruitment curves (SRC, 100-150% RMT). Paired-pulse TMS evaluated short-latency intracortical inhibition (SICI) and intracortical facilitation (ICF). Ipsilateral participants (I+), defined by having ipsilateral MEPs ≥ 0.05mV at 120%RMT in ≥ 5/20 trials, were compared to contralateral only (I-) children. Assisting Hand and Melbourne assessments quantified motor function.

**Results:** Complete data compared 25 I+ with 12 I- participants (n=37). I+ had worse motor function. SRC to unaffected hand were comparable between I+ and I-. I+ subjects had lower intensity ipsilateral SRC. Ipsilateral MEP latencies were prolonged (23.5 ± 1.8ms versus 22.2 ± 1.5ms contra, p<0.001). Contralateral SICI was comparable between I+ and I- (-42%) and present but reduced ipsilaterally (-20%). Contralateral ICF was also comparable (+43%) and similar ipsilaterally (+43%). All measures (SRC/SICI/ICF) correlated between contralateral and ipsilateral measures in I+ participants. Procedures were well tolerated.

**Conclusions:** Neurophysiology of non-lesioned M1 and its relationship to motor function is measureable in children with PS. Correlation of excitability and intracortical circuitry measures between contralateral and ipsilateral sides suggests common control mechanisms.

**Keywords:** Movement Disorders, Stroke

## Headache

**142. Physical and Mental Comorbidity of Pediatric Migraine in the Philadelphia Neurodevelopmental Cohort**

**Lateef TM (Washington, DC), He J, Calkins ME, Gur R, Merikangas KR**

**Objective:** To examine the pattern and extent to which other physical and mental conditions are comorbid with migraine and other headaches in children using a large, systematically obtained pediatric registry.

**DESIGN/METHODS:** Sample: 9,014 youth ages 8-21 (4,349 males and 4,665 females; 3,585 under age 13y, 1,751 ages 19-21y) from the Philadelphia Neurodevelopmental Cohort identified through pediatric clinics at the Children's Hospital of Philadelphia (CHOP) healthcare network by the Center for Applied Genomics (CAG). Measures: Physical conditions, based on electronic medical records (EMR) and interview data on 42 physical conditions of 14 organ systems, and mental disorders based on an abbreviated version of the structured Kiddie-Schedule for Affective Disorders and Schizophrenia psychiatric diagnostic interview. Migraine diagnosis was based on modified ICHD-II criteria.

**Results:** Children with any headache and specifically children with migraine reported higher rates of other neurologic (OR 2.8 [95% CI: 1.9-4.1]) and developmental (OR 1.6 [95% CI: 1.3-4.1]) conditions and also of cardiac (OR 2.3 [95% CI: 1.3-4.1]) and hematological problems (OR 2.3 [95% CI: 1.2-2.3]). Anxiety (OR 2.0 [95% CI: 1.3-3.0]) and Mood (OR 3.5 [95% CI: 2.4-5.2]) disorder were also more prevalent among youth with migraine compared with non-migraineurs. Children with any headache type were more likely to have ADHD (OR 1.2 [95% CI: 1.02-1.5]).

**Conclusions:** Pediatric migraine is associated with other physical and mental disorders suggesting that comorbid conditions should be evaluated comprehensively while treating youth with headache. Such comorbidity may be an important source of clinical and etiologic heterogeneity in migraine.

**Keywords:** Headache/Migraine

**143. Dihydroergotamine Treatment for Status Migrainosus in Children—Efficacy and Tolerability**

**Liang SN (Saint Louis, MO), Vargo V, Mar S**

**Objective:** There is limited evidence about status migrainosus management in children, and lack of an established protocol. This study examines the effectiveness and tolerability of intravenous dihydroergotamine (DHE) in children requiring admission for status migrainosus.

**Methods:** This is a retrospective chart review of 29 patients and 40 admissions, ages 12-20 years, who failed other first line medications in the emergency department, and were admitted to the St. Louis Children's Hospital from January 2008 to February 2010, for further management with DHE only. Data were collected on: duration of presenting migraine; initial interventions used in the emergency department; effectiveness of the treatments based upon pain scores; dose, duration, and frequency of side effects of DHE; and length of admission.

**Results:** The emergency department usually tried IV fluids, IV NSAIDs, and antiemetics first. Average duration of presenting headache was 5.9 days. One dose of DHE (0.5-1 mg) did not improve the pain score in 64% of patients, but additional doses provided further benefit (average 3.9 doses). About 95% reported decreased pain, and 10% were headache-free upon discharge. HR and BP increases are uncommon (<10%) and do not seem clinically significant. A third of children had nausea/vomiting. Length of stay was 1-3 days.

**Conclusions:** DHE can be an effective therapy for status migrainosus in children, even after IV NSAID and antiemetic use, but may require several doses. Blood pressure and heart rate changes were not therapy-limiting. Despite concurrent antiemetic use, nausea and vomiting occur in about a third of patients.

**Keywords:** Headache/Migraine

**144. Primary Stabbing Headaches (PSH) in Children and Adolescents**

**Rothner AD (Cleveland, OH), Mandel G**

**Objective:** To review the clinical presentation, natural history, evaluation and treatment of PSH in Children.

**Introduction:** PSH were described 50 years ago. Other names include: ice pick headache and stabs and Jabs. Data concerning PSH in children is scarce. It is considered an indomethacin sensitive headache and is characterized by a stabbing pain, lasting seconds. We report our experience with 44 children and adolescents seen at the CCF.
TABLE 1. Pediatric Literature Review Data from 5 Studies Results (Abstract 144)

<table>
<thead>
<tr>
<th>Pediatric Literature Review</th>
<th>CCF Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>158</td>
</tr>
<tr>
<td>Female: Male 1:1 (53%)</td>
<td>2:1 (66%)</td>
</tr>
<tr>
<td>Average Age of Onset</td>
<td>7.7</td>
</tr>
<tr>
<td>Range on Onset</td>
<td>2.4-18.5</td>
</tr>
<tr>
<td>Extra-trigeminal</td>
<td>27%</td>
</tr>
<tr>
<td>Laterality</td>
<td>Unilateral – 37%</td>
</tr>
<tr>
<td>Bilateral – 50%</td>
<td>Unilateral – 50%</td>
</tr>
<tr>
<td>Alternating – 15%</td>
<td>Alternating – 20%</td>
</tr>
<tr>
<td>Family Headache History</td>
<td>51%</td>
</tr>
<tr>
<td>Other Headaches (TTH, CH, CPH, HC, Rebound)</td>
<td>7%</td>
</tr>
<tr>
<td>Migraine</td>
<td>11%</td>
</tr>
<tr>
<td>Treatment</td>
<td>Indomethacin, Carbamazepine, Hydroxytryptophan + riboflavin, amitriptyline</td>
</tr>
<tr>
<td>Melatonin, indomethacin, lamictal, topirimate, cyproheptadine</td>
<td></td>
</tr>
</tbody>
</table>

Methods: Literature review 1964-2012. Review of CC records 2010-2014. Included were patients meeting the criteria. IRB approval.

Results: Table I - Literature Review and Table II – CCF patients

Discussion: PSH is not rare in children. PSH may present under age 5 and become more frequent after puberty. They may be unilateral or bilateral. They may occur in the trigeminal or extra trigeminal region. 50% occur daily and last seconds. Almost half have co-morbid primary headaches and > 50% a positive family history of headaches. Many disappear spontaneously and others respond to Indomethacin or Melatonin.

Literature review noted 158 children and adolescents with PSH. Major differences noted in our patients included a female to male ration of 2:1 an older age of onset 12 vs 7 years, and a larger number with co-morbid headaches.

Conclusions: Physicians caring for children and adolescents should recognize and differentiate PSH from trigeminal neuralgia and the trigeminal autonomic cephalgia of headaches. It is not rare in children and adolescents. No underlying etiology is noted. Treatment should be initiated with Melatonin. Spontaneous remission may occur.

Keywords: Headache/Migraine

Translational/Experimental Therapeutics

145. AFQ056 in Adults and Adolescents with Fragile X Syndrome: results of randomized, double-blind, placebo-controlled trials


Objective: Basic research spanning a decade and encompassing over 30 papers has shown that mGluR5 negative allosteric modulators (NAMs) normalize excessive pathway signaling and reverse phenotypes in the fmr1 knockout mouse model of fragile X syndrome (FXS). The work presented here sought to confirm the finding of behavioral improvement relative to placebo in adult FXS males with complete methylation of FMR1 during a phase 2a trial of AFQ056 (Novartis), a highly selective mGluR5 NAM.
Methods: Two larger phase 2b, randomized, double-blind, placebo-controlled, parallel-group trials were conducted in adults (n=175, 18-45 years) and adolescents (n=139, 12-17 years) with FXS. Participants were stratified by methylation status and received AFQ056 (25, 50, or 100mg bid) or placebo over 12 weeks.

Results: AFQ056 did not demonstrate benefit over placebo in either of these trials at any dose for the primary efficacy endpoint of behavioral improvement on the Aberrant Behavior Checklist-Community Edition using the FXS specific algorithm (ABC-CFX), nor on multiple additional behavioral outcomes including the ABC-CFX subscales, CGI-I, Repetitive Behavior Scale, and Social Responsiveness Scale. Neither methylation status nor younger age predicted efficacy. Discontinuation due to adverse events was similar between AFQ056 and placebo groups. The safety profile of AFQ056 was similar to earlier studies.

Conclusions: These results raise important concerns about the value of mouse models for predicting human response to disease-targeted drugs, and about the paradigm for translation of disease-targeted treatments from animal models to humans with developmental disorders, suggesting that success may be difficult to see with standard drug development strategies.

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

146. Objective Clinical Efficacy Outcome Measures for Cyclodextrin Treatment in Niemann-Pick Type C (NP-C): A Five Domain Approach

Berry-Kravis E (Chicago, IL), O'Keefe J, Hoffmann A, Chin J, Robertson E, Winston A, LaGorio L

Objective: To develop a system for tracking function in key clinical domains to evaluate the impact of hydroxypropyl-beta-cyclodextrin (HP-b-CD) treatment on the course of disease in NP-C.

Methods: Three patients with NP-C at various stages of disease were treated with HP-b-CD through an expanded access IND. Disease course was tracked with the NP-C Rating Scale and repeated objective assessments based on functional level every 2 or 6 months in 5 clinical domains impacted by NP-C: (1)Cognitive/language-NIH Toolbox cognitive battery, WISC/WAIS/Mullen (cognition), WRAML (memory), CELF (language), D-KEFS (executive) (3-48 scores depending on patient); (2)Gait/balance-Neurocom (balance), instrumented TUG and 2 minute walk (gait speed and stability) (24-42 scores); (3)Fine motor–Purdue and 9-hole pegboards, NEPSY tapping (6-8 scores); (4)Swallowing (2 scores); and (5)Eye movements–vestibulonystagmogram (28 scores). Percent of scores improved by >10%, changed by <10%, and worsened by >10% from baseline to present (8-14 months) was quantified in each domain.

Results: The NP-C Rating Scale improved by 0-4 points. Eye movements showed a higher percent of scores worsening than improving. Swallowing showed only improvement in all patients. Eye movements showed a higher percent of scores worsening than improving.

Conclusions: This system provides pilot data on measures sensitive to change in NP-C and defines a model which can be combined with repeated measures analyses to quantify chronic impact of an intervention across symptom domains in patients with a rare disease, to potentially guide treatment decisions.

Keywords: Translational/experimental therapeutics

147. The Effect of Everolimus on Growth and Sexual Maturation in Patients Treated for Subependymal Giant Cell Astrocytoma Associated with Tuberous Sclerosis Complex: Results from the 4-Year Final Analysis of EXIST-1

Franz DN (Cincinnati, OH), Kuperman R, Flamini JR, Wu J, Berkowitz N, Niolat J, Sparagana S

Objective: To assess the effect of everolimus on growth and sexual maturation in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex in the EXIST-1 study (NCT00789828).

Methods: Patients with ≥1 SEGA lesion (longest diameter ≥1 cm) were randomized (2:1) to 4.5 mg/m²/day everolimus (target trough 5-15 ng/mL) or placebo. After achieving positive results for the primary endpoint (SEGA response rate, cutoff March 2, 2011), all patients were offered open-label everolimus in an extension phase. Tanner stage assessments for sexual development were completed annually. Patient growth (in patients aged <18 years) was assessed through standard deviation scores (SDS) for height and weight.

Results: In total, 111 patients (median age 9.5 [range, 1.1-27.4] years) received ≥1 dose of everolimus. At study end (October 2, 2014), the median duration on everolimus was 47.1 months (range, 1.9-58.3). More than half (34/64 male patients, 27/47 female patients for breast development, and 25/47 female patients for pubic hair) were at Tanner stage 1 at baseline. Normal progression in Tanner stage was usually seen; median age to attain Tanner stage 2 was 12.1 years for genitalia and 12.0 years for pubic hair in males (range: 9.5-14.9), and 10.4 years for breast development and 11.0 years for pubic hair in females (range: 6.6-13.0). SDS for height and weight in patients aged <18 years were comparable to and after starting everolimus.

Conclusions: Final clinical data from more than 4 years of treatment in EXIST-1 did not show an impact of everolimus on growth and development or sexual maturation.

Keywords: Brain Tumors/Oncology, Genetics

148. A Novel Clinical Trial Design to Evaluate the Efficacy and Safety of Two Exon-Skipping PMOs, SRP-4045 and SRP-4053, in Patients with Duchenne Muscular Dystrophy (DMD)

Kaye EM (Cambridge, MA), Laforet GL, Saoud J

Objective: DMD, an X-linked myopathy caused by mutations in the DMD gene, results in the inability to produce functional dystrophin, an essential protein for muscle fiber function. Exon-skipping phosphorodiamidate morpholino
oligomers (PMOs) direct alternative splicing of dystrophin pre-mRNA, restore the mRNA reading frame and enable translation of an internally truncated dystrophin protein. SRP-4045 and SRP-4053 are two PMO drug candidates designed for patients with mutations amenable to exon 45 and 53-skipping, respectively (16% of total DMD population).

**Methods:** A double-blind, placebo-controlled, multi-center, 48-week study will evaluate the effects of the two PMOs on ambulation, endurance and muscle function as measured by the 6-Minute Walk Test. Secondary endpoints will evaluate restoration of dystrophin in muscle tissue measured from muscle biopsies, and respiratory muscle function as measured by pulmonary function tests. Patients (n=99) will be randomized by genotype 2:1 to active-treatment (SRP-4045 or SRP-4053) or placebo. All patients will undergo 2 muscle biopsies, one at baseline and one at either Week 24 or 48. Safety assessments will include adverse event monitoring, ECG, ECHO, and safety laboratory tests. The primary analysis of clinical outcomes will be based on the combined cohort receiving either SRP-4045 or SRP-4053 compared to those receiving placebo.

**Conclusions:** The study design highlights a novel approach in combining two exon-skipping drug candidates (SRP-4045 & SRP-4053) within a single trial. This is important for future exon skipping therapies in DMD as they will target increasingly smaller patient-populations, making it difficult to conduct separate, well-powered clinical trials for each compound.

**Keywords:** Genetics, Neuromuscular disorders, Translational/experimental therapeutics

149. Migration of Human Oligodendrocyte Progenitor Cells in the Young Adult Rat Brain
Osorio MJ (Rochester, NY), O’Neil S, Goldman S

**Objective:** To evaluate the migration and expansion competence of human oligodendrocyte progenitor cells (OPCs) upon transplantation in the postnatal brain.

**Background:** We have previously shown the ability of human OPCs to efficiently remyelinate the congenital dysmyelinated brain when transplanted in the neonatal mouse brain, making these cells attractive therapeutic strategies for leukodystrophies. However, given that treatment often will require transplantation beyond neonatal age, it is imperative to evaluate the ability of these cells to migrate and populate the young adult brain.

**Design/Methods:** 16 young adult congenitally immuno-deficient athymic nude rats were transplanted with human OPCs derived from second trimester fetal human forebrain tissue. A total of 100,000 CD140a+ OPCs were delivered into the corpus callosum and the animals were sacrificed after 4, 8, 12, 16 and 32 weeks.

**Results:** Human OPCs followed the major white matter structures. The mean distance travelled increased progressively after transplantation, to achieve a mean of $3.26 \pm 0.01$ mm (SEM) and a maximum distance travelled of $9.64 \pm 0.32$ mm by 16 weeks post transplantation (32

**FIGURE 1:** Example of 3D reconstruction of human cells within the rat brain at different timepoints upon intracerebral transplantation (each dot represents a human cell) (Abstract 149).
weeks data in progress). The number of human cells expanded significantly and reached a 25-fold increase after 16 weeks. Most cells remained within the oligodendroglial lineage (defined by the expression of the Olig2 marker) and a smaller proportion differentiated to astrocytic fate.

Conclusions: Human OPCs derived from fetal brain are capable of extensive migration and expansion throughout the young adult brain, thus can be considered as feasible therapeutic vectors for treatment of postnatal pediatric and adult disorders of myelin.

Keywords: Demyelinating Disorders, Translational/experimental therapeutics

150. Nonclinical Pharmacokinetic Evaluation of Eteplirsen, SRP-4045, and SRP-4053; Three Phosphorodiamidate Morpholino Oligomers (PMOs) for the Treatment of Patients with Duchenne Muscular Dystrophy (DMD)

Sazani P (Cambridge, MA), Charleston JS, Shanks C, Zhang J, Carver M, Saud J, Kaye E, EM

Objective: DMD, a rare, X-linked recessive, degenerative neuromuscular disorder caused by mutations in the DMD gene, results in the inability to produce functional dystrophin, a key structural protein in muscle fibers. PMOs can direct alternative splicing of dystrophin pre-mRNA, restore the mRNA reading frame and enable translation of an internally truncated dystrophin protein. Eteplirsen, SRP-4045, and SRP-4053 are investigational PMO drug candidates, designed to skip dystrophin exons 51, 45, or 53 respectively, targeting ~29% of the total DMD population.

Methods: Studies conducted to evaluate in vitro pharmacologic and pharmacokinetic properties of these PMOs included analysis of plasma protein binding and metabolic stability in hepatic microsomes of four species. Induction and inhibition of human cytochrome P450 isoenzymes were also evaluated.

Results: All three PMOs exhibited low protein binding in all species, no evidence of in vitro metabolism by hepatic microsomes, no clinically relevant inhibition of the major drug-metabolizing cytochrome P450 isoenzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5, and no induction of CYP1A2, CYP2B6, or CYP3A4 at biologically relevant concentrations. In vivo pharmacokinetic profiles for the three PMOs were similar and showed comparable Cmax, AUC, and clearance, and displayed similar dose proportionality across the doses examined in non-human primates (5, 40, and 320 mg/kg).

Conclusions: Together, these results suggest that PMOs as a class have similar pharmacokinetic profiles, have a low potential for drug-drug interactions based on the lack of significant metabolism, enzyme inhibition/induction and plasma protein binding, and have the potential to address all DMD patients that could benefit from the exon skipping approach.

Keywords: Genetics, Neuromuscular disorders

151. Rapamycin Prevents Neuroinflammation and Neuronal Death in a Mouse Model of Cerebral Palsy

Srivastava IN (Philadelphia, PA), Shperdeja J, Bayhis M, Crino PB

Objective: The mammalian target of rapamycin (mTOR) pathway governs cellular responses to hypoxia and inflammation including induction of autophagy and cell survival. Cerebral palsy (CP) is a prevalent neurodevelopmental disorder linked to hypoxic and inflammatory injury to the brain, however, a role for mTOR modulation in CP has not been investigated. Thus, we hypothesized that mTOR inhibition would diminish inflammation and prevent neuronal death in a mouse model of CP.

Methods: Mouse pups were subjected to hypoxia-ischemia and lipopolysaccharide-induced inflammation (HIL), a model of CP causing neuronal injury within the hippocampus. Pups received rapamycin (an mTOR inhibitor; 5mg/kg) following HIL, and then for 3 subsequent days. Phospho-activation of the mTOR effector ribosomal S6 protein and expression of hypoxia inducible factor 1 (HIF-1a) were assayed. Neuronal cell death was defined with Fluoro-Jade C (FJC) and autophagy was measured using Beclin-1 and LC3II expression. Iba-1 labeled, activated microglia were quantified.

Results: Neuronal death, enhanced HIF-1a expression, and numerous Iba-1 labeled, activated microglia were evident at 24 and 48 hours post-HIL. Basal mTOR signaling was unchanged by HIL. Rapamycin treatment significantly reduced neuronal death, HIF-1a expression, and microglial activation, coincident with enhanced expression of Beclin-1 and LC3II, markers of autophagy induction.

Conclusions: mTOR inhibition prevented neuronal death and diminished neuroinflammation in this model of CP. Persistent mTOR signaling following HIL suggests a failure of autophagy induction, which may contribute to neuronal death in CP. These results suggest that mTOR signaling may be a novel therapeutic target to reduce neuronal cell death in CP.

Keywords: Infections/Neuroimmunology, Neonatal neurology, Translational/experimental therapeutics

History/Teaching of Child Neurology

152. Utility and Effectiveness of a Self-Directed Interactive Learning Tool for Adult Neurology Residents

Byler DL (Hershey, PA), Lowden MR, Moser EM

Objective: To explore the acceptability and effectiveness of a self-directed e-learning program for compulsory pediatric neurology education for adult neurology residents.

Methods: This is a mixed methods study utilizing standardized test scores from residency in-training examinations and a Likert scale questionnaire examining attitudes and
self-reported efficacy in treating children with neurologic diseases. Participants took a self-directed case-based internet course on pediatric neurology essentials. Eight control subjects and 8 study subjects were evaluated.

**Results:** All participants achieved significant improvement over baseline test scores (p<.002); control subjects had variable results with no significant change. Comparison with controls was limited by baseline differences in test scores between the groups. Participants had significant improvement in self-reported efficacy over baseline in all areas (p<0.01) except headache treatment age 13-18. Residents reported satisfaction with the length, complexity and utility of the curriculum approach.

**Conclusions:** This case-based interactive e-learning course was enthusiastically received by the learners. When compared to baseline scores, all study subjects improved. Comparison to control group was limited by baseline test score discrepancies. The format allowed for standardization of clinical curriculum easily embraced by the learner. A global shortage of providers in pediatric neurology necessitates creative methods for medical education of allied specialties.

**Keywords:** History/Teaching of Child Neurology

153. ACGME NAS: Do Child Neurology Programs Have What it Takes?

**Feist TB** (Cincinnati, OH), **Campbell JL**, **Labare JA**, **Gilbert DL**

**Objective:** In preparation for the implementation of the Next Accreditation System (NAS) in Child Neurology (CN), the authors organized the first annual meeting of child neurology program coordinators to characterize the Program Coordinator workforce and determine program readiness for implementation of the ACGME NAS requirements.

**Methods:** A workforce and program-readiness survey was delivered prior to the meeting to all Child Neurology (CN) Coordinators. A post-conference survey was distributed to all coordinators in attendance.

**Results:** Response rate was 56%. Job titles varied widely. Most respondents (65%) also managed one or more fellowships. Most worked in graduate medical education (GME) for less than 5 years (53%), with no career path (88%), supervised by someone with no GME experience (85%), in divisions where faculty knowledge was judged inadequate (72%). A small proportion of programs had established clinical competency committee policies (28%) and felt ready to implement milestone-based evaluations (56%). 92% of attendees felt more prepared to implement NAS after the conference.

**Conclusions:** Child Neurology programs were not ready for the complexity of residency program management in the NAS era, and continue to face barriers to implementation. This supports substantive modifications to the program coordinator role, including a defined career pathway, managerial classification, administrative support, and continuing education.

**Keywords:** History/Teaching of Child Neurology

154. Improving Ability to Recognize Neonatal Encephalopathy: utility of a web-based video tool

**Ivy AS** (Stanford, CA), **Bahm SM**, **Clark C**, **Wusthoff CJ**

**Objective:** Neonatal encephalopathy resulting from hypoxia-ischemia is associated with significant morbidity and mortality. Early identification and treatment with hypothermia can reduce this risk. However, recognizing HIE can be challenging for examining physicians who may not encounter the diagnosis frequently. We created an online teaching tool, consisting of videos highlighting exam features of normal neonates, as well as those with mild, moderate or severe neonatal encephalopathy. The purpose of this study was to test the utility of this tool in improving physicians’ abilities to categorize degree of encephalopathy based on exam findings.

**Methods:** We tested pediatric residents’ correct categorization of exam findings in neonatal encephalopathy before and after using our online video tool. During testing, participants were asked to categorize exam findings as normal, or consistent with mild, moderate, or severe encephalopathy. Four exam domains were tested: spontaneous activity, level of alertness, posture/tone, and reflexes/autonomic responses. Pre- and post-test results were analyzed with paired t-tests followed by post-hoc Sidak’s multiple comparisons test.

**Results:** Participants’ test scores improved by 38% after watching teaching videos (p<0.0001). Pre-to post-test scores improved in all domains, and improved the most in the categorization of spontaneous activity and reflexes (45% improvement in both categories; p<0.05).

**Conclusions:** Residents improved their ability to recognize mild, moderate, and severe neonatal encephalopathy after accessing an online video teaching tool. These results support use of such a tool to train providers in appropriate identification of neonates with suspected neonatal encephalopathy.

**Keywords:** History/Teaching of Child Neurology, Neonatal neurology

155. Child Neurology Outreach Clinic: sharing an experience of five decades

**Qaiser S** (Lexington, KY), **Zafar M**, **Jones KS**, **Baumann RJ**

**Objective:** Thriving for more than half a century, the specialty of Child Neurology is still concentrated in urbanized areas owing to the proximity to tertiary care centers and professional isolation in rural areas. To address the needs of rural population, regional Outreach Clinics to underserved area was started in Kentucky 5 decades ago.

**Methods:** It is a retrospective chart review study. We looked at disease spectrum, number of cases, socio-economic status of areas served and team experience within last 15 years to ascertain effectiveness of the outreach program. We compared our results with the study published in 1978.

**Results:** In eastern Kentucky we have 9 regional clinics with 81 clinic days and 23 telemedicine days. We saw 1639(40%)more patients in 2014 as compared to annual average of 992/year from 1990-2001 with 60-70% show rate. 13% of cases were seen via telemedicine. On average
5-7% underwent Video EEG monitoring, 15% routine EEG, 7-10% MRI of head and 3% nerve conduction studies. Based on ICD code, these diagnosis were given: 66% epilepsy, 8% migraine, 7% developmental delay, 5% cerebral palsy 4%, movement & neuromuscular disorder, 3% congenital structural or metabolic disorder, and 2% neoplastic brain lesion.

**Conclusions:** Travel clinics not only provide excellent medical care for neurology patients in rural areas but provide a good learning/training endeavors for residents and change the trend by horizontal distribution of resources rather than concentrating in urban areas.

**Keywords:** Epilepsy, History/Teaching of Child Neurology, Neuromuscular disorders

**156. Trust but Verify: misrepresentation of publications among child neurology residency applicants**

Weisleder P (Columbus, OH), Campbell JL

**Introduction:** The authors of several publications have demonstrated that misrepresentation of publication records is commonplace among residency applicants. The prevalence of this practice ranges from 17.6% in pediatric surgery to 1.9% in ophthalmology.

**Objective:** We sought to determine the percentage of Child Neurology residency applicants that falsify information about publications in the documents submitted to the Electronic Residency Application Service (ERAS).

**Methods:** The data of all individuals who applied to our residency program for the past 2 years (194 individuals) was analyzed. Publications were verified by searching databases including PubMed, Google Scholar, Embasa, and Ulrich Periodicals Directory. Searches were conducted using all available information (author names, article title, journal name) in combination and separately. Articles in inaccessible publications, and those listed as “in press” or “accepted” were disregarded. Misrepresentation was recorded if one of the following was identified: misattributing authorship; listing a nonexistent article; listing a nonexistent article; promoting the applicant’s name on the authors’ list; and reporting the article as published in a more prestigious journal.

**Results:** Over a two-year period, we found that 12 candidates (6.2%), submitted unquestionably fraudulent information regarding their publications record. In 11 instances the candidate was not an author, in 7 the paper did not exist, and in 2 the article was published in a less prestigious journal than that reported.

**Conclusions:** Unfortunately, Child Neurology residency applicants are as apt to submit fraudulent information to ERAS as those to other specialties. Stringent review of applications before interview invitations are issued, and NRMP lists are submitted is warranted.

**Keywords:** History/Teaching of Child Neurology

**157. Improving Skills in Amplitude-integrated EEG (aEEG) in the Neonatal Intensive Care Unit**

Williams CY (Stanford, CA), Van Meurs KP, Randall KS, Wusthoff CJ

**Objective:** Amplitude-integrated electroencephalography (aEEG) is an increasingly popular bedside tool used in the Neonatal Intensive Care Unit (NICU), and is highly dependent on user experience and skill. However, there is no widely used method for training or certifying users in aEEG interpretation. The goal of this study was to evaluate the utility of a focused online training program to improve NICU staff skills in aEEG use and interpretation.

**Methods:** We created a 1-hour online video training module in aEEG use and interpretation. We assessed NICU staff skills before and after completion of the module in four areas: aEEG theory, aEEG practices, aEEG interpretation, and “raw” EEG interpretation. Improvement was assessed using McNemar and paired t tests. ANOVA was used to determine whether any particular group of NICU staff differed in their improvement.

**Results:** 57 participants completed the intervention and online post-test. Within group comparisons revealed that participant group mean scores significantly improved at post-test as compared with pre-test knowledge for all groups of healthcare practitioners (table). This improvement was seen for all of the question types represented: aEEG theory, aEEG practices, aEEG interpretation, and “raw” EEG interpretation. Improvement was assessed using McNemar and paired t tests. ANOVA was used to determine whether any particular group of NICU staff differed in their improvement.

**Conclusions:** These results suggest that a one-time, online training module can improve aEEG skills. Such an intervention may be useful for staff using aEEG in their NICUs.

<table>
<thead>
<tr>
<th></th>
<th>Pre-Test: mean score (SD), of 23 max possible, % correct</th>
<th>Post-Test: mean score (SD), of 23 max possible, % correct</th>
<th>Repeated Measures t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean of Differences, %</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>Attendings</td>
<td>9.73 (3.99), 42.3%</td>
<td>18.60 (1.84), 80.9%</td>
<td>8.87, 38.6%</td>
</tr>
<tr>
<td>Fellows</td>
<td>12.53 (3.20), 53.6%</td>
<td>18.33 (2.06), 79.7%</td>
<td>6.25, 27.2%</td>
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<tr>
<td>Nurse Practitioners</td>
<td>9.47 (2.20), 41.2%</td>
<td>15.67 (1.88), 68.1%</td>
<td>6.2, 27.0%</td>
</tr>
<tr>
<td>RNs</td>
<td>10.81 (3.53), 47.0%</td>
<td>14.50 (3.67), 63%</td>
<td>3.69, 16.0%</td>
</tr>
<tr>
<td>All subjects</td>
<td>10.19 (3.49), 44.3%</td>
<td>16.44 (3.08), 71.5%</td>
<td>6.25, 27.2%</td>
</tr>
</tbody>
</table>

© 2015 American Neurological Association  S223
Keywords: History/Teaching of Child Neurology, Neonatal neurology

158. Standardized Handoffs Improve Patient Care and Provider Satisfaction on Inpatient Child Neurology Services
Yuskaitis CJ (Boston, MA), An S, Kim SY, Ozonoff A, Maski KP

Objective: Communication among healthcare providers is a frequent and preventable cause of medical errors. Standardized handoffs have reduced medical errors in a general pediatric inpatient service and improved the completeness, accuracy, and resident satisfaction of handoffs on an adult neurology service. We hypothesized that a standardized written handoff tool would improve medical error rates and provider satisfaction on inpatient child neurology services.

Methods: 17 child neurology residents at a single institution were included. Intervention consisted of integrating the pre-intervention handoff document into a standardized format generated by the electronic medical record which includes updated laboratory and medication data. Medication-related adverse events via the hospital safety event reporting system (SERS) was obtained for the 6 months (Feb. 2013 - Aug. 2013) prior to intervention and 10 months (Sept. 2013 - Jun 2014) after intervention. Pre- and post-intervention surveys of residents (n = 17) satisfaction and perception of the written handoff tool was collected and analyzed.

Results: Implementation of the standardized written tool resulted in a 63% decrease in medication-related SERS reports on the inpatient child neurology services. Comparison of pre- and post-intervention surveys of residents resulted in a 60% increase in ease of access and 45% decrease in perceived time updating the standardized handoff document. Importantly, the standardized written handoff increased resident satisfaction by 48%.

Conclusions: Implementing a standardized and integrated written handoff document decreases reported medication-related adverse events and increases work efficiency on inpatient child neurology services. Future research includes measuring the impact of standardizing both the written and verbal handoff components.

Keywords: History/Teaching of Child Neurology

159. Pay Gap Exists for Female Physicians in Neurology
Zecevati N (Washington, DC), Oyegbile TO, Peeples C, Santos C

Objective: To assess whether gender differences in compensation and productivity exist among child neurologists in the United States.

Methods: An analysis of the 2012 and 2013 data presented in the Neurology Compensation and Productivity Report published by the American Academy of Neurology (AAN) was performed.

Results: Compensation data from 606 (2012) and 881 (2013) neurologists was analyzed in the form of aggregate data extracted from the AAN Compensation and Productivity Report. Eight percent of these responders (N=48) identified their primary subspecialty as child neurology in 2012 and 10% (N=86) in 2013, representing the 3rd and 4th highest responder groups, respectively. In 2012, median compensation by gender showed that at the 25th% female neurologists earned $128,926 vs. $181,521 for males. At the 50th% percentile the gap expanded to $176,484 for women vs. $242,778 for men. At the 75th%, the gap expanded further to $234,146 for women vs. $314,000 for men representing a $79,854 difference. While median physician revenue by gender was not assessed in 2012, in 2013, median physician revenue was $344,593 for women and $450,000 for men. In 2013, the overall median annual compensation for women was $209,653 vs $250,000 for men.

Conclusions: Based on this data, there appears to be a disparity in compensation between female and male neurologists, including child neurologists. Female physicians also generate less revenue suggesting that factors such as childbirth and maternity leave may hinder a female neurologist’s ability to achieve parity in pay when compared to their male counterparts.

Keywords: History/Teaching of Child Neurology

Association of Child Neurology Nurses (ACNN) Poster Presentations

160. Glut1 Transporter Deficiency presenting as Alternating Hemiplegia of Childhood
Ward K (Memphis, TN), Ledet D, Shab N

GLUT1 is a rare metabolic disorder characterized by low cerebrospinal fluid (CSF) glucose level caused by decreased activity of the glucose transporter protein. The typical presentation is that of infantile-onset refractory epilepsy, movement disorder, developmental delay, and acquired microcephaly. This presentation highlights a case of Glut1 deficiency with recurrent transient hemiparesis and focal dystonia as the presenting symptoms.

A 3 year old male first presented at 27 months with transient hemiparesis and focal dystonia. He was born full term and had normal growth and development with mild expressive speech delay. At his initial presentation, differential diagnoses included transient ischemic attack and seizure with postictal weakness. Neuroimaging was normal (MRI and MRA); his EEG showed mild left posterior slowing. Over the next four months, he had three similar episodes of transient hemiparesis. Symptoms were at longest 2-3 hours and his exam was normal other than a mild ataxic gait. Investigations and genetic studies for AHC were sent including ATP1A2, SCN1A, CACNA1A2, plus SLC2A1, all of which were normal except a variant of SLC2A1. CSF studies revealed aglucose of 33 with a corresponding serum glucose of 74 (ratio 0.44). The diagnosis of Glut1 transporter deficiency was confirmed and the ketogenic diet was
started. He has not had any further episodes of hemiparesis or dystonia since being on the ketogenic diet and continues to have developmental progression.

Conclusions: GLUT1 deficiency is a unique, treatable metabolic encephalopathy with varied clinical presentations. High index of suspicion and CSF studies for glucose levels should be performed in children with alternating hemiplegia and focal dystonia. This case highlights the importance of early recognition, diagnosis, and treatment of this rare disorder in a child with recurrent hemiparesis and dystonia.

161. Patient Engagement in the Research Process
Duffy L (Boston, MA)

Objective: The purpose of this study was to gain knowledge that can be applied to the development of a decision support tool to better aid families of children and adolescents with pediatric onset multiple sclerosis (POMS) in the decision-making process surrounding disease-modifying therapy. This study utilizes the approach supported by PCORI of engaging patients in each phase of the research process to help improve patient outcomes. The specific aim of this study was to describe the experience of decision making related to the use of disease-modifying therapy in patients with POMS and their parents.

Methods: Focus groups were conducted with four populations: 1) young adolescents ages 12 to 15 years with POMS, 2) adolescents ages 16 to 18 years with POMS, 3) young adults ages 19 to 24 years with POMS, and 4) parents of children ages 12 to 24 years who have a diagnosis of POMS. Participants were recruited from a pediatric MS clinic at an urban quaternary academic medical center.

Results: Data collection is currently ongoing. Analysis of the data obtained from the focus groups will include: Field notes about the environment, and participant observation, context, and tone will be added, In vivo codes will be identified and a codebook will be developed. Similar codes will be clustered, content validity will be assessed by initial focus group participants and also a group of multidisciplinary content experts

Conclusions: Findings from this study will inform the development of educational resources and a decision-making support tool to facilitate shared decision making regarding disease modifying therapy in POMS. Patient-reported outcome measures will be used to evaluate the effectiveness of the decision support tool. Findings from this study can be generalizable to a variety of chronic conditions that would benefit from patient engagement in the decision making process.

162. New Seizure Diagnosis: Educating the Caregivers
Atkinson C (Boston, MA), Kelly T, Duffy L

Objective: To develop a process of providing consistent, relevant information to caregivers of children with seizures. To initiate routine interventions using skills and teach-back to assure caregivers understand the diagnosis, seizure first aide, and medication administration and potential side effects prior to discharge.

Background/Significance: A new multidisciplinary approach to Quality Assurance/Performance Improvement (QAPI) was undertaken several years ago. A leadership triad of physician, nurse and MPH support specialist met with representative clinical stakeholders in inpatient and outpatient settings. The goal was to identify one area of clinical care we could improve to benefit our patients and families.

Findings: Patient education provided at the time of new seizure diagnosis was chosen because of its high volume and increased risk for calls to outpatient before first followup visit, return to the emergency department, readmission and medication side effect. The educational materials currently used were reviewed, edited and supplemented with additional materials. A dynamic checklist tool “Ticket Home” was utilized to track the completion of each aspect of the education provided.

Implications/Next Steps: The result is an educational packet of consistent materials, supplemented by unique materials such as medication information sheets, provided to all families of children with diagnosis of new onset seizure. At time of follow-up visit, a RedCap survey was administered to measure retained knowledge and query regarding the usefulness of materials distributed. Based on the response, the materials were again modified and edited and the second cycle of review is underway. One topic, SUDEP, originally omitted is now included at the physician’s discretion. This educational packet has now been available in the outpatient Epilepsy and Neurology settings for both new and established patients and in the inpatient setting for established families requesting a refresher.

163. Initiative to Prevent EEG Lead-Related Pressure Ulcers
Atkinson C (Boston, MA), Quigley S, Hamilton S

Objective: To develop a process for prevention of skin breakdown in patients undergoing continuous EEG monitoring. To initiate routine interventions in the management of patients on continuous EEG monitoring.

Background/Significance: Availability of medical technology to support clinical care can lead to increase usage and in some cases extending the duration of continuous electroencephalogram monitoring. In some instances monitoring is interrupted for testing, such as MRI, and resumed thereafter. Adverse effects of prolonged testing and the removal and reapplication of leads, are pressure ulcers and other skin-related issues.

Findings: In response to a pressure ulcer event, a multidisciplinary team, now referred to as the "EEG Skin Task Force", convened to review prior adverse event reports and current practice. The group determined the guideline for managing patients on EEG monitoring could be revised to include more specific steps the technologist, nurse and physician could institute to prevent skin injury while maintaining the quality of studies. A policy and procedure was adopted and hospital- wide education was rolled out with the support of the Skin SME and EEG Skin Task Force. Communication has improved through the use of a Power Form tool in the patients’ electronic medical record.
Implications/Next Steps: The change in practice has improved awareness in the clinical providers of the vulnerability of patients on continuous monitoring. The number of EEG lead skin-related events has decreased. A 100% review of all continuous EEG monitoring is done weekly for adherence to the updated policy and shared with the staff. A risk cause analysis is done on all reports of EEG lead skin issues. The technologists continue to explore available products and setup techniques. And as a team, thoughtful review of extended studies is discussed. The EEG Skin Task force will continue to meet quarterly.

164. Improving the Hospital Experience for Individuals with Intellectual Disabilities
Akinson C (Boston, MA), Marti C, Pixley L

Objective: Development of a process to proactively prepare not only the care team, but the patient and family for the medical experience. Initiate a preadmission screening for patients identified by the provider as aggressive or possibly behavioral. Formulate and institute an individualized plan of care.

Background/Significance: An increasing number of cognitively challenged and impaired children, including children on the autism spectrum, are elective admissions to our Inpatient Neuroscience and Epilepsy Monitoring Unit to facilitate diagnostic evaluation. Our response to behavioral issues was crisis intervention mode.

Methods: The admission coordinator who activates the outpatients with behavioral issues is shared with a core inpatient clinical team and triaged for a telephone interview by either the behavioral response team (BRT) or child life specialist (CLS). This contact establishes a relationship with the caregivers and a mutually developed behavioral plan, as well as a crisis management plan for the duration of the hospitalization is prepared and entered into the EMR.

Findings: Understanding unique triggers and de-escalation techniques for the individual has improved the patient experience in the medical environment. Although the intensity of resources and additional preparation and training to care for this patient population was identified by the care team of nurses (RN), technologists and CLS, our success rate accomplishing the goals for admission have improved substantially.

Implications/Next Steps: For the program, this quality improvement project developed a process to proactively prepare not only the care team, but patients with intellectual disabilities and their family, for the medical experience. The process has improved patient and staff safety, improved the overall hospital experience and resulted in staff and family satisfaction.

165. Comprehensive Care and Management of Leigh Syndrome at the UT Mitochondrial Center of Excellence
Minor L (Houston, TX), Williams S, Adejuoro R

Objective: To review the clinical presentation, neuroimaging findings, and management of patients with genetically confirmed Leigh syndrome at a comprehensive Leigh Syndrome clinic.

Findings: We reviewed the clinical presentations, imaging findings, and management of 15 genetically confirmed Leigh syndrome patients followed at the University of Texas Mitochondrial Center of Excellence. Of our 15 patients, 9 were male and 6 were female. The age of first symptom onset was birth in 6 (40%), less than two years in 4 (26%), and more than three years in 5 (33%). The most frequent presenting symptoms were hypotonia (11, 73%), developmental regression (n=11, 73%), hypertonia (n=4, 26%), and ataxia (n=4, 26%). Genetic studies showed mitochondrial DNA mutations in 11 and nuclear mutations in 4. MR findings included lesions in the brainstem in 7 patients (46%), basal ganglia in 12 (80%), thalami in 3 (20%), cerebellar white matter in 2 (13%), and global atrophy in 2 (13%). Medical life-saving interventions were needed for 7 patients (47%). Gastrostomy tubes were placed in 7 (47%) and 5 out of 15 (33%) required supplemental oxygen with 2 (40%) of these involving mechanical ventilation. Each of these cases required substantial nursing intervention and coordination.

Conclusions: Leigh syndrome is a devastating neurodegenerative disorder with multi-system involvement requiring comprehensive nursing management. Historically it is described as presenting in infancy with death by 2 years. Diverging from the classic descriptions, we found a significant proportion of patients presenting after the third year of life (33%). Nursing coordination increased dramatically in those surviving beyond the previously described life expectancy. As expected by their presentation, the majority of patients with Leigh syndrome and diagnosed and managed in a pediatric neurology setting making it imperative that neurology nurses are familiar with the management of this condition.

166. Cardiac Neurodevelopment: good fit for a Neurology APN Clinic
Greene-Roethke C (Wilmington, DE)

With medical and surgical advances, babies with congenital heart disorders are now living well into adulthood, meaning that the focus of care needs to shift from survival to quality of life. Recent investigations have highlighted the many potential neurologic complications that may accompany congenital heart disease and their impact on childhood development. I partnered with the Developmental Psychologist who performs assessments for research within our cardiac surgery program to launch a neurodevelopmental program that was instituted in our hospital two years ago. The program combines neurology assessments at the bedside and outpatient, family support and education that begin in the perioperative stage, and ongoing neurodevelopmental evaluations with a team that includes Therapists and Dieticians. Anecdotally, parents report greater satisfaction and professionally we feel we are contributing positively to the body of knowledge in this area.
Late Breaking Posters

167. Thyroid Hormone Disruption Effects Lamination of the Neocortex but Not the Cerebellum in a Model of Developmental Hypothyroidism
VanDine SE (New York, NY), Gilbert ME, Ramos RL

Objective: Research on neurodevelopmental changes resulting from thyroid hormone (TH) disruption in utero has important clinical implications; subclinical hypothyroidism has been linked to mild cognitive and psychomotor deficits in neonates, infants, and children. Previous rodent models demonstrated hypothyroidism in utero can cause the formation of subcortical band heterotopia, indicating that TH plays a role in neuronal migration during corticogenesis. This present study seeks to analyze effects of subclinical levels TH disruption on neocortical and cerebellar development.

FIGURE 1: Developmental hypothyroidism induces a bilateral malformation, a heterotopia, in the corpus callosum of the rat. A, Nissl-stained section from control animal. B, Nissl-stained section from a PN23 rat exposed to 10PPM PTU from GD6.

FIGURE 2: A. Nissl-stained midsagittal section of the rat brain with a heterotopia of the primary fissure. B. Higher magnification of heterotopia reveals a lack of pia at adjacent molecular layers compared to normal folia.

FIGURE 3: Cortical lamination is not altered remotely, in the anterior cortex, nor surrounding SBH in pups given 10p.p.m. PTU in the gestational and postnatal period. (a)–(c) Neurons belonging in layer VI are not disrupted in the anterior cortex, nor present in SBH. (d)–(f) Neurons belonging in layer IV/V are not disrupted in the anterior cortex, nor present in SBH. (g)–(i) Neurons belonging in layer II/III are not disrupted in the anterior cortex, nor present in SBH. (a), (d), (g) Demonstrate cortical sections from the anterior cortex at 4X magnification. (b), (e), (h) Demonstrate bilateral SBH (4X magnification). (c), (f), (i) SBH (10X magnification).
Methods: Pregnant rats were administered propylthiouracil (PTU) via the drinking water from gestational day 6 until postnatal day 21. Brains from adult offspring from PTU dose groups were harvested for Nissl staining and immunocytochemical analysis to visualize cell types and lamination defect in the cerebellum and neocortex. Chi-square analysis was used to compare across groups.

Results: All doses of PTU tested produced a heterotopia in the cortex, which increased in size with increasing dose level and were correlated with reduced serum levels of T4. In contrast, no cerebellar lamination defects were observed at any dose, although the presence of heterotopia was observed in all groups. Analysis indicated no significant dose-dependent increase in prevalence of heterotopia.

Conclusions: Although hypothyroidism produces robust and permanent neo-cortical malformations, cerebellar lamination and foliation appear intact when assessed in adult tissue. However, examination of neonatal and juvenile cerebellar tissue from treated rats may reveal migration delays. Together with the previous findings, these data indicate that mild TH disruption can affect brain development, but these effects are both timing- and region-specific.

Keywords: Cognitive/Behavioral Disorders

168. Long Term Efficacy and Safety of Low-dose Fenfluramine Treatment in Dravet Syndrome
Schoonjans A-S (Antwerp University Hospital, Belgium), Marchau F, Paelinck B, Lagae L, Ceulemans B

Introduction: Fenfluramine (FFA) has demonstrated antiepileptic activity. A Belgian Royal decree permitted use of

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>- Male (N, %)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>- Female (N, %)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Current age (Mean, SD)</td>
<td>23.5 year (+/- 8.83 y)</td>
</tr>
<tr>
<td>Age when Fenfluramine Started</td>
<td>6.3 year (+/- 5.25 y)</td>
</tr>
<tr>
<td>Current weight (Mean, SD)</td>
<td>63.7 kg (+/- 20.56 kg)</td>
</tr>
<tr>
<td>Starting Dose of Fenfluramine</td>
<td>12 mg (+/- 5.88 mg)</td>
</tr>
<tr>
<td>Current Dose of Fenfluramine</td>
<td>16 mg (+/- 4.59 mg)</td>
</tr>
<tr>
<td>Duration of Fenfluramine Therapy</td>
<td>191.9 months (+/- 93.31 months)</td>
</tr>
<tr>
<td>Cumulative Dose of Fenfluramine</td>
<td>96 240 mg (+/- 871 mg)</td>
</tr>
</tbody>
</table>

FIGURE 4: Nissl stained mid-vermal sections of the cerebellum, demonstrating: (a) Foliation pattern with no MLH in control pup, 0p.p.m. PTU (2X). Lobules labeled i-x. fp = primary fissure; sf = secondary fissure. (b) Higher magnification of lobules iii and iv separated by the primary fissure(10X). (c) Foliation pattern with MLH in pup given 10p.p.m. in the gestational and postnatal period (2X). (d) Higher magnification of MLH as seen in (b)(10X).

TABLE 1. Demographic data of the included patients

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| Patient number | Gender | Current Age (yrs) | Current weight (kg) | Age at start with fenfluramine (yrs) | Starting daily dose Fenfluramine (mg/d) | Current daily dose Fenfluramine (mg/d) | Interruption fenfluramine treatment (Y/N) | Duration Fenfluramine treatment (months) | Clinical signs of valvulopathy or pulmonary hypertension (Y/N) | Echographic signs of valvulopathy (Y/N) | Previous echocardiography's performed (N/Y) | Echographic signs of valvulopathy (Y/N) | Number of echocardiography's performed | Echographic signs of valvulopathy (Y/N) |
|----------------|--------|------------------|--------------------|-------------------------------|----------------------------------|------------------------------------|-----------------------------------------|---------------------------------------------|----------------------------------------------------------------------------------;---------------------------------------------------------------------------------|----------------------------------------------------------------------------------;---------------------------------------------------------------------------------|----------------------------------------------------------------------------------;---------------------------------------------------------------------------------|----------------------------------------------------------------------------------;---------------------------------------------------------------------------------|----------------------------------------------------------------------------------;---------------------------------------------------------------------------------|----------------------------------------------------------------------------------;---------------------------------------------------------------------------------|----------------------------------------------------------------------------------;---------------------------------------------------------------------------------|
| 1              | M      | 30               | 75                 | 6                             | 20                               | 20                                 | N                                       | 278                                                        | N                                                                                 | N                                                                                 | Y (aortic valve)                                                                            | Slightly thickened aortic leaflets Stable since 2010                                    |                                                                      |                                    |
| 2              | M      | 20               | 61                 | 2                             | 5                                | 15                                 | Y                                       | 153                                                        | N                                                                                 | N                                                                                 | Normal                                                                               | Slightly thickened AML (2013)                                                   |                                                                      |                                    |
| 3              | F      | 7                | 21.9               | 2                             | 10                               | 10                                 | Y                                       | 52                                                       | N                                                                                 | N                                                                                 | Normal                                                                               | Normal                                                                               |                                                                      |                                    |
| 4              | F      | 26               | 99                 | 13                            | 20                               | 20                                 | N                                       | 158                                                        | N                                                                                 | N                                                                                 | Slightly thickened AML (2014)                                                   | Normal                                                                               |                                                                      |                                    |
| 5              | M      | 22               | 51.6               | 1                             | 10                               | 10                                 | Y                                       | 241                                                        | N                                                                                 | N                                                                                 | Slightly thickened AML (2014)                                                   | Normal                                                                               |                                                                      |                                    |
| 6              | F      | 17               | 64                 | 7                             | 2                                | 20                                 | Y                                       | 120                                                        | Y                                                                                 | N                                                                                 | Normal                                                                               | Slightly thickened AML (2012)                                                   |                                                                      |                                    |
| 7              | F      | 29               | 80                 | 2                             | 10                               | 10                                 | Y                                       | 309                                                        | N                                                                                 | N                                                                                 | Normal                                                                               | Normal                                                                               |                                                                      |                                    |
| 9              | M      | 19               | 52.5               | 12                            | 10                               | 10                                 | N                                       | 72                                                         | N                                                                                 | N                                                                                 | Normal                                                                               | Normal                                                                               |                                                                      |                                    |
| 10             | F      | 40               | 74                 | 15                            | 10                               | 20                                 | Y                                       | 287                                                        | N                                                                                 | N                                                                                 | Normal                                                                               | Normal                                                                               |                                                                      |                                    |
TABLE 3. Effect Fenfluramine

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Current AED (in combination with FFA)</th>
<th>Number of TC seizures in the year before the last consultation</th>
<th>EEG (at last consultation)</th>
<th>Duration seizure freedom (if appropriate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>VPA</td>
<td>0</td>
<td>Normal</td>
<td>Seizure free since 13 years</td>
</tr>
<tr>
<td>2</td>
<td>VPA, TPM, Ethyl loflazepate</td>
<td>1</td>
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<td>Seizure free since 2 years</td>
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Conclusions: FFA provides long term, clinically meaningful, seizure control with 60% of this group continuing to experience long intervals of seizure freedom. There were no signs of clinically relevant cardiovascular side-effects and FFA was generally well tolerated. Phase 3 trials will begin at the end of 2015.

Keywords: Epilepsy

169. Anticonvulsants in Sturge-Weber Syndrome
Kaplan EH (Baltimore, MD), Kossoff EH, Bachur CD, Ghodston M, Hahn J, Widlus M, Comi AM

Objective: This study aimed to determine which anticonvulsants best control seizures in subjects with Sturge-Weber (SWS) and their side effects.

Methods: 108 research subject records from a single SWS center were retrospectively analyzed for SWS brain involvement, epilepsy, SWS neuroscores, and currently used anticonvulsants.

Results: The first-line anticonvulsants chosen were carbamazepine/oxcarbazepine or levetiracetam. Those whose...
seizures at most recent visit were fully controlled (seizure-free) for ≥6 months were more likely to have ever tried, or currently use carbamazepine/oxcarbazepine than those with uncontrolled seizures. 39 were seizure-free of 69 with carbamazepine/oxcarbazepine history versus 11 of 35 without, p<0.05; 38 were seizure-free of 62 currently taking these AEDS versus 12 of 42 not taking them, p<0.01. Seizure scores at the most recent visit were also significantly better in those with current carbamazepine/oxcarbazepine use than those without (p<0.01). Patients with ≥6 months of seizure control were less likely to have ever tried, or to currently be on levetiracetam than those without control. 16 were seizure-free of 56 with levetiracetam history versus 34 of 48 without, p<0.0001; 14 were seizure-free of 43 currently taking levetiracetam versus 36 of 61 not taking it, p<0.01. When topiramate was added as second line medication, 5/9 showed decreased seizure severity and worsening of glaucoma was not reported.

**Conclusions**: Carbamazepine/oxcarbazepine was associated with better seizure control than levetiracetam in this SWS patient cohort and so may be preferred as initial therapy. When used as adjunctive therapy, topiramate was effective in this limited analysis without clear increased incidence of glaucoma.

**Keywords**: Epilepsy, Stroke

### 170. Novel Gene Discovery in the Epilepsies Using Diagnostic Exome Sequencing

**Bergner AL** (Aliso Viejo, CA), **Helbig KL, Powis Z, Shinde DN, Hagman KE, Tang S**

**Objective**: Although diagnostic exome sequencing (DES) is transforming understanding and management of neurological diseases, the diagnostic rate reported by clinical laboratories analyzing only characterized genes has rarely exceeded 25–30%. DES simultaneously interrogates virtually all coding genes, providing unprecedented opportunities for novel gene discovery.

**Methods**: 314 unselected cases recently submitted to our lab with an indication of epilepsy underwent DES with analysis of characterized genes and, if negative, evaluation of variants in novel genes.

**Results**: Our diagnostic rate was 38.2% (120/314), with novel genes accounting for 12.5% (15/120) of positive cases. Additionally, 12.8% (5/39) of all uncertain/possibly positive cases involved novel genes. Altogether, these 20 cases represented 24 novel genes, with multiple novel genes found in three cases. Following our reporting of these genes, 37.5% (9/24) were subsequently reported in at least one publication with a median delay of 29.7 weeks and four (COQ4, DNM1, IL21R, PURA) were confirmed as dedicated disease genes in independent publications, on average within 20 weeks.

**Conclusions**: The inclusion of novel gene analysis as part of DES is of significant diagnostic value in the epilepsies. Novel gene interpretation for singleton cases is challenging and such findings cannot be definitively stated as causative. However, the 12.5% positive rate and the 37.5% corroboration rate in our cohort thus far demonstrate that overall clinical utility outweighs uncertainty for reporting novel findings. Novel gene reporting can both add to the growing body of evidence for Mendelian disease etiology in the epilepsies and aid in healthcare management of affected individuals.

**Keywords**: Epilepsy, Genetics

### 171. Non-Canonical Mechanisms and Therapeutic Targets of Mitochondrial Hyperfunction in Tuberous Sclerosis

**Pomerantz DJ** (Nashville, TN), **Armstrong LC, Armour EA, Carson RP, Eus KC**

**Objective**: The primary goal of this research is to determine Tuberous Sclerosis Complex (TSC) disease specific roles of mammalian target of rapamycin complex 2 (mTORC2) and MEK ERK signaling in mitochondrial function, neural development and aging.

**Methods**: A homozygous knockout of TSC2 gene and a conditional knockout (CKO) of RICTOR were created in two lines of MEFs. Skin cells from control human patients and TSC patients with TSC2 gene mutations were biopsied and undifferentiated through pluripotent stem cell induction. iPSCs were differentiated into neural progenitors with dual-Smad neural induction media for 7 days. NPCs were grown in low adherent plates for 72 hours to generate neurospheres. Cells and neurospheres were treated with Vehicle, Rapamycin, a selective mTORC1 inhibitor, or Torin2, a dual inhibitor of mTORC1 and mTORC2 for 24 hours. Mitochondrial Membrane Potential of iPSCs, NPCs and MEFs was assessed by a JC-1 assay via Red/Green Fluorescence Ratio of individual cells. Neurospheres were grown in vehicle, Rapamycin and Torin2 media conditions for 48 hours in a neurosphere migration assay.

**Results**: Relevant results, graphs and images attached in separate document.

**Conclusions**: Mitochondrial hyperfunction in TSC is associated with increased mTORC1, decreased mTORC2 and increased MEK/ERK signaling pathways. TSC

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**FIGURE 1: A Model for non-canonical mechanisms and therapeutic targets of mitochondrial hyperfunction in tuberous sclerosis**

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FIGURE 2: Mitochondrial Membrane Potential is hyperpolarized in a RICTOR dependent pathway but is rescued by Rapamycin therapy. (A) Representative pictures of individual Mouse Embryonic Fibroblasts with labeled pharmacologic conditions. (B) RICTOR KO and TSC2−/− MEFs cells have a 1.6–1.8 fold increase in JC-1 Red/Green ratio which is normalized by Rapamycin therapy but not equivalent Torin2 therapy. (Data not shown- TSC2−/−; p53−/− JC-1 Red to Green Ratio not significantly different from CRE-RICTOR)

FIGURE 3: Mitochondrial Membrane Potential is hyperpolarized in Heterozygous Mutant TSC induced pluripotent stem cells and is rescued by Rapamycin therapy. (A) Representative pictures of individual induced pluripotent stem cell colonies with labeled pharmacologic conditions. (B) TSC heterozygous mutant cells have a 1.5 fold increase in JC-1 Red/Green ratio which is normalized by Rapamycin therapy but not equivalent Torin2 therapy.
FIGURE 4: Mitochondrial Membrane Potential is hyperpolarized in Heterozygous Mutant TSC neural progenitor cells and is rescued by Rapamycin therapy. (A) Representative pictures of individual neural progenitor cell colonies with labeled pharmacologic conditions. (B) TSC heterozygous mutant cells have a 1.5 fold increase in JC-1 Red/Green ratio which is normalized by Rapamycin therapy but not equivalent Torin2 therapy.

FIGURE 5: Tuberous Sclerosis Patient Stem Cells express Tuberin and Hamartin but do not activate mTORC1 signaling (A) Representative pictures of Western Blots of Hamartin and Tuberin, the gene products of TSC1 and TSC2. Quantitative analysis demonstrate no significant difference in expression level. (B) Representative pictures of Western Blots of pS6, an intracellular signaling marker for increased mTORC1 signaling. Quantitative analysis demonstrate no significant difference in expression level.
FIGURE 6: MEK-ERK Signaling is Increased in TSC Heterozygous mutant iPS Cells and RICTOR CKO MEFs. (A) Significant Increase in P-ERK signaling in TSC Heterozygous Mutant iPS cells compared to control patient iPS cells (B) Significant Increase in pERK signaling RICTOR KO and TSC2−/−; p53−/− compared to control MEF lines.

FIGURE 7: Neuroprogenitor migration from TSC2 heterozygous mutant neurospheres is inhibited in a rapamycin/torin insensitive manner (A) Representative Pictures of Neurospheres plated for 48 hours in matrigel migration assay. Migration measured from circumference of sphere to circumference of furthest migrated cells. (B) Significant Decrease in Neurosphere Migration in TSC patient derived neurospheres which is not rescued by Rapamycin or Torin2 therapy.
dependent mitochondrial hyperfunction, but not mTORC2 nor MEK/ERK signaling can be partially rescued via Rapamycin therapy. Heterozygous TSC2 mutations in neural progenitors reduces migration distance but is not recovered by mTORC1/2 inhibition therapies. Future research should explore potential contributions of mTORC2 agonists and MEK/ERK inhibitors in long term management of aging TSC patients.

**Keywords:** Genetics

172. Potential Role of GABA-A alpha 3 Subunit Containing Receptors in the Adverse Effects of Benzodiazepine Exposure on the Preterm Brain

**Porter J** (Charlottesville, VA), Gunter SA, Jansen LA

**Objective:** We hypothesized that exposure of immature neurons to benzodiazepines may alter neuronal maturation and survival through activation of alpha 3 subunit containing GABA-A receptors.

**Methods:** Immunohistochemistry was performed on human and mouse cortex to determine the developmental stages of neurons that express the alpha 3 subunit. Embryonic mouse cortical cultures were treated with varying concentrations of diazepam and dexmedetomidine followed by immunohistochemistry.

**Results:** GABA-A alpha 3 subunit containing receptors were expressed in human cortex throughout mid to late gestation. Faint alpha 3 immunofluorescence was present in immature DCX-positive neurons, and became more intense as neurons matured and lost DCX expression. Pronounced alpha 3 expression was also present in neonatal mouse cortex. In cortical cultures, the alpha 3 subunit was present as early as DIV1 (~human 17 wk EGA). DIV4 cultures (~human 23 wk EGA) treated with diazepam showed a significant rate of apoptosis, and surviving neurons had blunted dendritic development. Dexmedetomidine, which does not activate GABA-A receptors, did not induce significant apoptosis at any treatment level.

**Conclusions:** At the developmental stage in which mouse cortical neurons express high levels of GABA-A receptor alpha 3 subunits, they are also susceptible to neuroapoptotic effects of diazepam. Human cortical neurons express alpha 3 subunits between 20 weeks gestation and term, a time period very relevant for infants in the NICU. Neurotoxicity caused by benzodiazepines could prove detrimental to the developing cortex, providing a rationale for selecting an alternative drug such as dexmedetomidine to sedate infants.

**Keywords:** Neonatal Neurology
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