FORTY-THIRD NATIONAL MEETING
OF THE CHILD NEUROLOGY SOCIETY

PLANNING COMMITTEE

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Roger Packer, Councillor  Washington, DC

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Keith Coffman  Kansas City, MO
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Sookyong Koh  Chicago, IL
Rebecca Lehman  Charleston, SC
Daniel Licht  Philadelphia, PA
Warren Lo  Columbus, OH
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John Mytinger  Columbus, OH
Marc Patterson  Rochester, MN
Steven Pavlakis  Brooklyn, NY
Mustafa Sahin  Boston, MA
Renee Shellhaas  Ann Arbor, MI
Elliott Sherr  San Francisco, CA
Peter Tsai  Boston, MA
Andrew Zimmerman  Lexington, MA

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

Presented at Hyatt Regency Columbus
Columbus, OH
October 22-25, 2014

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 The Nationwide Children’s Hospital and the Child Neurology Society. The Nationwide Children’s Hospital (NCH) is accredited by the ACCME to provide continuing medical education for physicians.

The Nationwide Children’s Hospital designates this educational activity for a maximum of 26.0 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 December 1, 2014
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- Kenneth Swaiman 1972-73
- Gerald Fenichel 1973-74
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- Richard Allen 1976-77
- Bruce Berg 1977-78
- N. Paul Rosman 1978-79
- Arthur Premsky 1979-80
- Paul Dyken 1980-81
- Mary Anne Guggenheim 1981-82
- Raymond Chun 1982-85
- David Stumpf 1985-87
- Marvin Fishman 1987-89
- Darryl C. De Vivo 1989-91
- Joseph J. Volpe 1991-93
- Michael E. Cohen 1993-97
- Alan K. Percy 1997-99
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- Nina Schor 2013-

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

**Secretary-Treasurer**
- Richard Allen 1972-75
- Raymond Chun 1975-78
- Robert Eiben 1978-81
- Lawrence Lockman 1981-84
- Marvin Fishman 1984-86
- Ira Lott 1986-89
- Peggy Copple (Ferry) 1989-93
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- Patricia Crumrine 1997-2002
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- Nina Schor 2004-2010
- Harvey Singer 2010-
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### CNS LIFETIME ACHIEVEMENT AWARDS

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

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<td>2011</td>
<td>Kyaw Linn</td>
<td>Myanmar</td>
</tr>
<tr>
<td>2012</td>
<td>Inga Talvik</td>
<td>Tartu, Estonia</td>
</tr>
<tr>
<td>2013</td>
<td>Samson Gwer</td>
<td>Nairobi, Kenya</td>
</tr>
<tr>
<td>2014</td>
<td>Jithangi Wanigasinghe</td>
<td>Dehiwela, Sri Lanka</td>
</tr>
</tbody>
</table>
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

Carolyn 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

Yoshima Sogawa
Schneider Children’s Hospital

Ignacio Valencia
St. Christopher’s Hospital

Adeline Vanderver
Children’s National Medical Center
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
2012
Partha Ghosh
Cleveland Clinic Foundation

J.J. Gold
University of California San Diego

Gayatri Mainali
Cleveland Clinic Foundation

Christopher B. Oakley
Johns Hopkins Medical Institute

2013
Anuja Jindahl
Pittsburgh Children’s Hospital

Archana Patel
Boston Children’s Hospital

Pilar Pichon
Loma Linda University

Mark Schomer
Boston Children’s Hospital

Mitchell Williams
Children’s Hospital of Michigan

2014
Jonathan Kurz
Children’s National Medical Center

Neggy Rismanchi
University of California San Diego

Siddarth Srivastava
Kennedy Krieger Institute

Kavita Thakkar
Pittsburgh Children’s Hospital

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
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
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 CLINIC
TRAINING PROGRAM DIRECTOR AWARD

2013
Harvey Singer
Baltimore, MD

2014
Steven Leber
Ann Arbor, MI

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
JoEllen Lee
Columbus, OH
THE CHILD NEUROLOGY SOCIETY GRATEFULLY ACKNOWLEDGES THE FINANCIAL SUPPORT OF

- Akron Children’s Hospital
- Arnold P. Gold Foundation
- Blue Bird Circle
- Eisai, Inc.
- Lundbeck
- Nationwide Children’s Hospital
- Questcor Pharmaceuticals, Inc.
- Sarepta Therapeutics
43rd Annual Meeting of the Child Neurology Society
Scientific Program
Columbus, Ohio
October 22 – October 25, 2014

Nina F. Schor, MD, PhD, President, CNS
Jonathan Mink MD, PhD, Chair, CNS Scientific Selection and Program Planning Committee

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

NCH designates this educational activity for a maximum of 26 AMA PRA Category 1 credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

PROGRAM

Wednesday, October 22

7:30 AM – 5:00 PM
Symposium I: Neurobiology of Disease in Children: Autism
Organizer: Bernard L. Maria, MD, MBA; Goryeb Children's Hospital, Morristown, NJ
Supported by the National Institutes of Health (5R13NS040925-09), the Child Neurology Society and Autism Speaks

7:30 AM – 7:40 AM
Opening Comments
Bernard L. Maria, MD, MBA
Story Landis, PhD; Director of NINDS, Bethesda, MD

7:40 AM – 9:55 AM
SESSION I: CLINICAL ASPECTS
Co-Director and Moderator: Stewart H. Mostofsky, MD; Kennedy Krieger Institute, Baltimore, MD

7:40 AM – 8:05 AM
Advances and Changes with DSM5
Sarah Spence, MD, PhD; Boston Children's Hospital, Boston, MA

8:05 AM – 8:30 AM
Epidemiology: Prevalence, Environment, Risk Factors
Craig J. Newschaffer, PhD; Drexel University, Philadelphia, PA

8:30 AM – 8:55 AM
Early Infant Development and Intervention
Lonnie Zwaigenbaum, PhD; University of Alberta, Edmonton, AB

8:55 AM – 9:20 AM
Co-Morbid Epilepsy and Sleep Disorders
Roberto Tuchman, MD; Miami Children's Hospital, Miami, FL

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

9:40 AM – 9:55 AM
Coffee Break

9:55 AM – 11:30 AM
SESSION II: PATHOGENESIS
Co-Director and Moderator: Stewart Mostofsky, MD

9:55 AM – 10:20 AM
Genetics
Jonathon Sebat, PhD; UCSD, La Jolla, CA

10:20 AM – 10:45 AM
MEG Insights into Neural Signaling and Connectivity
Tim Roberts, PhD; CHOP, Philadelphia, PA

10:45 AM – 11:10 AM
CNS Structure and Neuropathology
Cindy Schumann, PhD; UC Davis MIND Institute, Davis, CA

11:10 AM – 11:30 AM
Question and Answer Session

11:30 AM – 1:00 PM
Lunch and Presentation by Autism Speaks

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1:00 PM – 2:40 PM  
SESSION III: TARGETS AND TRANSLATIONAL OPPORTUNITIES  
Moderator: Emanuel DiCicco-Bloom, MD; Robert Wood Johnson Medical School, New Brunswick, NJ  
1:00 PM – TSC and mTOR Inhibitors  
1:25 PM Mustafa Sahin, MD, PhD; Boston Children's Hospital, Boston, MA  
1:25 PM – Sinai Shank3 and IGF1  
1:50 PM Joseph Buxbaum, PhD; Seaver Center Mt. Sinai, New York, NY  
1:50 PM – Rett Syndrome and BDNF  
2:15 PM David Katz, PhD; Case Western University Medical School, Cleveland, OH  
2:15 PM – Pharmacologic Interventions  
2:40 PM Diane Chugani, PhD; Children's Hospital of Michigan, Detroit, MI  
2:40 PM – Question and Answer Session  
3:00 PM – Coffee Break  

1:00 PM – 6:00 PM  
OPENING RECEPTION  
Supported by Nationwide Children's Hospital; Columbus, OH  
6:00 PM – 8:00 PM  
SIG Meetings  
Including Movement Disorders  
8:00 PM – 10:00 PM  

Thursday, October 23  

CONTINENTAL BREAKFAST  

SEMINARS  

Breakfast Seminar 1: Epilepsy Therapy Update  
Organizer: Sudha Kesler, MD; CHOP, Philadelphia, PA  
Epilepsy Therapy Update: Using the Literature to Inform our Choices  
New Medications for the Treatment of Focal Epilepsies  
Katherine Nickels, MD; Mayo Clinic, Rochester, MN  
New Medications for the Treatment of Lennox Gastaut Syndrome  
Renee Shellhaas, MD, MS  

Breakfast Seminar 2: Update on the Leukodystrophies  
Organizer: Adeline Vanderver, MD; Children’s National Medical Center, Washington, D.C.  
Introduction: New Information on Diagnosis, an Updated Algorithm and New Diseases  
Adeline Vanderver, MD  
Treatment of Common Symptoms  
Keith Van Haren, MD; Stanford University & Lucile Packard Children's Hospital  
Patient Care, Stanford, CA  
Established Therapeutics in Leukodystrophies  
Marc Patterson, MD; Mayo Clinic, Rochester, MN  
Clinical Trials in Leukodystrophies: Emerging Therapeutic Approaches  
Florian Eichler, MD; Massachusetts General Hospital, Boston, MA  

Breakfast Seminar 3: Neurodevelopmental Examination Using Telemedicine: the neuro exam in the era of mobile devices  
Organizer: Deepta Menon, MBBS; Kennedy Krieger Institute, Baltimore, MD  
Association of Child Neurology Nurses  
4:00 AM – 4:30 PM  
Professors of Child Neurology  
2:00 PM – 5:00 PM  

ADDITIONAL WEDNESDAY MEETINGS/SESSIONS  
8:00 AM – 4:30 PM  
Association of Child Neurology Nurses  
2:00 PM – 5:00 PM  
Professors of Child Neurology  

continued
Learning the Rules and the Technology of Telemedicine
Paul Lipkin, MD; Kennedy Krieger Institute, Baltimore, MD

Practical Application of Telemedicine in the Remote Assessment of Neurodevelopmental Disorders in Children
Deepa Menon, MBBS

Expanding Access: Telemedicine for Pediatric Rare Diseases Clinical Care & Research
Erika Augustine, MD; University of Rochester Medical Center, Rochester, NY

8:45 AM – 8:50 AM
Association of Child Neurology Nurses Claire Chee Award for Excellence
Jo Ellen M. Lee MSN APRN; Nationwide Children's Hospital, Columbus, OH

8:50 AM – 9:00 AM
CNS Lifetime Achievement Awards
• G. Robert DeLong, MD
• Richard Nordgren, MD

9:15 AM – 12:00 PM
Symposium II: Presidential Symposium: Plasticity and Learning in Recovery and Rehabilitation from Brain Injuries
Organizers: Jonathan Mink, MD, PhD and Nina Schor, MD, PhD; University of Rochester Medical Center, Rochester, NY

Regeneration and Repair after Cerebral Injury
Steven Back, MD, PhD; Oregon Health Sciences University, Portland, OR

Rehabilitative Strategies for Children's with CP – Current State of the Art
Darcy Fehlings, MD; University of Toronto, Toronto, ON

Constraint-Induced and Bimanual Therapy for Children with Hemiplegia
Andrew Gordon, PhD; Teachers College Columbia University, New York, NY

Locomotor Adaptation and Plasticity in Children with Brain Injuries
Amy Bastian, PT, PhD; Johns Hopkins University, Baltimore, MD

1:45 PM – 4:00 PM
Symposium III: Genetics & Biology of Early Life Epilepsies
Organizer: Alexander Paciorkowski, MD; University of Rochester Medical Center, Rochester, NY

The History of Epilepsy Classification and the Pediatric Epilepsy Research Consortium
Anne Berg, MD; Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL

Genes Active in the Nucleus and Early Life Epilepsies
Alexander Paciorkowski, MD

The Expanding Universe of Synaptic Acting Genes and Early Life Epilepsies
Annapurna Poduri, MD, MPH; Boston Children's Hospital, Boston, MA

Brain Growth Pathways and Early Life Epilepsies
Ghayda Mirzaa, MD; Seattle Children's Hospital, Seattle, WA

4:00 PM – 6:00 PM
CHILD NEURO NEWS BREAK: POSTER REVIEW
Supported by Eisai, Inc.

Friday, October 24

CONTINENTAL BREAKFAST

SEMINARS

Breakfast Seminar 4: A to ZZZZ's: CNS Hypersomnia Conditions in Children
Organizer: Kiran Maski, MD; Boston Children's Hospital, Boston, MA

Neurobiology of Sleep & Wake Systems
Kiran Maski, MD

Secondary Hypersomnia Conditions
Shelly Weiss, MD, FRCP; Hospital for Sick Children, Toronto, ON

Primary Hypersomnias
Suresh Kotagal, MD; Mayo Clinic, Rochester, MN

Breakfast Seminar 5: The Neurological Sciences Academic Developmental Award: The NINDS Physician-Scientist Career Development Award for Pediatric Neurology
Organizer: Bradley Schlagger, MD, PhD; Washington University School of Medicine St. Louis Children's Hospital, St. Louis, MO

Introduction to the NSADA Program
Deborah Hirz, MD; NINDS, Bethesda, MD

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Regulation of Vulnerability to Excitotoxicity in Developing Oligodendrocytes
Chris Elitt MD, PhD; Boston Children’s Hospital, Boston, MA

Potential Value of Health Information Exchange for People with Epilepsy
Zachary Grinspan, MD; Weill Cornell Medical School, New York, NY

Clinical Research in Tuberous Sclerosis
Tanjala Gipson, MD; Johns Hopkins University School of Medicine, Baltimore, MD

Assessment of Dissociative Steroid as Dexamethasone Substitute for Diffuse Intrinsic Pontine Glioma (DIPG)
Elizabeth Wells, MD; Children’s National Medical Center, Washington, D.C.

The Neurobiological Basis for HIV-Associated Neurocognitive Disorders and Depression in Horizontally-Infected Adolescents
Jen McGuire, MD; CHOP, Philadelphia, PA

Intraoperative EEG Monitoring in Congenital Heart Disease
Laurie Seltzer, DO; University of Rochester, Rochester, NY

Assessment of Functional Brain Development in Infants Using fMRI
Christopher Smyser, MD; Washington University School of Medicine, St. Louis, MO

Language Development and Cognitive Plasticity after Early Focal Brain Injury
Kevin Shapiro, MD; UCSF, San Francisco, CA

Source EEG Functional Networks Partially Reflect Underlying Structural Connectivity
Catherine Chu, MD; Massachusetts General Hospital, Boston, MA

Breakfast Seminar 6: Collaboration, Technology and Innovation in the Age of Health Care Reform: The Updated Child Neurology Encounter Guides
Organizer:
Julie M. Sprague-McRae, MS, RN, PPCNP-BC; Kaiser Permanente Medical Group Inc., Fremont, CA

The Child Neurology Encounter Guide Project and Innovative Electronic Patient Care Encounters
Julie M. Sprague-McRae, MS, RN, PPCNP-BC

Collaboration: The Child Neurology Society and the Association of Child Neurology Nurses
Leslie Morrison, MD; University of New Mexico, Albuquerque, NM

Child Neurology Encounter Guides in Action and Implications for Practice
Ruth Rosenblum, DNP, MS, RN, PPCNP-BC; Valley Foundation School of Nursing, San Jose, CA

8:30 AM – 10:15 AM

PLATFORM SESSIONS 1 & 2

Platform Session 1:

8:30 AM – 8:45 AM
PL1-1 Berry-Kravis E et al
Arbaclofen in Fragile X Syndrome: results of phase 3 trials

8:45 AM – 9:00 AM
PL 1–2 Chao HT et al
Context Dependent Modulation of GABAergic Gene Expression in Models of Rett Syndrome

9:00 AM – 9:15 AM
PL1–3 Franz DN et al
Everolimus for Subependymal Giant Cell Astrocytoma (SEGA) Associated with Tuberous Sclerosis Complex (TSC): EXIST 1 long-term efficacy and safety result

9:15 AM – 9:30 AM
PL1–4 Holder JL et al
SHANK3 Overexpression Causes Manic-Like Behavior with Unique Pharmacogenetic Properties

9:30 AM – 9:45 AM
PL 1–5 Jeste SS et al
Early Developmental Predictors and Behavioral Correlates of ASD in Infants with Tuberous Sclerosis Complex

9:45 AM – 10:00 AM
PL 1–6 Monani UR et al
Gene Therapy for Glut1 Deficiency Syndrome

10:00 AM – 10:15 AM
PL1–7 Tobe BTD et al; Evan Snyder, MD, PhD presenting
Using a “Molecular Can-Opener” to Model Complex Disease: probing lithium’s targets in bipolar hiPSC’s suggests a novel underlying developmental disorder

8:30 AM – 10:15 AM

Platform Session 2

8:30 AM – 8:45 AM
PL 2-1 Tully HM et al
Clinical Outcome of 237 Children with Developmental Hydrocephalus

8:45 AM – 9:00 AM
PL 2-2 Fayed N et al
Quality of Life among Children with Epilepsy from their Point of View

9:00 AM – 9:15 AM
PL 2–3 Khan SG et al
Hereditary Hypermanganesemia: a new potentially treatable metabolic disorder in four Pakistani siblings

9:15 AM – 9:30 AM
PL 2–4 Kirton A et al
Brain Stimulation and Constraint for Perinatal Stroke Hemiparesis: the plastic champs trial
9:30 AM – 9:45 AM
PL 2–5 McKnight D et al
High Positive Diagnostic Yield of Panel Testing and Whole Exome Sequencing for Patients with Epilepsy-related Neurodevelopmental Disorders

9:45 AM – 10:00 AM
PL 2–6 Olson HE et al
Genetic Mechanisms of Ohtahara Syndrome, A Cohort Study

10:00 AM – 10:15 AM
PL 2–7 Van Hove JLK
Outcome in Nonketotic Hyperglycinemia (NKH)

10:45 AM – 10:50 AM
Outstanding Junior Member Awards
M. Richard Koenigsberger Scholarship Award

10:50 AM – 10:55 AM
CNS/PCN Blue Bird Circle Training Program Director Award

10:55 AM – 11:05 AM
Arnold P. Gold Foundation Humanism in Medicine Award

11:05 AM – 11:15 AM
Child Neurology Foundation Scientific Awards

11:15 AM – 11:45 AM
Philip R. Dodge Young Investigator Award Lecture

11:45 AM – 12:30 PM
Bernard Sachs Lecture

12:45 PM – 2:00 PM
Lunch

2:15 PM – 4:30 PM
Symposium IV: Non Progressive Cerebellar Ataxia: Practical Pearls
Organizer: Michael Salman, MRCP, PhD; Children's Hospital, Winnipeg, MB
Epidemiology & Clinical Features
Michael Salman, MRCP, PhD
Cognitive & Behavioral Sequelae
Peter Tsai, MD, PhD; Boston Children's Hospital, Boston, MA

4:45 PM – 6:00 PM
Junior Member Seminars
Seminar 1: Med Students: Finding a Residency
Seminar 2: Residents: Finding a Fellowship
Seminar 3: Residents & Fellows: Finding a Job

7:00 PM – 10:00 PM
GALA RECEPTION

Saturday, October 25

7:00 AM – 7:30 AM
CONTINENTAL BREAKFAST

7:30 AM – 8:45 AM
SEMINARS
Breakfast Seminar 7: The Buzz on Medical Marijuana
Organizer: Kristen Park, MD; University of Colorado, Aurora, CO
Introduction
Kelly Knupp, MD; Children's Hospital Colorado, Aurora, CO
The ABC's of the Endocannabinoid System
Andrea Giuffrida, PhD; UT Health Science Center, San Antonio, TX
The Good, the Bad, and the Ugly: Clinical Uses of Cannabinoids
Francis Filloux, MD; Primary Children's Hospital, Salt Lake City, UT
Untangling the “Web” of Medical Marijuana: Lessons from Colorado
Kristen Park, MD

Breakfast Seminar 8: Neuroimaging Update in TBI: Clinical Perspectives & Research Advances
Organizer: Carolyn Pizoli, MD, PhD; Duke University Medical Center, Durham, NC
Prognostic Utility of Advanced MRI in Children with Moderate/Severe Traumatic Brain Injury
Stephen Ashwal, MD; Loma Linda University, Loma Linda, CA
Prospective Neuroimaging of Pediatric Mild Traumatic Brain Injury
Andrew Mayer, PhD; The Mind Research Network, U of New Mexico Health Science Center, Albuquerque, NM

Network Integrity after TBI: Insights from Functional Connectivity MRI
Carolyn Pizoli, MD, PhD

Breakfast Seminar 9: Neuro-Autoimmune Frontiers: Anti NMDAR Encephalitis & Related Conditions
Organizer: Jay Selman, MS, MD; Blythedale Children’s Hospital, Valhalla, NY
Introduction and Outcome in a Cohort of Severely Involved Children
Jay Selman, MS, MD

Clinical Presentations and Pathophysiology
Jessica Panzer, MD, CHOE; Philadelphia, PA

When the NMDA Receptor Antibody is Negative: Other Autoimmune Encephalitides in Pediatrics
Mark Gorman, MD; Boston Children’s Hospital, Boston, MA

9:00 AM – 9:45 AM
Hower Award Lecture
Michael Shevell, MDCM; McGill University, Montreal QC

10:00 AM – 12:15 PM
Symposium V: Code Stroke
Organizer: Catherine Amlie-Lefond, MD; Seattle Children’s Hospital, Seattle, WA
Moderator: Gabriele deVeber, MD, MSC; The Hospital for Sick Children, Toronto, ON

Preparing for a Childhood “Stroke Alert”
Timothy Bernard, MD; Children’s Hospital Colorado, Aurora, CO

Guidelines for Urgent Management
Michael Rivkin, MD; Boston Children’s Hospital, Boston, MA

Controversies for Urgent Management
Catherine Amlie-Lefond, MD

Outcome Measures: How Will I Know When I Get There?
Michael Dowling, MD, PhD; UT Southwestern Medical Center, Dallas TX
# Agenda for 2014 ACNN Conference Program

## Columbus, Ohio
October 22 – October 24, 2014

### Tuesday, October 21

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:00 PM</td>
<td>ACNN Welcome Reception (Nurses Only)</td>
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<tr>
<td>9:00 PM</td>
<td>Challenging Families: Trials, Tribulations and Triumphs</td>
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</tbody>
</table>

**Janet Brucker Keynote Address Project SEARCH**
J. Erin Richle, MSN, RN

### Wednesday, October 22

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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</thead>
<tbody>
<tr>
<td>7:00 AM</td>
<td>Registration &amp; Continental Breakfast</td>
</tr>
<tr>
<td>8:00 AM</td>
<td>Welcome &amp; Introduction</td>
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<tr>
<td>8:15 AM</td>
<td>Chronic Migraines in the Pediatric Population</td>
</tr>
<tr>
<td>9:00 AM</td>
<td>An Evidence Based Approach to Neuroimaging of Children with Chronic Headache</td>
</tr>
<tr>
<td>10:00 AM</td>
<td>Break</td>
</tr>
<tr>
<td>10:15 AM</td>
<td>A Nursing-Driven Pilot Study to Evaluate the Impact of a Personalized Plan of Care for Children with Autism Spectrum Disorder Preparing for Outpatient EEG’s with Anxiolysis</td>
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<tr>
<td>12:00 PM</td>
<td>Awards and Annual Business Meeting</td>
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### Thursday, October 23

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>12:00 PM</td>
<td>Lunch-SIG</td>
</tr>
</tbody>
</table>

### Friday, October 24

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:00 PM</td>
<td>Lunch-SIG</td>
</tr>
</tbody>
</table>

## Topics to be announced

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PLATFORM PRESENTATIONS

Platform Session 1
Friday, October 24
(8:30 AM - 10:15 AM)

PL1-1. Arbaclofen in Fragile X Syndrome: results of phase 3 trials

Objective: Arbaclofen rescues multiple abnormal phenotypes in animal models of fragile X syndrome (FXS), and showed promising results in a phase 2 clinical trial. The goal was to determine safety and efficacy of arbaclofen for social avoidance in FXS.

Methods: Two phase 3 placebo-controlled trials were conducted, a flexible dose trial in subjects age 12–50 (FX301), and a fixed dose trial in subjects age 5–11 (FX302). The primary endpoint for both trials was the FXS Social Avoidance (SA) subscale of the Aberrant Behavior Checklist (ABC). Secondary outcomes included other ABC subscale scores, CGI-I, CGI-S, and Vineland Socialization domain score.

Results: 119 of 125 randomized subjects completed FX301 (57 arbaclofen, 62 placebo); 159/172 completed FX302 (arbaclofen 5BID:38; 10BID:39; 10TID:38; placebo:44). There were no serious AEs, the most common adverse events included headache, vomiting, nausea, irritability/agitation, anxiety, hyperactivity, decreased appetite, and infections; many of which were also common on placebo. There were 12 discontinuations (11 arbaclofen, 1 placebo) due to AEs (all neurobehavioral). FX301 did not show benefit for arbaclofen over placebo for any measure. In FX302 the highest dose group only showed benefit over placebo on the ABC-FX Irritability subscale (p<0.05) and trends toward benefit on the ABC-FX-SA and Hyperactivity subscales (p<0.1).

Conclusions: Arbaclofen did not meet the primary outcome of improved social avoidance in FXS. Data from secondary measures and the long term treatment extension (improved Vineland Socialization) suggest some patients derive benefit, but these studies illustrate the challenges of translating targeted treatments from animal models to humans in FXS.

Keywords: Genetics, Translational/experimental therapeutics

PL1-2. Context Dependent Modulation of GABAergic Gene Expression in Models of Rett Syndrome
Chao HT, Peng Y, Han J, Heiman M, Gong S, Neul JL, Heintz N, Rosenmund C, Shaw C, Zoghbi HY (Houston, TX)

Objective: Rett syndrome (RTT) is a neurodevelopmental disorder due to mutations in MECP2, encoding methyl-CpG-binding protein 2, and is characterized by neurologic regression, impaired cognition, motor dysfunction, and autistic features. GABAergic-neuron specific MeCP2 deletion reproduced nearly all features of RTT. We hypothesize that MeCP2 regulation of GABAergic neuronal function is critical to disease pathogenesis via both a cellular-context dependent and independent manner.

Methods: We utilized mouse models of constitutive MeCP2 deficiency (Mecp2-/y) and GABAergic-neuron specific MeCP2 deficiency (Viaat-Mecp2-/y). Viaat-L10FP reporter was generated to express ribosomal protein L10 fused to enhanced green fluorescent protein in GABAergic neurons for cell type specific mRNA analysis via Affymetrix Mouse 430 2.0 microarrays. Genes were selected based on p<0.05 and log2 fold change of +/-0.5. n=3–4 per genotype.

Results: Distribution of down or up-regulated genes in cortical GABAergic neurons were similar between the two models of MeCP2 deficiency. 78 genes were shared, 18 genes down-regulated, 26 genes up-regulated, and 55 genes altered in opposite directions. Unbiased selection of 41 genes with the highest fold changes had ~70% qRTPCR validation rate (p<0.05). Gene ontology analysis reveals...
shared functions in cell communication, cell projection, growth factor activity, and metabolic processes.

Conclusions: GABAergic neuron specific gene expression profiles from MeCP2-/y and Viaat-Mecp2-/y models reveal that despite phenotypic similarity the majority of transcriptional alterations are not shared. These findings suggest that regulation of GABAergic function is influenced by the cellular context of MeCP2 deficiency and enable further elucidation of the role of GABAergic dysregulation in RTT and autism pathogenesis.

Keywords: Genetics

PL1-3. Everolimus for Subependymal Giant Cell Astrocytoma (SEGA) Associated with Tuberous Sclerosis Complex (TSC): EXIST-1 long-term efficacy and safety results
Objective: To examine the long-term safety and efficacy of everolimus, an mTOR inhibitor, in a randomized, double-blind, phase 3 trial (EXIST-1 [NCT00789828]; data cutoff January 11, 2013).
Methods: Patients (median age, 9.5 years [range, 0.8–26.6 years]) received 4.5 mg/m2/day oral everolimus (n=78; titrated to a target trough 5–15 ng/mL) or placebo (n=39). The primary endpoint, SEGA response rate, was defined as the proportion of patients with ≥50% reduction in sum of volumes of all target SEGA (≥1 cm in longest diameter) compared with baseline. Adverse events (AEs) were monitored at every visit.
Results: At the original cutoff (March 2, 2011) everolimus was superior to placebo for SEGA response rate (34.6% vs 0.0%; P<0.0001). Following positive results for the original cutoff, patients on placebo were offered open-label everolimus in the extension phase of the study. As of January 11, 2013, 111 patients had received ≥1 dose of everolimus and were included in the extension analysis presented here. The median treatment duration of everolimus was 29.3 months and the overall SEGA response rate was 48.6% (95% confidence interval, 39.0%-58.3%). The SEGA response rate with everolimus increased steadily up to week 96. The duration of SEGA response ranged from 2.1 to 31.1 months. Most AEs continued to be grade 1 or 2. The most frequent serious AEs occurring in more than 3% of patients were pneumonia (10.8%), pyrexia (4.5%), gastroenteritis (3.6%), and convulsion (3.6%).
Conclusions: Everolimus continued to reduce SEGA volume with no new safety concerns.
Keywords: Epilepsy and other paroxysmal disorders, Genetics

PL1-4. SHANK3 Overexpression Causes Manic-like Behaviour with Unique Pharmacogenetic Properties
Holder JL, Zoibiti HY (Houston, TX)
Objective: Haploinsufficiency of SHANK3 causes Phelan-McDermid Syndrome (PMS), a syndromic autism. In contrast, few cases of duplications of SHANK3 are known. Similarly, a mouse model of Shank3 overexpression has never been reported. Therefore, whether there are phenotypic consequences of SHANK3 overexpression is unclear. The goal of this work is to determine the phenotypic consequences of SHANK3 overexpression.
Methods: We interrogated the Baylor College of Medicine chromosome microarray database to identify the smallest 22q13 duplications encompassing SHANK3 ever reported. We reviewed the medical history of these patients to determine the phenotypic consequences of SHANK3 overexpression. Similarly, we created mice that overexpress Shank3 by bacterial artificial chromosome transgenesis. We performed detailed behavioral analysis and neurophysiologic characterization. We also identified in vivo protein-protein interactions of Shank3 by immunoprecipitation/mass spectrometry.
Results: Compared with wild-type littermates, Shank3 overexpressing mice are hyperactive, have increased sensitivity to amphetamine, decreased despair, altered circadian rhythm and hyperexcitability discharges with spontaneous seizures. The behavioral phenotypes are reversed by valproate treatment but not by lithium. Our interactome revealed an abundance of proteins involved in actin polymerization. We determined that elevated Shank3 levels results in increased actin polymerization.
Our patients with SHANK3 duplications similarly have neuropsychiatric disorders including attention deficit hyperactivity disorder and bipolar disorder with epilepsy.
Conclusions: SHANK3 overexpression results in a range of manic-like disorders in humans. In mice, elevated Shank3 levels result in manic-like behavior and epilepsy. Together, these data provide the first evidence of phenotypic consequences of SHANK3 overexpression and reveal a potential pharmacologic intervention for this disorder.
Keywords: Brain tumors/oncology, Genetics

PL1-5. Early Developmental Predictors and Behavioral Correlates of ASD in Infants with Tuberous Sclerosis Complex
Jeste SS, Varcin K, Wu JY, Sahin M, Nelson CA (Los Angeles, CA)
Objective: We performed a longitudinal cohort study of infants with Tuberous Sclerosis Complex (TSC) with the overarching goals of (1) defining early clinical predictors of autism spectrum disorder (ASD) and (2) more carefully characterizing the ASD phenotype in young children with TSC.
Methods: Infants with TSC and typically developing (TD) infants were recruited as early as 3 months of age and followed longitudinally until 36 months of age, with data gathered including standardized cognitive (Mullen Scales of Early Learning; MSEL) and social–communication measures (Autism Observation Scale of Infancy; AOSI and the Early Social Communication Scales; ESCS), comorbidities questionnaires (Child behavior checklist; CBCL), and a detailed seizure history. ASD diagnosis

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was made using the Autism Diagnostic Observation Schedule (ADOS) and confirmed using best clinical estimate at ages 18, 24, 36 months.

Results: 22/40 infants were diagnosed with ASD. The ASD group demonstrated (1) significantly greater cognitive delays by age 12 months and (2) a significant decline in non-verbal IQ from 12–36 months, compared to the non-ASD group. At 24 months, the ASD group had significantly greater cognitive impairment, higher anxiety symptoms, more sleep impairment, and a trend towards greater seizure severity. However, children not diagnosed with ASD still demonstrated sub-clinical evidence of social-communication impairment, particularly in language and play.

Conclusions: Cognitive impairment at age 12 months predicts a later ASD diagnosis in TSC. The relationship between intellectual disability and social-communication deficits in TSC requires further exploration, particularly in the context of diagnostic practices and early interventions targeting social communication function.

Keywords: Genetics

PL1.6. Gene Therapy for Glut1 Deficiency Syndrome

Objective: Heterozygous mutations in the SLC2A1 gene limit the facilitated diffusion of glucose across the blood brain barrier and result in the pediatric neurological disorder, Glut1 deficiency syndrome (Glut1 DS). The disease is characterized by infantile seizures, developmental delay, acquired microcephaly, low levels of glucose in the cerebrospinal fluid (CSF) – hypoglycorrhachia – and a complex movement disorder that is ataxic as well as dystonic. Ketogenic diets are the mainstay of current treatments but mitigate only certain disease symptoms. We sought to determine if restoring Glut1 in a preclinical model of the disease is effective in treating the disorder.

Methods: The murine Glut1 gene was packaged into adeno-associated virus 9 (AAV9) and systemically introduced into neonatal mutants. Injected mutants and relevant controls were assessed during adult life by examining 1) Glut1 mRNA and protein expression, 2) blood and CSF glucose levels, 3) brain and body weight and, 4) motor performance using the rota-rod and vertical pole assays.

Results: Glut1 model mice injected with PBS or AAV9-GFP expressed reduced Glut1 RNA and protein relative to wild type controls. Additionally, they exhibited evidence of hypoglycorrhachia, microcephaly and poor motor performance in the rota-rod and vertical pole tests. In contrast, in AAV9-Glut1 treated mutants, Glut1 RNA and protein levels rose, CSF glucose levels were restored, brain size was normalized and motor defects corrected.

Conclusions: Our results provide important proof-of-concept data of the therapeutic effects of restoring Glut1 protein function in Glut1 DS and constitute an important step toward treatment of the human disease.

Keywords: Translational/experimental therapeutics

PL1.7. Using a “Molecular Can-opener” to Model Complex Disease: probing lithium’s targets in bipolar hiPSCs suggests a novel underlying developmental disorder

Objectives: It has become common to make human induced pluripotent stem cells (hiPSCs) from patients with monogenic conditions. However, the greatest challenge for “Disease-in-a-Dish” modeling is approaching complex, polygenic, multifactorial disorders, the underlying pathophysiological mechanisms for which are poorly understood. Neuropsychiatric disorders are a prototype for such conditions. Of these, bipolar disease (BPD) is unique in that 50% of patients respond to lithium. Indeed, lithium-responsiveness is pathognomonic. Critically, lithium’s “mechanism-of-action” in BPD is unknown; however, were its target(s) to be identified, lithium could offer a molecular “handle” for discerning underlying mechanisms and deriving better treatments (lithium has unacceptable side-effects & a narrow safety index). As proof-of-concept, we show how exploiting a known functional agent in hiPSCs, even one whose action is unknown in a particular disease context -- such as lithium in BPD -- might provide a molecular “can-opener” for revealing heretofore unrecognized underlying pathophysiological mechanisms for such a disorder.

Methods/Results: By proteomic analysis of neurons generated from hiPSCs derived from lithium-responsive BPD patients, we discovered an unanticipated lithium target, "CRMP2", a molecule that mediates cytoskeletal reorganization and ion channel function based on its phosphorylation state. Lithium lowers p-CRMP2, which is excessively high in BPD neurons. Blunting p-CRMP2 promotes cytoskeletal reassociation and normalizes BPD behavior in animals.

Conclusions: These data help establish BPD as a heritable neurodevelopmental disorder with a novel “druggable” target with potentially wider uses. More broadly, we describe a strategy for using hiPSCs to unravel complex pathophysiological mechanisms & develop more effective drugs if there is a functional, molecular “hook”.

Keywords: Genetics, Translational/experimental therapeutics

Platform Session 2
Friday, October 24
(8:30 AM - 10:15 AM)

PL2.1. Clinical Outcome of 237 Children with Developmental Hydrocephalus
Tully HM, Rae T, Doherty D, Dobyns WB (Seattle, WA)

Objective: Developmental (congenital) hydrocephalus affects ~1/1000 infants and is heterogeneous in nature. Detailed clinical outcome has not been assessed systematically in these patients, and its main determinants are uncertain.

Methods: We reviewed imaging and clinical notes for 237 children with developmental hydrocephalus and assigned...
them to one of five clinical-anatomical subgroups. We assessed gender, age at diagnosis, Evans ratio (severity of ventricular dilatation), and surgical history. We also assessed the following clinical outcomes: ability to walk and eat independently, need for physical or speech therapy, presence of epilepsy, surgical revision rate, and mortality. We compared outcomes across subgroups and used regression analysis to determine features associated with developmental and surgical outcome, and mortality.

Results: At an average age of 4.6 years, 65% of children were walking independently and 87% could eat by mouth. 72% required physical therapy, 40% required speech therapy, and 17% had epilepsy; 6% were deceased. Among subgroups, we found significant differences in age at diagnosis (p<0.001), Evans ratio (p<0.0001), surgery history (p<0.001), need for physical therapy (p<0.001), speech therapy (p<0.04), independent mobility (p<0.001), and the presence of epilepsy (p<0.002). Developmental outcome was associated most strongly with Evans ratio (p=0.0004), though this effect was modified by age at diagnosis. Among patients who underwent surgery, revision rate was associated with both history of infection (p<0.0001) and hydrocephalus subgroup (p=0.006). Mortality was most associated with Evans ratio (p=0.01).

Conclusions: Evans ratio, hydrocephalus subgroup, and history of shunt-associated infection are the major determinants of clinical outcome in children with developmental hydrocephalus.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders, Neonatal neurology

PL2–2. Quality of Life among Children with Epilepsy from their Point of View
Fayed N, Davis A, Streiner DL, Boyle MH, Cunningham CE, Lach L, Rosenbaum PL, Ronen GM (Hamilton, Ontario)

Objective: Although seizure characteristics such as type, syndrome and severity have an impact on quality of life (QOL), so do child and family factors. The purpose of this study is to evaluate the extent to which seizure characteristics, when included among child and family factors, affect child-rated QOL.

Methods: We recruited children with epilepsy ages 8–14 with either a seizure within the previous 2 years or taking medication for seizure management, and with IQ>70 from neurology programs across Canada. The children completed 8 different health questionnaires during two visits. Demographic and biopsychosocial data were collected; the relative contributions of seizure, child and family characteristics were tested using SEM.

Results: 486 children with epilepsy self reported on their QOL. Mental health (B=0.46), as well the support children receive from parents (B=0.12) and peers (B=0.11) are related to QOL; neither seizure variables nor cognition were significant contributors. Moreover parental support had a strong indirect on QOL through child mental health (B=0.48).

Conclusions: In this first comprehensive study of factors that have an impact on child self-reported QOL study, when seizures and cognition are modeled in the presence of psychosocial factors, they lose their relative impact on QOL. Therefore, improving the child’s perception of the QOL is contingent on improving their mental health via supporting parent and peer acceptance. Longitudinal work is required to understand the underlying causes for the relationships observed.

Keywords: Epilepsy and other paroxysmal disorders

PL2–3. Hereditary Hypermanganesemia: a new potentially treatable metabolic disorder in four Pakistani siblings
Khan SG, Ibrahim S, Ahmed K (Jeddah, Saudi Arabia)

Objective: Hereditary hypermanganesemia is a newly described autosomal recessive disorder of manganese metabolism characterized by manganese accumulation in the brain. Mutations in the SLC30A10 gene, encoding a putative manganese transporter, have recently been identified as the cause of this syndrome. Affected individuals develop extrapyramidal dysfunction, polycythemia, severe hypermanganesemia, and variable hepatic dysfunction.

Methods: We describe the clinical features, magnetic resonance imaging, and laboratory findings in a family of four siblings with this disorder. Genetic basis of disorder, confirmed from University College London Institute of Child Health, led to the discovery of the first gene (SLC30A10) causing hereditary hypermanganesemia.

Results: Four of five siblings (2 girls and 2 boys) were affected. The age of onset was between 3–5 years with dystonia, polycythemia, and hepatic dysfunction. Blood manganese levels were markedly elevated (20–45 mg/dl; normal <2.5 mg/dl), and MRI brain showed T1 hyperintense and mild T2 hypointense signals in the basal ganglia and other regions of the brain. Whole genome mapping identified SLC30A10 as the affected gene. Subsequent sequencing identified a large deletion spanning exon 1 and 2 of the SLC30A10 gene. One sibling, treated with intravenous disodium calcium edetate chelation shortly after the onset, has mild disease.

Conclusions: We wish to highlight this rare potentially treatable inherited metal storage disorder, that otherwise can lead to permanent neurological disability and liver cirrhosis.

Keywords: Case studies/case series, Genetics, Neuromuscular disorders

PL2–4. Brain Stimulation and Constraint for Perinatal Stroke Hemiparesis: the plastic champs trial

Objective: Perinatal stroke causes hemiparetic cerebral palsy. Constraint therapy (CIMT) and repetitive transcranial magnetic stimulation (rTMS) may improve motor function in adult stroke but are untested in perinatal stroke.

Methods: PLASTIC CHAMPS (www.clinicaltrials.gov/ NCT01189058) was a blinded factorial trial of rTMS and CIMT in perinatal stroke hemiparesis. Children 6–18 years participated in a 2 week, goal-directed, peer-supported, motor learning camp. Subjects were randomized to daily inhibitory rTMS (1Hz, 1200 stimulations) over...
Conclusions: These data suggest that patients with NDD and epilepsy may benefit from a tiered testing approach including both targeted panel and WES, which could yield a diagnosis in about 40% of patients.

Keywords: Epilepsy and other paroxysmal disorders, Genetics

PL2–6. Genetic Mechanisms of Ohtahara Syndrome, A Cohort Study
Olsen HE, Sheidley BR, Tambunan D, Slain C, Pinky R, LaCoursiere CM, Libenson M, Bergin AM, Loddenkemper T, Takeoka M, Poduri A (Boston, MA)

Objective: To identify genetic causes of Ohtahara syndrome.

Methods: We enrolled 24 patients with a diagnosis of Ohtahara syndrome, an international cohort recruited to our study. For patients without an identified genetic etiology, next generation epilepsy gene panel testing and/or whole exome sequencing was performed.

Results: Genetic testing of 21 patients without brain malformations showed that six (29%) had de novo KCNQ2 variants, four (19%) had de novo STXBP1 variants, one (5%) had a SCN2A variant, and one (5%) was homozygous for a PNPO variant. All of the variants are predicted to be pathogenic. Three (14%) of the patients without malformations had suspected metabolic diagnoses of uncertain relationship to Ohtahara syndrome, including phenylketonuria, mitochondrial dysfunction, and cerebral folate deficiency (the latter combined with an STXBP1 mutation). For three additional patients with brain malformations, one with macrocephaly-capillary malformation syndrome with hemimegalencephaly and two with polymicrogyria, we have yet to identify a genetic etiology. The rest of the cohort remains unexplained. Apart from MRI imaging and/or metabolic findings, there are not clear differentiating features between the genetic causes of Ohtahara syndrome.

Keywords: Epilepsy and other paroxysmal disorders, Genetics, Neonatal neurology

PL2–5. High Positive Diagnostic Yield of Panel Testing and Whole Exome Sequencing for Patients with Epilepsy-related Neurodevelopmental Disorders
McKnight D, Retterer K, Juusola J, Suchy S, Richard G, Haverfield E (Gaithersburg, MD)

Objective: The abundance of genetic testing options for patients with epilepsy-related neurodevelopmental disorders can be overwhelming; we have compared the positive diagnostic rate of targeted epilepsy panels to whole exome sequencing (WES) for these patients.

Methods: Clinical testing of ~3500 epilepsy patients with various multi-gene epilepsy panels (next generation sequencing and deletion/duplication testing) was compared to 171 patients with neurodevelopmental disorders (NDD) and epilepsy tested by WES.

Results: Epilepsy panel testing revealed a clinical sensitivity of ~15% with the highest diagnostic rate (~20%) for a smaller set of genes linked to early-onset epilepsy. Using WES, ~34% of the patients with NDD and epilepsy had a positive result, slightly higher than the positive rate of WES for all test indications (30%, n=1327). Compared to the 15–20% positive rate for epilepsy panels, only 10% of patients tested by WES had mutations in the same set of genes sequenced on the panels. This discrepancy may be a combination of incomplete coverage and missed exon-level deletions/duplications by WES and sampling bias due to exclusion of patients with prior positive findings in one of these genes. The majority of WES positive results were in genes not included on the epilepsy panels. When looking at individuals who had both tests performed (n=30), epilepsy panel followed by WES, ~27% had a positive result by WES.

Keywords: Stroke, Translational/experimental therapeutics

PL2–7. Outcome in Nonketotic Hyperglycinemia (NKH)

Objective: Identify factors predicting prognosis in NKH.

Methods: We studied neurodevelopmental outcome, biochemical and molecular data in 124 NKH patients, stratified by developmental outcome as: neonatal death (n=26), severe (no developmental progress, n=56), attenuated poor (some...
developmental progress DQ < 20, n = 6), attenuated intermediate (DQ 20–50, n = 12), attenuated good (DQ > 50, n = 15), and attenuated without formal DQ (n = 9).

Results: Patients with severe NKH had more seizures; patients with DQ > 30 did not require anticonvulsants. Brain malformations occurred in 71% of severe NKH, but only in 8% with attenuated NKH (all hypoplastic corpus callosum). Within any outcome category, at least 50% of patients presented neonatally, but onset ≥ 4 months predicted attenuated good outcome. There was no difference by gender or affected protein. CSF glycine levels and CSF:plasma glycine ratio correlated inverse with DQ, CSF glycine > 230 predicted severe outcome, and CSF:plasma glycine ratio ≤ 0.08 predicted attenuated outcome. The glycine index differed between categories. Sequencing and deletion/duplication analysis identified 99% of mutant alleles, 85% GLDC and 15% AMT, with 98 new mutations identified. Recurring missense mutations in GLDC were expressed to identify residual activity, which occurred in amino acids near the active cleft. A mutation score based on identified dysfunction/duplication analysis predicted severe outcome, and CSF:plasma glycine ratio ≤ 0.08 predicted attenuated outcome. The glycine index differed between categories. Sequencing and deletion/duplication analysis identified 99% of mutant alleles, 85% GLDC and 15% AMT, with 98 new mutations identified. Recurring missense mutations in GLDC were expressed to identify residual activity, which occurred in amino acids near the active cleft. A mutation score based on identified dysfunction/duplication analysis predicted severe outcome, and CSF:plasma glycine ratio ≤ 0.08 predicted attenuated outcome.

Conclusions: Predictors help identify those attenuated patients potentially benefitting from early treatment.

Keywords: Epilepsy and other paroxysmal disorders, Genetics, Neonatal neurology

POSTER PRESENTATIONS

1. Anaplastic Ependymoma in a Child with Sickle Cell Disease: a case report highlighting treatment challenges for young children with CNS tumors and underlying vasculopathy

Crotty E, Wells EM, Mason G, Justus DG, Packer RJ (Washington, DC)

Objective: To report on a novel case of sickle cell disease and ependymoma and considerations to minimize potential treatment-related neurologic sequelae.

Methods: A 3-year-old male with sickle cell presented with progressive, daily emesis and partial left eye movement. MRI revealed nonmetastatic heterogeneous posterior fossa mass. Surgical resection left possible residual tumor along the medulla and pathology was anaplastic ependymoma, WHO grade III. Adjuvant radiation and chemotherapy were considered with focus on risk of adverse cerebrovascular events (CVE).

Results: Review of literature and expert discussion revealed no previous cases of ependymoma and very few reports of other CNS malignancies in patients with sickle cell disease. Stroke in 7% of sickle cell by age 14 translates to high baseline risk for CVE. The recent Children's Oncology Group study employed post-operative conformal radiotherapy alone for infants with fully-resected ependymoma.

Potential neurotoxicity includes neurocognitive deficits, hearing loss, secondary neoplasms, and CVE. Radiation-induced moyamoya syndrome is reported with underlying vasculopathy; radiation is avoided in neurofibromatosis type I. Chemotherapy to delay or avoid radiation is unproven in malignant ependymoma and risks renal disease which accounts for 16% of sickle cell deaths. The chosen treatment was focal proton beam irradiation without adjuvant chemotherapy, with prolonged transfusions to minimize anemia, another risk factor for CVE in sickle cell, and consideration of bone marrow transplant.

Conclusions: Treatment of CNS tumors requires balancing benefits/risks of multi-modal therapies. This unique case highlights treatment complexities for malignant brain tumors in patients predisposed to cerebral vasculopathy and need for further therapeutic alternatives.

Keywords: Brain tumors/oncology, Case studies/case series

2. Safety of Everolimus by Age Category for Subependymal Giant Cell Astrocytoma (SEGA) Associated with Tuberous Sclerosis Complex (TSC): results from the EXIST-1 trial

Franz DN, Brechenmacher T, Segal S, Jozwiak S (Cincinnati, OH)

Objective: To present a 90-day safety update by age category for patients who participated in the EXIST-1 trial (NCT00789828). At the original cutoff (March 2, 2011), everolimus was superior to placebo for SEGA response rate (34.6% vs 0.0%, P < 0.0001) and demonstrated an adverse event (AE) profile in TSC consistent with previous reports.

Methods: Patients (any age) with ≥ 1 SEGA lesion (longest diameter ≥ 1 cm) were randomized (2:1) to 4.5 mg/m2/day everolimus (target blood trough 5–15 ng/mL) or placebo. We report safety data for everolimus patients aged < 3 (n = 13), 3–17 (n = 55), and ≥ 18 years (n = 10) and placebo patients aged < 3 (n = 7), 3–17 (n = 26), and ≥ 18 years (n = 6).

Results: As of July 18, 2011 (90-day update), median treatment duration was 52 and 47 weeks (everolimus vs placebo). Stomatitis (< 3 and ≥ 18 years) and mouth ulceration (3–17 years) were the most common AEs for everolimus. For everolimus versus placebo, incidence of stomatitis was 69% versus 43% (< 3 years) and 40% versus 17% (≥ 18 years); incidence of mouth ulceration was 44% versus 8% (3–17 years). For patients < 3, 3–17, and ≥ 18 years, incidence of treatment-related grade 3–4 AEs was 46%, 13%, and 10% for everolimus and 14%, 8%, and 0% for placebo. Infections/infestations occurred in 100%, 71%, and 70% of everolimus patients and 100%, 69%, and 33% of placebo patients.

Conclusions: The safety of everolimus was comparable between age categories with the possible exception of a greater incidence of infections/infestations and stomatitis in younger patients. Small sample sizes may have limited the results.

Keywords: Brain tumors/oncology, Genetics
3. Embryonal Rhabdomyosarcoma of the Temporal Bone Presenting with Cranial Nerve Palsy

Ng E, Karkare S (New Hyde Park, NY)

Objective: Describe a case of Rhabdomyosarcoma involving right temporal bone and inner ear with right cavernous sinus infiltration that initially presented like a Bell's palsy in a 2-year-old boy and review the literature.

Methods: We describe the case of a 2-year-old boy who presented with 2 weeks history of right facial weakness, decreased right eye vision and hoarseness. He was treated for Bell's palsy before presenting to us. On examination, the child had right CN VI, CN VII, and CN XII involvement. MRI of Brain showed a large right-sided skull base mass involving the petrous and mastoid portions of the right temporal bone, with associated vascular encasement, inner ear involvement, and right cavernous sinus infiltration. MRI of spine showed leptomeningeal enhancement of T7, T8 and conus. Pathology on a biopsy specimen confirmed Rhabdomyosarcoma, embryonal type.. Patient was started on ARST 0431 and received Vincristine and Irinotecan. Review of literature was performed to compare clinical presentation, neuroradiologic finding, histopathologic findings, tumor staging, management and prognosis.

Results: Rhabdomyosarcoma is a highly malignant tumor of mesenchymal origin. 41% of pediatric rhabdomyosarcoma involves the head and neck and 8% of those tumors involve the temporal bone. They are aggressive neoplasms with propensity for local invasion and destruction. Rhabdomyosarcoma that spread to the petrous portion of the temporal bone may present with abducens and facial nerve palsy.

Conclusions: Temporal bone rhabdomyosarcoma should be considered in the differential diagnosis of patients with both CN VII and XII dysfunction. Tissue biopsy is important to diagnosis. The goal of therapy is local regional control and prevention or treatment of systemic metastasis.

Keywords: Brain tumors/oncology, History / Teaching of Child Neurology, Neuroimaging

4. Characteristics of Childhood Diffuse Intrinsic Pontine Gliomas (DIPGs) in Long-Term Survivors: a Children's National Medical Center (CNMC) experience

Sato AA, Wells EM, Packer RJ (Washington, DC)

Objective: Prognosis for childhood DIPGs is poor, with 90% of patients dying within 18 months of diagnosis; some investigators believe that there are no long-term survivors. This study sought to determine if there were long-term survivors with “classical” DIPGs and if survivors had distinctive demographic, clinical, and treatment characteristics, compared to non-survivors.

Methods: Retrospective chart review was performed on 152 patients with DIPG evaluated at CNMC between 1990 and 2013. Patients were a median of 6.5 years of age, ranging from 1 to 20 years; 66% were male. Bivariate analysis (Chi-square, t-test) compared 10 long-term survivors (more than 3 years) to 30 non survivors, including baseline demographic characteristics, clinical presentation, imaging, treatment regimens, and response to treatment.

Results: 10 of 152 patients (6.6%) were long-term survivors; 4 ultimately progressed. Non survivors had median survival of 14 months (range 4–33 months). There were no statistically significant differences between the two groups in all parameters studied, including radiographic features such as disease extent, the presence of cysts or necrosis and enhancement. 83% of patients were treated with radiotherapy. Types of adjuvant therapy, including chemotherapy or biologic therapy during or after radiation did not affect survival. Response to therapy also did not affect the likelihood of survival.

Conclusions: Some children with “classical” DIPG survived, and those who experienced prolonged survival had similar demographic, clinical, and even radiographic, features as non-survivors. Future investigations should evaluate the impact of molecular genetic characteristics on rate of survival.

Keywords: Brain tumors/oncology

5. Acute Brain Injury May be More Severe from Proton Beam Radiation (PBR) than from Conventional Radiation Therapy (CRT) for Young Pediatric Patients with Posterior Fossa Tumors


Objective: To investigate acute brain injury from proton beam radiation which is employed to decrease toxicity to surrounding tissue.

Methods: We evaluated 30 consecutive pediatric patients with posterior fossa tumors irradiated at multiple institutions between 2005 and 2013, without progressive disease 2 years later. 16 received PBR (mean age 6.1; range 1.4 – 16.3 years; 5 under 3 years) and 14 received CRT (mean age 8.0 years; range 1.1 – 15.8 years; 2 under 3 years). PBR group included 1 AT/RT, 7 ependymomas, 1 low grade glioma, 3 medulloblastomas, 1 brainstem PNET and 1 choroid plexus papilloma. CRT group included 1 AT/RT, 10 medulloblastomas, and 3 ependymomas. Radiation change on MRIs at 3 month intervals to at least 12 months post-radiation was graded 1: focal T2 increase in brainstem, cerebellum and/or cerebral white matter (no enhancement or diffusion restriction); 2: extensive T2 increase in brainstem, cerebellum, and/or cerebral white matter or focal abnormal enhancement without diffusion restriction; 3: extensive enhancement or diffusion restriction.

Results: PBR group showed 2 grade 2, 4 grade 3 injuries, and 1 pseudoprogression. 3 patients with brainstem change (all under age 3 treated with chemotherapy) died 3–7 months post-PBR with autopsy-demonstrated multifocal necrotizing leukoencephalopathy and demyelination. CRT group had 1 grade 2 and no grade 3, and no brainstem injuries. Radiation injury was more severe post-PBR (Chi-square 9.5, df 3, p<0.05).

Conclusions: PBR was associated with more severe acute brain injury than CRT, including 3 fatalities from brainstem
necrosis. PBR is increasingly recommended to spare long term adverse effects, but further research is needed.

Keywords: Brain tumors/oncology, Neuroimaging

6. Neurologic Sequelae in Brain Tumor Survivors in the Childhood Cancer Survivor Study (CCSS)


Objective: This study investigated longitudinal changes in treatment-related neurologic sequelae in survivors of childhood brain tumors.

Methods: Neurologic adverse events in 5 year survivors (n=1876) and siblings were evaluated longitudinally in the CCSS cohort. Multivariable regression determined risk for late onset neurologic sequelae, with hazard ratios (HR) and 95% confidence intervals (CI).

Results: 30 years post diagnosis, cumulative incidence for mortality was 25%, second malignant neoplasm (SMN) 4% and recurrence 21%. From 5 to 30 years, seizures increased from 27% to 41%, coordination problems 50% to 61%, weakness 21% to 35%, hearing loss 9% to 23%, and blindness 14% to 17%. Compared to siblings, survivors had elevated risk for seizures HR 27.2 (CI 15.9–46.5) for ages 5–14 and 8.8 (6.4–11.9) for 15+; coordination 24.3 (16.4–35.9) for ages 5–19 and 4.4 (3.2–6.2) for 20+; weakness 31.6 (18.0–55.5) for ages 5–19 and 3.9 (2.8–5.3) for 20+. Risk factors for coordination problems were radiation 1–49 Gy 1.9 (1.2–3.1) and >49 Gy 1.9 (1.2-2.8), recurrence 2.9 (1.9-4.4), and SMN 4.4 (1.8–11.2). Weakness risk factors were frontal radiation >49 Gy 2.0 (1.2–3.4), temporal >49 Gy 1.6 (CI 1.0–2.5), and recurrence 3.0 (2.1–4.4). Stroke gave a 7-fold increase (4.3–11.0) in later-onset coordination problems and 15-fold increase (10.6–21.7) in weakness.

Conclusions: Survivors of childhood CNS tumors experience new onset neurologic conditions as they age and remain at higher risk than siblings without cancer. Late onset stroke, SMN and primary tumor recurrence are independently associated with risk for a new neurologic condition.

Keywords: Brain tumors/oncology

7. NMDA Receptor Encephalitis Presenting with Apparent Migraine and Focal Seizure Evolving to ESES

Bernier RL, Acosta MT, Wells EM (Washington, DC)

Objective: To report a unique presentation of NMDA receptor (NMDAR) encephalitis and ESES, evolution of EEG, and treatment response.

Methods: We describe the case of a previously healthy right handed 15-year-old girl who presented with right focal seizure associated with new onset headache, visual blurring, irregular saccadic eye movements, and cognitive slowing who worsened over 4 days and developed emotional lability, anoma, and mild dysautonomia.

Results: Neurologic examination was normal except for cognitive slowing and word finding difficulties. Initial EEG revealed left mid-temporal slowing and differential diagnosis suggestive of migraine versus seizure. Patient clinically worsened 3 days later with new anxiety and mood instability with dysautonomia. Repeat EEG showed near continuous electrographic seizures from the left-temporal occipital region refractory to levetiracetam and fosphenytoin. Seizure control was achieved with oxcarbazepine, lacosamide, and high-dose diazepam (Boston ESES protocol). CSF cell count and protein were normal and brain MRI demonstrated increased perfusion of the left temporal lobe. CSF NMDAR antibody test was sent and positive. The patient was given IVIG 2 gram/kg with IV Solumedrol 1 gram every month for 6 months with gradual return to baseline. The treatment team included neurology, neuropsychology, psychology, physical therapy, and cardiology.

Conclusions: Testing for NMDAR encephalitis should be considered for patients with atypical focal epilepsy and ESES, even with minimal neurocognitive or psychiatric abnormalities that may seem post-ictal and without movement disorder. EEG may rapidly evolve. A multidisciplinary treatment approach promotes accurate surveillance to guide immunotherapy and improve quality of life.

Keywords: Case studies/case series

8. Orthostatic Intolerance in Atypical Concussion Recovery: a case series from Children’s National


Objective: To characterize a series of adolescent athletes with slow or atypical concussion recovery and orthostatic intolerance in order to better understand the association and opportunities for intervention.

Methods: 6 consecutive patients underwent retrospective chart review after referral to Cardiology for orthostatic intolerance that developed in the post-concussive period.

Results: The series included 6 patients (3 M, 3F) with mean age of 15.9 years (range 13.5–16.9) with sports-related concussion. At presentation to Cardiology at least 21 days post injury, all patients self-reported headache and dizziness and 5 of 6 had mental fogginess. Syncope (2), nausea (2), and abdominal pain (1) were less frequent. Family history of orthostatic intolerance was present in 100% of patients. All patients were symptomatic during formal tilt testing with orthostatic dizziness with or without headache. The mean increase in recorded heart rate amongst our patients was 41 (range 21–57). One patient was noted to have congenital long QT syndrome (type 1) without electrocardiographic evidence of torsade-de-pointe.

Conclusions: A subset of patients with post-concussion orthostatic intolerance likely have pre-existing orthostatic intolerance (or familial predisposition) that is aggravated post-injury. Cardiology referral is needed to evaluate for underlying orthostatic intolerance and possible arrhythmias. Future studies should investigate iatrogenic effects of excessive rest in previously active pediatric patients, and whether early exercise and use of dysautonomia medications might augment recovery from post-concussive symptoms, particularly in the subgroup of patients predisposed to orthostatic intolerance.

Keywords: Case studies/case series

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9. Diffuse Cerebral Hypometabolism with Focal Reduction in Somatosensory and Occipital Cortical Uptake on Brain FDG PET in a Case of Anti NMDA Receptor Encephalitis

Dayam N, Varma R, Muthukrishnan A, Goldstein A
(Pittsburgh, PA)

Objective: Anti N-methyl-D-aspartate receptor encephalitis (anti-NMDARE) is an under-recognized immune mediated encephalitis. The value of Fluorodeoxyglucose (FDG)-PET/CT in anti-NMDARE lies in the detection of any underlying malignancy, removal of which drastically improves the clinical outcome. However, the significance of the pattern of cerebral FDG metabolism has not been well studied. We present a patient with anti-NMDAR encephalitis with distinct pattern on brain FDG-PET/CT.

Methods: Case report and literature review

Results: A previously asymptomatic 17-year old female presented with sudden onset of flat affect, short-term memory loss, and bizarre behaviors. Subsequently, on evaluation she had catatonia, dyskinesia and autonomic instability. CT and MRI of the brain were normal. She was diagnosed with Anti-NMDARE after anti-NMDAR antibodies were identified on serology and CSF analysis. Extensive workup for neoplasms was negative. Brain FDG-PET/CT showed global cerebral hypometabolic activity, most pronounced in the somatosensory and the occipital cortex. She was treated with IVIG, IV solumedrol and rituximab.

Discussion: Clinical features include a viral like prodrome, psychiatric symptoms, memory disturbance, seizures, catatonic state, orofacial-limb dyskinesias and autonomic instability. Autoantibodies are usually detected in CSF and/or serum. Most patients respond to steroids, IVIG, plasmapheresis, and/or rituximab.

Conclusions: Most studies available in the literature describe global hypometabolism, at times with pronounced involvement of certain lobes/ global hypermetabolism/ focal FDG avid areas in the background of hypometabolism. Further research on FDG-PET uptake patterns would provide better insight whether imaging the normalization of pre-therapy metabolic patterns would help guide patient-specific therapy and assess clinical response to such therapies.

Keywords: Case studies/case series

10. Chiari I Malformation Causing Developmental Regression in a 4-month-old

Doll ES, Bonkowsky JL, Brown LL, de Havenon AH, Brockmeyer DL, Glasgow TS, Moria DN (Salt Lake City, UT)

Objective: Chiari I malformation is rarely reported in infants. Presenting symptoms in this population can be non-specific, including irritability and crying, dysphagia, and respiratory difficulties. We report a 4-month-old twin male with the novel presentation of loss of developmental milestones and Chiari I malformation.

Methods: A 4-month-old twin male infant presented with feeding intolerance, hyperreflexia in upper and lower extremities, and arm diplegia. Approximately one month before diagnosis, he stopped rolling over, lifting his head from the prone position, or reaching for objects. Pregnancy and prior medical history were unremarkable. There was no family history of Chiari I or other neurodevelopmental disorders. Brain MRI revealed a Chiari I malformation with 15 mm of tonsillar ectopia.

Results: Following suboccipital decompression and C1 laminectomy with tonsillar reduction, his neurological deficits improved and by 7 months of age he was developmentally normal. At most recent follow-up (15 months of age), he requires physical therapy for balance difficulties on uneven terrain and speech therapy for mild oral aversion.

Conclusions: Symptomatic Chiari I malformation can cause developmental regression in an infant. Surgical intervention can successfully treat this condition. The young age of presentation suggests an underlying genetic predisposition for development of symptomatic Chiari I malformation.

Keywords: Case studies/case series

11. Hyperextension Myelopathy: a rare ischemic injury of the spinal cord presenting in a 7-year-old cheerleader

Haralur-Sreekantaiah Y, Mruthyunjaya P, Skjei KL
(Louisville, KY)

Objective: Non traumatic spinal cord injury resulting in spinal cord ischemia as a result of hyperextension of the lower back is a relatively newly described entity. Thompson et al (2004) first observed such ischemic events in first time surfers and coined the term ‘surfer’s myelopathy’. The purposes of this study are to report for the first time, such injury in a pediatric patient and expand the spectrum of this myelopathy syndrome to include other causes of hyperextension.

Methods: Case report.

Results: We describe an ischemic injury to the spinal cord in a 7 year old cheerleader who performed repeated backbends after a long break from cheerleading. She presented with acute back pain, paraplegia, hypesthesia of the lower extremities and urinary retention. She was diagnosed with ischemic myelopathy based on clinical presentation and imaging findings. The mechanism of injury is thought to be similar to surfer’s myelopathy, and risk factors include repeated episodes of hyperextension of the lower back, lean body habitus, dehydration and mechanical tension on the cord.
Conclusions: Surfer's myelopathy is an ischemic injury of the spinal cord most likely from repeated hyperextension of the lower back in otherwise healthy individuals. Cheerleading exercises involving repeated hyperextension of the lower back may produce a similar syndrome. In patients presenting with signs of acute myelopathy, an initial work up should focus on acute transverse myelitis before considering cord ischemia. But in patients diagnosed with acute transverse myelitis without evidence of spinal cord inflammation, the possibility of hyperextension myelopathy must be explored.

References:

Keywords: Case studies/case series

12. Treatment Protocol in Anti-NMDA Receptor Encephalitis: pilot results from a survey of child neurologists
Kahn IL, Helman G, Wells EM, Vanderver A (Washington, DC)

Objective: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a multisite autoimmune disorder progressing from neuropsychiatric symptoms to catatonia, seizures, autonomic instability, and coma, with or without associated tumor. Over 250 research papers have been published since its 2007 discovery, however approaches to facilitate a higher index of suspicion for this condition and standardized immune modulating treatment are needed, and should be led by neurologists.

Methods: Members of the Child Neurology Society (CNS) were invited to complete an anonymous survey on their experience and treatments pursued in cases of NMDAR encephalitis through use of REDCap. We present pilot results from 14 members at 2 institutions.

Results: 64% of respondents reported they had treated 5 or more patients with anti-NMDAR encephalitis. 86% reported they would start immunotherapy based on a presumed diagnosis of autoimmune encephalitis, although a number of factors (i.e. fever (43%) and good cognitive function (50%)) would delay treatment until anti-NMDAR encephalitis was confirmed. Consensus treatment was a combination of IVIG and IV methylprednisolone (57%), with 64% of respondents (4 or higher on confidence scale) reporting they are very confident that patients should be treated initially with IVIG, steroids, and/or plasma exchange. In cases requiring further medical intervention, rituximab was the first choice disease modifying agent (86%).

Conclusions: A simplified approach to care guidelines is a difficult task that must combine expert opinion, provider experience, and evidence-based medicine. We provide a preliminary basis for establishing standard treatment guidelines amongst providers in cases of anti-NMDAR encephalitis, to promote patient safety and treatment efficacy.

Keywords: Infections/Neuroimmunology

13. Case Report: 2 patients with neurocutaneous melanocytosis harboring somatic NRAS gene mutations

Objective: The incidence of large congenital melanocytic nevi (LCMN) is 1/20,000 with 10–15% of children diagnosed with neurocutaneous melanocytosis (NCM). Nearly 70% of NCM patients become symptomatic (e.g., seizures, hydrocephalus) usually within the first 5 years of life. Of those with symptomatic NCM, 70% develop CNS melanoma. Prognosis remains poor for patients with symptomatic NCM, even in the absence of melanoma, with up to 90% mortality usually within 2–3 years after the onset of neurologic symptoms. While 40–60% of non LCMN/NCM associated melanomas harbor a mutation in the BRAF gene, Kinsler, et al demonstrated that 12/15 LCMN and NCM lesions had a mutant NRAS gene. We previously reported a patient with LCMN, NCM and seizures who underwent surgical resection for improved seizure control. The pathology was consistent with NCM without evidence of melanoma. A second patient with LCMN underwent biopsy of a spinal lesion and pathology was also consistent with NCM. We aimed to further elucidate the pathophysiology of NCM by confirming the presence of NRAS mutations, as previously described.

Methods: DNA from both lesions was isolated and subjected to an exon-capture based next generation sequencing platform developed at MSKCC: Integrated Mutation Profiling for Actionable Cancer Targets (IMPACT). This assay screens for mutations in 275 cancer associated genes.

Results: We identified a somatic Q61K mutation in NRAS in both patients with leisional DNA. No other mutations were identified in the remainder of genes sequenced.

Conclusions: We propose that the NRAS pathway may be a target for future therapy of patients with NCM.

Keywords: Brain tumors/oncology, Case studies/case series, Genetics

14. Malignant Migrating Partial Seizures in Infancy (MMPSI) or Coppola-Dulac syndrome: case report
Khan YK, Fenton G (Albuquerque, NM)

Background: The syndrome of malignant migrating partial seizures in infancy (MMPSI) is extremely rare, and is now included among the childhood epileptic syndromes. Seizures begin at <6 months of age and have no clear-cut structural or metabolic etiology. Treatment is difficult with pharmacoresistant seizures and development delay. Genetic mutations have been identified in some cases.[1]

Case: A 2 month old baby girl born at term. Apgar scores were normal and birth weight was 6 pounds 9 ounces. She presented to the University of New Mexico pediatric neurology clinic for uncontrolled seizures. Seizures were described as focal tonic type with involvement of head, eyes and trunk, to the left or right, with associated reddening of her face. Duration typically 30–40 seconds. She had an average of 10 seizures per hour.EEG showed a discontinuous background and ictal patterns arising independently from the right and left hemisphere, with a tendency to migrate to the opposite hemisphere. MRI was normal. Trials of phenobarbital, topiramate, levetiracetam, pyridoxine, pyridoxal phosphate, folinic acid, fosphenytoin, zonisamide, and oxcarbazepine provided only transient or no seizure control. Ezogabine, a novel antiepileptic compound which opens
KCNQ2/3 channels was initiated which resulted in complete seizure control.

Discussion: MMPSI is a rare epileptic encephalopathy of infancy that combines pharmaco-resistant seizures with developmental delay. The main features include normal development before seizure-onset, first seizures appearing generally in the first semester of life, nearly continuous electro-clinical focal seizures starting from different lobes and shifting from one hemisphere to the other, and progressive deterioration. Studies [2][3] have shown that potassium bromide may lead to seizure control or to a significant seizure reduction, generally in a few weeks. Ezogabine appears to be an effective agent in our patient, despite the demonstrated mechanism of action being on a different potassium channel subtype.

Conclusion: Although this is rare epileptic entity of infancy, neurologists need to be familiar with the clinical presentation and typical EEG pattern, as specific treatment options for seizure control are available.

References:

Keywords: Case studies/case series

15. Natural History of SSADH Deficiency Through Adulthood
Pearl PL, Lewis E, LaPalume-Remis, S, Schreiber J, Barrios E, Theodore WH, Gibson KM (Boston, MA)

Objectives: Typically SSADH deficiency, a defect of GABA metabolism, manifests as a relatively non-progressive encephalopathy with a median age of diagnosis of two years. The oldest previously reported patient at age of diagnosis was 25 years.

Methods: A 63-year-old man with longstanding intellectual disability was diagnosed with SSADH deficiency following hospitalization for progressive decline, escalating convulsions, and prolonged periods of altered consciousness. We reviewed our SSADH database adult cohort to derive natural history information.

Results: Of 102 patients in the database, there are 35 individuals age 18+ years (stratification: 24 patients aged 18 to 29 years, 9 in the thirties, one age 45, and the index case, now deceased at age 63). Only three of the 102 patients were diagnosed after 18 years old. Of the 35 adults, 22 (63%) have epilepsy. Predominant seizure types are generalized tonic-clonic, absence, and myoclonic. EEGs in adulthood were normal in 40%, showed background slowing or disorganization in 35%, and interictal epileptiform discharges in 30%. Psychiatric symptoms were prominent with anxiety, sleep disturbances, and severe obsessive-compulsive disorder. Hyperactive behaviour was described at some time in their history in 80%.

Conclusions: We identified 35 SSADH patients in our database over age 18 years of age following diagnosis of the first reported case over age 45. The illness had a progressive course with escalating seizures in the index case with fatality at age 63. Epilepsy is more common in the adult than pediatric SSADH cohort; neuropsychiatric morbidity remains prominent.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders, Genetics

16. Improving Communication of Imaging Results to Families: a quality improvement project
Rimer A, Filloux FM, Rogers JE, Rimer EG, Hughes AM, Kerr LM (Salt Lake City, UT)

Objective: Caring for children with neurological disorders often requires phone communication with families regarding imaging results and subsequent plan of care. We applied quality improvement (QI) methods to enhance communication of imaging results in our academic child neurology practice.

Methods: We compared resolution time, defined as the duration (in days) between availability of the imaging report and successful communication to the family, before and after QI intervention. The average number of “handoffs” between staff and providers for each communication was also compared. Both measures were determined by sampling ~10% of brain MRIs ordered by each provider (76 charts/12 months pre-intervention; 26 charts/3 months post-intervention). Utilizing established methods of QI including process analysis, annotated run charts and PDSA cycles, interventions were implemented. Major interventions included altering the triage process for obtaining and relaying results, and creating standard scripting for staff communicating these results. Independent samples t-test determined if there was a significant difference between resolution time before and after intervention.

Results: Average resolution time decreased from 10.2 (before intervention) to 3.1 days (after intervention), respectively (p < 0.001; d = .78). Brain MRI results resolved within 3-days increased from 25% to 54%. The average number of handoffs remained stable at 3.

Conclusions: Our data indicates that established QI methods can be successfully applied to care delivery in pediatric neurology. Similar approaches could also enhance communication of laboratory and EEG results. Ongoing monitoring is needed to ensure long-term effectiveness of interventions. Additional analysis of patient satisfaction surrounding communication of results is also warranted.

Keywords: Case studies/case series, Neuroimaging

17. Nicotine and Amphetamine Participate in Sensitized Motivational Behaviors and Acetylcholine-interneuron Firing
Bamford NS, Storey GR Gonzalez-Fernandez G, Heimbigner L, Minayan A, Walwyn WM (Seattle, WA)
Objective: The striatum is a central neural network that is critical for cue-dependent behaviors and motor learning. Several lines of evidence suggest that the striatum contributes to neuropsychological diseases, including attention deficit disorder and Tourette syndrome. These disorders can respond to both nicotine and the dopamine releaser amphetamine, but the unifying mechanism remains unclear. We hypothesized that nicotine and amphetamine modify behaviors by modulating acetylcholine-releasing striatal interneurons (ACh-I).

Methods: We used a model of operant drug-taking behaviors in which C57BL/6J mice (n=15), aged 4–9 weeks, self-administered amphetamine (0.05 mg/kg i.v.) through an in-dwelling jugular catheter. This was followed by a period of abstinence, drug-primed reinstatement, and ex vivo analysis of ACh-I activity. Nicotine (0.25–1.0 mg/kg i.p.), at doses which selectively increase Ca2+ influx through nicotinic receptors, blocked amphetamine-primed reinstatement, and blocked amphetamine-induced locomotor sensitization. Ex vivo electrophysiology showed a reduction in ACh-I activity following self-administration. An amphetamine challenge in vitro (10 μM) reduced spontaneous firing in saline-treated controls and increased TAN activity in mice responding to conditioned reinforcement, while physiological concentrations nicotine (100 nM) blocked both of these effects.

Conclusions: Our data demonstrates for the first time that amphetamine can promote drug seeking behaviors in mice. Results suggest that nicotinic receptors reduce sensitized behaviors following repeated amphetamine and modify the associated paradoxical changes in TAN firing. Further investigations are needed to determine whether selective targeting of nicotinic receptors can modify the symptoms and signs of neuphysiological disease.

Keywords: Translational/experimental therapeutics

18. Survey of Psychopharmacological Treatment in Children with Autism Spectrum Disorder Compared to General Pediatric Population in Israel
Gabis LV, Cohen EG, Leon O, Raz R (Rehovot, Israel)
Objective: It is estimated that between 30% and 60% of children with ASD are prescribed psychoactive medication for coping with aggression, irritability, hyperactivity and other behavioral problems. The prevalence and usage of medications in pediatric population in Israel was not yet assessed.

Methods: In this survey we examined the prevalence and patterns of medication use in children with ASD compared to a sample of 18000 general population of children same age range, using a phone interview and HMO database.

Results: From a total of 253 children diagnosed with ASD age 4–10 years old, 26% (n=66, 52 males) received pharmacotherapy, compared to 4% in general population. The usage increased with age both in ASD group as in general group. Among the group of 4-year-old children, only 1.6% of ASD children used medication (mainly Risperidone), while in the 10-year-old group 5.5% of ASD used medication. The most widely used was Risperidone (a third of children on medication), followed by methylphenidate (27%). Risperidone and stimulants were utilized more by males (twice more in boys than girls), utilization of SSRI’s had equal gender distribution.

Conclusions: Psychostimulants are widely used in the treatment of comorbidity in children with ASD and administration increased by 0.5- 1% each year for 4–10 years old children.

Keywords: Case studies/case series

Gabis LV, Amir BC, Leon O, Vusicker Y, Shefer S (Rehovot, Israel)
Objective: Global developmental delay below age three is considered to predict intellectual disability (ID). However, the trajectory may be different in children diagnosed of Autism Spectrum Disorder (ASD) compared to children with delays without ASD.

Methods: Children (n=88) diagnosed with global developmental delay (delay of more than 2 SD in two or more areas of development), and assessed with Bayley 2 developmental test, were followed and reassessed after age four using cognitive tests (WPPSI, Kaufman and WISC-R). They were divided in two groups according to definite diagnosis of ASD (n=38, 26 males) or GD without ASD (n=50, 37 males).

Results: As expected, a positive correlation was found between lesser degree of developmental delay as measured by MDI and subsequent IQ, in both groups. From ASD group, 60.1% scored with significant delayed performance on developmental test and 66% from GD group without ASD were significantly delayed. Subsequently, on cognitive tests after age 4 years, 20% of the non-ASD GD group scored with an IQ less than 70 and 28.9% from ASD group scored with comorbid intellectual disability.

Conclusions: MDI score less that 65 on Bayley 2 performed before age 3 years, predicts lower IQ (less than 70), on subsequent cognitive assessments. However, developmental delay trajectory is more stable in ASD group than in globally delayed children.

Keywords: Case studies/case series

20. Reduced Cortical Inhibition during a Novel Response Inhibition Task
Gilbert DL, Shabana N, Huddleston DA, Lauw CS, Wu SW, Mostofsky SH (Cincinnati, OH)
Objective: Response inhibition can be tested quantitatively in a variety of computerized tasks. Our objective was to develop a method to understand cortical neuropsychological mechanisms engaged during response inhibition tasks in children.

Methods: We modified the Sloter Hamel response inhibition task to include a race car controlled by the first digit on a game-controller. In a successful Stop trial, the participant inhibits releasing the button. The Stop difficulty adjusts to achieve approximately 50% successful inhibition. We used paired pulse Transcranial Magnetic Stimulation
(TMS) (Magstim Bistim 200) to measure “short interval cortical inhibition” (SICI) at baseline and during Go and Stop trials. For validation, we compared behavior and physiology in twenty-one healthy adults and 8–12 year old children. 

**Results:** On Go trials: Adults operated the car optimally more often than children (p = .06). On Stop trials: As intended, the percent successful inhibition was 55% for adults and 50% for children. The mean response inhibition time was better for adults (p = .06).

Cortical Inhibition: TMS-SICI did not differ between adults and children at baseline or during the tasks. However, compared to baseline, average SICI during the Slater Hamel task was 34% less (p = .0003). During inhibition, SICI was 15% less in failed versus successful trials (p = .03).

**Conclusions:** This new version of the Slater Hamel task quantifies behavioral differences and is suitable for TMS studies in children. Cortical inhibition appears to “disengage” during this task, particularly when inhibition fails.

**Keywords:** Neuroimaging


Gjolay N, Guy W, Kumar A, Chorgani HT, Behen ME (Detroit, MI)

**Objective:** We investigated the incidence of neurocognitive impairment as a function of duration of deprivation in a large sample of children raised from birth in international orphanages, in order to determine potential thresholds or sensitive periods for functional impairment.

**Methods:** One hundred and fifty-four children (mean age=9.7+2.4 years, 60 males; mean duration of orphanage experience=29.4+19.9 months; adoptive home=89.5+33.6 months), raised from birth in international orphanages underwent neuropsychological evaluations. Summary scores for ten neurocognitive domains were obtained; standard scores 2 or more SD below the mean of the normative population were considered impaired. To evaluate potential sensitive periods, incidence of impairment(s) was evaluated across durations of orphanage stay: <6 months, 7–19 months, 20–36 months, and >36 months.

**Results:** Less than 20% of children with 6 months duration or less evidenced any area of impairment. The likelihood of impairment increased to >50% after 6 months of orphanage stay and remained similar through 36 months. Beyond three years, incidence of impairment in at least one domain, rose to >80%. Chi-square analyses revealed significant differences in the incidence of impairment between orphanage duration categories (p=0.005), with significantly reduced or increased likelihood of impairment in those with <6 (p<0.005) or >36 (p=0.001) months of orphanage stay.

**Conclusions:** Exposures shorter than 6 months are associated with low likelihood of impairment, but risk doubles beyond 6 months (up to 36 months) of exposure, suggesting a 6 month threshold. Importantly, our data suggest a second threshold: exposures beyond 36 months represent a highly increased likelihood of at least one area of impairment.

**Keywords:** Case studies/case series, Neonatal neurology

**22. Increased Correlation between Orthographic and Frontal Functional Connectivity following Accelerated Reading Intervention in Children with Dyslexia during Rest**

Horowitz-Kraus T, Key B, Wang Y, Holland SK (Cincinnati, OH)

**Objective:** Dyslexia/Reading difficulty (RD) is defined by slow and inaccurate reading accompanied by impairments in executive functions (Horowitz-Kraus et al., 2012). The Reading Acceleration Program (RAP), a computerized program that trains reading fluency and was found to increase activation in neural circuits related to reading as well as functional connectivity between these and regions related to executive-functions in these populations (Horowitz-Kraus et al., 2013). Here we examine the effect of RAP on the functional-connectivity in orthographic, language and executive-functions’ networks in children with RD during rest.

**Methods:** Eighteen children with RD and 18 TRs (8–12 years old), matched for IQ and attention ability participated in the study. Inclusion criteria for RD were reaching the lowest quartile for word/non-word reading tests (TOWRE: Torgesen, Wagner & Rashotte, 1999) and the GORT-IV (Wiederholt & Bryant, 1992). All subjects trained on RAP 5 times a week for four weeks, and were scanned using the resting-state functional-MRI and tested behaviorally before and after training.

**Results:** Both groups showed increased word recognition ability and faster contextual reading after training. Greater correlation between orthographic, fluency, attention, and DMN networks was found in children with RD as compared to TRs as well as to their performance before training.

**Conclusions:** These results may reflect a more automatic, efficient and monitored reading process in RDs post-intervention, and point at a general effect of RAP on the functional connections between reading, language and executive processes during rest.

**Keywords:** Neuroimaging

**23. Executive Function in Tuberous Sclerosis Complex**

Hsieh DT, Jennesson MM, Thiele EA (Ft. Sam Houston, TX)

**Objective:** Children with tuberous sclerosis complex (TSC) can manifest a wide range of neuropsychological impairments. Our objective was to evaluate the executive function behaviors in children with TSC.

**Methods:** The Behavior Rating Inventory of Executive Function (BRIEF) is an 86-item assessment of executive function behaviors, with a standardized mean score of 50, with higher scores reflecting greater executive dysfunction. We administered the parent BRIEF via the caretakers of 19 children with TSC.

**Results:** 19 children with TSC (9 female, 10 male) had an age range of 6–17 years old (mean 11.1 years), and a full IQ range of 52–108 (mean 82.6). The mean Global Executive Composite (GEC) score was 60.2, with patients scoring the highest on the subsets of Working Memory (mean 63.9) and Plan/Organize (mean 60.3). Clinically
significant elevations (t score >65) were reported most commonly in the subsets of Working Memory (58%) and Inhibit (47%). 37% of patients had at least 4 subsets with clinically significant elevations. However, 26% of patients had no clinically significant score elevations. Higher GEC scores tended to be reported for patients with epilepsy versus those without (p=0.056), for patients with higher Early Childhood Epilepsy Severity Scale (E-Chess) scores (p=0.175), for patients with a history of infantile spasms (p=0.0002), and for patients with a TSC2 mutation (p=0.188). Higher GEC scores were not associated with the number of frontal tubers on MRI or the presence of electroencephalogram frontal spike waves.

Conclusions: Children with TSC can manifest, and may need support for, impairments in executive function.

Keywords: Epilepsy and other paroxysmal disorders, Genetics

24. Neurocognitive Predictors of Social Functioning in Cognitively Intact Children with Histories of Early Deprivation

Huq F, Gjolaj N, Guy W, Chugani HT, Behen ME (Detroit, MI)

Objective: Children with histories of institution rearing are commonly reported to have developmental delays and behavioral difficulties, including social problems, which often persist into adulthood. This study evaluated the relative impact of demographic, neurocognitive and behavioral variables on persistent social problems in a sample of children with histories of early deprivation and intact intellectual functioning.

Methods: Eighty-four children, all raised from birth in international orphanages (mean age=9.6 ± 2.4 years, 34 males; mean FSIQ=98.9 ± 15.3), completed neuropsychological evaluations. Mean duration of orphanage exposure was 20.5 ± 14.2; duration in the adoptive home was 94.0 ± 29.8. Caregivers completed the Behavioral Assessment for Children-Second Edition, including the social skills subscale. Stepwise multiple regression analysis, with backwards entry, was used and included demographic variables (age, gender, caregiver education, and duration of orphanage exposure and duration in the adoptive home), neurocognitive (FSIQ, receptive and expressive language, executive function, motor dexterity) and behavioral (internalizing and externalizing behavioral problems, attachment) variables as predictors, and social skills as the outcome measure.

Results: The final overall model was significant (R=0.608; p<0.01). Variables contributing significant variance to the model included duration of orphanage exposure (p=0.05), expressive language processing (p=0.045), motor dexterity for the dominant hand (p=0.029), and internalizing behavioral problems (p=0.003).

Conclusions: Our findings reveal that both developmental (expressive language, motor competence) and behavioral factors contribute to caregiver report of social skills in children with histories of early institution rearing, and indicate the import of early intervention that addresses both neurodevelopmental delay/impairment, as well as psychosocial intervention for behavioral problems in children with such histories.

Keywords: Case studies/case series, Neonatal neurology

25. Whole Brain Connectivity Pattern Can Differentiate Between High and Low-Functioning Children With Autism Spectrum Disorder: a brain connectome study

Jeong JW, Kumar A, Behen M, Ashab R, Chugani HT, Chugani DC (Detroit, Michigan)

Objective: This study performed whole brain connectome analysis in young children with autism spectrum disorder (ASD) using diffusion-weighted-MRI (DW-MRI) and evaluated whether the connectome analysis could discriminate between children with high and low-functioning ASD.

Methods: Thirteen children with low functioning autism (LFA, age:44±12.1 months, 10 males, Vineland composite <70) and seven children with high functioning autism (HFA, age: 41±5.7 months, 5 males, Vineland composite >70) underwent 3 Tesla DW-MRI. A total of 116 regions were generated by fitting a deformable template, resulting in a 116x116 pair-wise connectivity matrix. Finally, two sample t-test and Pearson correlation analyses were performed to identify the pair-wise connections showing significant group difference and their correlation with ADOS scores and the children's Yale-Brown obsessive compulsive scales (CYBOCS).

Results: Compared with the HFA group, children with LFA showed a significant reduction in neural connectivity in left hemisphere (Fig. 1a). The connections with the largest difference and their correlation with ADOS scores, but the first three connections showed positive correlation with CYBOCS values (R=0.41,0.40,0.42, p-value<0.07).

Conclusions: The present study reports left sided decreases in structural connectivity in children with LFA, compared to children with HFA. The correlation with the CYBOCS scores suggests these neural substrates may underlie obsessions and compulsive behaviors in these children.

Keywords: Neuroimaging

26. Reduced Cortical Thickness in Brain Regions in Children with Histories of Early Deprivation

Kamson D, Tiwari V, Jeong JW, Chugani HT, Kumar A, Behen ME (Detroit, MI)

Objective: We investigated whether children with histories of early social deprivation (ED) evidence altered cortical thickness in fronto-temporal brain regions as compared to typically developing non-adopted children (NC).

Methods: Forty-one children with histories of ED (mean age: 10.3 ± 2.3, 17 males) and 41 right-handed healthy controls (NC; mean age: 11.4 ± 2.6 years, 20 males) underwent MR-SPGR. All ED children were raised from birth in European or Asian orphanages, subsequently adopted in the USA. Exclusionary criteria included pre- or perinatal problems, prematurity, focal neurological abnormality, medical problems. All children also underwent neurocognitive/neurobehavioral evaluation. Cortical thickness was determined
via surface-based approach using the FreeSurfer software suite. Between-group comparisons in brain structure were made using the Qdec analysis tool of FreeSurfer, with a false discovery rate of 0.05.

**Results:** The groups did not differ on age, gender, or IQ. Between-group comparisons revealed reduced cortical thickness in frontal, parietal, and cingulate cortices, more prominent in the right hemisphere, as compared to controls. Results also revealed that cortical thickness in the ED group in many regions had a weaker association with age than that observed for controls who evidenced a strong negative correlation between cortical thickness and age.

**Conclusions:** These findings are consistent with previous work demonstrating abnormal white matter in children with histories of ED, and may be associated with a lack of normal pruning associated with a lack of experience-expectant stimulation and/or exposure to chronic stress associated with a lack of consistent caregiver during early development.

**Keywords:** Neuroimaging

27. **Time-related Variables Predict Integrity of Fronto-temporal White Matter Pathways in Orphanage-reared Children**

*Kumar A, Behen ME, Jeong JW, Guy W, Gjolaj N, Chugani HT (Detroit, MI)*

**Objective:** In this study, we investigated the influence of timing (duration of orphanage stay, duration in adoptive home) as predictors of microstructural integrity of fronto-temporal white matter pathways.

**Methods:** Thirty-six right-handed children (13 males, mean age = 121.5 ± 29.2 months; mean FSIQ = 95.8 ± 18.2), raised from birth in orphanages in Eastern Europe or Asia and subsequently adopted in the US, underwent diffusion-weighted MRI and their duration of orphanage experience (Dورو = 25.6 ± 18.9 months) and duration in adoptive home (DURA = 93.5 ± 23.0 months) were obtained. Arcuate fasciculus, uncinate fasciculus, fornix, and cingulum were isolated using tractography and their fractional anisotropy (FA) and mean diffusivity (MD), indicating underlying microstructural integrity of the white matter, were calculated. Separate multiple regression analyses were conducted for individual tracts, with age and gender entered in the first step, and either Dورو or DURA in the second; with MD or FA for each tract as the outcome measure.

**Results:** DURO was found to be negatively associated with FA of the right fornix (p = 0.02), suggesting reduced microstructural integrity with longer duration in orphanage. DURA was negatively associated with MD for bilateral cingulum (left, p = 0.0001 & 0.01 for left and right, respectively) and bilateral arcuate fasciculi (p = 0.0001 & 0.02 for left and right, respectively), indicating better white matter integrity with longer durations in adoptive home.

**Conclusions:** Time-related variables account for significant variance in microstructural integrity of several fronto-temporal white matter tracts, with better underlying white matter integrity associated with shorter orphanage stays and longer periods in the adoptive home.

**Keywords:** Neuroimaging
28. Physical Comorbidity of Attention Deficit Hyperactivity Disorder (ADHD) among US adolescents

Lateef TL, Sheppard B, He J, Jameson N (Washington DC)

Objective: To examine the pattern and extent to which other physical and developmental conditions are comorbid with ADHD in youth in a representative sample of the US population

Methods: The National Comorbidity Survey-Adolescent Supplement is a face-to-face surveys of adolescents aged 13–18 years in the continental US. Sufficient information to assess the DSM-IV criteria for ADHD and all its subtypes was available in the diagnostic module. A caretaker/parental self-administered report was used to assess a broad range of other physical and developmental conditions, such as autism spectrum disorders and learning disability. The sample for these analyses was 6483 adolescents with systematic caretaker/parent reports.

Results: Adolescents with ADHD reported higher rates of other developmental disorders, including autism spectrum disorders (OR, 5.39; 95% CI, 2.40-12.08) and learning disability (OR 6.46; 95% CI, 4.72-8.83). Also, we report in a nationally representative sample that enuresis (OR, 1.95; 95% CI, 1.36-2.82), gastrointestinal problems (OR 2.06, 95% CI, 1.33-3.19), asthma (OR, 1.49; 95% CI, 1.04-2.14) and seasonal allergies (OR, 1.39; 95% CI, 1.01-1.91) were more common in adolescents with ADHD compared to their unaffected counterparts.

Conclusions: Adolescent ADHD is associated not only with other developmental disorders such as learning disability and autism spectrum disorders that affect cognitive processes but may also be a manifestation of broader multisystem conditions that involve inflammatory/immune processes. Our findings suggest that comorbid medical conditions should be evaluated comprehensively in determining treatment options in youth with ADHD. Such comorbidity also could be an important source of the clinical and etiologic heterogeneity in ADHD.

Keywords: Case studies/case series

29. Evolution of EEG Findings in Children with Autism

Golla S and Sirsi D, Esvau PA, Arnold ST (Dallas, TX)

Objective: To observe evolution of serial EEG findings in Autism.

Methods: A retrospective chart review of 18 patients with a known diagnosis of Autism who underwent 2 or more EEG’s was conducted.

Results: -14/18 were males. Median age at time of 1st EEG was 5 years (range 1-16) and median age at subsequent EEGs was 7.5 years (range 2-18). No significant difference in age at initial EEG between normal EEG vs spikes was observed (Median age 5 years vs. 4.5 years). 6/18 had spikes on the initial EEG (4 focal, 2 generalized). 3/12 (25%) without spikes on the initial EEG developed spikes on subsequent EEGs (2 on the 2nd and 1 on the 3rd EEG). 3/4 patients (75%) with focal spikes on the initial EEG developed generalized spikes (2 on the 2nd and 1 on the 3rd EEG) and 1 normalized later. 1/2 patients (50%) with generalized spikes on the initial EEG changed to focal spikes and the other normalized. There was no significant

difference between evolution of EEG’s in regressive autism vs. non regressive autism. There was no significant difference between evolution of EEG’s in regressive autism vs. non regressive autism.

Conclusions: 25% patients with initial normal EEG had spikes on subsequent EEG’s. Repeat EEG’s increase yield of abnormalities especially when clinical suspicion for seizures is high. Selection of AEDs is frequently based on presence of focal vs generalized spikes but epileptiform discharges may change with time (50–75% changed in this study). Serial EEGs may guide AED therapy changes if clinically indicated.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders

30. Visual Processing in Infants with Tuberous Sclerosis Complex

Vargar KJ, Jeste SS, Nelson CA (Boston, MA)

Objective: Tuberous sclerosis complex (TSC) is an autosomal disorder that presents with a high penetrance of autism spectrum disorder (ASD) and intellectual disability. Rooted in evidence from mouse models of TSC that demonstrate aberrant visual cortical connections, we investigated low level visual processing and visual attention in TSC in the first years of life. This study comprised a part of a comprehensive longitudinal study of atypical development in TSC.

Methods: Infants with TSC and typically developing controls were followed as early as 3 months through to 36 months. We collected behavioral and electrophysiological assays of development within the visual domain; specifically, infants underwent developmental testing on the Mullen Scales of Early Learning (MSEL), an assessment of social-communicative skills using the Autism Observation Scale of Infancy (AOSI), and electrophysiological assessments of i) early visual processing using a visual-evoked potential (VEP) paradigm, and ii) face processing.

Results: Infants with TSC demonstrated atypical face processing and delays in the visually mediated behavioral measures (e.g., in visual reception, attention and tracking) as early as 6 months of age. These atypicalities did not stem from abnormal low level visual processing, as the TSC group demonstrated robust VEPs of comparable amplitude and latency to age matched controls over the first years of life.

Conclusions: Taken together, our results suggest that specific impairments in visually mediated behaviors in TSC do not appear to be rooted in disturbances in low-level visual processing. Instead, atypical development in the visual domain may be better explained by aberrations in networks associated with the processing of complex visual stimuli.

Keywords: Epilepsy and other paroxysmal disorders, Genetics, Neuroimaging

31. Steroid Treatment for Autism Spectrum Disorder: results from the CAST (corticosteroids for autism - a scientific trial) study


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Objective: To assess prednisolone efficacy as a treatment for autism spectrum disorder (ASD) in young children.

Methods: This is a double-blind, randomized, placebo-controlled, prospective clinical trial involving 3–7-year-old boys diagnosed with ASD according to DSM-IV criteria. Workup included brain MRI, lumbar puncture, prolonged electroencephalogram, karyotype, biochemical panel, PPD, and non-verbal intelligence test PTONI. The clinical trial spanned 24 weeks, during which prednisolone dosages were 1 mg/kg/day for 8 weeks, followed by 1 mg/kg qod for 8 additional weeks, then tapering during 8 weeks. The primary outcome measures were two language assessment tools developed in Brazil (ABFW, ADL) that were applied four times throughout the study. Childhood Autism Rating Scale (CARS), the secondary outcome measure, was applied prior to and in the end of the clinical trial.

Results: 20 children were randomly assigned to the prednisolone group, and 20 to the placebo group. Two subjects from the former abandoned the study. Initially, there was no statistically significant difference between the two groups regarding age (p = 0.9136), body weight (p = 0.1009), language scores (ABFW, p = 0.6524; ADL, p = 0.2033), or CARS score (p = 0.9060). The prednisolone group showed greater increase in expressive language scores than the placebo group, but this difference only approached statistical significance (p = 0.0862). Median CARS score decreased from 46.3 to 35.3 in the prednisolone group, versus a decrease from 45.8 to 43.0 in the control group (p = 0.0026).

Conclusions: Prednisolone significantly reduced ASD core symptoms as assessed by CARS score in a sample of severely autistic children.

Keywords: Translational/experimental therapeutics

32. Neuropsychological Testing Supports Involvement of the Dentate Gyrus in the Pathogenesis of Intellectual Disability Seen in Kabuki Syndrome

Weisman JR, Vaurio R, Bjornsson HT (Baltimore, MD)

Objective: Kabuki syndrome (KS) is a genetic syndrome caused by mutations in two different chromatin modifying genes, MLL2 and KDM6A. These patients have well-established characteristic features including cognitive impairment. However, the specific cognitive impairments in children with KS have not been well characterized to date nor have the brain regions involved.

Methods: We reviewed 5 cases of patients with KS who received neuropsychological testing at the Kennedy Krieger Institute.

Results: Of the 5 patients, only 2 met criteria for intellectual disability. However, all 5 children showed specific deficits (both by standardized scores and relative to their verbal problem solving and adaptive function) in fine motor control, visual spatial tasks (visuospatial problem solving and construction and visuospatial memory), and executive functioning (particularly planning and organizing tasks and processing speed).

Conclusions: Previous studies have shown that the dentate gyrus appears specifically associated with visuospatial memory and learning. Interestingly, our group has demonstrated that a mouse model of KS demonstrates hippocampal memory defects associated with a significant reduction in neurogenesis in the granule cell layer of the dentate gyrus, a site of active adult neurogenesis. These findings suggest that the dentate gyrus might be a neuroanatomical location of interest for KS and that the cognitive deficits seen may demonstrate more flexibility than those seen in other causes of intellectual disability. Finally, ascertaining cognitive profiles from patients with KS as done here and expanding it to a larger population of KS patients may provide specific measures for treatment outcome studies for this syndrome.

Keywords: Case studies/case series, Genetics

33. Abnormal Neurophysiologic Motor Cortex Plasticity in Children and Adolescents with Autism Spectrum Disorders

Wu SW, Pedapati EV, Shahana N, Huddleston DA, Laue CS, Gilbert DL (Cincinnati, OH)

Objective: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication, restricted interests and repetitive behaviors. Recent research points to a role for maladaptive neuroplasticity; however, tolerable, non-invasive methods for quantifying this in children are lacking. We sought to use a brief, low intensity Transcranial Magnetic Stimulation (TMS) protocol to evaluate a Long-Term Potentiation (LTP)-like property in children and adolescents. We present initial results from a pilot study.

Methods: Right-handed ASD subjects (13yoF, 14yoM, 18yoM) and Typically-Developed Controls (TDC; 10yoM, 11yoM, 13yoM, 15yoF) were included. Diagnosis of ASD was confirmed by the Autism Diagnostic Observation Schedule by a trained clinician. Using Magstim SuperRapid2, Intermittent Theta Burst Stimulation (iTBS; 3 pulses per burst at 30Hz with bursts repeated every 200msec for 2 seconds; total of ten 2-second trains with inter-train interval of 8sec) was delivered over dominant motor cortex (M1) at an intensity of 0.7*Resting-Motor Threshold (RMT). Single-pulse TMS was performed before and after iTBS to examine its neurophysiologic effects on M1.

Results: No serious adverse events occurred. Both TDC and ASD participants demonstrated dominant M1 LTP after iTBS. However, M1 LTP increase in the ASD group was significantly higher than the TDC group (Repetied-Measures ANOVA; Group*Time interaction F9,45 = 2.98, p = 0.007).

Conclusions: iTBS delivered to dominant M1 safely elicited LTP in seven children and adolescents but produced excessive M1 LTP in ASD subjects. This brief, well-tolerated repetitive TMS procedure may serve as a potential biomarker for maladaptive plasticity in ASD.

Keywords: Translational/experimental therapeutics

34. Longitudinal Diffusivity Changes and its Relationship to Disease Activity and Cognition in Pediatric MS

Aung WY, Massoumzadeh P, Najmi S, Benzinger TLS, Mar S (Saint Louis, MO)

Objective: To evaluate the longitudinal diffusivity changes in brain tissue integrity in pediatric MS and correlate with disease activity and cognition.
BACKGROUND: Diffusion Tensor Imaging (DTI) is a non-invasive, quantitative magnetic resonance imaging technique which measure brain tissue integrity. Recent studies have shown that childhood onset has a higher relapse frequency and lesion load on MRI, and shorter time to disability compared to adult onset.

Methods: Ten children with MS (mean age 16.2 ± 1.3) were imaged serially with at least one follow up scan (mean follow-up duration 10.3 ± 7.6 months). Twenty-five age matched healthy children were included as controls. Regions of interest (ROI) were drawn on lesions and corpus callosum normal appearing white matter (NAWM). Available cognitive data of children with MS were obtained from medical records (n = 5).

Results: On lesion analysis, the majority of the patients who had DTI closer to the disease onset (n = 7) did not have statistically different diffusivity ratios from the controls. 86% of patients had increased AD and RD, and 43% had low FA on follow up DTIs. The diffusivity measures did not change significantly over time except for 2 patients. There is no relationship between diffusivity ratios and lesion load, number of relapses or EDSS. On ROIs of corpus callosum NAWM, RD is persistently high in patients with significant cognitive impairment and normal in patients with minimal or no cognitive difficulty.

Conclusions: Diffusivity changes occur over time, and high RD in NAWM of corpus callosum may correlate with cognitive dysfunction in children with MS.

Keywords: Demyelinating Disorders, Neuroimaging

35. Pediatric Multiple Sclerosis: Demographic Features and Clinical Findings from the US Network of Pediatric MS Centers


Objective: To describe demographic/clinical features of a large US cohort of pediatric MS patients. Pediatric onset occurs in 2.7-5% of those with MS, data from US samples are incomplete.

Methods: Individuals with pediatric MS (< 18 years) were prospectively enrolled in a longitudinal observational study across 9 sites forming the US Network of Pediatric MS Centers.

Results: Demographic: Of 340 cases; girls: boys = 2:1. Percentage of girls increased from 53% (< 11 yrs) to 71% (> 12 yrs). Mean age of onset was 13.7 yrs (girls); 12.7 yrs (boys).

Race was self-identified as Caucasian (67%), African-American (20%), multi-racial (7%), other (6%). Race did not differ by gender (p = 0.59) or age (p = 0.40); Ethnicity: Hispanic (31%), non-Hispanic (69%). Among cases, 38% had one or both parents born outside the US, most frequent: Mexico (29%), Puerto Rico (9%), Dominican Republic (8%). 5.3% of cases were foreign born. Clinical: 31% of children had a prodrome before the first event: infectious (67%), closed head trauma (10%), vaccination (9%). Monofocal (60%) vs. polyfocal (40%) presentation, p < 0.01. Encephalopathy (5%) was more frequent among the youngest ≤ 11 yrs (14%) vs. > 12 yrs (2%) p < 0.01. Optic neuritis (27%) was highest among those ≤ 11 yrs (34%) vs. > 12 yrs (24%) (p = 0.07). At the initial visit, 77% had EDSS < 3. Mean ARR = 0.49 (n = 256) with > 1 yrs follow-up.

Conclusions: Individuals from the US with pediatric MS vs. adult MS differ demographically with fewer Caucasians and many first generation Americans. Overall, the female ratio increases with age; encephalopathy is more common among the youngest.

Keywords: Demyelinating Disorders

36. A Next-Generation Diagnostic Algorithm for the Diagnosis of Leukodystrophies


Objectives: Leukodystrophies are a large group of inherited diseases of CNS myelin. There are few treatments and a majority of patients do not receive a final genetic diagnosis. We report five patients with complex constellations of neurological symptoms and brain MRIs showing leukodystrophy. Despite extensive testing, a specific diagnosis was unable to be determined.

Methods and Results: Recently, we performed next-generation sequencing (NGS) on the five patients (from 3 families), revealing two novel pathogenic mutations in the PLP1 gene; and a novel mutation in the b-tubulin gene TUBB4A. PLP1 mutations are found in Pelizaeus-Merzbacher disease and Hereditary Spastic Paraplegia type 2. TUBB4A is a cause of hereditary dystonia type 4 (DYT4) and recently of hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC). This report expands the phenotypic spectrum of TUBB4A-associated neurological diseases to include static hypomyelinating leukodystrophy, and supports the clinical relevance of NGS.

Conclusions: These cases illustrate the utility of NGS to end diagnostic odysseys in patients where extensive genetic heterogeneity would make step-wise genetic diagnosis logistically difficult and prohibitively expensive. As ethical and financial issues resolve, NGS continues to become more accessible and may become integral to the diagnosis of leukodystrophies. We propose an algorithm for leukodystrophy diagnosis that is rational and cost-effective with a tiered approach to testing. There is utility in making an expedient diagnosis by excluding treatable forms of leukodystrophies, curtailing other expensive and lengthy testing, and providing valuable reassurance and prognostic information to the patient and their family.

Keywords: Case studies/case series, Demyelinating Disorders

37. Effect of Age on Efficacy of Fingolimod Treatment: young adult patients with multiple sclerosis demonstrate higher relative reduction of relapse rates

Chitnis T, Karlsson G, Häring DA, Ghezzi A, Pohl D, Putzki N (Boston, MA)

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Objective: Evaluation of effect of age on annualized relapse rates (ARR) in young adult Multiple Sclerosis (MS) patients receiving fingolimod 0.5mg versus intramuscular interferon beta-1a (IFNβ1aIM)/placebo in Phase 3 studies, to confirm sample size of PARADIGMS study (fingolimod versus IFNβ1aIM) in pediatric MS.

Methods: A post-hoc analysis of ARR using negative binomial regression was conducted in intent-to-treat populations of FREEDOMS, FREEDOMS II (versus placebo) and TRANSFORMS (versus IFNβ1aIM); ARR was estimated at ages 20 and 30 years.

Results: Proportion of patients aged ≤20 and ≤30 years were FREEDOMS, 28/1272 (2.2%) and 325/1272 (25.6%); FREEDOMS II, 17/1083 (1.6%) and 150/1083 (13.9%); TRANSFORMS, 40/1292 (3.1%) and 355/1292 (27.5%) with mean MS duration of 2.8–5.2 years and 1.5–1.7 mean number of relapses in previous year. Estimated ARR in 20 years/30 years/overall fingolimod 0.5mg groups was: FREEDOMS, 0.16/0.19/0.18; FREEDOMS II, 0.27/0.24/0.21; and TRANSFORMS: 0.14/0.17/0.16; in control groups ARR was: FREEDOMS, 0.73/0.57/0.40; FREEDOMS II, 0.67/0.51/0.40; and TRANSFORMS, 0.60/0.48/0.33. Estimated relative reduction in ARR by fingolimod 0.5mg versus controls was (20 years/30 years/overall): FREEDOMS, 0.73/0.57/0.40; FREEDOMS II, 0.16/0.19/0.18; and TRANSFORMS: 0.14/0.17/0.16; in control groups ARR was: FREEDOMS, 0.73/0.57/0.40; FREEDOMS II, 0.67/0.51/0.40; and TRANSFORMS, 0.60/0.48/0.33. Estimated relative reduction in ARR by fingolimod 0.5mg versus controls was (20 years/30 years/overall): FREEDOMS, 0.79/0.67/0.54%; FREEDOMS II, 59%/53%/48% and TRANSFORMS, 77%/64%/52% (all p<0.001).

Conclusions: Fingolimod 0.5mg groups showed low ARR irrespective of age, whereas controls showed higher ARR in young patients, versus overall population. The relative effect of fingolimod 0.5mg versus controls was consistently higher in young adult patients versus overall population. These results provide further evidence supporting investigations of fingolimod in pediatric MS patients. Approximately 190 patients will be randomized to receive fingolimod/IFNβ1aIM (1:1) in the PARADIGMS study currently recruiting globally.

Keywords: Demyelinating Disorders, Infections/Neuroimmunology, Translational/experimental therapeutics

38. ALD Connect, An All-inclusive Consortium with the Goal to Eradicate X-linked Adrenoleukodystrophy


Objective: X-linked adrenoleukodystrophy (X-ALD) is a devastating neurological disorder caused by mutations in the ABCD1 gene, which is responsible for transport of CoA-activated very long chain fatty acids from the cytosol into the peroxisome for degradation. In children, this causes rapid progressive brain demyelination that can only be halted in its early stages by hematopoietic stem cell correction. In the present study, we used AAV9 encoding human ABCD1 (AAV9-hABCD1) to assess gene correction in vitro and in vivo.

Methods: Primary cultured brain glia cell mixture from ABCD1-/- mice was transduced with different doses of AAV9-hABCD1. In vivo, AAV9-hABCD1 was delivered intravenously and by stereotactic intraventricular (ICV) injection.

Results: In ABCD1-/- mouse brain cell culture, AAV9-hABCD1 reduced very long chain fatty acid (C26:0 LPC, lyso-phosphatidylcholine) levels in a dose-dependent manner. In vivo, C26:0 LPC levels in mouse brain and spinal cord were reduced more effectively by intravenous (IV) than ICV delivery. IV delivery targeted a broader range of cell types (astrocytes, microglia, neurons, endothelial cells, oligodendrocytes) than ICV delivery (astrocytes, microglia, neurons). Immunofluorescence showed co-staining of the ABCD1 protein and catalase, indicating localization of ABCD1 to the peroxisome.

Conclusions: We conclude that AAV9-mediated ABCD1 gene transfer is able to reach target cells in the nervous system and reduce very long chain fatty acids in culture and in a mouse model of X-ALD. It remains to be seen whether

39. AAV9-Mediated Gene Therapy for X-linked Adrenoleukodystrophy (X-ALD)

Gong Y, Maguire CA, Mu D, Moser A, Ren JQ, Eichler FS (Boston, MA)

Objective: X-linked adrenoleukodystrophy (X-ALD) is a devastating neurological disorder caused by mutations in the ABCD1 gene, which is responsible for transport of CoA-activated very long chain fatty acids from the cytosol into the peroxisome for degradation. In children, this causes rapid progressive brain demyelination that can only be halted in its early stages by hematopoietic stem cell correction. In the present study, we used AAV9 encoding human ABCD1 (AAV9-hABCD1) to assess gene correction in vitro and in vivo.

Methods: Primary cultured brain glia cell mixture from ABCD1-/- mice was transduced with different doses of AAV9-hABCD1. In vivo, AAV9-hABCD1 was delivered intravenously and by stereotactic intraventricular (ICV) injection.

Results: In ABCD1-/- mouse brain cell culture, AAV9-hABCD1 reduced very long chain fatty acid (C26:0 LPC, lyso-phosphatidylcholine) levels in a dose-dependent manner. In vivo, C26:0 LPC levels in mouse brain and spinal cord were reduced more effectively by intravenous (IV) than ICV delivery. IV delivery targeted a broader range of cell types (astrocytes, microglia, neurons, endothelial cells, oligodendrocytes) than ICV delivery (astrocytes, microglia, neurons). Immunofluorescence showed co-staining of the ABCD1 protein and catalase, indicating localization of ABCD1 to the peroxisome.

Conclusions: We conclude that AAV9-mediated ABCD1 gene transfer is able to reach target cells in the nervous system and reduce very long chain fatty acids in culture and in a mouse model of X-ALD. It remains to be seen whether
this approach will be safe or more effective than currently available therapies in patients with X-ALD.

**Keywords:** Demyelinating Disorders, Genetics, Translational/experimental therapeutics

### 40. Whole Exome Sequencing in a Cohort of Unsolved Leukodystrophies

**BACKGROUND:** Unsolved leukodystrophies remain a diagnostic challenge for practitioners with nearly 50% of cases remaining unresolved. Leukodystrophies are a heterogeneous group of disorders characterized by abnormal signal of the white matter on brain magnetic resonance imaging. Diagnosis and characterization of the disorders has traditionally been based on MRI pattern recognition and classification.

**Methods:** Whole exome sequencing (WES) was performed on a cohort of 70 patients with unsolved leukodystrophy with non-specific radiologic findings or previously negative diagnostic testing. Patients were collected prospectively in the Myelin Disorders Bioregistry Project, as referrals were made for patients with unsolved leukodystrophies. Analysis was performed on trio or greater family groups in all cases. Sanger sequencing was used to validate and perform segregation analysis of all candidate mutations.

**Results:** WES and pathogenicity confirmation permitted resolution of 46% of families in our unsolved cohort, including novel and known genes in mitochondrial cytopathies (n=5), epileptic encephalopathy (n=4), aminoacyl transferases (n=3), hypomyelinating leukodystrophies (n=8) and other genes (n=13). The remaining cases (n=37) remain unsolved despite WES.

**Conclusions:** The advent of WES has been clinically significant in rare and undiagnosed disease, in particular leukodystrophies, where over half of affected patients never achieve a diagnosis with standard testing. We present the first large cohort of patients with genetic leukoencephalopathies undergoing WES, solving nearly half of unresolved cases. Based on this data, with the use of WES approaches, it may be possible to decrease the number of patients with an unresolved genetic disorder of the white matter to 25%.

**Keywords:** Demyelinating Disorders, Genetics, Neuroimaging

### 41. Mutations in CNTNAP1 Cause Severe Arthrogryrosis Multiplex Congenita with Distinct Neuroradiologic Features

**Objective:** Approximately 50% of patients with leukodystrophy do not have a clear genetic diagnosis. Targeted diagnostic efforts have previously been made on the basis of distinct MRI features. Two patients with an unsolved leukodystrophy and similar brain MRI and clinical features presented to the Myelin Disorders Bioregistry Project (MDBP). The MDBP aims to identify genetic etiologies of disease and develop new tests for leukodystrophies.

**Methods:** MRI imaging and medical records were reviewed and whole exome sequencing with Sanger confirmation was performed in a research setting.

**Results:** Two unrelated patients presented at birth with respiratory failure, arthrogryposis, severe congenital demyelinating neuropathy and leukoencephalopathy. Both patients developed bilateral hearing loss. Family history was significant for older siblings who passed away in the neonatal period; both were described as having similar phenotypes to our patients. Brain MRI imaging included persistent delays in myelination, immature appearing gyri with rapid atrophy, disproportionate inferior/temporal horn dilation, and thalamic signal abnormality. In both patients, biallelic nonsense mutations were identified in the CNTNAP1 gene; Patient 1 is compound heterozygous for c.319C>T (R107*) and c.967T>C (p.C323R); Patient 2 is homozygous for c.1163G>C (p.R388P).

**Conclusions:** The CNTNAP1 gene encodes a contactin-associated protein (CASPR) and is transcribed predominantly in the brain. It has been associated with severe arthrogryposis multiplex congenita. The identification of these two families may expand the disease spectrum and identify brain MRI characteristics to assist clinicians in making diagnostic testing decisions.

**Keywords:** Demyelinating Disorders, Genetics, Neuroimaging

### 42. A Novel Catastrophic Presentation of X-Linked Adrenoleukodystrophy

**Objective:** We report a novel presentation of childhood cerebral adrenoleukodystrophy, characterized by status epilepticus followed by abrupt and catastrophic developmental regression.

**Methods:** A description of the clinical presentation, laboratory evaluation, and imaging findings leading to a diagnosis of X-linked adrenoleukodystrophy.

**Results:** A previously healthy 3-year-old male with mild speech delay presented with fever, diarrhea, and status epilepticus requiring a 72 hour pentobarbital coma. Admission labs were notable only for a glucose level of 22, which stabilized after correction. The child never returned to his prior neurological baseline, with complete loss of gross motor, fine motor, and speech skills. Serial brain MRI/MRS were notable for progressive diffuse cortical signal changes with swelling, diffusion restriction, and ultimately laminar necrosis. An extensive metabolic workup revealed only a low CSF methyltetrahydrofolate level. Eight months after his initial presentation CSF protein and MRS lactate were persistently elevated, leading to testing for lysosomal and peroxisomal disorders. Very long chain fatty acids were elevated. Identifying the pathogenic ABCD1 mutation confirmed the diagnosis of X-linked adrenoleukodystrophy.

**Conclusions:** Boys with childhood cerebral X-linked adrenoleukodystrophy typically present with gradual behavioral changes. Rare reports of boys presenting with transient altered mental status or status epilepticus describe a recovery to their pre-presentation baselines. To our knowledge this is
43. SAFETY: safety, awareness and familiarity with epilepsy in teenage years

Agarwal RL, Patel R, Set K, Zidan M, Sivaswamy L (Detroit, MI)

Objective: To evaluate the understanding of adolescent patients with epilepsy regarding their disease.

Methods: The SAFETY questionnaire (Content Validity Index: 0.96, Flesch-Kincaid Grade level: 6.8) was administered to 165 cognitively normal adolescents with epilepsy (85 females, Mean age: 15.2 ± 1.6 years, range: 13–18 years). The questionnaire was devised to evaluate knowledge about epilepsy and seizure medications (SAFETY-K: 7 questions) and about lifestyle modifications and safety (SAFETY-S: 10 questions). Female participants answered 5 additional questions related to reproductive health (SAFETY-R).

Results: The average rate of correct responses for the SAFETY-K and SAFETY-S questions were 47.9% and 53.9% respectively. The SAFETY score (maximum possible score 17) was higher in adolescents between 16–18 years (vs. those between 13–15 years: 9.7 ± 2.9 vs. 8.1 ± 3.2; p=0.002), Caucasians (vs. African-Americans: 9.4 ± 3.4 vs. 8 ± 2.7; p=0.03), and in children whose parents were in professional occupation (vs. service occupation, 9.4 ± 3.2 vs. 8.2 ± 3.1, p=0.04). The score did not correlate with the duration of epilepsy, seizure control, number of antiepileptic medications; or with parental educational and (un)employment status. The mean rate of correct responses for the SAFETY-R questions amongst the teenage girls was 17.4%.

Conclusions: There is lack of awareness about epilepsy and its associated lifestyle modifications in majority of adolescents with the disease. This is especially true in young adolescents, African-American patients, and those whose parents are in service occupations. Teenage girls with epilepsy appear to have limited knowledge with respect to contraception and child-bearing.

Keywords: Epilepsy and other paroxysmal disorders, Translational/experimental therapeutics

44. EEG Response In Children Receiving Continuous VPA Infusion For Status Epilepticus And Breakthrough Seizures

Albuja AC, Stewart AM, Baumann RJ, Cook AM, Bensalem-Owen M (Lexington, KY)

Objective: To study the efficacy of valproic acid (VPA) continuous infusion as an abortive therapy for seizures, comparing VPA levels and electroencephalographic response.

Background: Intravenous VPA has been used for partial, absence, myoclonic and mixed seizure disorders, leading to a reduction in seizure activity. As continuous infusion, it offers steady therapeutic levels with minimal side affects.

Methods: This is a retrospective chart review of patients admitted to Kentucky Children's Hospital from August 2009 through August 2012 who were treated with VPA continuous infusion for status epilepticus and breakthrough seizures. Our protocol consisted of VPA load of 20–30mg/kg followed by continuous infusion of 1 mg/kg/hour. Serum VPA levels were measured 4 hours post-load and 24 hours after infusion initiation. Target serum concentration was 75–100mcg/mL. The primary outcome was change in electrographic seizure activity following VPA. Response was classified as complete cessation; >50% reduction; or no response/worsening.

Results: Thirteen patients were included (7 females). Ages ranged from 3 months to 12 years (mean 5.51 years, SD1.6 years, range: 13–18 years). Six patients (46.2%) had a complete response, 3 (23%) had >50% reduction, and 4 (30.8%) were non-responsive. Mean VPA 24 hour concentration was 92mcg/mL (SD11.5) for the group who showed a complete response, 78mcg/mL (SD36.43) for patients with >50% reduction, and 67mcg/mL (SD43.75) for non-responsive patients. Two patients (15.4%) reported nausea as adverse effect.

Conclusions: Continuous VPA infusion is a well-tolerated, effective therapeutic option for status epilepticus and breakthrough seizures in children. Initial serum concentrations at the high end of the therapeutic range may be associated with better clinical response.

Keywords: Epilepsy and other paroxysmal disorders, Translational/experimental therapeutics

45. Variability in Care and Outcome in Patients with Convulsive Status Epilepticus among 45 Children's Hospitals

An S, Kapur K, Loddenkemper T (Boston, MA)

Objective: To assess variability of care and outcomes in pediatric patients with convulsive status epilepticus treated at 45 different children's hospitals.

Methods: We conducted a retrospective cross-sectional analysis of patients 1) between age 1–21 years, 2) whose discharge diagnosis was ICD-9 345.3 (grand mal status) and APR-DRG 53 (seizure) and who were admitted at 45 US children’s hospitals within the Pediatric Health Information System (PHIS) database4 between 2009–2013 with care utilization rates and outcome measures across the children's hospitals.

Results: 13,637 admissions (10,544 patients) including 54% (7,321) males at a median (p25-p75) age of 5 years (2–9 years old) are included. EEG, CT and MRI, excluding 618 observations from three hospitals without this data, are utilized at overall rates (ranges) of 51% (21 – 93%), 31% (2.5 – 49%) and 20% (7 – 37%), respectively. The overall rate (range) of utilization of mechanical ventilation is 36% (19 – 58%). Overall rate of readmission within 30 days (range) is 20% (8 – 32%) while the overall length of stay and mortality rate are 2 days (1 – 3 days) and 0.7%, respectively. Among the hospitals, the variability in the
readmission and length of stay are significant (p<0.001) whereas the variability in mortality rate is not significant (p=0.100).

Conclusions: There is variability in clinical care and outcome, such as readmission and length of stay, for this population across different children's hospitals. Variability of care may provide insights on the relationship between different care approaches and outcome.

Keywords: Epilepsy and other paroxysmal disorders

46. Targeted Treatment of Malignant Migrating Partial Seizures of Infancy with Quinidine


Background: Malignant partial seizures of infancy (MMPSI) is an early onset epileptic encephalopathy syndrome characterized by frequent, migrating focal seizures beginning before the sixth month of life that are refractory to pharmacotherapy. The genetic basis of the syndrome has recently been described with approximately half of all cases thought to be secondary to gain of function mutations in the potassium channel KCNT1, suggesting that blockade of KCNT1 may be a rational pharmacotherapy for this condition. The cardiac anti-arrhythmic drug quinidine is a partial antagonist of KCNT1, making it a candidate drug for treatment of this condition.

Methods: We describe a 29-month old female with malignant partial seizures of infancy who was found by whole exome sequencing to have a heterozygous missense mutation in KCNT1 (c.1283G>A; p. Arg428Gln). The patient was refractory to conventional anti-epileptic drug therapy, but treatment with quinidine led to a 6-week seizure free period, a reduction in seizure duration and severity, electroencephalographic improvements, and improvement in psychomotor development.

Conclusions: This case demonstrates the importance of a specific genetic diagnosis in epilepsy syndromes for targeted treatment and is proof of concept for the possibility of pharmacologic blockade of KCNT1 as a treatment strategy for MMPSI. Further studies are necessary to identify the optimal strategy for blockade of KCNT1, identify an optimal dosing range, and definitively assess the efficacy of quinidine.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders, Genetics

47. Amantadine: an alternative to treat refractory electrical status epilepticus in sleep

Bhatt R, Sankar R, Husain S (Los Angeles, CA)

Objective: Electrical Status Epilepticus in Sleep (ESES) is associated with disruption of cortical information processing and manifests with cognitive and language impairment. Many patients are often refractory to traditional pharmacologic treatments, including diazepam, IVIG, and oral corticosteroids. This study was conducted to evaluate the electrographic and clinical response of ESES to amantadine therapy.

Methods: Patients with ESES who received amantadine from 2005 to 2013 were retrospectively identified. All 8 patients had prolonged EEG monitoring prior to initiation of amantadine and at least one month after treatment. Medical records, EEGs, clinical history, and neurologic examination were reviewed to determine clinical and electrographic response to amantadine.

Results: Five of eight patients had both electrographic and clinical improvement following treatment with amantadine. All five responders had been refractory to conventional treatments including diazepam, IVIG, corticosteroids, other AEDs, and immunosuppressants. Four patients received amantadine alone, and one patient was administered amantadine with low dose oral diazepam. Three patients exhibited complete resolution of ESES on sequential overnight EEG evaluation, and two patients showed a dramatic reduction in spike-wave burden. All five responders had improvement in language, four had improvement in other areas of school performance, and all five exhibited improvements in behavior. Among the three non-responders, two exhibited neither electrographic nor clinical improvement, and one did not titrate to therapeutic dose.

Conclusions: ESES is a treatable cause of developmental regression in children but can be refractory to traditional treatment. Amantadine therapy was well tolerated and accompanied by substantial clinical and electrographic improvement.

Keywords: Epilepsy and other paroxysmal disorders

48. Injuries from Seizures are a Dreadful, Capricious Problem in Childhood Onset Epilepsy: a population-based study

Camfield PR, Camfield CS (Halifax, Nova Scotia)

Objective: To document the frequency, types and risk factors for injuries caused by seizures for people with childhood onset epilepsy.

Methods: We contacted patients with all types of epilepsy except childhood absence epilepsy from the Nova Scotia Childhood Epilepsy population-based cohort. Seizure onset was between 1977–1989. Patients and parents were asked about serious injuries resulting from a seizure. Serious injury was defined as severe enough for an urgent physician or dentist visit.

Results: Of 600 eligible patients, we contacted 433 (72%). Overall 52 (12%) had ≥1 serious injury during an average follow up of 27±5 years. Of all injuries, 23 (29%) were lacerrations requiring sutures, 15 (19%) bone fractures, 14 (16%) broken teeth, 4 (5%) burns, 4 (5%) concussions and 20 (25%) other. “Other” included 1 fatal drowning, 2 near drownings, 3 shoulder dislocations and 1 severe eye injury. 4 injuries occurred with the first seizure; all others occurred after a long gap from seizure onset (range 1.5–30 years). Injuries occurred in all epilepsy syndromes, most common with symptomatic generalized epilepsy (19% vs 7.5% p=0.005) and intractable epilepsy (28% vs 7.6% p=0.000). Most injuries occurred during normal daily activities and were not easily preventable.

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Conclusions: During ~30 years of follow up 1 in 8 patients with epilepsy had a serious injury as the result of a seizure. Most injuries occurred years after the initial diagnosis and were more common when seizures were more frequent. The only practical solution to injury prevention is better seizure control.

Keywords: Epilepsy and other paroxysmal disorders

49. Optimizing Care with a Standardized Management Protocol for Patients with Infantile Spasms
Fedak E, Patel A, Wood E, Heyer GL, Mytinger JR (Columbus, OH)

Objective: The management of infantile spasms (IS) varies among clinicians. Developing a best-practice model that standardizes care could improve IS outcomes. As part of a quality improvement (QI) project, we implemented a standardized management protocol based on the best available data and expert consensus.

Methods: Starting September 2012, all IS patients at Nationwide Children's Hospital were managed using a standardized treatment protocol. Length of stay (LOS) and the use of first-line therapies (ACTH, corticosteroids, and vigabatrin) as initial treatment were compared between a pre-standardization cohort (January 2009 to October 2012) and a post-standardization cohort (September 2012 to March 2014).

Results: The percentage of patients receiving first-line therapy as the initial treatment was 62.7% (32/51) in the pre-standardization cohort and 100% (31/31) in the post-standardization cohort. There was no significant change in the median LOS between pre- and post-standardization cohorts even when analyzed by treatment type. The longest LOS in both groups occurred in patients treated with ACTH and management standardization did not reduce LOS. For the entire cohort, we noted that the median LOS for oral corticosteroids (2.2 days) was significantly less (<0.001) than the LOS for ACTH (5.1 days) despite similar monitoring and caregiver education.

Conclusions: Management standardization led to all IS patients receiving first-line treatment as initial therapy, but it did not reduce LOS. The need for insurance approval prior to discharge likely explains the longer LOS with ACTH. Future QI projects will target LOS optimization with ACTH treatment.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders

50. Utility of Long Term Video EEG Monitoring for Children with Staring
Haridas B, Steven J, Patel AD (Columbus, OH)

Objective: Staring is a common referral to a child neurology center. A clinical history can assist in determining if staring is a symptom of an epileptic seizure. However, long term video EEG monitoring (LTM) is often utilized as a method to differentiate these episodes. The goal of our study was to assess whether LTM would be useful in the analysis of staring as a symptomatic complaint.

Methods: After obtaining IRB approval, LTM reports and electronic medical records were analyzed over a 4 year period. LTM reports as well as the action(s) taken following the LTM report were analyzed.

Results: 276 patients were included with an age range of 0.16 to 22 years of age. 52% of the patients were male subjects. 45% of the subjects had a baseline diagnosis of epilepsy. The average LTM duration was 35.69 hours. The staring spell occurred during the inpatient stay in 51.8% of the 276 patients. Among those in whom the spell was captured, 20.3% had an electrographic correlate. However, in the 276 patients presenting for LTM with staring, 10.5% had an electrographic correlate. Among the 184 subjects with any type of abnormal result on LTM, 48.4% had an actionable abnormality, defined as a change in treatment.

Conclusions: Based on the results, it appears the yield of LTM for identifying a seizure during a staring episode is low. Given its considerable time and financial expense, LTM monitoring may not be cost effective when determining the etiology of staring spells in children.

Keywords: Epilepsy and other paroxysmal disorders

51. Predictors of Surgical Outcome for Lesional Infantile Spasms
Harini C, Nagarajan E, Bergin A, Takeoka M, Kapur K, Bolton J, Loddenkemper T (Boston, MA)

Objective: To determine outcome and predictors in patients with lesional infantile spasms (IS) undergoing epilepsy surgery.

Methods: We performed a retrospective chart review of patients with active or resolved IS between 2002–2010. Patients with structural MRI lesions who underwent surgery at our center for IS and/or associated epilepsy and had minimum follow-up of 3 months after surgery were included. Demographics, seizure semiologies, EEG, MRI, PET, SPECT, and seizure outcome at follow-up were collected and analyzed for predictors of seizure outcome.

Results: Among 446 patients with IS, 217 (71% males) met inclusion criteria. Mean age at spas onset was 4.8 months (1 day - 22 months), mean duration of follow-up 3.5 years (0.4 – 11.63). Predominantly unilateral MRI-lesions were noted, including malformations of cortical development (8), hemimegalencephaly (4), tumor, stroke, TS and others accounting for the remainder. Seventeen had active IS at surgery, 15/17 underwent surgery for treatment of IS, while 2/17 underwent surgery for another seizure type (drop seizure). Four patients with remote history of IS had surgery for focal seizures. Ictal EEG had generalized (8), generalized with a leading spike (5) and focal (8) seizure patterns. PET/SPECT were done in 50%. Surgery included hemispherectomy (11), lobar/multilobar resections (8) and corpus callosotomy (2). Favorable outcome (Engle I & II) was seen in 62%. None of the factors examined, including duration of spasms, laterality of ictal EEG, or concordance of PET/SPECT scans, predicted seizure outcome. Lateralized semiology (focal tonic, asymmetric spasm) predicted favorable outcome at 6 months after surgery (p=0.042).
Conclusions: Surgery for IS with unilateral lesions provides favorable seizure control. Lateraled seizure semiology may be of value in predicting outcome.

Keywords: Epilepsy and other paroxysmal disorders

52. Investigations of Qudexy XR (Topiramate) Extended-Release Capsules Administration through Feeding Tubes

Holmøy M, Heintz MJ, Pellock JM (Maple Grove, MN)

Objective: USL255 (Qudexy XR) is a once-daily, extended-release capsule of topiramate formulated to reduce drug plasma fluctuations. USL255 was recently approved as monotherapy for partial-onset seizures (POS) or primary generalized tonic-clonic (PGTC) seizures (patients ≥10 years old), and adjunctive therapy for POS, PGTC, or seizures associated with Lennox-Gastaut syndrome (patients ≥2 years old). USL255 capsules can be taken whole or opened and the beads sprinkled. The objective of these experiments was to determine if USL255 beads can be administered through 14, 16, and 18 French gastric and jejunum tubes (G-/J-tubes).

Methods: The tube sizes selected are those most commonly used for pediatric and adult patients. For the 16/18 French tubes, contents of an entire 200mg USL255 capsule or 4 divided doses of 50mg each were diluted in 10mL deionized water. Suspended beads were drizzled into pre-moistened G-/J-tubes, repeated (if necessary) until entire dose was given, followed by a 15mL flush. Bead recovery was then determined. A similar procedure for smaller 14 French tubes is being tested, but using diluent with glidant properties, gentle pressure, and lower doses.

Results: Nearly 100% bead recovery was obtained when adding USL255 into pre-moistened 16/18 French tubes in ~50mg (5mg/mL) increments. Total fluid volumes ranged from 70–110mL, not including the 15mL pre- and post-flushes. Clogging occurred when the entire 200mg (20mg/mL) capsule content was added at once or a low-profile (ie, right-angle bend) feeding tube was used.

Conclusions: USL255 beads may be a useful once-daily treatment option for patients with G-tubes or J-tubes.

Keywords: Epilepsy and other paroxysmal disorders

53. Clobazam Higher Evening Differential Dosing as an Add-on Therapy in Refractory Epilepsy

Jackson MC, Thome S, Klehm J, Kadish NE, Fernández IS, Loddenkemper T (Boston, MA)

Objective: Clobazam has been used as an add-on therapy for several seizure types with satisfactory results. We evaluated patients who used clobazam as an add-on therapy with differential dosing, using a higher evening dose for treatment of predominantly nighttime and early-morning seizures. We compared seizure reduction rates between patients who received differential and equal dosing.

Methods: We retrospectively reviewed patients with refractory epilepsy who used clobazam differential dosing at a tertiary pediatric center between 2001 and 2013. Each differential dose patient was matched to two non-differential dose controls by age, etiology, seizure type, and MRI-lesion. Differential dosing was defined as higher clobazam dose administration after six p.m. and providing more than 50% of the total daily dose at that time. Seizure reduction was calculated from baseline (three months prior to clobazam introduction) to first follow-up.

Results: Twenty-seven patients were treated with differential dosing (median age: 9.1 years, IQR: 5.5–10.3). Median follow-up was nine months (IQR: 5–19). Genetic etiology was observed in six (22.2%), structural/metabolic in twelve (44.5%), and unknown etiology in nine (33.3%) patients. Differential dose patients exhibited a median seizure reduction of 75% (IQR: 60–100), as compared to 50% (IQR: 20–83.33) seizure reduction in controls (p<0.001). Patients with generalized seizures benefitted the most from differential dosing with a 77.5% (IQR: 63.33–100) seizure reduction, as compared to 50% (IQR: 20–93.03) in controls (p=0.017).

Conclusions: Clobazam differential dosing improves seizures, particularly in patients with generalized seizures. Chronotherapy based upon times of highest seizure susceptibility may improve care in epilepsy patients.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders, Neuroimaging, Translational/experimental therapeutics

54. Intramuscular Lorazepam for Breakthrough Seizures in Children with Refractory, Symptomatic Epilepsy

Johnson PJ, Carter C, Pham Q, Harrison DL, Nguyen A, Ng YT (Oklahoma City, OK)

Introduction: To evaluate intramuscular (IM) lorazepam’s effectiveness in managing prolonged seizures. Children admitted to The Children’s Center often experience prolonged/repetitive seizures. A treatment protocol was developed using IM lorazepam for seizures >5 minutes and a repeat dose was administered 15 minutes after the first dose if the seizures persisted.

Methods: Children, 0–19 years were included in this study from June 1, 2007 through May 1, 2012, who received at least one dose of IM lorazepam for seizures. Because many patients had frequent seizures, only the first 5 seizure episodes were included for analysis. Multiple logistic regression was employed to the assess the relationship between seizure resolution and independent variables. Data analyses were conducted using Stata v13.1, with alpha set at p< 0.05.

Results: There were 62 patients with 194 separate seizure episodes. Median age of patients was 6.5 years (range 0.6–19). Mean number of lorazepam doses administered per episode was 1.2 ± 0.05. The mean IM lorazepam dose administered was 1.4 ± 0.8 mg or 0.07 ± 0.05 mg/kg/dose. With the first dose of IM Lorazepam, seizure resolution was noted in 143 episodes (90.5%). Children administered more than 1 dose of IM lorazepam had a 79.5% decrease in the odds of seizure resolution (odds ratio, 0.205; 95% confidence interval 0.046-0.909; p=0.037), while controlling for other factors.

Conclusions: IM lorazepam was extremely effective in stopping seizures in this very refractory group of epilepsy patients. Administration of more than 1 dose of IM lorazepam had a 79.5% decrease in the odds of seizure resolution (odds ratio, 0.205; 95% confidence interval 0.046-0.909; p=0.037).
lorazepam was associated with decreased odds of seizure resolution.

**Keywords:** Epilepsy and other paroxysmal disorders, Translational/experimental therapeutics

### 55. Early Predictors of Epilepsy Severity and Cognitive Abnormalities in Children with Sturge-Weber Syndrome

**Juhata C, Aiano E, Behen ME, Guy WC, Chugani HT**

(Detroit, MI)

**Objective:** Reliable markers of neuro-cognitive outcome during the early disease course of Sturge-Weber syndrome (SWS) have not been established. In this longitudinal study of children with SWS, we have evaluated if clinical, EEG, or neuroimaging variables could predict seizure frequency and cognitive functions.

**Methods:** Seizure variables, interictal scalp EEG abnormalities (background attenuation/slowing, spike frequency), and extent of brain involvement on imaging (MRI and glucose PET, expressed as the number of affected lobes) were measured at baseline and correlated with seizure frequency and cognitive functions assessed at follow-up in 37 young children with SWS (mean age: 3.2 years at baseline) who were followed for 1–10 years (mean: 2.4 years; no surgery during follow-up). Both univariate (Pearson’s) correlations and multivariate regression analyses were performed.

**Results:** In univariate analyses, poor cognitive outcome was predicted by young age at seizure onset (p=0.007), high seizure frequency (p=0.03), high EEG spike frequency (p=0.002), and severe EEG background abnormalities (p=0.002); early seizure onset and high spike frequency remained significant independent predictors in the multivariate analysis (p≤0.02). High seizure frequency at baseline was the only independent predictor of high seizure frequency at follow-up (r=0.65, p<0.001).

**Conclusions:** Early onset of seizures and high interictal spike frequency are independent predictors of poor cognitive outcome in young children with SWS; while initial seizure frequency is the strongest predictor of seizure outcome. On the other hand, the number of affected lobes, as seen on baseline neuroimaging, is not a good predictor of either cognitive or seizure outcome in this patient population.

**Keywords:** Epilepsy and other paroxysmal disorders, Neuroimaging

### 56. Epilepsy, Nystagmus and Myopathy in Timothy Syndrome: expanding the neurologic phenotype

**Kalnser L, Ionita C, Madan Cohen J**

(Hartford, CT)

**Objective:** Timothy Syndrome (TiS) is a multisystem disorder caused by mutations in the L-type Cav1.2 calcium channel leading to failure of inactivation of calcium channels. It is recognized as a cause of prolonged QT interval (QTi) in infancy, but a distinct neurologic phenotype has not been previously defined. We have identified a pattern of neurologic involvement in TiS including epilepsy and myopathy.

**Methods:** Case report and complete literature review.

**Results:** The cardinal feature of TiS is prolongation of the QTi. Affected children may have other manifestations including syndactyly, structural cardiac defects and hypoglycemia. Developmental impairment and autism spectrum disorder are recognized neurologic manifestations. Seizures have been reported, though often attributed to hypoglycemia or ischemic/anoxic injury. Muscle weakness has also been observed, with nemaline rods on muscle biopsy in two patients. We report a child with TiS associated with prolonged QTi and mixed epilepsy syndrome including infantile spasms and focal seizures. He has severe muscle weakness and remains profoundly impaired with global delay. He has cortical visual impairment with pendular nystagmus. This pattern of deficits, though reported in scattered cases, has not been recognized as a distinct neurologic phenotype in this condition.

**Keywords:** Epilepsy and other paroxysmal disorders, Genetics, Neuromuscular disorders

### 57. Familial Hyperekplexia with Catastrophic Intractable Infantile Epilepsy: Comparison to Literature and Review of Commercially Available Genetic Panels

**Kielian A, Bicknese AR**

(Chicago, IL)

**Objective:** Infantile epileptic encephalopathy is catastrophic and can result in death. Genetic testing is revolutionizing diagnostic approach to seizures and many laboratories offer infantile epileptic gene panels. Each is expensive and provides a different collection of genes, adding to the diagnostic challenge.

**Methods:** We describe siblings (male and female) who presented at two weeks with hyperekplexia, normal EEG and progressed to intractable myoclonic and multifocal seizures. We reviewed over 100 articles describing genes associated with infantile seizures and compared to commercially available genetic panels. When available, we linked the genes to phenotype in order to create a model that would facilitate the approach to genetic investigation. We include the genes more frequently associated with infantile seizures, including Ohtahara Syndrome, early myoclonic epileptic encephalopathy, Dravet syndrome, and others.

**Results:** We identified over 100 genes with known association to infantile-onset intractable epilepsy in commercially available tests. All reviewed panels included: SCN2A, ARX, STXBP1, SPTAN1, SLC25A22, PNKP. Most panels offered KCNQ2, SCN8A, CDKL5, PLCB1, ALDH7A1, PNPO, SCN1A, GABRG2, PCDH19. A group of 15 genes were offered in only 3 panels and remaining 85 genes were offered in only 1 to 2 panels. We compare and rank these genes and panels.

**Conclusions:** Infantile-onset epileptic encephalopathy is a complex condition and requires extensive diagnostic efforts. Navigating through genetic panels is challenging as panels are not all-inclusive and offer variety of genes specific to
58. Interim Review of Safety and Tolerability of 1 Hz Deep rTMS for Treatment of Temporal Lobe Epilepsy

Oberman L, Gersner R, Zangen A, Rotenberg A (Boston, MA)

Objective: Repetitive transcranial magnetic stimulation (rTMS) is a method for focal noninvasive brain stimulation where small intracranial electrical currents are induced by fluctuating extracranial magnetic fields. When applied in low frequency (≤1 Hz) trains, rTMS leads to suppression of cortical excitability. Whereas conventional rTMS stimulates the cortex superficially, recent advances enable deep rTMS and stimulation of the mesial temporal structures. Accordingly, we adapted the deep rTMS system to test whether 1 Hz rTMS, delivered in 10-day 30 min/day treatment blocks suppresses seizures in temporal lobe epilepsy (TLE). A randomized placebo-controlled trial is in progress. We report an interim review of the safety and tolerability of the deep rTMS technology in patients with TLE.

Methods: We reviewed all per-session patient safety and tolerability questionnaires and mini-mental examination (MME) scores. Per treatment block, at baseline and subsequent to treatment, EEG, clinical seizure frequency and performance on the Wechsler Memory Scale or the Children’s Memory Scale were also analyzed.

Results: Complete safety data sets were obtained form eight subjects. Deep rTMS was well-tolerated by all. No adverse change in MME or memory metrics was recorded. Atypical seizure, status epilepticus and epilepsy exacerbation did not occur. One subject withdrew prior to randomization and stimulation due to anxiety. One subject withdrew from the placebo arm, citing nausea and mood change. Transient headache, a common rTMS side effect followed 11% of treatment sessions.

Conclusions: On interim review, 1 Hz deep rTMS appears well-tolerated in patients with TLE.

*Dr. Oberman and Gersner contributed equally to this study.

Keywords: Epilepsy and other paroxysmal disorders, Translational/experimental therapeutics

59. Cost Analysis of Epilepsy Surgery in Children with Drug-resistant Epilepsy

Oldham MS, Tsevat J, Horn P, Standridge S (Cincinnati, OH)

Objective: Approximately 20% of children with epilepsy are drug-resistant, incurring a considerable amount of resources. Epilepsy surgery can be an effective intervention in this population. This study provides an initial look at the costs associated with surgical management of children with drug-resistant epilepsy, as compared with medical management alone.

Methods: In a retrospective cohort study of children with drug-resistant epilepsy referred for possible surgical intervention, we compared direct costs of those treated surgically versus those managed medically, and assessed the difference in seizure frequency between the groups.

Results: The median cost of epilepsy surgery was $118 400 [$101 900, $143 800]. Total median follow-up costs, not including the cost of surgery itself, were not significantly different between the surgical and medical groups at 1-year or 2-year follow-up. However, the surgical patients who achieved seizure freedom (ILAE class 1) had a significant reduction in median costs both 1-year and 2-year post-operation as compared with pre-operation, and significantly lower costs as compared with the medical group. Subjects in the surgical group had significantly fewer weekly seizures as compared with the medical group at 1-year follow-up (5.6 vs 8.9, respectively, p=0.02).

Conclusions: Epilepsy surgery is an expensive intervention. While the overall costs of surgical and medical management are the same after 2 years, the subset of patients who achieved seizure freedom after surgery had lower costs as compared with those in the medical group. This study highlights areas of further evaluation that could provide information on reducing the societal economic burden of epilepsy.

Keywords: Epilepsy and other paroxysmal disorders

60. Seizure Recurrence After Resolution of Presumed Childhood Encephalitis


Objective: To evaluate the risk of seizure recurrence after resolution of presumed childhood encephalitis.

Methods: We prospectively identified 217 consecutive patients with suspected encephalitis who had been referred to the California Encephalitis Project (CEP). Inclusion criteria included encephalopathy lasting 24 hours and at least one of the following: fever, seizure, focal neurologic signs, pleocytosis, or EEG or neuroimaging evidence concerning for encephalitis. We studied a cohort of these patients who previously did not have prior seizures, abnormal brain MRIs, or pre-existing neurologic conditions. In this cohort, we analyzed their hospital course and identified risk factors for seizure recurrence after resolution of the illness.

Results: Risk of seizure recurrence in comparing age groups showed that children < 1 yo were twice as likely to have recurrent seizures after hospitalization. Children requiring continued antibiotic treatment after discharge had a 52% chance of seizure recurrence after resolution of the encephalitis. Abnormal EEGs after hospital discharge indicated a higher likelihood of seizure recurrence after encephalitis. 93% of those with abnormal EEGs after hospital discharge had recurrent seizures.

Conclusions: In analyzing our cohort of previously neurologically normal children who recovered from presumed encephalitis, risk factors for seizure recurrence were identified. These risk factors include age < 1yo, children requiring continued antibiotic treatment after discharge, and abnormal EEG findings after discharge.

Keywords: Epilepsy and other paroxysmal disorders
61. *Chronological Evolution of Radiological Findings in Case Series of Patients with Febrile-Infection Related Epilepsy Syndrome (FIRES*)


**Objective:** To describe and analyze the chronological evolution of the radiological findings in 7 children with FIRES.

**Methods:** This is a retrospective study describing the radiological findings and evolution on 7 children with FIRES who presented from 2009 to 2013.

**Results:** Six males and one female age range 3 months to 9 years presented with status epilepticus preceded by a febrile illness. Extensive investigations for infectious, autoimmune and metabolic etiologies were negative. Multiple anti-epileptic medications were tried including drug-induced coma in all of them with poor response. Immunotherapy with intravenous steroids and IVIG were tried in 6 of 7 patients with poor response. Ketogenic diet was initiated in 4 of 7 patients with limited response. Serial neuroimaging studies were done from initial presentation up to 18 months of follow up showing evolution from normal imaging to severe cerebral atrophy. Progressive cytotoxic edema involving mostly bilateral hippocampi and temporal lobes was appreciated in 1–3 weeks. At 1 month from seizure onset, mild to moderate cerebral atrophy and hippocampal sclerosis was appreciated that continued to progress over the next year. By 6 months most of the patients showed moderate to severe cerebral atrophy and by 1 year cerebellar atrophy was also appreciated.

**Conclusions:** FIRES is a catastrophic epilepsy syndrome of unknown etiology associated with progressive clinical deterioration and rapid radiological evolution. These radiographic findings may help with early diagnosis and provide some clues to the underlying pathophysiology of this devastating epilepsy. Early diagnosis and therapeutic intervention may improve long term neurological outcome.

**Keywords:** Epilepsy and other paroxysmal disorders, Neuroimaging

62. *Seizure Action Plans do not Reduce Healthcare Utilization in Pediatric Seizure Patients*

**Rivas-Coppola MS, Choudhri A, Wheless J, Shah NS (Memphis, TN)**

**Objective:** Management of pediatric epilepsy requires coordination of care between patients, their families, and their providers. Measures to improve communication and planning are believed to improve health outcomes and reduce healthcare utilization. As a quality improvement measure, a "Seizure Action Plan" (SAP) was developed for all patients with seizures, to be generated at the time of clinic visit or hospital discharge. The SAP included a list of current anti-epileptic medications and dosages; instructions for use of rescue medications when necessary; instructions for breakthrough seizures, and a specific follow-up plan. Our hypothesis was that an improved at-home seizure management care plan would reduce subsequent emergency department utilization and hospitalizations.

**Methods:** We conducted a retrospective case-control study of 120 patients, consisting of 60 consecutive patients each with seizures before and after SAP implementation, in two distinct 18-month epochs.

**Results:** There was no difference in the demographics of the study groups. There were no statistically significant differences in emergency department visits, hospital admissions, follow-up visits, telephone calls to the office, or the percentage of emergency department visits that resulted in hospitalization.

**Conclusions:** Our results show no significant decrease in several measures of pediatric epilepsy patient healthcare utilization following implementation of a seizure action plan. This study suggests that pediatric epilepsy quality improvement measures may require more complex planning and implementation to achieve significant differences in outcomes. Further, our work demonstrates that healthcare measures that may be adopted by healthcare organizations should also be tested for actual efficacy.

**Keywords:** Epilepsy and other paroxysmal disorders

63. *Management of Children with Refractory Epilepsy: a decision analysis comparing medical versus surgical treatment*

**Sánchez Fernández I, An S, Loddenkemper T (Boston, MA)**

**Objective:** To quantify the life expectancy of surgically-eligible children with refractory epilepsy comparing two treatment strategies: medical treatment only versus epilepsy surgery.

**Methods:** Decision analysis model populated with available parameters from the literature. Outcome: life expectancy. Time horizon: lifetime.

**Results:** Across the range of pediatric ages, epilepsy surgery yielded a higher life expectancy than medical treatment only for both patients with temporal and extratemporal lobe epilepsy. For a cohort of 10-year-old children with refractory epilepsy, the gain in life expectancy with epilepsy surgery (compared to medical treatment only) was 5.9 years for temporal epilepsy and 5.6 years for extratemporal epilepsy. One-way and two-way sensitivity analysis demonstrated the robustness of results across a wide range of values in individual parameters. Second-order Monte-Carlo simulations demonstrated the robustness of epilepsy surgery as the preferred strategy considering parameter uncertainty in the literature. There was no adjustment for quality of life but we estimated the percentage of life expectancy spent in seizure freedom for each strategy. For a cohort of 10-year-old patients with refractory epilepsy: 1) in temporal epilepsy, epilepsy surgery yielded 48.9% of life expectancy years in seizure freedom while medical treatment yielded 14.3%; and 2) in extratemporal epilepsy, epilepsy surgery yielded 43.0% of life expectancy years in seizure freedom while medical treatment yielded 14.3%. Surgical complications were infrequent.

**Conclusions:** Epilepsy surgery yields a substantially higher life expectancy than continued medical treatment for surgically-eligible children with refractory (temporal or
extratemporal) epilepsy. This conclusion is robust across a wide range of parameter variations.

**Keywords:** Epilepsy and other paroxysmal disorders

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**64. Phenobarbital and Neonatal Seizures Affect Cerebral Oxygen Metabolism: a near-infrared spectroscopy study**

*Sokoloff MD, Plegue MA, Barks JDE, Chervin RD, Shellhaas RA (Ann Arbor, MI)*

**Objective:** Near-infrared spectroscopy (NIRS) measures tissue oxygen metabolism and is increasingly used for monitoring critically-ill neonates. Yet, the implications of NIRS-recorded data in this population are poorly understood. We evaluated NIRS monitoring for neonates with seizures.

**Methods:** In neonates monitored with video-EEG, NIRS-measured cerebral regional oxygen saturation (rSO2) and systemic O2 saturation were recorded every 5 seconds. Mean rSO2 was extracted for 1-hour blocks before, during, and after each phenobarbital dose. For each electrographic seizure, mean rSO2 was extracted for a period of 3-times the duration of the seizure before and after the ictal pattern, and during the seizure. Linear mixed models with interactions were developed to assess the impact of phenobarbital administration on rSO2 and fractional tissue oxygen extraction (FTOE), adjusted for dose. Linear mixed models and post-hoc pairwise comparisons were employed to evaluate seizure data. Bonferroni-adjusted p-values are presented.

**Results:** For 20 neonates (EGA 39.6±1.5 weeks), 61 phenobarbital doses and 40 seizures were analyzed. Cerebral rSO2 rose (p<0.001), and FTOE declined (p=0.009) with increasing phenobarbital doses (range 2–22mg/kg; Figure). rSO2 declined during seizures, compared with baseline and postictal phases (81.2 vs. 77.7 vs. 79.4; p=0.004). FTOE was highest during seizures (p=0.006).

**Conclusions:** Cerebral oxygen metabolism decreases after phenobarbital administration, and increases during seizures. Whether these clear, but small, metabolism changes have clinical consequences remains to be determined. NIRS reveals pathophysiological information, but may not contribute to clinical management of neonatal seizures.

**Keywords:** Epilepsy and other paroxysmal disorders, Neonatal neurology

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**65. The Boston Bumetanide Trial in Newborns with Seizures: initial pharmacokinetics and safety findings**

*Soul JS, Hayes B, Fortuno CR, O’Reilly D, Stopp C, Vinks A, Staley K (Boston, MA)*

**Objective:** Bumetanide (BTN) shows great promise as an antiepileptic drug for newborns in synergism with GABAergic drugs. We aimed to determine the pharmacokinetics (PK) & safety of BTN in newborns with seizures.

**Methods:** We enrolled newborns aged 34–44 weeks with seizures in a double-blind, randomized, controlled trial of BTN as add-on therapy to phenobarbital (PB), with stratification by hypothermia Rx. We measured serum BTN levels by LC/MS/MS at 2–6 points after study drug administration, and relevant clinical data for PK & safety analysis.

**Results:** A two-compartment PK model best described data in 7 subjects receiving 0.1mg/kg of BTN. Mean t1/2 was 8.73 hours (range 3.07–13.69), mean clearance 0.021 L/h/kg (0.003-0.077), and mean volume of distribution 0.24 L/kg (0.16-0.29). There was large between subject variability in clearance and volume. There was no significant effect of weight, age, gender, race, hypothermia or hepatic/renal dysfunction on PK. Safety data compared between the groups showed no statistically significant differences in hearing loss, fluid balance, electrolytes, bilirubin and cardiorespiratory support.

**Conclusions:** The PK of BTN are similar in newborns with seizures compared with published data from newborns with fluid overload. Variability among patients is likely multifactorial, but there was no consistent effect of hypothermia or hepatic/renal dysfunction. Data from 0.2 mg/kg dose group will be available for presentation at the meeting. A standard therapy control group allows comparison of safety data between treated and control groups for often systemically ill newborns with expected high rates of organ dysfunction that could be falsely attributed to BTN.

**Keywords:** Neonatal neurology

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**66. Cerebral Glucose Hypometabolism is Associated with Mitochondrial Dysfunction in Patients with Intractable Epilepsy**

*Tenney JR, Rozhkov L, Horn P, Miles L, Miles MV (Cincinnati, OH)*

**Objective:** Metabolic imaging studies, such as positron emission tomography (PET), assess physiological...
functioning of the brain and [18F]fluoro-2-deoxyglucose (FDG) - PET is a common technique for pre-surgical epilepsy evaluation. Focal inter-ictal decreases in glucose consumption are concordant with the ictal onset area but the underlying mechanisms are poorly understood. This study tests the hypothesis that areas of glucose hypometabolism, determined by FDG-PET, are associated with mitochondrial dysfunction in patients with medically intractable epilepsy associated with isolated focal cortical dysplasia (FCD).

**Methods:** Measures of electron transport chain (ETC) functioning and mitochondrial abnormalities (ETC complex biochemistry, Akt1, GFAP) were assessed in surgical resection specimens that had hypometabolic abnormalities and those that were normal on FDG-PET. Determination of FDG-PET abnormalities was made based on co-registration of statistical parametric mapping (SPM) results with postsurgical images (Fig 1).

**Results:** 22 patients (11 males, 11 females; mean age at surgery $10.5 \pm 4.4$ years), with pathologically confirmed FCD, were included in this retrospective review. Complex IV function was found to be significantly reduced in areas of hypometabolism ($p = 0.014$) while there was a trend towards a significant reduction in complexes II and III function in areas of hypometabolism ($p = 0.08$, $p = 0.059$, respectively) (Fig 2). These decreases were independent of FCD severity ($p = 0.321$) and other clinical epilepsy measures.

**Conclusions:** This study demonstrates a relationship between glucose hypometabolism and reduced mitochondrial complex IV functioning, which is independent of the degree of cortical dysplasia. This supports the role of cellular energy failure as a potential mechanism for intractable epilepsy.

**Keywords:** Epilepsy and other paroxysmal disorders, Neuroimaging

Figure 1. Examples of (A) a resection specimen which was deemed FDG-PET abnormal and (B) a resection specimen which was deemed FDG-PET normal.
67. Protocoled Treatment of Infantile Spasms at a Tertiary Care Center
Thodeson DM, Sogawa Y (Pittsburgh, PA)

Objective: Infantile spasms (IS) lends itself to protocoled treatment and evaluation due to its relatively stereotypic clinical presentation, frequent seizures, and EEG findings. We implemented an IS treatment protocol in December 2012 at our institution as a departmental quality improvement project.

Methods: A retrospective cohort (pre-protocol) was identified between September 2009 – September 2012. These results were discussed at a divisional meeting to develop the protocol in Nov 2012. A prospective cohort (post-protocol) group was started December 2012. Short-term response was defined as resolution of spasms and no hypsarrhythmia on EEG within 3 months of treatment initiation. Treatment was divided into three groups: vigabatrin, steroid (ACTH and prednisolone), and other therapies.

Results: There were 65 patients pre-protocol and 20 patients post-protocol who met inclusion criteria and had sufficient follow up data. There was a change in choice of initial treatment (p<0.0001). Initial treatment choice was vigabatrin (62%), other therapies (30%) and steroid (8%) in the pre-protocol cohort and steroid (63%), vigabatrin (33%) and other therapies (4%) post-protocol. Short-term response has improved in the post-protocol group (15/20, 75% vs. 34/65, 52%, p=0.028). In the post-protocol group, there was no statistical difference in short-term response by etiology of IS (4/4, 100% in cryptogenic etiology vs. 11/16, 69% in symptomatic etiology, p=0.530).

Conclusions: Use of a standardized protocol for IS treatment and evaluation has improved the short-term treatment outcome of IS at our center. Implementation of standardized diagnostic and treatment algorithms is vital to improving outcomes and conducting future research in children with epilepsy.

Keywords: Epilepsy and other paroxysmal disorders

68. Brief Cognitive and Behavioral Screening in Children with New-Onset Epilepsy: acceptability, feasibility, and preliminary results
Triplett RL, Bone M, Asato MR (Pittsburgh, PA)

Objective: Brief tools to identify cognitive and behavioral comorbidities requiring formal assessment and remediation among children with epilepsy are currently an unmet clinical need. We piloted a computerized cognitive battery and a behavioral questionnaire to: 1) determine clinical feasibility and acceptability to parents and patients, and 2) detect changes associated with newly-diagnosed epilepsy and treatment.

Methods: In an ongoing study, we recruited 36 medication-naïve children (ages 8–17 years) with recent-onset seizures from the Children’s Hospital of Pittsburgh Neurology Clinic. At enrollment (T1), several months (T2), and one year (T3) after medication initiation, children completed the CNS Vital Signs computerized cognitive battery (CNSVS). Parents completed the Strengths and Difficulties Questionnaire (SDQ) and were surveyed for test acceptability.

Results: All patients completed computerized testing in under 40 minutes. CNSVS scores were lower and SDQ behavioral symptom rates were higher than age-matched norms at T1, with no differences from T1 to T2 and ongoing T3 data collection. Higher CNSVS and lower SDQ scores correlated. Parents rated testing in clinic as highly convenient and important, expressing strong interest in learning about the potential cognitive and behavioral impact of epilepsy and medication. A significant proportion
of patients had parental reports and/or performance indicating that a formal neuropsychological evaluation would be appropriate.

Conclusions: Our brief battery was easily tolerated and well-received. Computerized testing in conjunction with parent questionnaires provide an acceptable, clinically accessible means to detect early cognitive and behavioral difficulties requiring medical or educational support.

Keywords: Epilepsy and other paroxysmal disorders

69. Psychosis in 3 Young Adults with a History of CSWS
Urion DK (Boston, MA)

Objective: To review the case histories of 3 individuals with electrical status epilepticus during sleep with continuous spike-wave sleep (ESES-CSWS complex) who had experienced early recovery of language on anti-epileptic therapy and then had significant behavioral and psychiatric disorders in their third decade.

Methods: Chart review

Results: 3 individuals (2 males, 1 female) presented as toddlers with language regression and were found to have CSWS, with spike density > 70%. They were treated with daily anti-epileptic therapy. All three experienced substantial improvement in their EEG (2 normalized, one had infrequent spike-wave complexes in sleep), as well as significant language recovery. All three had non-lesional CSWS (3T MRI). All three attended public schools with special education support. All three had AED therapy discontinued in their teens. They presented in their early-mid 20’s with increasingly disordered thought patterns, paranoid ideation, and hallucinations. None had evidence of recurrence of CSWS. None had any family history of significant psychiatric illness.

Conclusions: ESES-CSWS has been considered multi-phasic, with periods of normal development, onset of EEG abnormalities and variable forms of epilepsy, and subsequent language regression. Language and behavioral dysfunction have been posited to disruptions of memory consolidation during sleep. A recovery period and "plateau phase" have been described. The later behavioral decline reported here may suggest another phase of the disorder that does not appear to be associated with recurrence of CSWS, and may reflect early disruptions in language acquisition or consequences of early repetitive electrical discharges in critical circuits.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders

70. Centrotemporal Spikes Affect Language Networks in Children with BECTS
Vannest J, Maloney TC, Tenney JR, Hibbard KC, Morita D, Szaflarski JP, Glauser TA (Cincinnati, OH)

Figure 1. Regions of group activation in a) BECTS patients and b) healthy controls during the story processing task. Increases in activation for words are shown in hot colors, for noise in cool colors. FSL cluster correction p<.05. Images are in radiologic orientation.
Objective: Children with BECTS have frequent electrographic centrotetemporal spikes (CTS) with variable frequency and laterализation across patients. Previous studies suggest BECTS patients have subtle cognitive deficits, which may be due to frequent CTS. Using functional MRI, we examined how CTS affect language skill and reorganization of language networks.

Methods: Participants were right-handed native English speakers, 16 healthy children (ages 5–12, 8F); 16 BECTS patients (ages 6–11, 7F, not taking medication). 4 showed greater left-sided CTS activity, 2 had bilateral CTS, 9 had greater right-sided CTS. Participants completed a Story Processing (Schmithorst et al., 2006) fMRI task. This task used a 30-second block design in which stories were auditorily presented during active periods, alternating with broadband noise to control for auditory processing. Language skill was assessed using the Clinical Evaluation of Language Fundamentals (CELF, Semel et al., 2003).

Results: BECTS patients showed a trend toward lower CELF scores (mean 98.0, 106.6 for controls (p = 0.053). During the Story Processing task, BECTS patients showed an atypically left-lateralized pattern of activation for stories > noise (Figure 1). The degree of left-lateralization (as measured by a lateralization index in the temporal lobe region active in the group) was positively correlated with CELF scores \(r^2 = 0.23, p < 0.05\).

Conclusions: Results suggest that CTS affect lateralization of language networks. This change in lateralization is not related to poorer language skill; children with BECTS may be able to compensate for changes in language organization. However, this sample examined children primarily with right-CTS; left-CTS may affect language skill to a greater degree.

Support: NIH/NINDS R01-NS065840

Keywords: Epilepsy and other paroxysmal disorders, Neuroimaging

71. Infantile Spasms Respond Poorly to Topiramate Monotherapy
WEBER AB, COLE JW, MYTINGER JR (COLUMBUS, OH)

Objective: To determine the rate of infantile spasms (IS) remission with topiramate monotherapy.

Methods: We retrospectively analyzed the rate of clinical remission for all IS patients treated with topiramate monotherapy from January 2009 to March 2014. For responders, the post-treatment electroencephalogram (EEG) was reviewed to assure electrographic remission. Clinical remission was assigned to those without IS for 28 days starting within one month of topiramate initiation.

Results: All 39 patients identified received topiramate prior to the implementation of a standardized management protocol in September 2012. After this time, topiramate was no longer used. Six patients who started topiramate concurrently with first-line therapy (ACTH, oral corticosteroids, or vigabatrin) and one in whom remission could not be determined were excluded. Thirty-two topiramate monotherapy patients were analyzed. Topiramate was used as the initial treatment in 17 patients. Other patients received topiramate as the second (10), third (4) or fourth (1) treatment. We identified two patients with a clinical remission. These patients received topiramate as the second or fourth treatment. Although the EEG improved in one patient, he later experienced clinical and electrographic relapse. While the other patient’s EEG normalized with prior ACTH treatment, IS did not resolve until after starting topiramate.

Conclusions: The rate of clinical remission with topiramate was 6% (2/32). Temporary electrographic improvement occurred in one of these patients. This study included a relatively large number of patients who received topiramate as the first or second treatment for IS. These findings suggest that topiramate is not an optimal therapy for IS.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders

72. Phenotypic Analysis of Epilepsy in the MELAS-associated mtDNA A3243G Mutation
DEMAREST ST, WHITEHEAD MT, TURNACIAGLU S, PEARL PL, GROPMAN A (WASHINGTON, DC)

Background: The A to G mtDNA point mutation at position 3243 (A3243G) is the most common cause of Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke like Episodes (MELAS) a systemic multi-organ disease. Epilepsy is common in a common finding but there is wide phenotypic variation that has not been thoroughly explored.

Methods: This is a retrospective analysis of the epilepsy phenotypes of seven patients with the A3243G mutation. Clinical context is provided with discussion of associated stroke like episodes and overall clinical course.
Results: Most of the patients presented with typical MELAS and epilepsy characterized by infrequent prolonged focal seizures including: Epilepsia partialis continua, hemi-clonic status epilepticus, nonconvulsive status and occipital status epilepticus. Seizures usually occurred during the acute phase of a stroke like episodes. Periodic lateralized epileptiform discharges (PLEDs) may be seen electrographically. There was a poor correlation between the frequency and severity of stroke like episodes and overall burden of epilepsy between the stroke like episodes. Some patients with this mutation are completely asymptomatic or have mild symptoms typical for mitochondrial diseases. Slow spike-wave consistent with Lennox-Gastaut syndrome and electrographic status epilepticus was seen in one patient who responded to ethosuximide. This patient never suffered any stroke like episodes.

Conclusions: Prolonged focal seizures are often associated with acute stroke like episodes and PLEDs may be seen electrographically, but there is minimal epilepsy burden between stroke like episodes in most patients. The phenotypic spectrum is wide and includes asymptomatic patients and Lennox-Gastaut syndrome without stroke like episodes.

References:

Atypical MELAS

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders, Genetics

73. Metabolic Strokes in Glutaric Aciduria Type 2 (MADD) – A Case Report and Review of the Literature
Jülich K, Anselm I, Prabhu SP, Fayad M, Berry G, Neelan E (Boston, MA)

Objective: Based on a patient with metabolic strokes during an episode of metabolic stress, we discuss imaging findings in glutaric aciduria type 2.

Methods: We performed a review of the patient chart and literature.

Results: Glutaric Aciduria Type 2 or Multiple Acyl-CoA Dehydrogenase Deficiency (MADD) is a rare metabolic...
disorder caused by mutations of the electron-transferring flavoprotein genes ETFα, ETFβ, and the dehydrogenase ETFDH. Affected individuals present with severe acute neonatal encephalopathy (type I and II), or later in life with encephalopathy and CK elevation with metabolic stress (type III). Rare case reports describing imaging findings of cerebral malformations including gray matter heterotopias, temporal lobe hypoplasia, bilateral basal ganglia injury, callosal hypoplasia, cerebellar vermian agenesis, and periventricular white matter abnormalities.

Our patient is a 7 year-old girl who underwent brain imaging during an episode of metabolic acidosis with headache, vomiting, fatigue and subjective leg weakness. Her MRI showed an unusual pattern of focal areas of restricted diffusion in the corpus callosum, subcortical and deep white matter, in addition to other cerebral and cerebellar white matter abnormalities indicating remote injury. She had no focal deficits on neurologic exam. Follow-up imaging one year later showed expected evolution of the injury.

Conclusions: Patients with MADD appear to be susceptible to metabolic strokes during phases of metabolic stress. Based on the literature, imaging findings vary with multiple areas of the brain affected, although basal ganglia and white matter seem to be predisposed to injury.

Keywords: Case studies/case series, Genetics, Neuroimaging

74. Reduced Fronto-Parietal Functional Connectivity in Ornithine Transcarbamylase Deficiency
Pacheco-Colon I, Washington S, Shattuck K, VanMeter J, Gropman AL (Washington, DC)

Objective: To investigate differences in default-mode network (DMN) resting state activity in patients with OTCD versus controls. DMN, a network of brain regions is active when an individual is at wakeful rest, and suppressed during cognitively demanding tasks.

Methods: Resting-state fMRI data (TR/TE=2000/30 ms, 36 slices, 4.0 mm3 resolution) was collected to examine the DMN. Standard processing was done using SPM8. Motion was carefully assessed using Art Repair. We studied 22 Controls and 12 subjects. Independent component analysis (ICA) was used to extract components of the DMN of each group. ANOVA was conducted on functional connectivity between nodes of the DMN using ROIs based on the nodes in the control group's ICA followed by post-hoc t-tests.

Results: DMN of controls consists of medial prefrontal cortex, precuneus, and bilateral parietal cortex. All of these regions were present in the DMN of OTCD patients, but split into three different components. ANOVA revealed that patients have significantly reduced functional connectivity between all regions of the DMN relative to controls, F(1, 32) = 11.80, p = .001, the largest difference being between the medial prefrontal cortex and bilateral parietal cortex (right: p = .011; left: p = .055).

Conclusions: These results expand upon our previous findings of reduced frontal white matter integrity in OTCD by identifying reduced long distance functional connectivity within the DMN especially between the frontal and parietal nodes, most likely reflecting damage caused by episodes of hyperammonemia. This has implications in studying recovery from HA and residual damage and provides a quantitative noninvasive measure of anatomic damage.

Keywords: Genetics, Neuroimaging

75. Physiologic Biomarkers in SSADH Deficiency Treated with Chronic Taurine Therapy
Pearl PL, Schreiber JM, Dustin I, Wiggs E, Barrios E, Wassermann EM, Gibson KM, Theodore WH (Boston, MA)

Rationale: Taurine intervention for SSADH is rational due to partial GABA(A&B) receptor agonist effects and rescue in the null mouse from status epilepticus and premature lethality.

Methods: Subjects with confirmed SSADH deficiency were titrated onto taurine weekly from 50 to 200mg/kg/day (maximum 10 grams/day). Biomarkers including neuropsychological testing, MRI, flumazenil-PET, TMS, and CSF metabolites were studied following three months on versus off intervention.

Results: Eight patients (6M/2F; age range 12–33 yrs) were enrolled. Neuropsychological results indicate baseline average FS IQ (Wechsler Nonverbal) of 44.1 (range 34–55), 3.6 SD < mean. Of 6 who returned at 6-month follow-up, 5 completed testing (3M/2F) on therapy; average FS IQ = 43.4 (range 33–51), an insignificant difference. CSF biomarkers were (n=4): taurine: 9 + 1 mM (SEM); 26 + 6 (n=4, p<0.05 off/on): free GABA (ref range, 32–170 nM): 394 < 5 (range 29–45), an insignificant difference. CSF metabolites were (n=4): total GABA (ref range 3.3–12.1 mM): 14.3 ± 2.4 (p<0.05 off/on): total GABA (ref range 3.3–12.1 mM): 14.3 ± 2.4 (p<0.05 off/on): TMS confirmed previous findings at baseline and showed a trend towards a reduction in short interval intracortical inhibition and the cortical silent period after taurine administration.

Conclusions: Average nonverbal IQ score is 43.5 (range 33–55) in SSADHD and did not show changes with taurine intervention. TMS on taurine revealed trends towards reduced inhibition in two separate measures believed to be mediated through different GABA receptor subtypes.

Keywords: Case studies/case series, Translational/experimental therapeutics

76. Widening Phenotypic Spectrum of AADC Deficiency, A Disorder of Dopamine Serotonin Synthesis
Pearl PL, Helman G, Pappa MB (Boston, MA)

Objective: Aromatic L-amino acid decarboxylase deficiency presents with prominent extrapyramidal and autonomic features and CSF monoamine deficiency with increased 3-O-methyldopa, a byproduct of accumulated L-DOPA. Less than 100 cases have been identified. The disease is typically associated with a severe phenotype and worse prognosis in females. Gene transfer technology has been implemented using an adeno-associated virus encoding AADC in the putamen bilaterally.
Methods: We describe a cohort of five AADC deficiency cases showing a heterogeneous phenotype and variably intact response to pharmacologic therapy.

Results: Five patients (age range 2–10 yrs, mean 5 yrs, 3M/2F) with confirmed AADC deficiency are described. Four (3M/1F) have had improvement on combinations of dopaminergic agonists, MAO-inhibitors, pyridoxal-5-phosphate, and folinic acid. Each presented with hypotonia, decreased voluntary movement, dystonia, irritability, and oculogyric crises. Two (1M/1F) are independently ambulatory and are not dependent on gastrostomy-tube feedings. One female has a severe phenotype including recurrent hypoglycemic events associated with bradycardia, although the latter have resolved with chronic anticholinergic therapy. One Taiwanese boy had the common homozygous mutation and otherwise we describe five new DDC mutations (Table).

Conclusions: We report a wider phenotypic spectrum including intact response to pharmacologic management and milder outcome in a female, as well as four new mutations. Four of five patients have improved on combination therapy including a dopamine agonist, MAO inhibitor, pyridoxal-5-phosphate, and folinic acid. The advent of viral-mediated gene therapy in AADC deficiency renders expanded knowledge of the outcome increasingly important.

Keywords: Case studies/case series, Genetics

### MRI Findings in a Child with Acute Hepatic Encephalopathy Mimicking Hypoxic Ischemic Encephalopathy

**Objective:** To describe the MRI abnormalities mimicking hypoxic ischemic encephalopathy (HIE) and clinical outcome in a child after liver transplant for acute hepatic encephalopathy.

**Methods:** Case report.

**Results:** A 3-year-old boy presented to St. Louis Children's Hospital in idiopathic hepatic failure. Ammonia peaked at 207 mcmmol/L on day 6, accompanied by severe encephalopathy, but intact cranial nerves and a normal head CT. He underwent liver transplant on day 7. The following day, his neurologic status worsened, with loss of gag reflex. CT revealed diffuse gray-white hypoattenuation. MRI on day 10 showed diffuse diffusion restriction in a non-vascular pattern (Figure 1). His exam gradually improved over his 2-month hospitalization. MRI on day 27 showed improvement in diffusion restriction and increased T2/FLAIR changes (Figure 2). At 3-month follow-up, he speaks in 4–5 word sentences, follows commands, feeds himself, and walks independently.

**Conclusion:** Diffusion-restriction associated with hepatic encephalopathy can be confused with HIE. Our patient

### TABLE . Clinical Overview of AADC Patients

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current age (years)</td>
<td>4</td>
<td>10</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>16 months</td>
<td>7 years</td>
<td>10 months</td>
<td>13 months</td>
</tr>
<tr>
<td>AADC Enzyme Activity: &lt; 1.5 pmol/mm/mL</td>
<td>Stands; takes steps with support; G-Tube Dependent; Non-ambulatory; Non-verbal</td>
<td>Severe; G-Tube Dependent; Non-ambulatory; Non-verbal</td>
<td>Severe; G-Tube Dependent; Non-ambulatory; Non-verbal</td>
<td>Severe; G-Tube Dependent; Non-ambulatory; Non-verbal</td>
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*Newly reported DDC mutations*
demonstrates that this process can occur in the subacute period after the liver failure is corrected. The mechanism may be due to accumulation of glutamine in astrocytes causing increased intracellular osmotic pressures and cerebral edema, which is not quickly reversed. This cascade may explain our patient’s presentation of decompensation post-liver transplant. Reports of adults with hepatic encephalopathy have also found reversible cortical diffusion restriction radiographically indistinguishable from HIE.2,3,4,5. Our patient’s outcome was better than expected for HIE. Awareness of this phenomenon aids prognostication and directing goals of care.

References:

Figure 1: Diffusion weighted and FLAIR sequences from MRI on day 10 of hospitalization, demonstrating diffuse diffusion restriction throughout the periventricular, cortical and subcortical white matter with hyperintensity of the deep-grey structures.

Keywords: Case studies/case series, Neuroimaging

78. Autistic-like Behavior and Severe Purkinje Cell Degeneration in Lis1 Conditional Knockout Mice
Alkawaz M, Ross M, Sudarov A (New York, NY)

Objective: Investigating the role cerebellum plays in complex neurological disease such as autism spectrum disorder (ASD) is an ongoing topic of research. Recent study from our lab identified Lis1 as key factor in regulation of synaptic homeostasis with significant implications for autistic-like behaviors. The present study aimed to understand molecular and behavioral role of Lis1 exclusively in Purkinje cells, sole output of cerebellar circuitry.

Methods: To investigate the role of Lis1 in Purkinje cells we generated Lis1 conditional knockout animals using postnatal Purkinje cell specific L7-Cre driver (L7-Lis1cko). Cerebella of L7-Lis1cko and control animals were examined using immunohistochemistry to assess the cerebellar size, Purkinje cell morphology and synaptogenesis. To identify the cognitive and motor impairments in L7-Lis1cko animals we used 3-chamber social interaction, gait analysis and rotarod with challenge test.

Results: L7-Lis1cko cerebella are hypoplastic (p <0.03) in comparison to controls. Purkinje cells of L7-Lis1cko mutants are severely disorganized and dislaminated. The ectopic Purkinje cells have immature and stunted dendritic arborization (p <0.015) but maintain synaptic integrity. Additionally, we found an increase in cell death (p<0.0029), neuronal inflammation, and phagocytizing macrophages. Loss of Lis1 in Purkinje cells resulted in neuronal degeneration of their synaptic targets, cerebellar nuclei, as evidenced by a reduction in the axonal bouttons. We found no significant motor impairments or ataxia, but social behavioral deficits (p<0.003) in L7-Lis1cko animals.

Conclusions: Here we demonstrate that loss of Lis1 in postnatal Purkinje cells is associated with autistic-like behaviors. Furthermore, our study highlights the important contribution of cerebellum to the pathogenesis of ASD.

Keywords: Genetics

79. Radiologic Features Predicting Clinical and Neurodevelopmental Outcome in Schizencephaly
Almugbil MA, Moghaddam MH, Sour M, Shevell M, Poolin C, Rasmussen L, Amron D, Anderman E (Montreal, Quebec)

Objective: The aim of this study is to determine the radiologic features that predict the neurodevelopmental and clinical outcome.

Methods: We performed a comprehensive retrospective chart review of 33 individuals with schizencephaly. All imaging was systematically reviewed. Two-sided Fisher’s exact test was used to assess associations between radiologic
features of schizencephaly and specific clinical features, including neurodevelopmental outcome and epilepsy.

**Results:** The distribution of schizencephaly subtypes were as follows: 45% (15/33) individuals had unilateral closed lipped, 27% (9/33) unilateral open-lipped, 15% (5/33) bilateral closed lipped and 12% (4/33) bilateral closed lipped. The presence of unilateral versus bilateral involvement was not significantly associated with a difference in severity of developmental delay nor presence of seizure or seizure intractability. The presence of an open-lipped schizencephaly ($p = 0.001$) or midline abnormalities (such as agenesis of the corpus callosum or septum pellucidum) ($p = 0.017$) were significantly associated with increased severity of developmental delay.

**Conclusions:** Schizencephaly is associated with a heterogeneous and variable severity in neurodevelopmental outcome and epilepsy. Surprisingly, bilateral cerebral involvement is not predictive of the worse neurodevelopmental or clinical outcome, whereas presence of an open-lipped abnormality or associated midline abnormality were associated with a poorer clinical outcome.

**Keywords:** Case studies/case series, Genetics, Neuroimaging

### 80. Hypomyelination Secondary to Oligodendrocyte Specific Deletion of the Tuberous Sclerosis Complex 2 Gene

**Carson RP, Fu C, Kelm ND, West KL, Does MD, Ess KC** (Nashville, TN)

**Objective:** A link between myelin abnormalities and morbidity in tuberous sclerosis complex (TSC) is supported by human MRI findings correlating myelin abnormalities with autism. This is further reinforced by myelin abnormalities in mouse models of TSC, though the cells types responsible and the mechanisms underlying the myelin abnormalities remain unclear.

**Methods:** To determine the role of cell-autonomous alterations in mTOR signaling in oligodendrocytes, we generated an oligodendrocyte specific conditional knock-out (CKO) mouse using Cre-recombinase and the Olig2 promoter to inactivate the Tsc2 gene.

**Results:** CKO mice demonstrated a high-frequency appendicular tremor similar to that seen in mouse models of hypomyelination. Despite the tremor, no changes in coordination were seen with Rotarod testing. No clear evidence for anxiety was seen with elevated zero-maze testing, though total distance traveled in the open arm and entries to the open arm were reduced in CKO mice. Diffusion-weighted MRI imaging studies demonstrated reductions in fractional anisotropy and increased radial diffusion in white matter tracks in CKO mice, consistent with that seen in human disease and further supporting abnormal myelination (Figure 1). Decreases in myelin constituent proteins were further demonstrated with immunofluorescence microscopy and Western blotting. Coincident with hypomyelination, extensive gliosis was seen in both cortex and white matter tracks.

**Conclusions:** Loss of Tsc2 in oligodendrocytes results in hypomyelination and diffuse gliosis. Gliosis may suggest alterations in glial cell fate, possibly due to changes in mTOR activity. Additional ongoing studies are aimed at determination of the molecular substrates for the pathologic and possible cell fate changes.

**Keywords:** Epilepsy and other paroxysmal disorders, Neuroimaging, Translational/experimental therapeutics

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Figure 1. Altered myelin structure following loss of Tsc2 from oligodendrocytes. Axial images from P60 control and Olig2-Tsc2 CKO mouse brains were obtained with a 15.2T MRI scanner. Fractional anisotropy (FA) is decreased secondary to increased radial diffusion (RD), supporting abnormal myelin in CKO mouse brains.
81. Tuberous Sclerosis: a quality improvement multidisciplinary approach
Ciobanu M, Wong M, Silvia MT (Salem, NC)

Objective: To develop a practical multidisciplinary QI approach in order to improve tuberous sclerosis care. Tuberous sclerosis complex is a highly variable inherited condition presenting a relentlessly progressive course over the lifetime of an affected individual. Accurate early diagnosis is fundamental to implementation of appropriate medical surveillance and treatment.

Methods: As part of a QI initiative to develop a multidisciplinary tuberous sclerosis clinic for achieving the surveillance and management recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference, we retrospectively reviewed the charts of 28 patients with tuberous sclerosis followed by epilepsy clinic. The chart review revealed that the TS patients at our institution received fragmented services and lacked interdisciplinary care coordination.

Results: We designed a tuberous sclerosis program at Wake Forest Medical Center to improve patient care and outcomes. We identified quality improvement (QI) practice changes and implemented a multidisciplinary approach that focuses on surveillance, anticipatory and preventive measures as well as active interventions to address the primary and secondary aspects of the disorder. Our aims were to establish closer collaboration and an interchange of knowledge between TS providers and different disciplines.

Conclusions: Morbidity and treatment burden of TS manifestations is significant, suggesting substantial economic and humanistic burden for the families and society. Medical care is thus best provided by a team of medical specialists and health professionals working closely together in an interdisciplinary fashion. Standardized care can also facilitate planning for multicenter trials and help with the identification of areas in which care can be improved.

Keywords: Genetics

82. Leptomeningeal Vessel Phosphorylated ERK Expression Correlates with Sturge-Weber Syndrome Brain Involvement
Comi AM, Mateo M, Shotwell L, Verina T, Marchuk D, North P (Baltimore, MD)

Objective: Sturge-Weber syndrome (SWS) consists of a facial capillary malformation, choroid angioma of the eye and leptomeningeal angioma. We recently identified the causative somatic mosaic mutation in GNAQ which increases ERK phosphorylation, however the cell type(s) involved are currently unknown. We aimed to determine SWS leptomeningeal blood vessel ERK phosphorylation status.

Methods: Surgical formalin fixed SWS surgical brain tissue samples. The most intense labeling was in endothelial cells of leptomeningeal arteries and arterioles; the expression in endothelial cells of veins and venules was much less intense. The average p-ERK expression score was positively and significantly correlated with the Sturge-Weber brain involvement scores ($r=0.62$, $p=0.02$).

Conclusions: We hypothesize that the hyperactivating somatic mutation in GNAQ, or alternatively blood stasis with resulting hypoxia-ischemia, results in increased endothelial cell p-ERK expression in abnormal leptomeningeal vessels. The distribution of the intense p-ERK expression within endothelial cells of leptomeningeal vessels with the morphologic features of arteries suggests that their further study is warranted. Inhibitors of the Ras-Raf-MEK-ERK pathway may in the future prove useful in the treatment of patients with SWS.

Keywords: Epilepsy and other paroxysmal disorders, Genetics, Stroke, Translational/experimental therapeutics

83. An Uncommon Pattern of Subcortical Band Heterotopia
Holler YF, Brown CP (Lubbock, TX)

Introduction: Subcortical Band Heterotopia (SBH) is a cortical malformation complex with a strong genotype-phenotype correlation. The majority of cases of SBH are due to mutations in the DCX (doublecortin or XLIS) gene. MRI findings in SBH caused by DCX gene mutations demonstrate anterior dominant or generalized subcortical band heterotopias. There have been no cases of posteriorly restricted subcortical band heterotopias due to a DCX mutation.

Case: A 2 year old girl presented with rotary eye movements that occurred upon awakening. The initial head CT suggested a cortical malformation. The subsequent MRI findings were significant for posteriorly restricted SBH and a subtle SBH in the inferior temporal lobes. A heterozygous missense mutation (c608,c>G) was found in the DCX gene. This child also was determined to have focal epilepsy; two years later the seizures have been refractory to several anti-epileptic medications.

Discussion: This missense mutation on the DCX gene was previously reported in an affected female as part of a kindred. That affected female had the MRI findings of a diffuse thin subcortical band. The child in this case presents with an uncommon pattern of SBH, showing greater involvement in the posterior, more than anterior brain regions; not previously described. Since the child has epilepsy that is refractory to medication, it is possible that the mutation in this child caused a more severe phenotype that has not been previously reported. Therefore, testing for the DCX gene mutation should be considered in girls who have posterior SBH.

Keywords: Case studies/case series, Genetics, Neuroimaging

84. PI3K/AKT Pathway Mutations Cause a Spectrum of Dysplastic Brain Malformations from Syndromic Megalencephaly to Focal Cortical Dysplasia

Results: Phosphorylated ERK expression was increased in the endothelial cells lining leptomeningeal vessels in the SWS surgical brain tissue samples. The most intense labeling was in endothelial cells of leptomeningeal arteries and arterioles; the expression in endothelial cells of veins and venules was much less intense. The average p-ERK expression score was positively and significantly correlated with the Sturge-Weber brain involvement scores ($r=0.62$, $p=0.02$).

Conclusions: We hypothesize that the hyperactivating somatic mutation in GNAQ, or alternatively blood stasis with resulting hypoxia-ischemia, results in increased endothelial cell p-ERK expression in abnormal leptomeningeal vessels. The distribution of the intense p-ERK expression within endothelial cells of leptomeningeal vessels with the morphologic features of arteries suggests that their further study is warranted. Inhibitors of the Ras-Raf-MEK-ERK pathway may in the future prove useful in the treatment of patients with SWS.

Keywords: Epilepsy and other paroxysmal disorders, Genetics, Stroke, Translational/experimental therapeutics

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Adams C , Tupal S, Ojemann JG, Shendure J, Dobyns WB (Charlottesville, VA)

Objective: Malformations of cortical development containing dysplastic neuronal and glial elements, including dysplastic malformations (DMEG), hemimegalencephaly (HMEG), and focal cortical dysplasia (FCD), are common causes of intractable pediatric epilepsy and neurocognitive impairment. In this study we analyzed the clinical, genetic, imaging, pathologic, and immunohistologic phenotypes of 33 children who underwent surgical resection of dysplastic cortex for the treatment of intractable epilepsy.

Methods: Genomic DNA was isolated from frozen cortex obtained at epilepsy surgery. Targeted sequencing was performed using molecular inversion probe capture technology. Extracts of frozen cortex were submitted to Western blotting. Formalin fixed, paraffin-embedded sections were used for fluorescence immunohistochemistry studies.

Results: We identified mosaic activating mutations in PIK3CA and AKT3 in this cohort, including cancer-associated hot spot PIK3CA mutations in DMEG, HMEG, and FCD IIa. A germline PTEN mutation was identified in a boy with HMEG but no peripheral manifestations of Cowden or Bannayan-Riley-Ruvalcaba syndromes. A spectrum of clinical, imaging and pathologic abnormalities was found in this cohort that did not predict mutation status. Elevated levels of phosphorylated S6 ribosomal protein were identified in both neurons and astrocytes of all HMEG/FCD specimens. In contrast, expression patterns of the T308 and S473 phosphorylated forms of AKT discriminated between control cortex, mutation-positive dysplastic cortex, mutation-negative dysplastic cortex, and non-dysplastic epilepsy cortex.

Conclusions: Our findings identify PI3K/AKT pathway mutations as an important cause of epileptogenic brain malformations and establish DMEG, HMEG, and FCD as part of a single pathogenic spectrum.

Keywords: Epilepsy and other paroxysmal disorders, Genetics, Neuroimaging

85. Examining a Correlation Between Congenital Heart Disease and Neurofibromatosis I
Mientkiewicz L, Erenberg P, Rothner AD, Moodley M (Cleveland, OH)

Background: The exact risk of congenital heart disease in patients with neurofibromatosis type 1 (NF1) is not known, though smaller studies have suggested that there is an increased incidence. We examined a larger cohort of pediatric patients with NF1 to assess the incidence of congenital heart disease.

Objective: To assess the incidence of congenital heart disease in pediatric patients with NF1 at a single center.

Methods: Retrospective chart review of all patients less than 21 years of age diagnosed with NF1 from January 2009 to August 2013. Data collected included demographics, family history of NF1, physical exam findings, vitals and echocardiogram results.

Results: 132 patients with NF1 were identified. 15 (11.4%) had heart defects. 60 (45%) were female with ages 0–21 years (mean 11 years). The most prevalent defects included coarctation of the aorta (4/15), mitral valve prolapse (MVP) (4/15), pulmonary stenosis (PS) (4/15) and atrial septal defect (ASD) (3/15). Patient had a ventricular septal defect (VSD).

Conclusion: There is a correlation between NF-1 and congenital heart disease. In our study, the overall incidence of congenital heart disease in patients with NF1 was 11.4%, considerably higher than the incidence in the general population, which is about 0.8-1%. Our study is the largest to date to evaluate this incidence. Further research may be needed, but a cardiac screening program for children with NF1 should be considered.

Keywords: Case studies/case series

86. IQSEC2: a cause of neurodevelopmental disability with Rett-like features in females
Olson HE, Tambunan D, LaCoursiere CM, Sheidley BR, Khwaja O, Ha E, Kaufmann W, Poduri A (Boston, MA)

Objective: To assess the role of IQSEC2, a gene associated with X-linked intellectual disability in males, with neurodevelopmental disabilities and Rett-like features.

Methods: We performed whole exome sequencing for 11 patients with Rett syndrome or Rett-like features, who had previously tested negative for mutations in MECP2.

Results: Among the 11 patients, we identified de novo predicted pathogenic variants in IQSEC2 in two girls with Rett-like features not meeting criteria for Rett syndrome. The first patient lacked regression but had severe global delays, atypical features, and paroxysmal events. Rett-like features included deceleration of head growth, somatic growth retardation, hypotonia followed by spasticity and rigidity, breathing disturbances, scoliosis, cold extremities, bruxism, and tremors. The second patient had developmental regression and met all major criteria for Rett syndrome with the exception of loss of hand skills. Rett-like features included breathing disturbances, abnormalities in muscle tone, and inappropriate laughing and screaming spells. Prior literature reports include 2 female probands and one family of 3 females with disruption of the gene IQSEC2 (Xp11.2) by translocation or de novo mutation resulting in developmental delays, intellectual disability, and in some cases epilepsy.1–3 One of the girls had a clinical diagnosis of Rett syndrome.

Conclusions: Based on our cases and prior literature, we suggest that mutations in the gene IQSEC2 are associated with developmental delay and intellectual disability with or without epilepsy in females. IQSEC2 should be part of the differential diagnosis for girls with Rett syndrome and Rett-like features who test negative for MECP2.

References:

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders, Genetics

87. Decreased Anterior-Posterior Connectivity in Neurofibromatosis Type 1
Resting-state functional MRI (rs-fMRI) is a noninvasive means of assessing the brain’s intrinsic functional architecture and has not been widely investigated in the NF1 population.

Objective: The purpose of this study was to evaluate brain connectivity in individuals with NF1 using rs-fMRI with novel graph theory analysis methods.

Methods: Thirty individuals with NF1 (mean age 27±12 years; 12 males) and 30 healthy controls (29±11 years; 16 males) underwent a resting state fMRI for 5 minutes. fMRI data was divided into 112 brain regions using the Harvard-Oxford Atlas. Partial correlations were used and resulting Markov networks indicated direct relationships between two regions of interest and reduced variability in subject graphs. Novel R3 strategy was implemented to sparsify networks and determine subject- and group-level differences.

Results: More anterior-posterior connections were found in the controls. Thirty-one edges found in controls did not exist in the NF1 subjects. NF1 subjects had 13 edges that were not found in controls. NF1 subjects also showed more lateralization, atrophied modular clustering than controls. NF1 subjects were similar to controls in global metrics such as sparsity and modularity.

Conclusions: Using a novel R3 strategy to inquire into detailed edge structure and modular clustering, we found that NF1 subjects had significantly fewer anterior-posterior connections than controls. NF1 subjects also had different modular organization than controls. These results provide further insights into the etiology of neurocognitive deficits in NF1.

Keywords: Neuroimaging

88. Carotid Dysplasia and Cerebrovascular Insufficiency as a Novel Manifestation of the PTEN Hamartoma Syndrome
Taylor JM, Vadivelu S, Abruzzo T (Cincinnati, OH)

Objective: We report for the first time the observation of bilateral carotid dysplasia and cerebrovascular insufficiency associated with PTEN Hamartoma Tumor Syndrome and discuss a proposed mechanism.

Methods: A 3 year old male with PTEN Hamartoma Tumor Syndrome (Y68H missense mutation) underwent brain MR imaging because of marked macrocephaly and global developmental delay. Peripartum hypoxemia was suspected as the patient was delivered full term by emergent caesarean section due to cephalopelvic disproportion. Brain MR imaging, MR angiography, and MR perfusion with acetazolamide challenge are reviewed and ascribed to the pathogenesis of PTEN mutations.

Results: Symmetric leukomalacia in the MCA/PCA watershed territory with sparing of the cerebral cortex suggested a chronic hypoperfusion injury pattern. Time of flight MR angiography revealed aplasia/hypoplasia of the right internal carotid artery (C1-C6 Bouthillier segments) and of the left internal carotid artery (C6 Bouthillier segment). The C7 segment of both internal carotid arteries were reconstituted by the posterior communicating arteries. Acetazolamide MRI perfusion challenge was suggestive of minimal vasoreactivity to carbonic anhydrase inhibition consistent with depletion of cerebrovascular reserve. Both carotid canals were diminutive. Previous reports of animal models with PTEN dysregulation have similarly shown occlusive intimal hyperplasia following vascular injury. In our patient, peripartum hypoxemia and/or birth trauma likely comprised the injury that triggered intimal hyperplasia and failure of normal internal carotid artery development.

Conclusions: Patients with PTEN Hamartoma Tumor Syndrome are at risk for carotid dysplasia and cerebrovascular insufficiency. We report for the first time this novel vascular finding as a clinical manifestation of PTEN dysregulation.

Keywords: Case studies/case series, Neuroimaging, Stroke

89. Effect of TUBB4A Mutations on Tubulin Polymerization and Axonal Transport: molecular mechanisms of hypomyelination with atrophy of the basal ganglia and cerebellum

Objective: An expanding number of mutations and a spectrum of hypomyelinating and dystonic phenotypes with TUBB4A mutations are now being identified. It remains to be determined how TUBB4A mutations disrupt critical tubulin and axonal function in affected cells. We studied the effect TUBB4A mutations on tubulin polymerization in affected versus control cells. We identified that H-ABC (Hypomyelination with Atrophy of the Basal Ganglia and Cerebellum) was caused by heterozygous denovo mutations in TUBB4A, with a majority of patients with a single pathogenic mutation, c.745G>A (p.Asp249Asn).

H-ABC is a leukodystrophy with paucity of development of myelin (hypomyelination) and selective atrophy of the putamen and cerebellum, but little is known about its pathogenesis.

Methods: To determine the effect of mutant tubb4a on tubulin dynamics in the relevant cell type, we used high-resolution subcellular imaging to define microtubule dynamics in fibroblasts expressing either WT or mutant tubb4a. Fibroblasts (Wild type and TUBB4A mutated) cells were harvested by lysis and centrifuged according to previously established techniques[1–3]. The percent of unpolymerized tubulin vs. microtubules was calculated by: 100*(supernatant)/(supernatant+pellet) using immunoblotting approaches.

Results: Overall, H-ABC tubulin shows a trend to a lower percentage of polymerized microtubules than control suggesting instability of microtubules (see Figure 1).

Conclusions: H-ABC is a progressive neurologic disorder with no known treatment. The above results suggest that TUBB4A mutations are dominant negative in this condition, and the H-ABC may result from a disruption of tubulin stability and axonal transport.

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Bibliography:

Keywords: Demyelinating Disorders, Genetics, Translational/experimental therapeutics

90. Etiology of Global Developmental Delay at a Pediatric Neurology Clinic and Yield of Metabolic Testing
Armour J, Agarwal RL, Scussel L, Huq AHM (Detroit, MI)
Objective: To evaluate the profile of patients with global developmental delay (GDD) seen at a tertiary care pediatric neurology clinic and establish the yield of metabolic testing.

Methods: Retrospective analysis of 157 patients (91 males, 58%) with GDD referred to a pediatric neurogeneticist from July 2000 to December 2010.

Results: Mean age of referral was 52.9 ± 59.1 months (Range: 2–528 months). Seizures were the most commonly associated co-morbidity (82 patients, 52%). Seventy-three patients (46%) had abnormal neurological exam (abnormal tone, involuntary movements, cranial nerve deficits). Genetic studies were diagnostic in 18/119 patients (15.1%) with abnormalities detected on karyotype (3/84), FISH (3/57), microarray (4/29) and targeted gene testing (8/45). A "screening" metabolic workup (urine organic acids, plasma amino acids, ammonia, lactic acid, serum acylcarnitine profile) was abnormal in 49/157 patients (31.2%). Despite the high rate of abnormalities on metabolic screening, only 7/157 patients (4.4%) were eventually diagnosed with an inborn error of metabolism (IEM) which included non-ketotic hyperglycinemia (2), Niemann-Pick Type C (1), glucose transporter type-1 deficiency (1), mitochondrial encephalopathy (2) and metachromatic leukodystrophy (1). Screening metabolic workup was suggestive of an IEM in only 1 of these seven patients who had an underlying mitochondrial disorder and showed elevated arginine, hyperammonemia and lactic acidosis.

Conclusions: Inborn errors of metabolism represent less than 5% of patients with GDD. Nonetheless, a significant number of patients with GDD have inconclusive abnormalities on metabolic screening. Whether these abnormalities represent physiological variants, milder forms of enzyme deficiencies or unknown metabolic pathways remains to be elucidated.

Keywords: Genetics

91. International Web-Based Survey on Evaluation of Global Developmental Delay
Bhatia P, Cohen B (Akron, OH)
Objective: Testing paradigms for the evaluation of Global Developmental Delay (GDD) without regression have evolved dramatically over the last decade. This study was developed to compare the current practice and preferences among Neurology and Developmental-Behavior (DB) providers (physicians and nurse practitioners (NPs)) with respect to the 2003 American Academy of Neurology (AAN) and Child Neurology Society (CNS) Practice Parameter, and the 2011 AAN and CNS Evidence-based Report summarizing the value of diagnostic testing for these patients.

Methods: A 26-Question, web-based survey was distributed to members of Child Neurology Society, and DB Pediatrics Discussion Board, with a request to share it with other providers in their field. The survey included 19 diagnostic evaluation items for the evaluation of GDD without regression. These items were selected from the AAN and CNS Practice Parameter (2003) and Evidence-based Report (2011), and modified to reflect current testing practices. Seven demographics items were also included in the survey.

Results: There were 290 responses (225 neurologists, 23 neurology NPs, 32 DB physicians, 1 DB NP). 4.6% (13) of those who identified their specialty (281) were from outside US. The table summarizes and contrasts responses to major questions in the survey.

Conclusions: Although the evaluation varies, the majority practice within the domain of Practice Parameter and Evidence Report. The use of tests nearing obsolescence has declined (subtelomeric FISH and routine karyotype), and many providers have a more rigid definition of GDD than defined (more than 2 spheres required). X-linked Intellectual Disability gene panel (relatively newer test) is probably being used less than what is suggested in the 2011 evidence report, while thyroid testing is being used more frequently. Notably, based upon the extent of response, the results of this survey are mainly applicable to practice within US only.

Keywords: Genetics

92. Introduction to Genomics for Child Neurology: an educational program for educators and clinicians
Objective: Genetics plays a role in many neurological disorders. While genetics is presented early in medical school, many residencies and fellowships lack continued education, whereas Neurology board examinations are heavy in genetic content. Objective: To address this gap, we developed a program called “Introduction to genomics for Child Neurology" for child neurology educators and clinicians developed in collaboration between NCHPEG and the Children's National Medical Center.

Methods: It is appropriate for practicing clinicians, medical students, residents, and fellows. Curriculum includes four one-hour workshops that educators can implement at their own institutions. Topics include genomic risk assessment, evaluation and testing decisions, genetic testing ordering and interpretation, and communication with families about genomic data; as well as point of care tools and interactive Web cases for clinicians to practice genomic skills.

Results: The program is available as a resource to educators and clinicians. Educators can use the comprehensive
curriculum materials to implement local workshops for child neurology providers. Clinicians can use interactive Web cases and point of care tools to build skills.

Conclusions: This presentation will review the content and suggestions for use and how it can be implemented within a fellowship or residency program as well as in the private practice setting.

Keywords: Genetics

93. Clinical Whole Exome Sequencing in Child Neurology Practice
Objective: Whole exome sequencing (WES) represents a significant breakthrough in clinical genetics as a powerful tool for etiological discovery in neurodevelopmental disorders. To better characterize the genetic landscape of neurodevelopmental disorders, we analyzed patients in our pediatric neurogenetics clinic who underwent WES.

Methods: We performed a retrospective cohort study on 78 patients with various neurodevelopmental disabilities and unifying workup prior to WES. We characterized their molecular diagnoses, clinical features, and whether their previous treatment plan changed due to WES results.

Results: The overall diagnostic rate for our cohort was 41% (n=32 out of 78 patients). Nineteen patients had a single autosomal dominant (AD) disorder, 11 had a single autosomal recessive (AR) disorder, one had an X-linked dominant disorder, and one had both an AD and AR disorder. The 32 patients with positive mutations exhibited various neurobehavioral and neuroimaging abnormalities, including: intellectual disability/developmental delay (n=28), cerebral palsy-like encephalopathy (n=11), autism spectrum disorder (n=5), delayed/hypomyelination (n=7), and cerebellar abnormalities (n=9). The results of WES affected management for all patients with a positive diagnosis, triggering reproductive planning (n=27), disease monitoring initiation (n=5), investigation of systemic involvement of the disorder(s) (n=6), alteration of presumed disease inheritance pattern (n=7), changing of prognosis (n=10), medication discontinuation (n=5) or initiation (n=2), and clinical trial education (n=3).

Conclusions: The high diagnostic yield of WES supports its use in pediatric neurology practices. It may also lead to earlier diagnosis, impacting medical management, prognostication, and family planning. WES therefore serves as a critical tool for the child neurologist.

Keywords: Case studies/case series, Genetics

94. Off-label Use of Citrate in the Treatment of Combined D- and L-2-Hydroxyglutaric Aciduria
Objective: Combined D- and L-2-hydroxyglutaric aciduria is a rare inborn error of metabolism typically manifesting as severe neonatal epileptic encephalopathy, developmental delay, respiratory insufficiency and feeding issues. It is an autosomal recessive condition that results from mutations in the SLC25A1 gene which encodes a mitochondrial citrate transporter. We present a 6-month-old term baby girl with delayed milestones, hypotonia and frequent episodes of respiratory distress, resulting in admission to the PICU after an initial evaluation was nondiagnostic. To help identify a diagnosis, she was enrolled in a rapid whole genome sequencing study. Two compound heterozygous missense variants, c.578C>G (p.Ser193Trp), and c.82G>A (p.Ala28Thr), both predicted to be pathogenic, were identified in the SLC25A1 gene. While urine glutaric acid was not elevated, there was an initial mild elevation of 2-OH-glutaric acid that increased over time. Enantiomer testing revealed elevations of both D-2 and L-2 enantiomers in urine and plasma.

Methods: Because this disorder is so rare, there are no standardized protocols for treatment. However, investigators in Germany recently published successful treatment with supplemental citrate. Our patient was treated with supplemental citrate, 1500 mg/kg/day for 4 divided doses.

Results: After 6 weeks of treatment her 2-OH-glutaric acid level fell from 519 (reference value <89) to 159 with clinically improving head control and ptosis.

Conclusions: We present a case where early whole genome sequencing in the PICU allowed for an intervention that is thus far well-tolerated and offers promise for effective therapy in this rare inborn error of metabolism.

Keywords: Case studies/case series, Genetics, Translational/experimental therapeutics

95. Intermediate Size Patient Population Ind For 2-Hydroxypropyl-ß-Cyclodextrin (Hp-ß-Cd) Outpatient Treatment Of Siblings with Neimann-Pick Type C1 (Np-C) and Disparate Rates of Progression: exploration of outcome measures and biomarkers
Berry-Kravis E, O'Keefe J, Hoffmann A, Chin J, Pournardjian T, Porter FD, Algam S, Haldar K, Ory D (Chicago, IL)
Objective: To evaluate biomarkers and clinical markers of response in 14- and 15-year old siblings (non-eligible for concurrent NIH trial) with NP-C treated with intrathecal hydroxypropyl-ß-cyclodextrin (HP-ß-CD) through an intermediate size patient population IND (21CFR 312.315).

Methods: The siblings, compound heterozygotes for mutations in NP-C1 (c10C>T and c2000C>T), are highly discordant for clinical severity: sibling 1 had severe cognitive and motor skills impairment and intractable seizures, sibling 2 had subtle cognitive deterioration and minimal vertical gaze abnormality. The HP-ß-CD treatment protocol was modeled after the NIH phase 1 trial protocol modified for an outpatient setting. An initial LP with saline infusion was followed by infusions every two weeks of HP-ß-CD 200 mg for 6 infusions, followed by dose escalation to 300 mg, then 400 mg. Safety and efficacy outcomes were assessed at baseline and monitored throughout the treatment protocol, including ABRs, swallow evaluations, language/cognitive testing, NP-C rating scale, parent-reported PROMIS, audiology; EKGs, standard laboratory testing, and blood and CSF biomarkers (24-hydroxycholesterol and...
lysozyme). Gait/balance was tracked with a Neurocom system and inertial sensors and eye movements with VNG.

**Results:** There have been no safety issues or clinically significant changes in laboratory parameters. Sibling 1 had resolution of choking, decreased seizures, increased use of language and steadier gait by the 4th infusion. Additional safety data and results of clinical and biomarker outcomes after 10 months of treatment will be presented.

**Conclusions:** These outcomes will help inform treatment timing and dose, safety monitoring, and outcomes for future phase 2/3 trial design.

**Keywords:** Case studies/case series, Genetics, Translational/experimental therapeutics

96. The Challenges of Clinical Trials in Rare Diseases: Lessons from Batten Disease


**Objective:** There are numerous challenges to the conduct of clinical trials for rare diseases: wide geographic dispersal of participants, requisite small sample size, and limited availability of resources to support rare disease trials. We developed novel infrastructure for a clinical trial in Juvenile Batten disease. Our goal was to address the above challenges and reduce travel burden for vulnerable child participants.

**Methods:** We developed a hybrid model combining elements of single- and multi-center trial infrastructure. In this randomized placebo-controlled clinical trial of mycophenolate mofetil, participants completed four visits at the University of Rochester (UR) and four visits with a local physician collaborator. UR was the central site for screening, consent, drug dispensing, and tolerability and efficacy assessments.

**Results:** Eleven of fifteen (73%) local collaborators had no prior experience as an investigator for a clinical trial. Six collaborators (40%) reported support from a study coordinator. Mean start-up time was 9.6 months. Access to study coordination support was associated with shorter site start-up time ($t=4.11$, df=13, $p=0.001$).

**Conclusions:** Our novel design has the potential to improve recruitment, retention, and safety oversight for rare disease clinical trials. However, we found that using this model, we engaged a high proportion of new investigators who lacked research support. Absence of clear regulatory guidelines for site initiation among private practices, requirements related to federally-funded trials, and research training for collaborators, resulted in a lengthy site-initiation process. Structured procedures are needed to ensure timely site startup and training in order to further improve this research model.

**Keywords:** Translational/experimental therapeutics

97. Standardization and Improvement of Management for Concussion Patients: concussion SCAMPS

*An S, Kuenmerle K (Boston, MA)*

**Objective:** To develop an algorithm for clinical management for concussion patients and use clinical decision and outcome data to adjust the algorithm.

**Methods:** Prospective cohort study. Management algorithms and concussion intake questionnaires were distributed and completed at each visit 1) for concussion patients 2) of 6 years old or older 3) between 5/29/12 and 1/21/14 at a tertiary pediatric hospital.

**Results:** 319 patients (144 male) were enrolled. 16% of patients are 6–10 years old, 55% are 11–15 years old and 27% are 16 years old or older. Based on the post-concussion symptom score, 214 (67%) have low total score of $<50$ out of 150 and 104 (33%) have high total score of $>50$. At an initial visit, 100% of patients (n=3) with abnormal neurological exam were requested to obtain MRI.
With and without abnormal neurological exam, patients (n = 33) received MRI at a visit > = 4 weeks post-concussive event, of which 0 patient presented signs of brain injury confirming the recommendation on the algorithm and 3 had abnormal neurological exam. During the first phase, the actions taken by clinicians for patients seen within and after 4 weeks were similar, except for a decrease in frequency of providing education (96% vs. 57%), recommending physical and cognitive test (67% vs. 17%) and providing symptomatic treatment (73% vs. 17%). The latter two were removed from algorithm accordingly.

Conclusions: The data support some recommendations while prompting to edit others. Further analysis is required to understand the impact of care provided.

Keywords: Headache/Migraine

98. Utility of Continuous EEG Monitoring in Children with Suspected Nonaccidental Traumatic Brain Injury
Carpenter JL, Dean N, Bansal S, Kebede T (Washington, DC)
Objective: We aimed to determine the utility of EEG monitoring in children with suspected non accidental traumatic brain injury for the detection of electrographic seizures.

Methods: We identified 54 children, aged 4 weeks to 28 months, with suspected NAT brain injury admitted to a single center PICU from June 2008 to March 2014 from a prospective Neurocritical Care database. Data from their course was supplemented with a retrospective review of the record.

Results: Fifty four consecutive patients with NAT were identified of which 44 underwent continuous EEG monitoring. All but 1 patient received seizure prophylaxis per institutional pathway guidelines. Twenty nine patients (53%) developed acute symptomatic seizures. Of the children monitored with EEG (n = 44), 47% had nonconvulsive seizures and 14% had only nonconvulsive seizures. Of the children with seizures (n = 29), 72% had nonconvulsive seizures. Patients with NAT and associated hypoxic-ischemic injury (n = 21) had a high rate of seizures 76% of which all had nonconvulsive seizures identified on EEG.

Conclusions: Continuous EEG monitoring is useful in identifying and characterizing acute symptomatic seizures in patients with nonaccidental traumatic brain injury. The high rate of nonconvulsive seizures suggests routine monitoring of this population with continuous EEG is reasonable.

Keywords: Epilepsy and other paroxysmal disorders

Choe MC, Zeiger M, Fischer J, Yudovin S, McArthur D, Giza CC (Los Angeles, CA)
Objective: 1.7 million people sustain traumatic brain injuries in the US annually. Historically, injury severity is determined by Glasgow Coma Scale (GCS), with mild TBI (mTBI) defined as GCS>12, moderate GCS 9–12, and severe GCS<8. The term "complicated mild" has been suggested for those traumatic brain injuries with GCS 13–15 and intracranial findings on acute imaging, excluding non-displaced fractures. We aimed to determine whether demographics and outcomes of complicated mTBI patients differ significantly from those with moderate and/or mild injuries.

Methods: Data was prospectively collected from 399 individuals 0–22yrs of age presenting to clinic with TBI. Statistical analyses was performed using R version 2.15.1.

Results: 214 patients had mTBI (53.7%), 73 complicated mTBI (18.3%), 56 (14.0%) moderate, and 56 (14.0%) severe. Gender was not significantly different between the groups. However, mean age at injury was significantly different between complicated mild (8.0yrs) and mTBI groups (13.9yrs, p<0.001), but not between complicated mild and moderate (7.1yrs) groups. Those with mild injuries were 11.3x (CI 5.25, 28.33) more likely to have post-traumatic headache (PTHA), but there was no significant difference in post-traumatic seizure incidence. Conversely, patients with complicated mild injuries did not differ significantly in PTHA or seizure incidence from those with moderate injuries.

Conclusions: Whereas complicated mild TBIs are characterized by GCS identical to mTBI, demographics and outcomes may be more similar to moderate injuries. Continued investigation may elucidate other significant differences in outcomes, and help to determine whether complicated mild injuries warrant their own categorization.

Keywords: Headache/Migraine

100. Topiramate as Migraine Prophylaxis in Pediatric Patients: results of an integrated analysis
Ford L, Shi Y, Shalayda K, Maniipitsipalk P (Raritan,NJ)
Objective: To assess overall treatment effect of topiramate as prophylaxis for migraine in pediatric patients from five randomized double-blind placebo-controlled studies in an integrated efficacy and safety analysis.

Methods: 309 pediatric patients (6–17 years old) from studies TOPMAT-MIG-3006 (N = 103), age 12–17 years, fixed-dosed topiramate 50–, 100 mg/day [n = 70], or placebo), CAPSS-122 (N = 157), age 6–15 years, flexibly-dosed topiramate 2–3 mg/kg/day [n = 108], or placebo), and subgroup of adolescents (N = 49), age 12–17 years from TOPMAT-MIGR-001/002/003 (adult and pediatric) (N = 1505). TOPMAT-MIGR-001 and TOPMAT-MIGR-002 were fixed-dosed topiramate 50–, 100–, 200 mg/day, or placebo. TOPMAT-MIGR-003 was fixed-dosed topiramate 100–, 200 mg/day, placebo, or propranolol 160 mg/day).

Results: Key efficacy endpoints: 1) percent reduction in average monthly migraine attack rate (baseline to last of 12-week double-blind phase); TOPMAT-MIG-3006: 100 mg/day group (72%) was significantly (p = 0.0164) efficacious versus placebo (44%);50 mg/day (45%); CAPSS-122, no significant effect of topiramate versus placebo (58% versus 48%); TOPMAT-MIGR-001/002/003: trend in 100 mg/day group (72%) was significantly (p = 0.0164) efficacious versus placebo (44%);50 mg/day (45%); CAPSS-122, no significant effect of topiramate versus placebo (58% versus 48%); TOPMAT-MIGR-001/002/003: trend in 100 mg/day-treated versus placebo (75% versus 37%). 2) 50% reduction in responder rate: TOPMAT-MIG-3006: topiramate 100 mg/day group (83%) had significantly (p = 0.0048) higher percentage of responders versus placebo (45%); 50 mg/day (46% [p = 1.000]); no significant effect
for topiramate versus placebo in CAPSS-122 (56% versus 49%) or TOPMAT-MIGR-001/002/003 (69% versus 33%). Safety profile was consistent with established topiramate safety profile; most common treatment-emergent adverse events were influenza-like symptoms, language problems, and paresthesia.

Conclusions: Overall, a significant therapeutic benefit of topiramate for migraine prophylaxis in adolescents (12–17 years) was demonstrated. Most consistent results occurred with topiramate 100 mg/day total dosage which was safe and well-tolerated.

Keywords: Headache/Migraine

101. Early MRI Findings and 1-Year Outcomes in Pediatric Complicated Mild TBI
Holshouser B, Pivonka-Jones J, Tong K, Ghosh N, Randquist M, Ashwal S (Loma Linda, CA)

Objectives: We present MRI findings on a subgroup of pediatric TBI patients who had CT evidence of intracranial hemorrhage despite “mild” GCS scores, and their relation to one-year neurologic and neuropsychological outcomes.

Methods: Patients (4–18 years) were enrolled if they sustained a moderate/severe TBI (GCS score <13 or intracranial hemorrhage on CT). Patients underwent MRI (3T), acutely (6–17 days), including SWI, MRS and DTI. The number/volume of hemorrhagic lesions, regional DTI metrics and MRS ratios were compared to neurologic (PCPCS) and neuropsychological outcomes at 12 months, specifically general measures of memory (Children’s Memory Scale), attention (TEACH G score), and intelligence (WASI: Full Scale IQ).

Results: 22 children had “mild” GCS scores of 15 (n=17), 14 (n=3) or 13 (n=2). They were injured in vehicle/bike accidents (9), falls (8), sports-related injuries (4), or assaulted (1). The average number (32) and volume (2.5 cc) of hemorrhagic lesions were lower than the larger group of 52 patients (87 lesions, 12.0 cc hemorrhage) and did not show correlation with neuropsychological measures at 1-year. ADC values in the deep hemispheric regions (BG, THAL, CC) and global NAA/Cr ratios were significantly different in these children, compared to control subjects. All 22 patients had good neurologic outcomes. FA values in subcortical white matter were significantly correlated with attention scores at one-year.

Conclusions: There are limitations to the GCS score, particularly with regards to TBI patients with milder injuries. These children can have imaging abnormalities that correlate with neuropsychological measures at one-year follow-up.

Support: NIH/NINDS: R01-NS054001

Keywords: Neuroimaging

102. Report Of Longitudinal MRS and DTI after Moderate/Severe Pediatric TBI
Holshouser B, Ghosh N, Tong K, Pivonka-Jones J, Randquist M, Ashwal S (Loma Linda, CA)

Objective: We present our findings on a prospective study of MRS and DTI measures in pediatric TBI patients acutely and at 1-year after injury.

Methods: Patients (4 to 18y), were enrolled if they sustained a moderate/severe TBI (GCS <13 or intracranial injury on CT). Patients underwent 3T MRI with DTI and proton MRS acutely (6–17 days post TBI) and at 1 year. TBI and control regional DTI metrics (FA, ADC, AD, RD) and MRS ratios (NAA/Cr, NAA/Cho, Cho/Cr) at both time points were compared and correlated to neurologic (PCPCS) and 12-month neuropsychological outcomes (general measures of memory, Children’s Memory Scale; attention, TEACH G score; and intelligence, WASI: FSIQ).

Results: We studied 58 children (43M/15F); age 12.2 ±3.5 yrs (5.2–17.9 yrs); initial GCS (Mild=23; Moderate=8; Severe=27) and 54 control children; mean age 12.1 ±3.3 yrs (5.5–17.4 yrs). Initial studies were done at 11.5 ±3.4 days after injury and follow-up studies were done at 12.2 ±3.5 months for TBI patients and 12.1 ±3.3 months for controls. Total and regional NAA/Cr ratios and total, corpuscallosal, parietal and temporal white matter mean FA and AD measures were 1) significantly reduced initially compared to controls; 2) significantly correlated with neurologic outcomes, FSIQ and General Memory scores; and 3) did not recover in patients with initial severe injury at 1 year.

Conclusions: Metabolite and DTI measures that remain reduced at one year in patients with severe injury suggest that neuronal loss and axonal injury contribute to long term intellectual and memory deficits

Support: NIH/NINDS:R01-NS054001

Keywords: Neuroimaging

103. Unusual (and not-so-unusual) Sequelae of Pediatric Traumatic Brain Injury
Ng AS, Choe MC, Yudovin S, Fischer J, McArthur DL, Giza CC (Los Angeles, CA)

Objective: According to the CDC, an estimated 1.7 million people sustain a traumatic brain injury (TBI) annually. Pediatric TBI causes disability and death and accounts for almost 500,000 emergency department visits annually. We report demographic data and unusual neurologic sequelae following TBI from a tertiary care center.

Methods: A retrospective, cross-sectional chart review on 393 consented patients seen at the UCLA Pediatric TBI Clinic between May 2001 to February 2014 with age at TBI ranging from birth to 19 years was conducted. Data regarding gender, severity, mechanism, and sequelae was collected.

Results: Average age at injury was 10.47 years. Male:Female ratio was 1.89. Leading mechanisms of injury were falls (39.2%), blunt (37.7%), motor vehicle accidents (16.0%), and abusive head trauma (7.1%). Mechanism of injury was related to severity (p<0.01) with most blunt mild and AHT moderate/severe. Age at injury and severity have an inverse relationship (p<0.001).
This registry reports clinical characteristics for 68 cases of new-onset post-traumatic seizures (including 4 - infantile spasms, 2 - primary generalized epilepsy), 66 cases of new-onset post-traumatic migraines, 8 cases of post-traumatic cranial neuropathies (CN3 [2], CN4 [1], CN7 [5], CN12 [1]), 6 cases of dysautonomia, and 4 cases of new-onset tic disorders.

CONCLUSION: Pediatric TBI is a common problem with a myriad of sequelae. Clinicians providing these patients specialty care should be comfortable managing common sequelae such as post-traumatic seizures and migraines, but also be aware of unusual sequelae.

**Keywords:** Case studies/case series, Epilepsy and other paroxysmal disorders, Headache/Migraine

105. The Association between Migraine and Congenital Heart Disease

Zhu C, Friedman NR (Cleveland, OH)

**Objective:** The goal of this study is to identify the prevalence of migraine headaches in children with congenital heart disease.

**Methods:** Prospective study - consecutive cohort of children ages 5–18 in the general pediatric outpatient clinics (controls) and pediatric cardiology clinics. All patients and parents completed a headache diagnostic questionnaire. IRB #13–447

**Results:** 125 patients with CHD and 139 controls. Migraine was classified both by expert opinion and by strict ICHD-2 classification. Migraines were classified as “definite” or “probable” based on standardized criteria. Four comparisons were made between CHD patients and controls with p-values determined using Fischer’s exact test. For migraine only using the ICHD-2 criteria, the p-value was 0.62. For migraine only using the expert classification, the p-value was 0.31. For migraine + probable migraine using the ICHD-2 criteria, the p-value was 0.52. For migraine + probable migraine using the expert classification, the p-value was significant at 0.003. Four comparisons were also done for the CHD group against national controls. The incidence of migraines in national control populations is estimated at 7%. P-values for these comparisons was done through the use of one sample test of binomial proportions against national controls of 7%. Each comparison was found to be significant with p-values of <0.001.

**Conclusions:** Migraine headaches are a significant and unrecognized morbidity in children with CHD. Further studies looking at optimal treatments and drug safety in this unique population is warranted.

**Keywords:** Headache/Migraine

106. Maternal HIV is a Risk Factor for Pediatric Cerebral Palsy in Botswana

Bearden DR, Karuna E, Monokwu N B (Philadelphia, PA)

**Objective:** To determine if maternal Human Immunodeficiency Virus (HIV) is a risk factor for cerebral palsy in children in Botswana

**Background:** Cerebral palsy is common among children in the developing world, but there are few published studies that address potentially preventable risk factors. Maternal HIV is an important candidate risk factor that may be a major contributor to cerebral palsy in low resource settings and is potentially modifiable through antiretroviral therapy.

**Methods:** We conducted a case control study among HIV uninfected children in Gaborone, Botswana comparing 55 cases of cerebral palsy to 55 unaffected controls and examined the contribution of maternal HIV and other potential risk factors.

**Results:** Maternal HIV is significantly associated with pediatric cerebral palsy (OR 3.5, 95% CI 1.2–10.5, p=0.3).

**Conclusions:** Further studies are necessary to confirm these findings and delineate the mechanisms by which maternal HIV may contribute to cerebral palsy.

**Keywords:** Infections/Neuroimmunology, Neonatal neurology
107. Dysautonomia is Associated with Increased Morbidity and Prolonged Hospitalization in Children with Encephalitis
Farias-Moeller R, Wells EM, Carpenter JL (Washington, DC)

Objective: Dysautonomia in children with neurologic disease is understudied. We sought to investigate risk factors for dysautonomia and whether it was associated with increased morbidity in patients with encephalitis.

Methods: Patients with encephalitis were identified from a single center, prospective pediatric Neurocritical care database. Dysautonomia was defined as lability in heart rate and/or blood pressure, hyperthermia, tachypnea and/or agitation without other cause. Statistical analysis was performed using t-test and chi-square to compare outcomes (length of ICU stay, hospital stay, need for inpatient rehabilitation and mortality), and risk factors (demographics, cause of encephalitis, laboratory findings and radiographic variables) between patients with and without dysautonomia.

Results: 69 patients with encephalitis were identified and 58 met inclusion criteria. Dysautonomia was found in 23/58 (40%) children. Mean length of ICU stay for encephalitis with dysautonomia was 23.5 days (range 1–87) compared to 7.3 days (range 1–38) without dysautonomia (p<0.001). Mean length of hospitalization with dysautonomia was 37.3 days (range 6–87) compared to 17.6 days (range 2–69) without (p=0.001). The groups showed no differences in mortality or need for inpatient rehabilitation. Risk factor analysis found no differences in age, gender, or cause of encephalitis. Radiographic abnormalities of the diencephalon or brainstem occurred in 6/23 (26%) children with encephalitis with dysautonomia compared to 4/35 (11.4%) without dysautonomia. (p=0.15).

Conclusions: Dysautonomia is associated with increased duration of ICU and overall hospitalization in patients with encephalitis. Further research should evaluate causes of dysautonomia in critically ill patients with encephalitis and means to decrease morbidity associated with this condition.

Keywords: Infections/Neuroimmunology

<table>
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<td>Died, n (%)</td>
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108. HIV Related Cognitive Difficulty in Vertically Transmitted HIV in Myanmar
Mar SS, Meddles K, Heapi J, Isbell S, Sirivichayakul S, Linn K (St. Louis, MO)

Objective: To determine the impact of HIV on neurocognition in children with perinatally-acquired HIV in Myanmar by using a demographically-matched sample of seronegative control subjects

Background: The majority of neurocognitive studies in HIV-infected children have been performed in the United States and Europe. The outcome of these studies is not directly applicable to resource poor countries where perinatal HIV infection is most prevalent. Myanmar has one of the highest HIV-1 prevalence rates in Southeast Asia. We hypothesized that HIV+ orphans would perform significantly worse on cognitive indices compared to HIV- orphans from the same socioeconomic environment.

Methods: A series of neurocognitive tests measuring learning, attention, psychomotor speed and motor speed were administered to 22 children with perinatally-acquired HIV+ and 22 HIV- children (8 to 14 years old) from orphanages in Yangon, Myanmar. Most children with HIV were started on ART after 18 months of age.

Results: Comparison of groups using independent t-tests indicates that the HIV+ children perform more poorly than HIV- children across all tests including verbal earning Test-Revised and recall tests, digits forward, digits backwards, digit symbols, letter-number sequencing, trails A, semantic fluency, and finger tapping.

Conclusions: HIV+ children in Myanmar survive with significant cognitive problems. Understanding the viral and host determinants, timing of the treatment, and the choice of ART on cognition may be important in the treatment of HIV in children.

Keywords: Infections/Neuroimmunology

109. Cerebellar and Cortical Abnormalities in Paediatric Opsoclonus-Myoclonus Syndrome

Objective: Paediatric Opsoclonus-myoclonus syndrome (OMS) is a poorly understood condition with long term cognitive and motor sequelae. Neuroimaging in the acute phase is normal. Previous studies have indicated volume loss in cerebellar vermis in the chronic phase. This does not fully explain the cognitive problems. Understanding the viral and host determinants, timing of the treatment, and the choice of ART on cognition may be important in the treatment of HIV in children.

Methods: Nine OMS patients and ten controls participated in a magnetic resonance imaging (MRI) session to acquire T1-weighted structural images, diffusion-weighted images and, magnetic resonance spectroscopy. Voxel-based morphometry (VBM) was used to determine changes in grey matter volume, tract-based spatial statistics (TBSS) was used to analyse differences in white matter integrity and analysis of cortical thickness across visual and motor cortices was also undertaken.

Results: Whole-brain analysis indicated that cerebellar grey matter was significantly reduced in OMS patients, particularly in the vermis and the superior cerebellum. A region-of-interest analysis indicated significantly lower cerebellar grey matter volume, particularly in patients with greatest OMS scores. Diffusion-weighted images did not show effects at a whole brain level, but all major cerebellar tracts showed increased mean diffusivity when analysis was restricted to the cerebellum. There was highly significant reduction in cortical thickness across motor and visual areas in OMS group, indicating involvement beyond the cerebellum.

Conclusions: There is considerable cerebellar atrophy, particularly in the vermis and flocculonodular lobes. Symptomatic OMS patients showed greater cerebellar atrophy than the asymptomatic group. Beyond the cerebellum, there was decrease in cortical thickness across motor and visual regions.

Keywords: Infections/Neuroimmunology, Neuroimaging, Neuromuscular disorders, Stroke

110. Dopamine Promotes Plasticity in Striatal Nicotinic Receptors
Bamford NS, Ross JC (Seattle, WA)

Objective: Excitatory glutamatergic inputs from most areas of the cerebral cortex form synapses on striatal spiny projection neurons (SPNs). This pathway promotes cue-dependent behaviors and motor learning and is modulated by several neurotransmitters, including dopamine, acetylcholine, and γ-aminobutyric acid (GABA). Episodic increases in striatal dopamine as modeled by repeated amphetamine are known to promote long-lasting plasticity in corticostriatal function that is dependent on acetylcholine, but the synaptic mechanism remains unclear. We hypothesized that this corticostriatal plasticity is dependent on de-sensitization of striatal nicotinic receptors.

Methods: We used electrophysiology in brain slices from saline- and amphetamine-treated (2 mg/kg/d, 5 d) genetically-modified mice to determine how the reported reduction in acetylcholine availability following the use of amphetamine can modify nicotinic receptors on GABA interneurons and SPNs. We used Lhx6-EGFP (n=5) mice with fluorescently labeled GABA interneurons and targeted SPNs using enhanced green fluorescent protein (EGFP) bacterial artificial chromosome mice (n=8) with fluorescently-labeled D1 and D2 receptor-expressing cells.

Results: In saline-exposed mice, physiological concentrations of nicotine excited both GABA interneurons and SPNs and desensitized the nicotine receptor (Fig. A-C). In amphetamine-treated mice however, nicotine had little effect on SPNs and GABA interneurons and nicotinic receptor desensitization was more prominent (Fig. D-E).

Conclusions: These data demonstrate that repeated dopamine can produce down-stream plasticity in corticostriatal activity through striatal nicotinic receptors. Given the dependence of cue-dependent behaviors on striatal acetylcholine, this mechanism may encode critical aspects of normal striatal function and participate in neurodevelopmental disorders of childhood, including attention deficit and Tourette syndrome.

Keywords: Translational/experimental therapeutics

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111. Targeting HCN Channels on Cholinergic Interneurons in Parkinsonism

Bamford NS, Darvas M (Seattle, WA)

Objective: Parkinsonism in children is caused by a disruption in dopamine signalling. The lack of dopamine alters striatal acetylcholine release, which may contribute to the motor disability by promoting dyskinesias and impulse control disorders during treatment. We hypothesized that dopamine depletion would modify the activity of striatal acetylcholine-releasing interneurons (ACh-I).

Methods: We used electrophysiological and biochemical techniques in novel genetically-modified mice to determine how dopamine depletion modifies hyperpolarization-activated cation (HCN) channels that encode pacemaking activity in ACh-I.

Results: We created a model for Parkinsonism using Slc6a3DTR/+ (DAT-DTR) mice that expresses the diphtheria toxin receptor in dopamine neurons. The selective ablation of dopamine neurons by diphtheria toxin (50 mg/kg, i.m.) at 6 days reduced striatal dopamine to ~10% of normal, decreased motor function, and promoted dyskinesias following L-dopa (50 mg/kg i.p.). ACh-I from DAT-DTR mice demonstrated a reduction in HCN channel currents and autonomous firing rates; this was not found in control mice that received the dopamine-depleter reserpine (5 mg/kg i.p.) 12 hr prior to sacrifice. The depression in ACh-I activity was found in virally-rescued DbhTh/++;Ths/fs mice, where insertion of a stop cassette in front of the Th gene reduced dopamine to ~0.5% of normal and injection of canine adenovirus expressing Cre recombinase reactivated the Th alleles, thereby restoring dopamine.

Conclusions: Reduction in HCN channel-dependent pacemaking characterizes late-onset plasticity in ACh-I in dopamine deficiency. This plasticity was resistant to dopamine restoration in vivo, suggesting that targeted manipulation of HCN channels will improve motor function in Parkinsonism and reduce the untoward effects of pharmacotherapy.

Keywords: Translational/experimental therapeutics

112. 35-Year Experience with Tourette Syndrome at a Single Center with Follow-up into Adulthood

Byler DL, Chan, L, Ahmad, S, Brown, A, Berlin, C (Hershey, PA)

Objective: A retrospective analysis of a 35 year single center experience with pediatric tics and Tourette syndrome was conducted. Patient characteristics, treatment and comorbid conditions over time were reviewed. Follow-up contact
was made to determine clinical and social outcomes of these patients as adults.

Methods: Charts from 482 patients seen from 1972 to 2007 were reviewed. Historical features and clinical course was documented. Follow-up surveys were mailed to last known address and 83 patients responded (17%). Response rate was affected by long time interval from last visit; contact information was most often the address of patient as a child.

Results: Population was predominantly male (84%). Mean tic onset was at 6.6 years. Multiple motor tics were seen at initial visit in 83% and more than 50% had comorbidities noted on first visit. Follow-up showed positive clinical and social outcomes in 73/83 survey responses. Of those patients indicating a poor outcome, the mean educational level was lower and number of current psychiatric comorbid conditions higher. Tic burden was not the main determining factor.

Conclusions: Patient characteristics did not change significantly over time. 44% required only one visit and most less than 10 visits. Outcome appeared affected more by comorbidities such as ADHD, OCD and learning disabilities rather than tic burden as adults. Access to caregivers with knowledge about TS was a problem for adult patients. A shortage of specialists may be in part addressed by interested general pediatricians as was the case in this practice.

Keywords: Case studies/case series

113. Orthostatic Intolerance is an Under-Recognized and Treatable Cause of Astasia Abasia in Adolescents

Jarjour IT, Needham JM, Jarjour LK (Houston, TX)

Objectives: Inability to stand and walk in the absence of other neurologic abnormalities (astasia abasia, AA) leads often to extensive testing and diagnosis of psychogenic gait disorder. Orthostatic leg weakness as a potentially treatable cause of AA has not been reported. We describe clinical and diagnostic findings in adolescents with AA and orthostatic intolerance (OI).

Methods: We reviewed the medical records of patients presenting to a Tertiary Care Hospital with leg weakness and difficulty walking and standing, normal strength while supine, normal deep tendon and plantar reflexes, and no focal neurologic deficits. We assessed orthostatic vital signs using standing and tilt tests.

Results: 11 patients met inclusion criteria (8 females; age 13.9±2 years). Mean follow up in 9 was 10 months. Initial diagnosis was psychogenic gait disorder (5), OI (4), and probable transverse myelitis (2). Orthostatic symptoms included: bilateral leg weakness (11), lightheadedness (7), headache (5), leg numbness (4), blurred vision (4), syncope (3), and leg pain (3). Autonomic symptoms included: voiding dysfunction (3) and decreased sweating (1). Orthostatic vital signs showed postural tachycardia (7), and hypotension (3). Brain MRI showed normal or incidental findings (10/10). Spinal MRI was abnormal in 1/9 (focal myelitis). LP was abnormal in 1/5 (aseptic meningitis). Treatment included fluids and salt intake (11), fludrocortisone (4), iron (9), vitamin D (6), and antidepressants (2). At last follow up, 7/9 (78%) patients had full recovery.

Conclusions: Orthostatic leg weakness is a potentially treatable, under-recognized cause of AA. Prompt recognition of OI-related AA prevents unnecessary testing and may lead to early effective treatment.

Keywords: Case studies/case series, Neuromuscular disorders

114. Comparison of the Effect of Robotic Reinforced Movement Learning Technology on the Development of Prone Locomotion in Infants with and without Risk for Cerebral Palsy

Kolobe THA, Fagg AH, Ng YT (Oklahoma City, OK)

Objective: To determine whether an integration of robotic and sensor technologies self-initiated prone progression crawler (SIPPC), would improve prone locomotion in infants with cerebral palsy (CP).

Methods: Repeated measures experimental design with 3 groups: experimental group (SIPPC-E), and 2 control groups (SIPPC-T and SIPPC-C). Measures were collected twice a week for 12 weeks. Participants were 27 infants, 4–6.6 months old, with or without risk for CP. Inclusion criteria: A TIMP z-score >-1.0 for controls and z-score<-1, a confirmed diagnosis of CP, or positive MRI results for study patients. The SIPPC consists of device-based wheel position sensors and limb-mounted inertial measurement units (IMUs) that measure movement performance and can be used to trigger locomotion assistance. The patients were randomly assigned to the groups.

Results: The mean distance for all groups increased over the 12 week period with the largest increase in the SIPPC-T group (p=.001) followed by the SIPPC-C group (p=.01). The mean increase for the SIPPC-C group was not statistically significant (p=.067). Correlation coefficients between the movement patterns and the distance traveled ranged from r=.71-.94 for the SIPPC-T, r=.55-.83 for the SIPPC-E, and r=.32-.56 for the SIPPC-C group, respectively.

Conclusions: The differences in the mean distance travelled by the infants in the SIPPC-E compared to those in the SIPPC-C group suggest that infants as young as 4.5 - 6 months of age are capable of using reinforcement offered by robotic sensors such as the SIPPC to learn a complex and high dimensional movement like prone locomotion.

Keywords: Neuroimaging, Translational/experimental therapeutics

115. Abstract Withdrawn

116. Novel Mutations in TITF1 Cause Benign Hereditary Chorea, Hypothyroidism and Neonatal Respiratory Distress Syndrome

Meijer IA, Michaud J, Tran L, Rosignol E, van Vliet G, Deladèvre J, Chouinard S, Bernard G (Montreal, QB)

Objective: Benign hereditary chorea (BHC) is characterized by hypotonia, motor delay and a childhood onset non-progressive movement disorder. BHC is the neurological
presentation of the brain-thyroid-lung syndrome, a highly penetrant autosomal dominant syndrome caused by mutations in the TITF1 gene (OMIM610978). Patients can also present with a neonatal respiratory distress syndrome and/or congenital hypothyroidism. The aim of this study was to determine the genetic cause of a shared non-progressive movement disorder in a pediatric cohort.

Methods: Five French-Canadian patients with a non-progressive movement disorder, pulmonary symptoms and/or hypothyroidism were assessed by a movement disorder expert. The sixth patient presented with congenital hypothyroidism and severe neonatal respiratory distress. In the patients presenting with movement disorder, extensive metabolic testing was performed followed by comparative genomic hybridization analysis. The TITF1 gene was assessed by sequencing and multiplex PCR amplification in all patients. Variants were analyzed for pathogenicity using functional prediction tools, conservation and segregation analysis.

Results: TITF1 mutations were identified in 4 out of the 6 patients and include a novel frameshift (p.Tyr116-LeufsX323) and three missense mutations (p.Pro291Arg, p.Arg209Pro, p.Asn241Asp).

Conclusions: We report 3 novel TITF1 mutations causing a spectrum of the brain-thyroid-lung syndrome. The frameshift mutation led to a severe neonatal pulmonary phenotype. Interestingly, there was no common French-Canadian mutation. The absence of mutations in two patients suggests genetic heterogeneity or unidentified mutations in upstream regulatory elements. This study further demonstrates the phenotypic variability of TITF1 mutations and underlines that TITF1 should be considered in children presenting with movement disorder in association with thyroid or pulmonary dysfunction.

Keywords: Case studies/case series, Genetics

117. Improving Developmental and Behavioral Outcome of Children with Opsoclonus-Myoclonus Syndrome (OMS)

Mitchell WG, Wooten AA, O'Neil SH (Los Angeles, CA)

Objective: Children with OMS, with or without neuroblastoma (NB) frequently have long-term cognitive, behavioral and motor deficits1–4. Experience and literature has led us to increase immunosuppression, particularly adding rituximab5. We studied a new group of OMS patients, aggressively treated, to see if cognitive and behavioral outcomes were improved.

Methods: 15 families consented to participate. We reviewed records for OMS etiology (NB vs no NB), initial and subsequent treatment, relapses, and most recent status. Study visit included neurological examinations, brief developmental/cognitive testing, motor assessment. Parents completed ABAS-II and CBCL. We compared current subjects to 26 previously reported OMS subjects2. See table for subscales and ages.

Results: 14 subjects completed testing and questionnaires. Symptom onset was at 10–35 months (median=17). Interval from onset to diagnosis: 2 days-15 months. Nine had NB, all non-N-myc amplified (7 favorable histology, 2 unfavorable histology). Initially, 12 received corticotropin (Acthar®), 3 oral steroids. All received IVIg (2 grams/kg usually monthly), 10 rituximab, 5 cyclophosphamide, 1 monthly bolus intravenous dexamethasone. Outcome: Current subjects: age at testing ranged from 2.5–10.3 years. Adaptive Behavior (11 subjects), mean 93.5; Estimated IQ/DQ mean 93.5; Motor scale: mean 92.8. Comparison to previously reported OMS subjects showed improved outcomes: Age range was similar. ABI and IQ/DQ were significantly higher (P<.0001) in new subjects. (figures 1 and 2).

Conclusion: Cognitive and behavioral outcomes for children with OMS have significantly improved with more aggressive immunosuppression, primarily including rituximab. Currently, most OMS survivors are functioning at or near normal.

References:
TABLE . Measures used:

<table>
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<th>Measure Used</th>
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<th>New Group</th>
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<tr>
<td>IQ or DQ estimate</td>
<td>Up to 42 months: Bayley Scales of Infant Development II, Mental Development Index</td>
<td>Up to age 4 years: Bayley III, Cognitive Scale</td>
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<td>3.5 to 6 years: WPPSI-R</td>
<td>Age 5 and above: Adaptive Behavior Assessment System, second edition (ABAS-II), ages 5–21 scale</td>
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<td>6 years and up: WISC-III</td>
<td>Motor Scores</td>
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<tr>
<td>Average of Verbal IQ and (Nonverbal) Performance IQ</td>
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<td>Old Group</td>
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<td></td>
<td>Old Group</td>
<td>New Group</td>
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<td>Adaptive Behavior</td>
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<td>Up to age 5 years: Adaptive Behavior Assessment System, second edition (ABAS-II), 0–5 year scale</td>
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<td>4 years to 5 years, 11 months: WPPSI-IV</td>
<td>Age 5 and above: Adaptive Behavior Assessment System, second edition (ABAS-II), ages 5–21 scale</td>
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<td></td>
<td>6 years and up: WISC-IV</td>
<td>Motor Scores</td>
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<tr>
<td></td>
<td>Average of nonverbal (Matrix Reasoning) and verbal (Similarities) subtests.</td>
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<tr>
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<td>Adaptive Behavior</td>
<td>New Group</td>
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<td>New Group</td>
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<td>Vineland Adaptive Behavior Scale</td>
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<td>Under age 5 years: Bayley Scales of Infant and Toddler Development II, motor scale</td>
<td>Age 5 and above: Adaptive Behavior Assessment System, second edition (ABAS-II), ages 5–21 scale</td>
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<td></td>
<td>Age 5 years and above: Bruininks-Oseretsky Test of Motor Proficiency</td>
<td>Motor Scores</td>
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<td>New Group</td>
<td>Old Group</td>
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<td></td>
<td>Under age 4 years, Motor Scale of Bayley III</td>
<td>New Group</td>
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<td>Age 4 and above: Bruininks-Oseretsky Test of Motor Proficiency 2, brief form</td>
<td>Under age 4 years, Motor Scale of Bayley III</td>
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<td>Age 4 and above: Bruininks-Oseretsky Test of Motor Proficiency 2, brief form</td>
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118. Missense Mutations of DST (Encoding Dystonin) Cause Neonatal Feeding Difficulty, Hypotonia, Dystonia, Choreoathetosis, and Hypoalgesia


Homozygous mutation of the DST gene was reported as causing a lethal form of hereditary sensory and autonomic neuropathy (HSAN6) in a large consanguineous family of Ashkenazi Jewish descent (1). A spontaneous mutation in the mouse homologue, dst, causes dystonia musculorum, characterized by sensory neuropathy, dysautonomia, and contractures secondary to cytoskeletal disorganization (2).

The proband is a 4.5 year-old male who was born normally at term. He had a poor suck. He was hospitalized at 1 week with poor feeding, dehydration and hypothermia. He did not cry with needle sticks. At 3 weeks, he developed urinary retention and had a distended bladder. He required a feeding gastrostomy and intermittent bladder catheterization. At 2 months, his muscle tone was low, and he was described as having "facial diplegia". His cognitive development was normal, and he made slow but steady progress in his motor skills. Findings at age 2: lack of facial expression, absent corneal reflex, poor head control and axial hypotonia, constant athetoid movement, variable tone in limbs with dystonia, and hypoactive tendon reflexes. Studies including MRI of the brain and spine, array CGH, EMG/NCV, CSF studies, metabolic screens, and muscle biopsy did not lead to a specific diagnosis. A mitochondrial disorder was suspected.

Proband and parents were studied by family-based whole exome sequencing. Phased, compound heterozygous variants (p.Lys1270Arg – maternal; p.Ser365Cys - paternal) were identified in the DST gene. These missense mutations are associated with a milder phenotype than previously reported with HSAN6.

Keywords: Case studies/case series, Genetics, Neuromuscular disorders

119. A Novel GNAL Mutation Identified by Whole Exome Sequencing Is Associated With Familial Generalized Chorea

Parnes MS, Stocco AJ (Houston, TX)

Objective: To report a unique case of familial chorea and a likely genetic etiology identified using whole exome sequencing.

Methods: Whole exome sequencing is a relatively new technology that is revolutionizing the way in which physicians diagnose rare genetic diseases. Although there are numerous causes of hereditary chorea, in the absence of clues to a specific diagnosis on history, examination, and/or neuroimaging, the etiology may prove elusive without sophisticated genetic testing. We describe a 6 year-old boy with global developmental delay who was noted at 2 years of age to develop ongoing, random-appearing involuntary movements that interfered with walking. His mother also had onset of chorea in childhood and struggles with impulsivity, and has basal ganglia abnormalities on MRI. The estranged maternal grandfather also was affected with chorea. After an extensive workup was unrevealing, the patient underwent whole exome sequencing.
Results: Whole exome sequencing revealed a novel mutation in the GNAL gene. FISH analysis confirmed the same mutation in his mother. Deleterious mutations in GNAL are known to be the cause of dystonia 25 (DYT25), an autosomal dominant focal dystonia that typically involves the neck and face, but have not previously been described in association with chorea.

Conclusions: Whole exome sequencing has quickly become a powerful tool in determining specific gene defects related to heritable disorders. The use of this and emerging technologies like whole genome sequencing is vital to the identification and, optimistically, the eventual molecular treatment of disorders such as this.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders, Genetics

120. Horizontal Head Titubation in Infants with Joubert Syndrome: a new finding
Poretti A, Christen HJ, Elton LE, Baumgartner M, Korenke GG, Sukhudyan B, Hethey S, Cross E, Steinlin M Boltshauser E (Baltimore, MD)

Objective: Head thrusts are well known in Joubert syndrome (JS) and oculomotor apraxia (OMA). We provide a detailed clinical characterization of head titubation (HT) in 13 children with JS.

Methods: Detailed description of HT as assessed by targeted clinical evaluation and/or analysis of videos.

Results: 13 children with confirmed diagnosis of JS (presence of the molar tooth sign on axial neuroimaging) were included in this study. In 12 out of 13 children, HT was first recognized in the first 2 months of life and decreased in severity until spontaneous resolution. In all children, HT was horizontal, high frequency (about 3 Hz), had a small amplitude (5–10°), was never present during sleep, could not be interrupted by holding the head and did not interfere with the neurodevelopment during infancy. In the majority of children, emotion, anxiety and tiredness were worsening factors for HT. At the last follow-up, OMA with characteristic head thrusts was present in 12 out of 13 children. In all these patients, HT and OMA occurred independently.

Conclusions: HT is a benign, early presentation of JS. HT in hypotonic infants should prompt a careful search for JS. Awareness of its occurrence in JS may avoid unnecessary investigations.

Keywords: Genetics

121. Glutamate and GABA in Children with ADHD and Complex Motor Stereotypies: a 7T 1H MRS study
Singer HS, Mahone EM, Horska A, Ryan M, Wang X, Edden R, Barker PB (Baltimore, MD)

Objective: Motor stereotypes are repetitive, rhythmic, fixed, purposeful but purposeless movements that stop with distraction. Previously thought to be secondary to autism, intellectual disability, or sensory deprivation, complex motor stereotypes (CMS) can also occur in otherwise typically developing children. Existing data suggests that “primary” CMS is a motor control abnormality localized within cortico-striatal-thalamo-cortical pathways. This study evaluated the hypothesis of cortical hyper-excitability (elevated glutamatergic or reduced GABAergic neurotransmission) using single-voxel magnetic resonance spectroscopy to measure brain glutamate (Glu) and GABA concentrations.

Methods: Medication free participants included 24 typically developing children (mean 7.5±1.4 years, 14 girls) and 19 with primary CMS (mean 6.7±1.3 years, 3 girls). MRI/MRS, preceded by 10–20 minutes of mock scanner training, was performed at 7T. Single voxel 1H MRS (TR/TE/TM=3000/14/26 ms, SW=3000 Hz, 2048 datapoints, NS=96) data were acquired in 5–9 ml voxels in the left anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), premotor cortex (PMC) and striatum (STR). Concentration ratios to creatine (Cr) were calculated and linear mixed-effect model analysis was used to examine group differences in metabolite concentrations, controlling for age and sex.

Results: The MRI/MRS protocol (45–60 min) was well-tolerated. GABA/Cr was significantly lower in CMS (age-adjusted mean: 0.19±0.06) than controls (0.24±0.07, p=0.004). The ACC (p=0.009) and STR (p<0.015) showed significant reductions in GABA/Cr. No group differences in Glu/Cr were observed. Figure 1.

Discussion: High-field MRS studies can assist in understanding the pathophysiology of movement disorders and guide the development of pharmacotherapy. Our study suggests that GABA metabolism may be impaired in children with primary complex motor stereotypes.
Conclusions: High-field MRS studies can assist in understanding the pathophysiology of movement disorders and guide the development of pharmacotherapy. Our study suggests that GABA metabolism may be impaired in children with primary complex motor stereotypies.

Keywords: Neuroimaging

122. Anomalous Putamen Development in Children with Primary Complex Motor Stereotypies

Singer HS, Mahone, EM, Crocetti, D, Klene, T, Mostofsky, SH (Baltimore, MD)

Objective: Motor stereotypies are repetitive, rhythmic movements that have a predictable pattern, seem purposeful but serve no obvious function, tend to be prolonged, and stop with distraction. While previously thought to be only associated with intellectual disability, sensory deprivation or autism, complex motor stereotypes (CMS) are now recognized to occur as a more "primary" form in otherwise typically developing children. Neuropsychologically, children with primary CMS show isolated deficits in motor skill development. Findings from animal models suggest that alterations within cortico-striato-thalamo-cortical circuits, more specifically the basal ganglia, may be involved in the pathophysiology of this disorder.

Methods: High-resolution anatomical (MPRAGE) images, acquired at 3.0T, were analyzed in 38 children ages 8–12 years (19 with primary CMS [11 boys] and 19 typically developing controls—matched on age, sex, handedness, and IQ). Cortical regions were delineated and measured using automated methods in Freesurfer; basal ganglia structures were manually delineated.

Results: There were no significant group differences in total cerebral volume (TCV; \( p = 0.64 \)), or in gray or white matter volumes in any lobar or sublobar cortical regions (all \( p > 0.20 \)). After controlling for TCV, the CMS group showed significant reductions in right putamen (\( p = 0.047, \eta^2 = 0.11 \)), and a trend for reduced left putamen volume (\( p = 0.073, \eta^2 = 0.09 \)—both with moderate to large effect sizes. There were no significant group differences in either caudate or globus pallidus volumes bilaterally (all \( p > 0.35 \)).

Conclusions: These findings, in conjunction the observed motor deficits in children with primary CMS, suggest (potentially selective) anomalous development of the habitual (premotor—putamen) circuitry that gives rise to the observed behavioral phenotype.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders

124. Acute Ataxia in Childhood: 10 year experience at a major pediatric referral center

Thakkar KP, Alper G (Pittsburgh, PA)

Objective: To categorize the causes of acute ataxia and characterize post-infectious cerebellar ataxia in the pediatric population of a large, urban medical center.

Methods: We defined patients with "acute ataxia" as those presenting to Neurology within 4 weeks of onset. We used chart review to retrospectively identify all acute ataxia patients seen from 2003–2013. Patients diagnosed with brain tumors, genetic or metabolic diseases were excluded.

Results: We identified 119 children with acute ataxia. Post-infectious cerebellar ataxia was the most common diagnosis in 65% (77/119), followed by drug intoxication (\( n = 10 \)), opsoclonus-myoclonus ataxia syndrome (\( n = 10 \)), episodic ataxia (\( n = 4 \)), acute cerebellitis (\( n = 3 \)), cerebellar stroke (\( n = 2 \)), ADEM (\( n = 2 \)), meningitis (\( n = 1 \)), cerebral vein thrombosis (\( n = 1 \)), Miller-Fisher syndrome (\( n = 1 \)) and concussion (\( n = 1 \)). Seven patients had no definite diagnosis.

Conclusions: Among the 77 patients with post-infectious cerebellar ataxia, 54% were male and 46% were female. Most (82%) were 1–6 years old, and most (84%) had a history of antecedent viral illness. CSF pleocytosis was present in 40% of patients; all had normal brain MRIs. Most (90%) recovered within 30 days. Immunotherapy with IVIG or corticosteroid was used in 7 patients. Three patients with abnormal imaging were diagnosed with acute cerebellitis.

Conclusions: Post-infectious cerebellar ataxia is the most common cause of acute ataxia in childhood. This condition is characterized by normal brain imaging and has a good
prognosis. Children with abnormal cerebellar imaging, despite having clinical overlap, should be distinguished from post-infectious cerebellar ataxia in terms of etiology and management.

Keywords: Case studies/case series, Infections/Neuroimmunology

125. Maternal High-fat Diet During Pregnancy and Lactation Decreases Progeny Brain Concentrations of an Endogenous Anti-Inflammatory Lipid Mediator

Barks JD, Djuric Z, Ren J, Liu YQ, Shangguan Y, Silverstein FS (Ann Arbor, MI)

Objective: Specialized pro-resolving lipid mediators (SPMs) are endogenous modulators of inflammation derived from polyunsaturated fatty acids (FA) including the neuroprotective FA docosahexaenoic acid (DHA), e.g. protectin-D1 (PD1)(10(R),17(S)-dihydroxy-DHA) and protectin-DX (PDX; 10(S),17(S)-dihydroxy-DHA). In a neonatal rat model of hypoxic-ischemic (HI) brain injury, acute DHA treatment improves sensorimotor outcomes, whereas pre- and post-natal exposure to maternal high-fat (HF) diet has opposite effects (worsening outcome). Thus, we evaluated the impact of maternal HF diet during pregnancy and lactation on neonatal brain DHA, PD1, and PDX concentrations.

Methods: Pregnant rats (n=6) were fed HF chow (34% fat calories) or standard low-fat chow (LF, 17% fat calories) beginning on E7. Seven-day-old (P7) progeny underwent right carotid ligation followed by 60 minutes 8% O2 exposure to elicit HI brain injury. Right cerebral hemispheres were collected 1h post-HI, along with normal control (NC) littermate samples. Free FA were extracted and metabolites analyzed by liquid chromatography-tandem mass spectroscopy.

Results: In all HF diet-exposed pups, there was a marked reduction of PDX, the DHA-derived SPM, and of free eicosapentaenoic acid (EPA); surprisingly, free DHA (unlike the membrane-bound fraction) and free arachidonic acid (AA) concentrations did not differ between diet groups (Table). Protectin-D1 was not detected. Concentrations of the three free FA's and of PDX were not influenced by HI.

Conclusions: These data provide the first evidence that a DHA-derived endogenous neuroprotective lipid mediator PDX is detectable in developing brain and suggest that its depletion may underlie the deleterious effects of maternal HF diet on recovery after neonatal brain injury.

TABLE

<table>
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<tr>
<th>Group</th>
<th>PDX (ng/mg protein)</th>
<th>Free EPA (ng/mg protein)</th>
<th>Free DHA (mcg/mg protein)</th>
<th>Free AA (mcg/mg protein)</th>
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<tr>
<td>LF NC (n=10)</td>
<td>3.3 ± 2.7</td>
<td>42.4 ± 10.7</td>
<td>37.9 ± 20.0</td>
<td>4.4 ± 3.0</td>
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<td>LF HI (n=11)</td>
<td>3.5 ± 2.4</td>
<td>46.1 ± 17.9</td>
<td>39.2 ± 20.7</td>
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<td>HF NC (n=6)</td>
<td>1.3 ± 1.0a</td>
<td>23.9 ± 4.2a</td>
<td>32.3 ± 19.2</td>
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<tr>
<td>HF HI (n=9)</td>
<td>2.0 ± 1.4a</td>
<td>18.5 ± 9.9a</td>
<td>36.7 ± 20.4</td>
<td>3.4 ± 1.9</td>
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</table>

*p<0.005 for diet, by 2-way ANOVA factoring diet and lesioning status.

126. Supratentorial Intracerebral Lobar Hemorrhage in Term Neonates: risk factors, imaging and outcome

Bassan H, Sarajlija j, Heiman, E, Beni L, Eshel R, Cowan FM (Tel Aviv, Israel)

Objective: To evaluate the perinatal factors, imaging, neonatal presentation and outcome in term neonates with supratentorial intracerebral lobar hemorrhage (SILH).

Methods: Term neonates from Hammersmith and Queen Charlotte's Hospital, Imperial College, London, and Tel Aviv Sourasky medical center, with SILH were included. MRI scans were reviewed. Perinatal data were compared to healthy control infants. Neurodevelopmental outcome at >2 years was documented.

Results: 34 infants were studied; mean gestational age and birthweight were 39.3±1.5 weeks and 3,438.3±561.7 grams, respectively. Compared to 229 healthy controls, infants with SILH had increased frequency of maternal autoimmune disorders, maternal inapartum fever, prolonged 2nd stage delivery, emergent caesarean section, neonatal resuscitation, and low Apgar scores (p<0.05). Thrombocytopenia occurred in 6/32(18.8%) and MTHFR homozygosity in 3/17 (17.6%). MRI findings: parenchymal haemorrhage involved the frontal (41%), temporal (32%) and parietal (26%) lobes. Supratentorial extraaxial hemorrhage accompanied 82.4% of cases. Midline shift with ipsilateral ventricular compression was more commonly seen with frontal (71.4%) than with parietal and temporal hemmorhages. Neonatal seizures occurred in 94.1% of infants: mostly apneic (65.4%) and focal motor (46%). Neonatal encephalopathy was documented in 30.3% infants. Outcome data was available in 26 children. One infant died. Seven (26.9%) had either cerebral palsy and/or developmental quotient <70, and one developed epilepsy.

Conclusions: SILH in term infants is associated with multiple risk factors apparently related to inflammatory processes, labor and delivery, hypoxia-ischemia and hematological variants. Although clinical and imaging findings at presentation are dramatic, approximately 75% of children had a good outcome.

Keywords: Neonatal neurology, Neuroimaging

127. Maternal Infections During Pregnancy and Cerebral Palsy in the Child

Bear JB, Wu YW (San Francisco, CA)

Objective: Chorioamnionitis is a risk factor for cerebral palsy (CP). The relationship between maternal infections

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outside the amniotic cavity and CP is less well studied. We determined the association between intra-amniotic and extra-amniotic infections diagnosed during a pregnancy hospitalization and CP in the child.

Methods: In a retrospective cohort study of six million Californian births, 1991–2001, we linked maternal and newborn hospital discharge abstracts to records of all children receiving services for CP at the California Department of Developmental Services. We identified maternal hospital diagnoses of chorioamnionitis, other genitalia, and respiratory infections occurring any time up to twelve months before delivery. We performed logistic regression adjusting for maternal age, education, socioeconomic status, and race, and infant sex.

Results: 6.3% of mothers had a hospital diagnosis of one of the three infections studied: chorioamnionitis (2.0%), other genitalia (3.1%), and respiratory (1.5%). We identified 8,473 individuals with CP (1.4 per 1000). These maternal infections were more commonly diagnosed in CP than non-CP cases (15.3% vs. 6.3%, P<0.001). All three maternal infections were associated with CP after adjusting for sociodemographic factors: chorioamnionitis RR 4.1, 95% CI 3.8–4.5; genitalia RR 1.7, 95% CI 1.5–1.9; respiratory RR 2.3, 95% CI 2.0–2.6. Genitalia and respiratory infections were associated with elevated risk of CP whether diagnosed during a prenatal or birth hospitalization.

Conclusions: Extra-amniotic infections are associated with increased risk of CP. These data support the role of the maternal inflammatory milieu in the pathogenesis of CP.

Keywords: Neonatal neurology

128. Predictors of Epilepsy After Neonatal Arterial Ischemic Stroke
Billinghurst LL, Beslow LA, Uohara M, Abend NS, Licht D, Ichord R (Philadelphia, PA)

Objective: Neonatal arterial ischemic stroke (NAIS) is a unique model of acquired epilepsy with utility for elucidating mechanisms of epileptogenesis. Prognostic factors for remote symptomatic seizures (RSS) and epilepsy are unknown. We sought to define clinical and electrographic features predictive of post-stroke seizures and epilepsy.

Methods: We evaluated 67 term infants with NAIS from a single-center prospective consecutive cohort enrolled 2006–2013. Charts were abstracted for treatment of acute symptomatic seizures (ASS), characteristics of acute and follow-up electroencephalogram (EEG), RSS and epilepsy outcome.

Results: EEG reports were available from acute (<7 days from first ASS) and follow-up recording (during acute hospitalization or after discharge) in 55/67 (82%). EEG was categorized as normal or abnormal. Acute EEG was abnormal in most (n=46/55; 84%) but normalization was typically found on follow-up (n=32/46; 70%). All neonates except two presented with ASS, and the majority (n=41/53, 77%) were discharged on anticonvulsant for a median duration of 71 days (IQR 60–88). No difference was found in RSS-free or epilepsy-free survival among those discharged on anticonvulsant therapy versus those not (p=0.12, log-rank and p=0.08, log-rank). Neonates with EEG normalization were less likely to develop RSS and epilepsy than those without (FIGURE), even when controlling for discharge on or off anticonvulsant [HR 11.6 (95%CI 3.5–38.2) and HR 10.8 (95%CI 2.8–42.4)].

Conclusions: Normal acute EEG and EEG normalization after NAIS predicts lower rates of future RSS and epilepsy. Clinicians should consider the prognostic value of follow-up EEG after NAIS.

Keywords: Epilepsy and other paroxysmal disorders, Neonatal neurology. Stroke

129. Epilepsy Outcome among Newborns with Hypoxic-Ischemic Encephalopathy Treated with Therapeutic Hypothermia
Cordeiro M, Tsichinda TN, Mabray P, Czech TM, Harris K, Masaro AN, Nelson KB, Chang T (Washington, DC)

Objective: To determine the prevalence of epilepsy and its potential risk factors among newborns with hypoxic-ischemic encephalopathy (HIE) treated with therapeutic hypothermia (TH).

Methods: This is a retrospective review of encephalopathic newborns treated with TH (criteria based on the NICHD protocol) between 2006 and 2010. Demographics, EEG and MRI data were collected for all patients. Follow up data were gathered by a phone survey or by chart review. Patients with at least 3 years of follow up were included in the analysis.

Results: During the study period 149 newborns met the inclusion criteria, of which 29 (19%) died in the NICU. At least 3 years of follow up was available for 70 infants (70/120, 58.3%). Epilepsy was diagnosed in 16 infants with a median age of onset of 1.51 years (3 months–3.9 years). 62% were male. EEG confirmed seizures during hypothermia were significantly higher in the epilepsy patients (p<0.001; RR 5.7, 95% CI 1.8–18.4). Severely abnormal initial EEG background (burst-suppression, extremely low voltage or inactive) [RR 10.8, 95% CI 3.4–33], status epilepticus (RR 6, 95% CI 2.9–12.2) and evidence of MRI injury (p=0.001) were strongly associated with epilepsy. Those lost for follow up had less EEG confirmed seizures and status epilepticus (p<0.01).

Conclusions: This study is limited by the lack of adequate follow up. However, we can conclude that epilepsy is more frequent among HIE infants treated with TH (16/
120, 13.3%) compared to the general population (1%). EEG and MRI abnormalities can help to identify infants at higher risk.

**Keywords:** Epilepsy and other paroxysmal disorders, Neonatal neurology

130. Cerebral Palsy following Neonatal Encephalopathy: how much is preventable?
Garfinkle J, Winternack P, Shevell Ml, Oskoui M (Montreal, QC)

**Objective:** To (1) estimate the proportion of cerebral palsy (CP) following moderate-to-severe neonatal encephalopathy (NE) that could be prevented by therapeutic hypothermia and (2) elucidate perinatal factors and outcomes that distinguish those who meet from those who do not meet physiologic criteria for hypothermia.

**Methods:** Using the Canadian Multi-Regional CP Registry, term-born (>36 weeks) children with CP following NE were categorized according to the presence or absence of physiologic criteria required to qualify for hypothermia. Perinatal, antepartum, intrapartum, and postpartum factors and outcomes were compared between the two groups. A number needed to treat of 8 (95% CI: 6–17) was used for calculations.

**Results:** Of 543 term-born children with CP, 155 (29%) had NE. Sixty-four of 155 (41%) met cooling criteria and 91/155 (59%) did not. 5.1% (95% CI: 2.4–6.6%) of CP following NE could be prevented by hypothermia. Shoulder dystocia was more common in those not meeting cooling criteria (OR 8.8; 95% CI 1.1–71.4). Thirty-two of 155 (21%) neonates and 39/96 (41%) placentas were criteria (OR 8.8; 95% CI 1.1–71.4). Thirty-two of 155 (41%) met cooling criteria and 91/155 (59%) did not. 5.1% (95% CI: 2.4–6.6%) of CP following NE could be prevented by hypothermia. Shoulder dystocia was more common in those not meeting cooling criteria (OR 8.8; 95% CI 1.1–71.4). Thirty-two of 155 (21%) neonates and 39/96 (41%) placentas were <10th percentile for weight. CP was significantly more severe (GMFCS IV-V: 65% vs 32%) and quadriparietic (62% vs 34%) and associated with more communication difficulties (53% vs 21%) in those meeting cooling criteria.

**Conclusions:** An estimated 2.4–6.6% of CP following term NE could be prevented by hypothermia. Fetal and placental growth restriction were prevalent in CP following NE regardless of group assignment. Those not meeting cooling criteria more commonly had shoulder dystocia, suggesting that current cooling criteria may be overly restrictive. Lastly, those meeting cooling criteria were more impaired.

**Keywords:** Neonatal neurology

131. Maternally Acting Gene Alleles (MAGAs) Contributing to Neurodevelopmental Disorders and to Disorders of Pregnancy
Johnson WG, Bayske SG, Stenroos ES (Piscataway, NJ)

**Objective:** Maternal gene alleles that act prenatally in the mother make a major contribution to the intrauterine environment, especially during the early part of pregnancy. We tested our hypotheses (i) that the range of MAGAs contributing to neurodevelopmental disorders might differ from those contributing to disorders of pregnancy and (ii) that they act by many independent mechanisms.

**Methods:** To test these hypotheses, we identified reports of prenatal maternal effects and excluded those resulting from: maternal environmental effects acting on the fetus or interacting with a fetal genotype; mitochondrial genes; microchimerism; or known genomic imprinting. We included MAGAs that affect phenotype of the embryo or fetus. We determined possible mechanisms of action, understanding that genes may have more than one mechanism and considering the possibility of ascertainment bias. We identified categories of mechanisms of the MAGAs.

**Results:** Among 161 reports of 41 MAGAs, some from our laboratory, we found that the majority of known MAGAs acted by detoxification/oxidative stress mechanisms (55%), many by folate/1-carbon mechanisms (22%), a few by immune mechanisms (4%); the rest (15%) did not fit these categories. We found that most categories and even the same genes contributed to both neurodevelopmental disorders and disorders of pregnancy.

**Conclusions:** Thus, most MAGAs known so far seem to act by one of three categories of mechanisms. This finding has major implications for the nature of their prenatal contribution to intrauterine environment and suggests approaches to ameliorating or preventing these disorders.

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

132. Intranasal Epidermal Growth Factor Treatment Ameliorates Hippocampal Dysfunction in a Mouse Model of Premature Brain Injury
Kurz JE, Edwards J, Scafidi S, Gallo V, Scafidi J (Washington, DC)

**Objective:** Very preterm infants are at risk for long-term neurodevelopmental and cognitive impairments. Using an established mouse-model of chronic hypoxia (postnatal day P 3–11), which recapitulates the phenotype of prematurity-related brain injury, we recently demonstrated cellular and functional recovery of hypoxia-induced white matter injury with intranasal epidermal growth factor (EGF) stimulation of EGF receptor (EGFR)-expressing progenitors. We hypothesized that hypoxia-induced hippocampal dysfunction and injury is also attenuated with intranasal EGF administration.

**Methods:** Investigations were performed in normoxia and hypoxia-reared groups, with either vehicle or intranasal EGF treatment administered from P11-P14. Hippocampal-dependent behaviors were analyzed via novel-object, Barnes-maze, and Y-maze at P30 and P60. Using immunohistochemistry against glial, neuronal, and proliferation-specific markers, we characterized short (P18) and long-term (P30) effects of hypoxia and EGF-treatment on specific cellular populations in the hippocampal subgranular zone (SGZ).

We performed fate-mapping of SGZ progeny cells derived from hGFAP-expressing (radial glia) and PDGF-FuR-expressing (oligodendrocyte progenitor, OPC) cells to determine the short and long-term effects of hypoxia and EGF treatment on the developmental fate of SGZ cells. Hippocampal metabolic function was evaluated using 1H-NMR spectroscopy.

**Results:** Intranasal EGF activated EGFR in the SGZ, and produced significant recovery of hypoxia-induced decreases in hippocampal-dependent behavioral
133. Effect of Hypothermia and Continued Administration of the Antiepileptic Drug Levetiracetam on Long Term Neurologic Function after Hypoxia-Ischemia in the Newborn Piglet

Legido A, Malaeb S, Anday E, Wacker E, Delivoria-Papadopoulos M (Philadelphia, PA)

Objective: Hypothermia (HT) is useful to treat newborns with acute hypoxic ischemic (HI) encephalopathy. The present study tests the hypothesis that combined HT and administration of the presynaptic Ca2+ channel inhibitor Levetiracetam (LEV), which dampens excitotoxicity after HI, further improves neuroprotection in newborn piglets.

Methods: Ventilated newborn piglets were exposed to HI [FiO2 0.07 for 1hr and hypotension (40% decrease in systolic BP)], then returned to FiO2 0.21 to restore O2 and BP. Piglets received either saline or LEV 80mg/kg loading dose i.v. immediately after HI, then cooled to 33°C for 4hrs and rewarmed over 6hrs. LEV 20mg/kg BID i.v. was continued for 7 days. Locomotion was assessed as number of lines crossed per minute (LPM) on a 9x6ft grid and problem solving ability as number of successful attempts to access covered food on 6 trials (M±SD). Normoxic (Nx)-HT were sham-controls.

Results: NxHT piglets (n=3) crossed 19.5±2.25 LPM and accessed covered food on 5.3±0.5 trials. HI-HT (n=3) crossed 8.5±4.8 LPM (p<0.05 vs NxHT) and accessed covered food on 1.7±1.2 trials (p<0.05 vs NxHT) 8 days after HI. LEV-treated HI-HT (n=3) crossed 15.5±1.18 LPM (p<0.05 vs HI-HT) and accessed covered food on 5.8±0.5 trials (p<0.05 vs HI-HT) 8 days after HI.

Conclusions: Newborn piglets had impaired locomotive and problem solving abilities after HI. Combined HT and LEV improved neurologic function compared to HT alone. LEV may be a novel neuroprotective adjunct therapy to HT following perinatal HI.

Keywords: Neonatal neurology

134. Neurologic and other Systemic Complications of Infants of Diabetic Mothers

Moodley M, Reed B, Worley S (Cleveland, OH)

BACKGROUND: There is limited data on neurologic complications and their long term outcomes in infants of diabetic mothers (IDMs). Despite advances in prenatal care leading to improved outcomes in infants in general, IDMs remain at increased risk for many perinatal complications due to the teratogenic effects of glucose on fetal development. Maternal hyperglycemia causes fetal hyperinsulinism which in turn can cause Pax-3 dysregulation linked to NTD and other neurological morbidities.

Conclusions: These results provide further evidence that targeting EGFR is a potential therapeutic intervention for common neurodevelopmental deficits associated with very preterm birth.

Keywords: Neonatal neurology, Translational/experimental therapeutics
cortical and subcortical injury. While majority (14/27, 52%) had normal EEG, 6 (22%) had abnormal EEG, 4 (15%) developed IS and 3 (11%) died. Diffuse brain injury was significantly associated with unfavorable outcome (death or IS) compared to an absence of subcortical involvement (7/27 vs. 0/33, p<0.003).

Conclusions: Brain stem injury is highly predictive of IS in head cooled neonates with HIE.

Keywords: Epilepsy and other paroxysmal disorders, Neonatal neurology, Neuroimaging

136. Perinatal Factors, In-Hospital Outcomes And Seizures In Neonatal Hypoxic Ischemic Encephalopathy

Objective: Neonatal encephalopathy due to hypoxic ischemic encephalopathy (HIE) is frequently accompanied by seizures, which are associated with poor developmental outcomes in HIE. However, it is difficult to predict which newborns will have seizures, particularly since the initiation of therapeutic hypothermia for treatment of HIE. We evaluated a large cohort of newborns with HIE to assess the relationship between perinatal variables and seizures in neonatal HIE.

Methods: We performed a retrospective analysis of 87 newborns treated at three referral centers from 2012–2013. Data collected for all subjects included if cooling was received, worst pH and base excess at presentation, Apgar scores, chest compressions, PPV, CPAP, blow-by oxygen, need for transport to a referral center for cooling and in-hospital mortality. The presence of seizures was confirmed on electroencephalogram.

Results: Seizures were not associated with acidosis or Apgar scores. Seizures were not correlated with any methods of resuscitation (compressions, PPV or CPAP). However, the association between seizures and in-hospital mortality was trending towards significance (p=0.095) and newborns requiring transport were more likely to have seizures (p=0.03).

Conclusions: The relationship between mode of resuscitation and seizures is not well defined for neonatal HIE. Seizures may be associated with increased in-hospital mortality, though this may reflect the increased mortality in neonates who require transport for cooling as shown by our group in a separate analysis (Sinha et al 2014). Our results support the need to further assess the risk factors for seizures in neonatal HIE.

Keywords: Neonatal neurology

138. Cerebellar Hypoplasia at Term Associated with Abnormalities in Neurological Examination at 18 Months in Preterm Newborns
Tam EWY, Chau V, Pokhit KJ, Synnes A, Zwicker J, Grunau RE, Miller SP (Toronto, ON)

Objective: To examine the relationship between cerebellar hypoplasia measured at term-equivalent age by MRI and neurological examination at 18 months in preterm newborns.

Methods: Preterm newborns (<32 weeks gestational age) were analyzed by semi-automated segmentation of the cerebellum on MRI performed at term-equivalent age. MRI scans were evaluated for brain injury, including intraventricular hemorrhage, white matter injury, and cerebellar hemorrhage. Neurological examination was completed at 18 months corrected age. Logistic regression analysis was performed to study the relationship of cerebellar volume at term and findings on neurological examination, adjusting for severity of brain injury.

Results: Of 95 subjects with MRI scans at term age (40.6±3.0 weeks), 79 (83%) had follow-up at 19.0±1.9 months. Adjusting for severity of brain injury, smaller
cerebellar volume at term was associated with increased odds of truncal hypotonia, abnormal station, and abnormal plantar response (P<0.01). If defined as <19cm³ by 40 weeks, cerebellar hypoplasia is associated with 10-fold increased odds of truncal hypotonia (P<0.001, area under ROC 0.73), 15-fold increased odds of abnormal station (P<0.001, area under ROC 0.77), and 5.5-fold increased odds of abnormal plantar response (P=0.015, area under ROC 0.67). No association was found between cerebellar volume and limb tone, power, or reflexes, retained primitive reflexes, or movement disorders.

Conclusions: Although previously associated with cognitive deficits in follow-up, this study demonstrates that cerebellar hypoplasia of prematurity is also associated with specific abnormalities on neurological examination, including truncal tone, abnormal station, and upgoing plantar response by 18 months corrected age.

Keywords: Neonatal neurology, Neuroimaging

139. Early Onset Limb-Girdle Muscular Dystrophy Caused by Mutation in Thymidine Kinase 2 Gene
Acadi G, Maian Cohen J, Wu Q (Hartford, CT)

Objective: Thymidine kinase 2 (TK2) gene is involved in mitochondrial DNA synthesis and mutations in the gene results in mitochondrial depletion. The clinical phenotype is variable and may involve multiple organs. We report a young child with progressive isolated myopathy caused by homozygous TK2 mutation.

Methods: We present the clinical features, muscle biopsy and genetic testing of nuclear mitochondrial genes of the patient.

Results: 1) Clinical presentation: The 22 months old female toddler was evaluated for falls, walking and climbing difficulty. The mother noticed decreased fetal movements during pregnancy but no perinatal problems. The motor development was not late but she has never walked normally. The neurological examination was significant for decreased muscle tone, proximal muscle and some distal weakness and waddling gait. 2) Laboratory tests: creatine kinase: 1103–1410 IU, lactate 4.7-7.6 and pyruvate 2.4 mM elevated alanin. 3) Muscle biopsy: dystrophic features with muscle fiber necrosis, fibrosis, fiber size variation, Type 2 fiber atrophy; ragged-red fibers, SDH and COX staining loss in some fibers. The EM showed large mitochondria and crystalline inclusions. 4) Genetic testing by exome sequencing of nuclear genes revealed a homozygous mutation (Thr108Met) in the TK2 gene.

Conclusions: TK 2 gene mutations have been described in early onset progressive disease with multi-organ pathology due to depletion of mitochondria. At 3 years of age, our patient has evidence of isolated skeletal myopathy and a histological features of dystrophy. Mitochondrial myopathy should be considered as a cause of early onset limb-girdle muscular dystrophy.

Keywords: Case studies/case series, Neuromuscular disorders

140. Lower Extremity Predominant Spinal Muscular Atrophy Caused by BICD2 Gene Mutation
Acadi G, Plemier K, Ounpuu S (Hartford, CT)

Objective: Dominant mutations in Bicaudal D homolog 2 (Drosophila) (BICD2) protein and Cytoplasmic dynein heavy chain (DYNC1H1) were recently described in patients with clinical characteristics of lower extremity predominant proximal weakness similar to spinal muscular atrophy (LED-SMA). We report the clinical and gait characteristics of a three-generation family with LED-SMA that was included in the original paper describing BICD2 mutations (Oates et al. 2013).

Methods: We collected longitudinal clinical history, family history, neurological examination, electrophysiological and computerized gait analysis data of a 7 year old patient. The genetic analysis of the family was carried out by next generation exom sequencing.

Results: The index case had cyanotic apneas at 2 months and later was noticed to have hypotonia and delayed onset in walking. An initial neurologic exam at 14 months showed no facial weakness, but muscle hypotonia and proximal lower extremity weakness. The deep tendon reflexes were preserved. A limited electrophysiological study showed normal NCVs and no signs of denervation at two years. She has gained some strength over the years, but she had more fatigue, lower extremity pain and cramps and an “awkward gait”. Her neurological exam at 6 years of age showed a lower more than upper extremity proximal weakness but some distal weakness as well. Her computerized gait analysis revealed a bilateral delayed heel rise due to ankle plantar flexor weakness and bilateral internal foot progression due to internal tibial torsion and forefoot inversion. Her “waddling” gait was correlated with increased lateral trunk lean due to hip abductor weakness. Compared to a previous gait study 2 years earlier, she had no major changes in walking kinematics and kinetics. She was able to walk 400 meters during the 6-minute walk test and her CMTPeds score was 17 suggesting a mild to moderate functional deficit. The mother, uncle and grandfather had similar clinical presentation.

Conclusions: We present the clinical characteristics of a 7-year-old girl and her three-generation family with LED-SMA caused by a dominant mutation in BICD2 gene. The condition appears more severe in males. The clinical features and gait test suggest a very minimal progression of disease over two years. Studying the molecular biology of BICD2 and DYNC1H1 may reveal involvement of convergent molecular pathways in SMA.

Keywords: Case studies/case series, Neuromuscular disorders

141. Clinical Course of Dystroglycanopathy Arising from POMGnT1 Mutations: a case series with up to 22 years of follow up
Crockett CD, Stephan CM, Mathews KD (Iowa City, IA)

Dominant mutations in alpha-dystroglycan glycosylation lead to a subset of highly variable muscular dystrophies known as the dystroglycanopathies. Dystroglycanopathies
due to mutations in POMGnT1 typically manifest as muscle-eye-brain disease. There are few reported cases with follow up over many years.

Methods: Medical records of four patients with mutations in POMGnT1 currently ranging from age 2 to 23 years were reviewed.

Results: All had onset of weakness in infancy and were classified either as MDDGA3 (OMIM 253280) or MDDGB3 (OMIM 613151). All patients older than 2 years of age walk independently. None reported loss of functional motor skills related to weakness, and weakness was not a prominent clinical feature. Eye involvement (including high myopia, cataracts, retinal atrophy, nystagmus, and hypoplastic optic nerves) is found in three patients. Brain MRI abnormalities (including pontine, cerebellar, and temporal lobe hypoplasia, polymicrogyria, cerebellar cysts, cortical dysplasia, and white matter abnormalities) and cognitive delay are present in all four. Three of the four patients have epilepsy. The patient followed for 22 years has had a relatively static course with regard to motor function, but seizures beginning at age 11 years have been difficult to control.

Conclusions: Adding to previous descriptions of progression in this rare disorder, these cases suggest individuals with POMGnT1 mutations may have slowly progressive weakness, ambulation maintained past age 20, and potential for development of seizures well after onset of weakness. This series also emphasizes the risk of missing POMGnT1 mutation-related diagnoses, as the muscle phenotype can be mild relative to other manifestations.

Keywords: Case studies/case series, Neuromuscular disorders

142. Comparison of Clinical Progression between Siblings with Dystroglycanopathy

Crockett CD, Mockler SR, Laubscher KM, Stephan CM, Mathews KD (Iowa City, IA)

Objective: The dystroglycanopathies are a phenotypically and genetically heterogeneous subset of muscular dystrophies arising from abnormal glycosylation of alpha-dystroglycan. We compared the clinical phenotype and disease progression of siblings with childhood-onset dystroglycanopathies.

Methods: Siblings with onset of weakness in childhood were identified from a cohort of subjects enrolled in a longitudinal dystroglycanopathy natural history study (NTC00313677). Participants were assessed with yearly, standardized clinical examinations. Data collection included manual muscle testing (MMT), timed function tests, and pulmonary function tests. Medical records were reviewed where possible.

Results: Eight pairs of siblings, including 2 sets of identical twins, were included in analysis. FKRP mutations were present in 6 sibling pairs and FKTN mutations in the other 2 sibling pairs. Disease progression was more similar between siblings for tests of strength and motor function (manual muscle testing, time to walk 10 meters, time to rise from supine, time to climb stairs, 6 minute walk test) than for pulmonary function assessments. One sibling pair displayed a considerable amount of difference in clinical progression across all measures compared to other sibling pairs. Identical twin sets showed varying degrees of clinical homogeneity across measures.

Conclusions: The clinical progression of siblings with dystroglycanopathy is generally concordant, although there are exceptions. The reason for the highly disparate phenotypes among some siblings is unknown; however, additional genetic modifiers or treatment differences might contribute.

Keywords: Neuromuscular disorders

143. Increasing the Index of Suspicion of Parry-Romberg Syndrome in Patients with Hemifacial Atrophy

Dasyam N, Goldstein A, Gardner K (Pittsburgh, PA)

Objective: Parry-Romberg syndrome (PRS) or progressive hemifacial atrophy, involves atrophy of skin, subcutaneous tissues and to varying extent, cartilage and underlying bones. We present a patient with suspected PRS in order to increase the awareness of the condition.

Methods: Case report and literature review.

Results: A 15-year old female was referred to our Neurofibromatosis Clinic for hyperpigmented lesions, migraines and chronic abdominal pain. Her past medical history is significant for facial asymmetry noted at age 4 years which progressed over 1 year and then stabilized. On examination, the skin and subcutaneous tissue on the right face, right upper lip and tongue were atrophic without associated facial weakness. In addition, she had several hyperpigmented, atrophic lesions on her back. CT at age 10 years showed facial asymmetry with hypoplasia of right maxilla and mandible.
Conclusions: The etiology of PRS is unknown but proposed hypotheses include autoimmune disease, viral or bacterial infection, trauma and hereditary disorder. The onset is in early childhood or adolescence, with a female-to-male ratio of 1.5:1. Facial atrophy is seen in the distribution of the trigeminal nerve branches. Nearly half of the patients have the coup-de-sabre linear scar in the face; hence, some patients are misdiagnosed with linear scleroderma. Neurological complications such as seizures especially partial seizures, trigeminal neuralgia and migraine are usually present. Ocular involvement manifests as progressive enophthalmos and Duane syndrome. The disease progresses for 2–10 years before stabilizing. There is no cure for PRS, though reconstructive plastic surgery can be offered for cosmetic purposes.

Keywords: Case studies/case series

144. Spectrum of Non-traumatic Neuropathies in Children
Ghosh PS, Sorenson EJ (Rochester, MN)

Objective: To analyze electrophysiological and etiological spectrum of neuropathies in children.

Methods: Retrospective review of patients ≤18 years over 10 years. Patients with referral diagnosis of mononeuropathies, peripheral neuropathies (PN), and plexopathies were reviewed after excluding children with post-traumatic neuropathies. Motor and sensory nerve conduction studies (NCS) were performed according to standard techniques and compared with age-specific controls to determine axonal or demyelinating features. Individual motor and sensory nerves were examined for mononeuropathies; ≥ 2 motor and ≥2 sensory nerves were examined for PN/plexopathies. Needle EMG were performed with standard concentric needle electrodes recording voluntary motor unit potentials and spontaneous discharges. Conscious sedation was routinely used for children ≤10 years of age.

Results: Fifty-six cases were included (age 1–17 years). Following observations were made: Group A: mononeuropathies (19): ulnar (6), sciatric (6), radial (2), median (2), femoral (1), peroneal (1), multiple mononeuropathies (1). Common etiological diagnoses in this group were: perineuroma (6), nerve tumors (2), carpal tunnel syndrome (2), tardy-ulnar nerve palsy (2), and inflammatory (2). Group B (plexopathies = 4; brachial (2), lumbosacral (2)). All were post-inflamatory. Group C (peripheral neuropathies = 18): demyelinating (4, all inherited neuropathies), axonal (14). Common etiological diagnoses in axonal neuropathies were: inherited (8), diabetes (2), post-chemotherapy (3). Group D (polyradiculoneuropathies = 15): demyelinating (14; AIDP=2, CIDP=12) and axonal (1).

Conclusions: Perineuromas and tumors should be considered in children with mononeuropathies. Inherited neuropathies were common in both demyelinating and axonal form of PN. Electrophysiological studies help to identify polyradiculoneuropathies which have important therapeutic implications.

Keywords: Neuromuscular disorders

145. Diagnostic Yield of Electromyography in Children with Myopathic Disorders
Ghosh PS, Sorenson EJ (Rochester, MN)

Objective: Interpretation of pediatric electromyography (EMG) interpretation in myopathic disorders is technically challenging. We assessed our EMG experience with respect to sensitivity and specificity in pediatric myopathy.

Methods: We did a retrospective chart review of patients ≤18 years between 2009 and 2013. 224 EMG studies were reviewed with the following referral diagnoses were reviewed: myopathy, muscle weakness, neuromuscular disorders, myositis, myalgia, myoglobinuria, myasthenia, myotonia, cramps, periodic paralysis, hypotonia, and developmental delay. Only children who had an EMG and muscle biopsy were included for analysis. Patients with neurogenic EMG and neuromuscular junction disorders were excluded. Myopathic EMG was defined as short duration, low amplitude, polyphasic motor unit potentials with rapid recruitment.

Results: Seventy-two cases were included, age range (6 months to18 years). The following observations were made: Group A: EMG myopathic or pathognomonic of muscle disease and biopsy or genetically confirmed myopathy (32 cases); Group B: myopathic EMG but biopsy normal or non-diagnostic (12 cases); Group C: normal EMG but biopsy or genetically confirmed myopathy (3 cases, all with metabolic myopathy) and Group D: EMG normal and biopsy normal or non-diagnostic (25 cases). The most common diagnoses were: congenital myopathy (7), metabolic myopathy (6), muscular dystrophy (6), genetically confirmed myopathy (5), myopathy, undefined (5), and inflammatory myopathy (4).

Conclusions: Pediatric EMG was 91% sensitive and 67% specific in myopathic disorders. The metabolic myopathies were commonly missed by EMG.

Keywords: Neuromuscular disorders

146. Efficacy of Antioxidants in Treatment of Friedreich Ataxia
Katz Y, Cotticelli GM, Wilson RB (Roanoke, VA)

Objective: Friedreich Ataxia (FA) is a genetic disorder with fatal neurodegenerative consequences, and no effective treatment currently exists. Decreased frataxin protein expression results in iron overload and oxidative damage. Selenium serves as a cofactor of glutathione peroxidase, and has potent antioxidant effects by means of replenishing the free radical scavenger glutathione. We hypothesized that treatment of frataxin-deficient cells with selenomethionine - a viable source of selenium - will result in increased cellular viability markers.

Methods: A validated model of frataxin-deficient murine fibroblasts was used. Cells were seeded in iron-enriched medium, with BSO (glutathione synthesis inhibitor) added 24h later. Compounds (idebenone - positive control, selenomethionine - treatment) were added 2h after BSO. Cellular viability (# of live cells in culture) was assessed 48h hours later via luminescence measurements of intracellular ATP content; two-sided t test was used to compare groups.

Keywords: Neuromuscular disorders

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Results: Selenomethionine (SeMet) was added to cultured frataxin-deficient fibroblasts at 500nM concentrations. Cellular viability was compared between SeMet-treated, idebenone-treated (positive control), carrier (deionized H2O), and non-treated groups (no iron/BSO and no treatment). Treatment with SeMet exhibited statistically significant increases in viability when compared to Idebenone-treated (positive control), carrier (deionized H2O), and non-treated (NT) ATP viability average (i.e., 100% survival).

Conclusions: The pathogenesis of Friedreich Ataxia is thought to implicate widespread cellular damage secondary to frataxin deficiency, resulting in mitochondrial dysfunction, iron overload, and oxidative damage. Selenomethionine exerts potent antioxidant effects in vitro by supplying selenium, which itself serves as a cofactor for a family of glutathione peroxidase enzymes that regenerate oxidized glutathione (GSSG) into its reduced form (GSH). By treating a well-validated cellular model of FA with SeMet, we observed increased survival of these cells in an environment of oxidative stress. These results shed light on a novel mechanism of clinical therapy for a currently-incurable disease.

References:
2. N. Calmels, et al., The first cellular models based on frataxin missense mutations that reproduce spontaneously the defects associated with Friedreich ataxia, 2009.

Keywords: Genetics, Neuromuscular disorders, Translational/experimental therapeutics

Objective: Decode Duchenne is a program of DuchenneConnect (DC) that provides genetic testing to U.S. Duchenne/Becker muscular dystrophy (DBMD) patients unable to access testing. DuchenneConnect is a self-report registry for DBMD patients. With mutation-specific therapeutics in the pipeline, genetic testing is increasingly important, but financial limitations can be a barrier. Decode Duchenne is funded by Sarepta Therapeutics.

Methods: Patients with no DNA testing or inconclusive testing were recruited. Emory Genetics Laboratory performed DMD CGH array analysis to identify deletions/duplications. If negative, sequencing was performed. If sequencing was negative, further testing was performed for other mutations as well as the Neuromuscular Gene Panel.

Results: To date, we received applications from 24 patients and results on 11. Nine previously had inconclusive testing while fifteen had no previous genetic testing. Most providers reported testing was denied by Medicaid or private insurance. Six patients had identified deletions/duplications. Sequencing was obtained on 5 patients and completed in 4. Sequencing identified a mutation in one; three were negative with results from further testing pending.

Conclusions: Mutation-specific therapy trials require genetic confirmation for participation. Obtaining testing has been difficult for some patients. While DNA testing is standard of care, some insurance providers do not cover testing. Our results highlight the utility of genetic testing to verify a diagnosis. Three out of 11 cases have no mutation identified by sequencing, which is unexpected. This is important for potential therapeutic interventions and reproductive risk counseling. The Decode Duchenne program provides access to genetic testing and highlights areas for future study.

Keywords: Case studies/case series, Genetics, Neuromuscular disorders

148. Timed Function Tests and Other Physical Function Outcomes in Ataluren-Treated Patients with Nonsense Mutation Duchenne Muscular Dystrophy (nmDMD)

McDonald C, Reha A, Elfring GL, Peltz SW, Spiegel RJ (Davis, CA)

Objective: A Phase 2b, controlled study of ataluren, an investigational drug, assessed changes in several measures of physical function, including timed function tests, over 48 weeks in ambulatory males ≥5 yrs old with nonsense mutation Duchenne muscular dystrophy (nmDMD). Outcomes were analyzed in subgroups of patients who, as revealed by emergent natural history data, entered the study at high risk of ambulatory decline.

Methods: An ambulatory decline phase subgroup was retrospectively defined as: ≥7 to ≤16 years old, ≥150 m 6MWD but ≤80%-predicted 6MWD at baseline, on corticosteroids. A subgroup of patients with baseline 6MWD...
<350 m, a pre-specified stratification factor and alternative indicator of compromised ambulatory capacity, was also analyzed.

Results: Differences in mean change in 6MWD at Week 48 between ataluren 40 mg/kg/day and placebo were 31.3 m (nominal p=0.0561) overall, 49.9 m (nominal p=0.0096) in the ambulatory decline phase subgroup, and 60.0 m (nominal p=0.0053) in the baseline 6MWD <350 m subgroup. Mean differences for stair-climbing, stair-descending, and walking/running 10 m were: -2.4, -1.6, and -1.4 seconds, respectively, overall: -2.9, -2.9, and -2.8 s in the ambulatory decline subgroup; and -6.4, -5.0, and -3.5 s in the baseline 6MWD <350 m subgroup.

Conclusions: Ataluren treatment effects on physical function may be obscured in younger patients with nmDMD still undergoing normal growth and development but are evident in the overall study population and to the greatest extent in patients in the ambulatory decline phase. These findings are consistent with ataluren’s mechanism of action as a dystrophin restoration therapy.

Keywords: Neuromuscular disorders, Translational/experimental therapeutics

149. Eteplirsen in Duchenne Muscular Dystrophy (DMD): 144 week update on six-minute walk test (6MWT) and safety

Objective: DMD, a rare, degenerative, genetic disease results in progressive muscle loss and premature death. It is caused by mutations in the dystrophin gene preventing production of the dystrophin protein. Eteplirsen is an investigational drug designed to enable functional dystrophin production in boys amenable to exon 51 skipping.

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 transitioned into an ongoing open-label extension with 30 or 50 mg/kg. FVC, FVC %–predicted, MIP, MEP, and MIP and MEP %–predicted were assessed every 12–24 weeks. For all 12 patients changes in function at Week 120 were examined from Week 1, and additionally from last assessment pre-eteplirsen administration for the placebo/delayed-treatment cohort (n=4). One-sample t-test was used for statistical analysis.

Results: Reported are results for all 12 patients, including two boys who became non-ambulant by Week 24. Median age at Week 120 was 12 years. Stability on all 6 PFT measures after 120 weeks of treatment was demonstrated by a statistically significant increase from baseline in MEP and no significant decline from baseline in the other 5 PFT parameters. Furthermore, individual patient PFT values for all 12 patients on all 6 parameters were generally consistent and exhibited stability over the same treatment duration. Week 144 data will be presented.

Conclusions: Eteplirsen dosed up to 120 weeks was well tolerated and demonstrated stability on PFT measures contrary to a steady decline expected in DMD patients of this age.

Keywords: Neuromuscular disorders

150. Pulmonary Function is Stable in Patients with Duchenne Muscular Dystrophy (DMD) Treated with Exon-Skipping Drug Eteplirsen in Phase 2b Study
Mendell JR, Lowes LP, Alfano L, Duda P, Saoud J, Kaye EM (Columbus, OH)

Objective: DMD, a rare, degenerative, genetic disease results in progressive muscle loss and premature death. Clinical pulmonary dysfunction often occurs when DMD patients become non-ambulant, preceded by subclinical deterioration of pulmonary function tests (PFTs). Eteplirsen is an investigational drug designed to enable functional dystrophin production in boys amenable to exon 51 skipping.

Methods: 12 boys were randomized 1:1:1 to weekly IV eteplirsen 30 mg/kg, 50 mg/kg or placebo for 24 weeks. All patients transitioned into an ongoing open-label extension with 30 or 50 mg/kg. FVC, FVC %-predicted, MIP, MEP, and MIP and MEP %–predicted were assessed every 12–24 weeks. For all 12 patients changes in function at Week 120 were examined from Week 1, and additionally from last assessment pre-eteplirsen administration for the placebo/delayed-treatment cohort (n=4). One-sample t-test was used for statistical analysis.

Results: Reported are results for all 12 patients, including two boys who became non-ambulant by Week 24. Median age at Week 120 was 12 years. Stability on all 6 PFT measures after 120 weeks of treatment was demonstrated by a statistically significant increase from baseline in MEP and no significant decline from baseline in the other 5 PFT parameters. Furthermore, individual patient PFT values for all 12 patients on all 6 parameters were generally consistent and exhibited stability over the same treatment duration. Week 144 data will be presented.

Conclusions: Eteplirsen dosed up to 120 weeks was well tolerated and demonstrated stability on PFT measures contrary to a steady decline expected in DMD patients of this age.

Keywords: Neuromuscular disorders

151. Consistent Safety and Pharmacokinetic Profiles of Eteplirsen, SRP-4045, and SRP-4053, Three Phosphorodiamidate Morpholino Oligomers (PMOs) for Treatment of Patients with Duchenne Muscular Dystrophy (DMD) Suggest PMOs are a Well-tolerated Therapeutic Class
Eteplirsen, SRP-4045, and SRP-4053 are three PMOs developed for DMD treatment. DMD is mostly caused by mutations in the dystrophin gene leading to a reading frame shift and premature translation termination. PMOs promote exon skipping during splicing of dystrophin pre-mRNA, restoring the reading frame and translation of internally truncated, but functional dystrophin protein. Eteplirsen, SRP-4045, and SRP-4053 are intended to treat patients with mutations amenable to exon 51, 45 and 53 skipping, respectively.

IND enabling preclinical studies were completed for eteplirsen, SRP-4045, and SRP-4053. In vitro metabolism data and PK profiles in animals were similar for all three PMOs. No adverse responses were detected in safety pharmacology studies in non-human primates (NHPs). Genotoxicity studies were negative. NHPs given 12 weekly IV doses up to 320 mg/kg showed no significant sequence-specific toxicities.

A clinical study of eteplirsen with weekly IV doses of 30 and 50mg/kg reported no clinically significant treatment-related adverse events through 120 weeks of treatment. A few cases of transient, mild urine protein elevation resolved without intervention or drug interruption. There were no hospitalizations, discontinuations, or clinically significant treatment-related changes for lab parameters, including liver enzymes, kidney function, coagulation, or platelet counts. Plasma Cmax and AUC increased dose-proportionally, and half-life was approximately 3 hours with no plasma accumulation observed.

The consistent preclinical profiles and lack of significant, sequence-specific toxicities for eteplirsen, SRP-4045, and SRP-4053 demonstrate PMOs to be a well-tolerated therapeutic class, with potential applications in a wide variety of disease indications.

**Keywords:** Neuromuscular disorders

152. Exonic Deletion of SLC9A9 in Autism with Epilepsy

**Wagle MR, Holder JL** (Houston, Texas)

**Objective:** Autism is a neuropsychiatric disorder that is associated with a higher incidence of epilepsy. Here we report for the first time an exonic deletion in SLC9A9 associated with autism and epilepsy.

**Methods:** The medical record of our patient was reviewed for pertinent findings associated with his SLC9A9 mutation.

**Results:** We have identified a patient with a ~0.5 kb deletion in 3q24 that includes exon 2 of SLC9A9. He was initially evaluated for delayed language development as he did not speak until five years of age. He was also noted to have poor socialization and eye contact. Neuropsychological testing confirmed a diagnosis of high functioning autism. Our patient had his first seizure at 15 years of age. His electroencephalogram revealed both a focus of epileptic activity in the frontotemporal region as well as abortive generalized spike and wave activity. Neuroimaging revealed a puncta of T2 prolongation in the left temporal pole potentially representing a focal cortical dysplasia.

**Conclusions:** Here, we describe a novel deletion of chromosome 3q24 encompassing exon 2 of SLC9A9. Our work confirms a role for SLC9A9 in autism and epilepsy and further clarifies the phenotypes associated with mutations of this gene. SLC9A9 encodes a Na+/H+ exchanger found in the recycling endosome. Exactly how loss of this protein causes neuropsychiatric disorders is unclear. However, identifying additional individuals with mutations of SLC9A9 will help clarify the genotype-phenotype relationship.

**Keywords:** Case studies/case series, Epilepsy and other paroxysmal disorders, Genetics


**Tiongson E, Pimentel N, Ramos-Platt L, Jaradeh SS** (Los Angeles, CA)

**Objective:** To present 2 cases of anti-ganglioside antibody positive patients, their presentation, and treatment course.

**Methods:** 2 case reports.

**Results:** Patient 1 presented at 17 years of age with a 3 year history of always feeling like he was choking. He had voice changes, palpitations, chest pain, heat intolerance, vision changes, ptosis, episodic dizziness, multiple GI complaints, and sleep disturbance. Tilt table testing supported autonomic dysfunction. QSART had abnormal sweating. Throat EMG demonstrated neurogenic changes in the laryngeal muscles. A sleep study demonstrated OSA. A GI emptying scan showed gastroparesis. Despite treatment trials with oral steroids, IV steroids, IVIG, Cellcept, and plasmapheresis, his symptoms and elevated antibody levels remain. He recently completed a Rituximab course. Patient 2 presented at 2 years of age initially as AIHP and a positive campylobacter stool culture. He was initially treated with IVIG. Although he has good strength after he was extubated, he remained areflexic. Lumbar puncture and spinal MRI were unremarkable. NCV demonstrated sensory neuropathy. He had corneal and skin ulcers from anhidrosis and alacrima. He also had gastroparesis (found on a GI emptying scan) and alternating constipation and diarrhea. He did not tolerate repeated IVIG doses. GI symptoms improved following weekly high dose methylprednisolone for 6 weeks but his antibody titer remains elevated.

**Conclusions:** These two cases contribute to the sparse autoimmune autonomic neuropathy pediatric literature and highlight the need for studies to create a set of diagnostic criteria and define optimal treatment regimens.

**Keywords:** Case studies/case series, Infections/Neuromunology, Neuromuscular disorders

154. Neuronal Ceroid Lipofuscinosis and Associated Sleep Abnormalities

**Lehwald LM, Pappa R, Steward S, de los Reyes E** (Columbus, OH)

**Objective:** Evaluate for sleep difficulties in children with Neuronal Ceroid Lipofuscinosis (NCL). Determine if there is a correlation between the form of NCL and the sleep abnormalities.
Methods: We recruited patients with a known diagnosis of NCL. Caregivers completed the Children’s Sleep Habits Questionnaire (CSHQ). A Total Sleep Disturbance Score and 8 subcategories of sleep behavior was calculated from the 33 item CSHQ. A Total Sleep Disturbance Score greater than 41 is sensitive and specific for a sleep disturbance.

Results: All but three of the 28 patients (89%) had a sleep disturbance based on a Total Sleep Disturbance Score greater than 41. The average Total Sleep Disturbance Score for all patients = 67.4, Standard Deviation = 15.3, 93% had at least one abnormal sleep subcategory. Four sleep subcategories were found to be of statistical significance: Sleep Onset Delay (p-value 0.0003), Sleep Duration (p-value 0.0002), Night Wakings (p-value 0.0065) and Daytime Sleepiness (p-value 0.0001).

CLN2 Patients, n=11
82% of patients considered to have a sleep disturbance. One sleep subscale variable was found to be of statistical significance: Sleep Onset Delay (p-value 0.0431).

CLN3 Patients, n=10
90% of patients considered to have a sleep disturbance. Three sleep subscale variables were found to be of statistical significance: Sleep Onset Delay (p-value 0.0330), Sleep Duration (p-value 0.0331) and Daytime Sleepiness (p-value 0.0041).

Conclusions: Children with NCL have an extremely high incidence of sleep disturbance. Different forms of NCL may have a unique pattern of abnormal sleep behavior. This information should be considered when developing a clinical treatment plan.

References:

Keywords: Genetics, Translational/experimental therapeutics

155. Utility of Repeat Surveillance Neuroimaging for Cerebral Arteriovenous Malformations in Children with Hereditary Hemorrhagic Telangiectasia
Anderson JL, White AJ (St. Louis, MO)

Objective: Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder of angiogenesis leading to epistaxis, mucocutaneous telangiectasias, and arteriovenous malformations. Children with HHT are susceptible to unexpected complications of cerebral arteriovenous malformations (CAVM’s) including hemorrhagic stroke. Current international guidelines recommend a single brain MRI in the first 6 months of life or at diagnosis. There are no published reports of a pediatric patient developing new CAVM after initial brain MRI, and no data exist to guide timing of repeat surveillance neuroimaging. We report our experience with 23 pediatric patients over 10 years in a single referral center.

Methods: A database of 154 children (age range 3 weeks to 21 years) with diagnosed or suspected HHT seen over 10 years in a pediatric HHT Center was reviewed. Of the 154 enrolled, 127 had initial brain MRI. Of those, 23 had repeat brain MRI.

Results: Of the 127 children with initial brain MRI, 13 (10%) were diagnosed with CAVM. 23 out of 127 children with initial brain MRI had repeat brain MRI. The average time to repeat brain MRI was 3.6 years (range in months, 12–117). None of these 23 children developed new CAVM’s on repeat neuroimaging.

Conclusions: It is important to screen children with diagnosed or suspected HHT for cerebral arteriovenous malformations at first presentation. The utility of repeat surveillance neuroimaging is in question. We have shown that after initial brain MRI, repeat surveillance imaging may not be indicated for several years or longer.

Keywords: Case studies/case series, Genetics, Neuroimaging

156. Human Neural Stem Cell Improve Water Maze Learning after Rat Pup Moderate Ischemic Injury Without Affecting Injury Volume
Ashwal S, Hartman R, Ghosh N, Tone B, Tian H, , Snyder EY, Obenaus A (Loma Linda, CA)

Objective: Stem cell (SC) transplantation is being evaluated for treatment of neonatal hypoxic-ischemic injury (HII). Critical issues are whether the degree of HII severity affects the potential for SCs to improve functional recovery and whether functional recovery can occur without significant reduction in injury volumes. We examined these issues in a rat pup unilateral HII model.

Methods: We transplanted hNSCs (250k) into the contralateral ventricle of rat pups 3d after HII. We examined lesion volumes using high field strength MRI at 2d and 90d post-injury and behavior at 90d followed by histology. HII severity was defined using a rat pup MRI-based severity score. Animals classified as mild were compared to those classified as moderate.

Results: In this study, hNSC transplantation did not significantly change lesion volume (neither core nor penumbra) when measured at 90d. When assessed at 90d, mild animals did not differ on any behavioral task (open field, rotarod, zero maze, water maze). However, moderate saline animals exhibited significantly worse spatial learning than moderate hNSC animals (p<.05), which performed similarly to mild animals.

Conclusions: In this study, hNSC transplantation did not affect 90d lesion volumes in mild or moderate animals. However, moderate hNSC-treated animals exhibited significantly better spatial learning than those receiving saline. Mild animals exhibited little to no behavioral impairment that could be ameliorated by hNSCs. These data suggest that despite not having significant effects on long-term HII volume, hNSC transplantation shortly after neonatal HII ameliorates long-term cognitive deficits, even in cases of moderate brain injury.

Support: NIH-1R01NS059770-01A2
Keywords: Neuroimaging, Stroke, Translational/experimental therapeutics

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157. Acute Susceptibility-Weighted MRI of Hemorrhagic Brain Lesions and One-Year Neuropsychologic Outcomes after Pediatric TBI

Tong KA, Al-Ramadhani R, Pivonka-Jones J, Rundquist M, Holdshower B, Ghosh N, Arhwal S (Loma Linda, CA)

Objective: We present an update on acute hemorrhagic injuries detected by MRI susceptibility-weighted imaging (SWI), and their relation to one-year neurologic and neuropsychological outcomes in 52 prospectively studied pediatric TBI patients.

Methods: Pediatric patients, aged 4 to 18, were enrolled if they sustained a moderate/severe TBI (GCS score <13 or hemorrhagic intracranial injury on CT). Patients underwent 3T MRI, acutely (6–17 days). The number/volume of hemorrhagic lesions were compared to neurologic (PCPSCS) and neuropsychological outcomes at 12 months, specifically general measures of memory (Children’s Memory Scale, General Memory score), attention (Test of Everyday Attention for Children; TEA-CH: Teach G score), and the Wechsler Abbreviated Scale of Intelligence (WASI: Full Scale IQ).

Results: We studied 52 children (38M, age 12.3 years), who were injured in vehicle/bike accidents (31), falls (12), sports-related injuries (7), or assaulted (1). The total number/volume of lesions were negatively correlated with one-year PCPSCS as well as one-year TEA-CH scores. Lesions in the corpus callosum were negatively correlated with FSIQ. Lesions in the frontal lobes and basal ganglia were negatively correlated with one-year CMS General Memory scores.

Conclusions: The extent of hemorrhagic lesions on acute MRI correlated with neurologic outcomes and specific neuropsychological outcome measures. SWI confirms that hemorrhagic shearing injuries have an important effect on many cognitive and neurologic domains. SWI can also be used in future models to predict long-term neuropsychological outcomes.

Support: NIH/NINDS:R01-NS054001

Keywords: Neuroimaging

158. Fainting in Teenagers is Not Always Faking

Avula S, Moodley M (Cleveland, OH)

Objective: Postural Orthostatic Tachycardia Syndrome (POTS) is now being recognized in increasing number in children. Currently available literature on POTS concentrates mainly on adult disorders with pediatric disorders being poorly defined. This issue will raise awareness of the expanding field of pediatric POTS.

Methods: We reviewed the medical records of all children < 18yrs seen at Cleveland Clinic Pediatric Neurology center, during 2011-13 presenting with syncope, dizziness, associated headaches and abdominal pain. 44 patients were included for study based on positive tilt test. We used the criteria of increase in HR >35 or HR>120 for positive tilt table test.

Results: 35 (79%) were females. 31 children had HR increment at or after 6 mins of tilt table. 14 out of 29 children tested for Qsart had abnormal test. 20 out of 29 children improved with treatment, out of which 5 children improved with Salt & water alone and 15 children improved with Salt & water, + Florinef or Metoprolol. 9 continued to have their symptoms with treatment. 16 out of 21 children had Low vit D levels.

Conclusions: It is easy to miss the diagnosis of POTS with bed side orthostatic vitals as we have observed that the max heart rate increments occur at or after 6 mins of Tilt table testing in majority of the patients. 76% of children had Low Vit D levels. Treatment with salt tablets improved symptoms but treatment with salt and water + Florinef or Metoprolol improved symptoms much better.

Keywords: Headache/Migraine, Neuromuscular disorders

159. Incidence of Epilepsy Following Pediatric Cerebral Sinovenous Thrombosis: a prospective cohort study

Billinghamurst LL, Beslow LA, Uohara M, Licht D, Ichord R (Philadelphia, PA)

Objective: While neurologic morbidity occurs in a significant proportion of pediatric cerebral sinovenous thrombosis (CSVT) survivors, the incidence of epilepsy is unknown. We measured the cumulative incidence of epilepsy in children after CSVT.

Methods: We evaluated 57 patients with CSVT (22 neonates, 35 children) from a single-center prospective consecutive cohort enrolled 2006–2013. Charts were abstracted for epilepsy timing, semiology, treatment, and severity. Cumulative incidence was assessed using survival analysis.

Results: 12/22 (54%) neonates and 8/35 (23%) children presented with acute symptomatic seizures. Among those with seizures, all were treated acutely; 12/12 neonates and 7/8 children were discharged on anticonvulsants. Venous infarction affected 9/22 (41%) neonates and 11/35 (31%) children (p=0.6). Intracranial hemorrhage occurred in more neonates than children (77% vs 17%; p<0.01) and neonates received anticoagulation less frequently than children (41% vs 82%; p<0.01). Median follow-up interval was 26 months in neonates (IQR 11–45) and 27 months in children (IQR 10–42). Epilepsy occurred in 10/57 (5 neonates, 5 children; 18%) at a median time of 4 months (range 1–54). Epilepsy-free survival at 36 months was the same in neonates and children, 80% (95% CI 47–94%) vs 83% (95% CI 63–93%) (p=0.53; log-rank test). Median Engel classification (0–5) in those with epilepsy was 1.

Conclusions: Epilepsy is common after pediatric CSVT. In our prospective cohort, we estimated 3-year cumulative incidence of epilepsy at 20% and 17% after neonatal and childhood CSVT, respectively. Further study is needed to identify predictors and potential therapeutic targets for epileptogenesis after pediatric stroke.

Keywords: Epilepsy and other paroxysmal disorders, Neonatal neurology, Stroke

160. Sensitivity and Specificity of an Adult Stroke Screening Tool in Childhood Ischemic Stroke

Gramling KL, Lo WD (Columbus, OH)

Objective: Stroke cards are widely used in adults to rapidly identify ischemic stroke. Uncontrolled studies in childhood
stroke suggest that deficits can be recognized with adult stroke cards. We performed a case-controlled study to test whether an adult stroke card is sensitive and specific for identifying childhood ischemic stroke.

Methods: An adult stroke tool developed by the Central Ohio Trauma System (COTS) was based upon the Los Angeles and Cincinnati Stroke tools. There are four elements: decreased consciousness, slurred speech, facial droop, and hemiparesis. A retrospective chart review identified patients with radiologically confirmed stroke at Nationwide Children’s Hospital (NCH) from 2006–2013. Stroke cases were compared with age and gender matched controls seen in the NCH ED diagnosed with hemiplegia or facial weakness not due to stroke. Documented physical findings for stroke cases and controls were evaluated using the categories of the COTS tool. A score of ≥3 was set as positive for stroke.

Results: A total of 59 stroke cases and 57 controls were identified. Chi square analysis showed no difference between stroke and control groups on the COTS scores (2.071, p = 0.196). Using a lower threshold for stroke (COTS score set at ≥2) also showed no difference (1.673, p = 0.134). Receiver operator curves revealed a low sensitivity and specificity for the COTS tool to distinguish between stroke and non-stroke cases (area under the curve = 0.526), with an effect size of only −0.134.

Conclusions: The COTS adult stroke tool is not sensitive or specific for identifying childhood stroke. This suggests that adult stroke tools cannot simply be applied to children, but that separate tools need to be developed. Such tools would need to consider unique characteristics in the pediatric population such as development-dependent functions and the frequency of seizures as a first sign of stroke. While a pediatric stroke tool would be an invaluable resource, future studies may need up to 300 subjects per arm for adequate power, which implies the need for a multicenter study. Rapid and accurate recognition of childhood stroke is the first step to implementing acute stroke interventions in the pediatric population.

Keywords: Stroke

161. Educational Placement and Neurological Outcome after Pediatric Intracerebral Hemorrhage

Hawks CE, Gindville MC, Ichord RN, Licht DJ, Beslow LA, Jordan LC (Nashville, TN)

Objective: This study describes educational placement of school-age children after spontaneous intracerebral hemorrhage (ICH) and to examine education placement in relation to hemorrhage volume and neurologic outcome.

Methods: Children with spontaneous ICH presenting from 2007 to 2013 were prospectively enrolled at 3 tertiary centers. The pediatric stroke outcome measure (PSOM) and a parental questionnaire gathered information about neurologic outcome, school attendance and educational services.

Results: The cohort of 92 children included 42 school-aged children (5–17 years) with ICH. Four died. Thus 38 completed 3-month follow-up and 30 have completed 1-year follow-up to-date. All survivors available for follow-up at 12-months post-ICH were attending school; 50% received regular age-appropriate programming, 37% attended school with in-class services, 13% were below grade level in a special-education program. No child was still receiving home-based services due to ICH-related deficits. Between the 3-month and 1-year visits, 40% of children improved their education status, 50% remained at the same education level, and 10% were reclassified at a “lower” education level, primarily due to appropriate implementation of an individual education plan. Median PSOM was 0.7, interquartile range, 0.5-3. PSOM ≥1 at 12 months, present in 50% of children, was associated with a need for educational services (p=0.03, Fisher exact test).

Conclusions: Neurological deficits were associated with remedial educational placement after pediatric ICH. Children return to school within a year of ICH; most show improvements with a reduction in the intensity of educational supports. A high need for educational services persists, however, as only 50% returned to regular classes.

Keywords: Stroke
anticonvulsants. Median age at last follow-up was 39 months (IQR 25–64 months). Epilepsy occurred in 12/67 (18%) children at a median age of 8 months (range 2–62 months). Epilepsy-free survival rates at 12, 24, 36, and 48 months were 89% (95% CI 79–95%), 88% (95% CI 77–94%), 85% (95% CI 73–92%), and 82% (95% CI 68–90%), respectively. Epilepsy was focal in 6/12 cases and infantile myoclonic in 6/12 cases. Median Engel-Classification (0–5) was 2 (<1 seizure/month).

Conclusions: We estimated 4-year cumulative incidence of epilepsy to be 18% after NAIS in a prospective cohort. This population is greatly in need of further study to identify biomarkers and potential therapeutic targets for epileptogenesis in the developing brain.

Keywords: Epilepsy and other paroxysmal disorders, Neonatal neurology, Stroke

163. Risk Factors for Neurodevelopmental Disorders in Pediatric Sickle Cell Disease
Lance El, Comi AM, Johnston MV, Casella JF, Shapiro BK (Baltimore, MD)

Objective: The primary objective of this study was to identify disease characteristics and complications associated with neurodevelopmental disorders in children with sickle cell disease.

Methods: The study was a retrospective case control study of children with sickle cell disease. A chart review of sickle cell disease subjects seen at either or both of two medical centers, Kennedy Krieger Institute (KKI) and Johns Hopkins Hospital (JHH), took place from May 2012 to March 2014. Charts from both hospitals were reviewed for documentation of neurodevelopmental diagnoses.

A total of 59 subjects were included in the overall chart review. Eighteen subjects were included in the KKI chart review and forty-one subjects were included in the JHH chart review. See Table 1 for additional subject characteristics.

Results: Prevalence of neurodevelopmental diagnoses and sickle cell disease related complications in the study group were presented in Tables 2 and 3. There was a significant difference between reported attention issues in children with different types of sickle cell disease (5% in HgbSS, 0% in HgbSC, 50% in HgbSβThal1, Fisher’s exact, p < 0.005). Additional significant results showed differences in reported developmental delay, behavioral issues, and academic performance between males and females and across different types and complications of sickle cell disease.

**TABLE 1. Characteristics of Pediatric Sickle Cell Disease Subjects (n = 59)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age at Last Visit</td>
<td>16.8 years (1.3 – 20)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male: 34 (58%)</td>
</tr>
<tr>
<td>Type of Sickle Cell Disease</td>
<td>Hgb SS: 37 (63%)</td>
</tr>
<tr>
<td></td>
<td>Hgb SC: 12 (20%)</td>
</tr>
<tr>
<td></td>
<td>Hgb Sβ Thal +: 6 (10)</td>
</tr>
<tr>
<td></td>
<td>Hgb SS and α Thal: 1 (2%)</td>
</tr>
<tr>
<td></td>
<td>Unknown: 3 (5%)</td>
</tr>
<tr>
<td>Sickle Cell Disease Treatment</td>
<td>Hydroxyurea: 24 (41%)</td>
</tr>
<tr>
<td></td>
<td>Chronic Transfusion Therapy: 11 (19%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Black: 57 (97%)</td>
</tr>
<tr>
<td></td>
<td>Caucasian: 1 (1.5%)</td>
</tr>
<tr>
<td></td>
<td>Other: 1 (1.5%)</td>
</tr>
<tr>
<td>School Services</td>
<td>Individualized Education Plan: 26 (44%)</td>
</tr>
<tr>
<td></td>
<td>None: 7 (12%)</td>
</tr>
<tr>
<td></td>
<td>504 Rehabilitation Act: 3 (5%)</td>
</tr>
<tr>
<td></td>
<td>Previous IEP: 1 (2%)</td>
</tr>
<tr>
<td></td>
<td>Unknown: 22 (37%)</td>
</tr>
<tr>
<td>Specific Learning Disability</td>
<td>17 (29%)</td>
</tr>
<tr>
<td>Math</td>
<td>7</td>
</tr>
<tr>
<td>Reading Comprehension</td>
<td>7</td>
</tr>
<tr>
<td>Reading</td>
<td>3</td>
</tr>
<tr>
<td>Poor Academic Performance</td>
<td>12 (20%)</td>
</tr>
<tr>
<td>Attention Deficit Hyperactivity</td>
<td>11 (19%)</td>
</tr>
<tr>
<td>Disorder (ADHD)</td>
<td>Inattentive Type: 5</td>
</tr>
<tr>
<td>Combined Type</td>
<td>1</td>
</tr>
<tr>
<td>Unknown Type</td>
<td>5</td>
</tr>
<tr>
<td>Developmental Delay</td>
<td>11 (19%)</td>
</tr>
<tr>
<td>Attention Issues</td>
<td>7 (12%)</td>
</tr>
<tr>
<td>Language Disorder</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Receptive and Expressive Language Disorder</td>
<td>2</td>
</tr>
<tr>
<td>Unknown Type</td>
<td>4</td>
</tr>
<tr>
<td>Behavioral Issues</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Language Delay</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Intellectual Disability</td>
<td>2 (3%)</td>
</tr>
</tbody>
</table>

*one subject had both a silent stroke and an ischemic stroke*
Conclusions: Children with certain types of sickle cell disease may have different risks for neurodevelopmental concerns such as attention issues. This preliminary study will aid in the design of prediction models to determine factors that may affect neurodevelopmental disorders in pediatric sickle cell disease.

Keywords: Genetics, Stroke

164. Inflammatory Markers in Acute Neonatal Arterial Ischemic Stroke
Mineyko A, Yusuf K, Narendran A, Kirton A (Calgary, AB)

Objective: The pathophysiology of perinatal stroke remains largely unknown. Inflammatory processes involving the placenta may explain pathogenesis and innate immune response may alter the degree of injury. The role of inflammation in acute neonatal arterial ischemic stroke (NAIS) has not been described.

Methods: We performed a prospective case-controlled pilot study. Inclusion criteria included term birth, acute NAIS diagnosed with diffusion MRI within 72 hours of birth, idiopathic stroke etiology, and no evidence of infection. A comprehensive panel of 65 chemokines and cytokines was analyzed using Luminex multiplex bead technology on serum of consecutive cases. Cord blood from birth, idiopathic stroke etiology, and no evidence of infection served as controls. Differservices in protein concentrations were determined by Student t-test and Wilcoxin Rank Sum.

Results: Nine NAIS cases and matched controls were enrolled (56% male). All cases presented with seizures and had middle cerebral artery AIS (56% left). Fourteen analytes were different between cases and controls. Cases showed elevations in IL-309, CTACK, MIP-1d, Flt-3L, IL-9, IL-4, MCP-1, IL-5, IL-8 and relative deficiencies in TARC, C6kine, TRAIL, G-CSF, and sCD40L. These cytokines and chemokines work synergistically to upregulate leukopoiesis and signal recruitment of mixed leukocyte lines.

Conclusions: A unique cytokine profile involving chemo-attractants and pro-inflammatory cytokines that act synergistically suggests a role of innate immunity in the pathophysiology of NAIS. Larger prospective studies determining cytokine network correlations are necessary to further elucidate this process.

Keywords: Infections/Neuroimmunology, Neonatal neurology, Stroke

165. Effect of Seizures on Attention in Children with Perinatal Stroke
Shi EL, Ballantyne AO, Trauner DA (La Jolla, CA)

Objective: To determine whether seizures beyond the neonatal period are associated with attention problems in children with perinatal stroke.

Methods: 34 children with perinatal stroke (PS) (17 with a history of seizures [PS+], 17 with no seizures [PS-]) and 34 typically developing controls were given the Test of Variables of Attention (TOVA) version 7.0.3, and Digit Span and Coding subtests from the WISC-3.

Results: There were no significant differences between controls and PS- on any of the measures. There was significantly poorer performance of the PS+ compared with controls on all measures. There was no clear relationship between medication and attention scores in the PS+ group.

Conclusions: The presence of seizures beyond the neonatal period significantly impairs attention in children with perinatal stroke. The results are consistent with the concept of attention resulting from network connectivity and functional communication, with seizures interfering with that connectivity. The results of this study add to the existing knowledge base on perinatal stroke and further efforts to predict, understand, and ameliorate the consequences so as to promote achievement as these children grow and learn.

Keywords: Epilepsy and other paroxysmal disorders, Stroke

166. Quality of Life in Children after Intracerebral Hemorrhage
Walker CH, Gindville MC, Ichord RN, Licht DJ, Beslow LA, Jordan LC (Nashville, TN)

Objective: While many studies have explored recovery after ischemic stroke in children, recovery after non-traumatic intracerebral hemorrhage (ICH) in children remains understudied. We assessed the relationship between neurological outcome and quality of life (QOL) in children with ICH.

Methods: A prospective study of non-traumatic ICH in children (≥ 37 weeks gestation–17 years) seen at three institutions from 2007 to 2012 assessed neurologic outcome at 3 and 12 months post-ICH via the pediatric stroke outcome measure (PSOM) and the Pediatric Quality of Life Inventory 4.0 (PedsQL). Parent-proxy (2–17 years) and child self-report (5–17 years) PedsQL forms were completed.

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Results: We assessed QOL in 23 children with ICH, median age 12.9 years, interquartile range (8–16 years), 58% male. At 12 months post ICH, moderate correlation was present between the PSOM and parent-proxy QOL physical functioning subscores (Spearman’s r = -0.61) and total QOL score (r = -0.49). Poorer PSOM cognitive-behavioral subscores correlated with reduced social and school QOL subscales (r = -0.57 and r = -0.68). Parent-proxy total QOL scores did not improve from 3 to 12 months (median increase of 1.1 points). Children rated their overall QOL higher than their parents 12 months post-ICH (child median 84.4, parent-proxy median 74.3), Wilcoxon signed-rank test p < 0.001. This pattern was also seen in the various subcategories of QOL.

Conclusions: Overall QOL decreases with increasing neurological deficits. Cognitive-behavioral deficits correlate with reduced social and school-related QOL. Children rate their QOL higher after ICH than their parents. Additional research is required to understand factors other than neurological deficits that impact QOL.

Keywords: Stroke

167. Increased Pediatric Functional Neurologic Symptom Disorders following the Boston Marathon Bombings: a case series
Guerrero RM, Pier DB, de Gusmão CM, Bernson-Leung ME, Maski KP, Urion DK, Waugh JL (Boston, MA)

Objective: Functional neurologic symptom disorders are frequently the basis for acute neurologic consultation. In children they are often precipitated by high-frequency, everyday stressors. The extent to which a severe traumatic experience may also precipitate functional neurologic symptoms is unknown.

Methods: For the two-week period following the Boston Marathon bombings, we prospectively collected data on patients whose presentation suggested a functional neurological symptom disorder. We assessed clinical and demographic variables, duration of symptoms, extent of educational impact, and degree of connection to the Marathon bombing. We contacted all patients at six months following presentation to determine outcome and accuracy of the diagnosis.

Results: In a parallel study we reported a baseline of 2.6 functional neurological presentations per week in our emergency room. In the week following the Boston Marathon bombings this frequency tripled. Ninety-one percent of presentations were delayed by one week, with onset around the first school day following a city-wide lockdown. Seventy-three percent had a history of a prior psychiatric diagnosis. At 6 months follow-up, no functional neurological symptom disorder diagnoses were overthrown and no new organic diagnosis was made.

Conclusions: Pediatric functional neurological symptom disorder may be precipitated by both casual and high-intensity stressors. The 3.4-fold increase in incidence following the Boston Marathon bombings and city-wide lockdown demonstrates the marked effect that a community-wide tragedy can have on the mental health of children. Care providers must be aware of functional neurological symptom disorders following stressful community events in vulnerable patient populations, particularly those with prior psychiatric diagnoses.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders

168. West Nile Encephalitis in a Breast-Fed Newborn Infant
Appavu BL, Condie J (Phoenix, AZ)

Objective: We present the first case of a breast-fed infant with West Nile Encephalitis.

Methods: A previously healthy, 59 day old breast-fed male infant presented with a four day history of facial rash, fevers, and subsequent status epilepticus. His mother experienced fevers and a body rash concurrent to his symptoms. He underwent electroencephalography, MR imaging, and transcranial doppler assessments in the ICU.

Results: The patient was brought out of status epilepticus with IV lorazepam. Electroencephalography during the first 48 hours revealed absent right hemispheric sleep spindles, which later improved. MR imaging revealed an infarction to the right lateral thalamus. Transcranial doppler analysis suggested increased cerebral vascular resistance in the posterior circulation. Cerebral spinal fluid returned positive for IgM West Nile Virus antibodies. He was treated with levetiracetam, aspirin, and IV fluids, and made a strong recovery. Breast milk was sent to the CDC, with analysis pending.

Conclusions: West Nile Encephalitis is caused by a RNA-containing flavivirus, is known to primarily affect older adults, and can lead to seizures and deep cerebral infarctions. There had been no prior reported cases of clinical illness with the West Nile Virus in breastfeeding infants, though there has been suspicion that it can be transmitted in breast milk. This case demonstrates that this encephalitis can occur in the newborn period, and manifest with seizures and thalamic strokes. Future assessments of breast milk in infants with West Nile viral infections, in conjunction with this case, may help further elucidate the risks of breast-feeding with infected mothers.

Keywords: Case studies/case series, Infections/Neuroimmunology

169. Continuous Intravenous Valproic Acid as an Abortive Therapy for Pediatric Migraine
Zafar MS, Cook AM, Stewart A, Baumann R (Lexington, KY)

Objectives: To study the efficacy of continuous intravenous valproic acid as an abortive therapy for pediatric migraine.

Background: Valproic acid (VPA) has been reported to be effective in status epilepticus and prophylaxis of migraine headache. IV VPA as bolus dose has also shown to be effective as an outpatient abortive therapy in children but its effectiveness is unknown.

Methods: This is a retrospective chart review of all children admitted to Kentucky Children Hospital from August 2009 to August 2012 and treated with IV VPA. Children in
migraine status were treated by standard protocol: IV VPA load 20mg/kg followed by continuous infusion of 1 mg/kg/hour. Serum VPA levels were checked at 4, 24 and 48 hours. The target serum concentration was 100(+/-10). Standard pain scoring (FACES for ages 4-8 and VAS for >8 year) was used. Response was graded according to reduction in pain scoring as Excellent (> than 50%) Moderate (> than 30% but < than 50%) and Poor (< than 30%).

Results: 78 subjects met criteria. They were 24 boys (32%), 54 girls (69%), ages 4 to 18 year (mean 12.9 +/- 3.34%). 59 (75%) reported an excellent response, 9 (11.5%) a moderate response and 10 (12.8%) a poor response. 68% with excellent response responded within first 12 hours. Age and gender did not affect the likelihood of response. The only reported side effect, Nausea, was noticed in 5 children.

Conclusions: Continuous infusion IV VPA is a safe, rapidly effective, abortive agent in pediatrics Migraine. Randomized, double blind, controlled studies are warranted.

Keywords: Headache/Migraine

170. Do Systemic Variables Add Predictive Value to Amplitude-Integrated EEG for Neonates with Hypoxic Ischemic Encephalopathy?
Kushwaha JS, Plegue MA, Selewski DT, Barks JDE, Shellhaas RA (Detroit, MI)

Objective: Amplitude-integrated EEG (aEEG) is a robust predictor of outcome after hypoxic ischemic encephalopathy (HIE). Cerebral and systemic near-infrared spectroscopy (NIRS) are commonly measured, but their predictive value is not well understood. Acute kidney injury (AKI) is associated with abnormal neuroimaging findings in neonates with HIE. We investigated the prognostic value of aEEG, cerebral and systemic NIRS, and AKI for 18-month neurodevelopmental outcome in neonates with HIE treated with therapeutic hypothermia.

Methods: Neonates were monitored with bilateral parietal aEEG, bilateral parietal and systemic NIRS during the 72-hours of therapeutic hypothermia. NIRS-measured rsO2 and objective aEEG data (average minimum, maximum, and mean amplitudes) were evaluated in 12-hour epochs during hypothermia. Modified KDIGO criteria were used to classify AKI based on rise in creatinine from a previous trough. 18-month Bayley Scales of Infant Development III (BSID) were recorded. Adverse outcome was death or BSID cognitive and language scores <85.

Results: Outcomes were available for 18 of 21 enrolled infants (5 adverse outcomes). There was no association between cerebral or systemic NIRS and BSID scores. Mean aEEG amplitude during hours 24-48 of cooling was higher among those with good outcomes (p = 0.027 to 0.032). The aEEG lower margin was also higher during hours 12-48 for those with good outcomes (p = 0.014 to 0.035). AKI did not predict outcome (p > 0.05).

Conclusions: In this pilot study, systemic variables did not predict outcome, but some aEEG variables during the first two days of cooling were confirmed to distinguish those who experience good versus adverse outcomes after HIE.

Keywords: Neonatal neurology

171. Prematurity and the Association between Periventricular Leukomalacia Laterality on MRI and Learning Disability Outcome
Huff HV, Urion DK (New Orleans, LA)

Objective: We hypothesized an association between history of prematurity and learning disability (LD) outcome, with the severity of disability associated with lateralization of periventricular leukomalacia (PVL) observed on brain MRIs.

Method: We undertook a retrospective analysis of cases referred to a tertiary-hospital-based LD program. MRIs were reviewed for all patients born prematurely to assess for structural brain abnormalities. Those with PVL were assessed for laterality of PVL. Additionally, the level of severity of current LD outcome for each patient with PVL was determined based on the child’s level of suggested service provision. This LD outcome was compared to the child’s PVL laterality.

Results: Of the 1940 children evaluated between 2000 and 2010 in the LD Program, 640 had a history of prematurity and 600 were found to have normal MRI. Of the 600, 520 were found to have PVL (roughly 40% had PVL predominantly on the left, 20% on the right and 40% were bilateral symmetric). The categorization of “very significant LD outcome” was given to 50% of the left sided PVL patients, nearly 70% of the right-sided PVL patients and all of the bilateral symmetric PVL patients. The proportion of patients with very significant LD outcomes is much greater than that in a comparable sample over the same period without a history of prematurity.

Conclusions: This study found that severity of LD outcome was highly associated with a history of prematurity, and that laterality of PVL on MRI in this population was differentially associated with LD outcome.

Keywords: Neonatal neurology, Neuroimaging

172. Interneuron-specific Loss of Tsc2 Causes Hyperactivity and Early Communicative Impairment
Fu C, Parker B, Eis KC (Nashville, TN)

Tuberous sclerosis complex (TSC) is a genetic neurodevelopmental disorder caused by mutations in either TSC1 or TSC2. Although it affects multiple organs, neurological morbidity is considerable with frequent occurrence of epilepsy and neuropsychiatric manifestations such as autism spectrum disorder and attention deficit-hyperactivity disorder. Despite advances related to the molecular pathogenesis and emergence of mTORC1 inhibitors as promising treatments for a subset of TSC symptoms, the neuropsychiatric manifestations remain refractory to mechanism oriented treatment. This discrepancy may stem from a knowledge gap related to underlying mechanisms at the developmental level. Emerging evidence suggests that GABAergic interneuron abnormalities contribute to neurological symptoms in TSC. We hypothesized that abnormal interneuron development contributes to neuropsychiatric morbidity in TSC. To test this hypothesis and explore the role of interneurons in TSC behavioral manifestations, we recently developed a

Keywords: Neonatal neurology
novel conditional knockout mouse model of TSC by inactivating Tsc2 in neocortical interneurons. These interneuron-specific Tsc2 knockout mice have abnormal neocortical interneuron development associated with increased mTORC1 activity. They exhibit significant delays in growth, early deficits in communicative behavior and exhibit significant hyperactivity in a novel environment. To our knowledge this is the first TSC mouse model exhibiting behavior traits modeling ADHD. Studies directed towards underlying mechanisms of altered interneuron development and contributions to hyperactivity in this model are ongoing and have great potential to inform mechanism based treatments for TSC related ADHD.

173. Safety, Pharmacokinetics and Preliminary Assessment of Efficacy of Dextromethorphan for the Treatment of Rett Syndrome

Objectives: Evaluate safety, tolerability and pharmacokinetic profile of Dextromethorphan (DM), and identify an effective dose to improve cognition, and seizures in girls with Rett Syndrome (RTT).

Methods: Girls ages 2–15 years with mutations in the MeCP2 gene were identified. Fast metabolizers of DM were determined by pK studies and randomized to one of three escalating doses of DM (0.25, 2.5 and 5 mg/kg/day). Routine laboratory tests, neurologic and behavioral assessments were performed pre and post-trial (6 months).

Results: Of the forty-nine enrolled subjects, thirty eight were randomized. Eleven slow metabolizers of DM and were excluded. Thirty-five completed the 6 month study without side effects. No hematologic, electrolyte, LFT or EKG abnormalities related to DM were noted in any of the three treatment groups. Two participants were discontinued due to inter-current illnesses and one was deferred due to imminent scoliosis surgery. A subsample was evaluated using the Mullen and Vineland Adaptive Behavior scales. Although, the scores at baseline were different in the three treatment groups, we report significant gain in receptive language, vis-sual reception and socialization skills post trial at a dose of 5 mg/kg/day. Despite lack of improvement in spike counts seven out of twenty-five participants showed improvement in clinical seizures, fifteen remained unchanged and three worsened. One subject showed reduction in myoclonus that returned to pre-trial levels post-trial.

Conclusions: Our study demonstrates that DM is safe and well tolerated in young girls with RTT. Preliminary data shows improvement in receptive language, socialization and clinical seizures.

Mintz M, Chadebume M, Barahat R, McKernan K, Boles RG, Marks H, Stanley C, Zare A (Gibbsboro, NJ)

Objective: To assess the clinical utility of large targeted NextGen DNA sequencing panels focused on genes of interest for mitochondrial function and/or ion channel transport ("relevant exomes") for individuals with Autism Spectrum Disorders and Intellectual Disabilities (ASD/ID), with and without Epilepsy.

Methods: Retrospective analysis of 65 individuals with ASD/IDs, with and without concomitant Epilepsy, who had comprehensive DNA sequence analyses of epilepsy-associated and nuclear mitochondrial genes, and mitochondrial genome sequencing, utilizing 450 to 1,200 gene panels (Courtagen Diagnostics Laboratory, Woburn, MA).

Results: There were 19 (29%) patients with genetic variants that were interpreted as likely associated with disease or the patient's phenotype; 28 (43%) had variants of uncertain significance (VUS), and 18 (28%) had variants likely not associated with disease/phenotype. Sanger sequencing of parental DNA was recommended for 48 patients and completed to date in 13; there was one "de novo" mutation and four "in trans". Of the 47 patients with positive or VUS findings, 34 (52% overall) had "actionable" findings defined as informing or changing clinical management, which included specific medication, supplement or dietary options, and/or additional specific diagnostic testing.

Conclusions: Utilization of targeted NextGen sequencing panels assessing relevant exomes provides high yields with actionable results and reduces incidental findings compared to whole exome sequencing (WES). Such panels should be considered as an initial and lower-cost alternative to WES, particularly for those with ASDs/IDs. As with all genetic testing, higher yields are dependent upon linkage of excellent comprehensive clinical information with well-analyzed sequence data by both physician and genomicist.

Keywords: Epilepsy and other paroxysmal disorders, genetics

175. Tracking Neurogenesis in Perinatal Stroke - Potential MR Applications
Felling RJ, Zhang J, Northington FJ (Baltimore, MD)

Objective: Studies in animal models of perinatal hypoxic/ischemic brain injury have demonstrated post-injury neurogenesis in the subventricular zone (SVZ). This presumably contributes to plasticity-based repair mechanisms, but we do not know to what extent neurogenesis occurs in the human brain after such injuries. We sought to identify potential magnetic resonance imaging (MRI) biomarkers of neurogenesis in perinatal stroke patients.

Methods: We identified a series of perinatal stroke patients who had diffusion weighted MRI (DW-MRI) in the first week of life. We defined a region of interest adjacent to the lateral ventricle (LV) ipsilateral to the stroke as corresponding to the SVZ and measured the average ADC signal. We compared this to the average ADC signal within the infarct core and in the contralateral SVZ.

Results: We identified 3 patients with perinatal arterial ischemic stroke from our recent experience who had DW-MRI in the first week of life. In these patients the ipsilateral SVZ demonstrated reduced ADC values compared to the contralateral, and these values were discordant with the adjacent infarct core.
Conclusions: We identified a unique signal on DW-MRI within the region of the SVZ in several patients with perinatal arterial ischemic stroke. The reduced ADC values were unique to the ipsilateral side, and differed from the adjacent infarct core, suggesting different processes. DW-MRI is generally used to demonstrate acute cytotoxic edema, but increased cellularity, for example, can demonstrate similar changes. This signal may result from increased SVZ cellularity reflective of neurogenesis occurring in response to stroke.

Keywords: Neonatal neurology, neuroimaging, stroke

176. Impaired Cognitive Performance after Exposure to Anesthesia in Premature Newborns
Gano D, Andersen SK, Glass HC, Rogers EE, Barkovich AJ, Ferriero DM (San Francisco, CA)

Objective: Exposure to anesthesia in early childhood is associated with an increased risk of adverse neurodevelopment, however it is not known if age at exposure affects neurodevelopmental outcome. Our objective was to evaluate the association of cognitive outcome to the number of surgeries required before and after term-equivalent age in premature newborns.

Methods: Cohort study of exposure to anesthesia for surgery among premature newborns (<33 weeks gestation) prospectively studied with neonatal MRI and the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) at 3-6 years blinded to anesthesia exposure. Multivariate linear regression was performed to analyze the association of composite IQ scores with the number of surgeries before term-equivalent age (<42 weeks postmenstrual age) and after (≥42 weeks), adjusting for clinical variables associated with surgery prior to term-equivalent age.

Results: Among 128 children evaluated with the WPPSI-III at 4.6 ± 0.6 years, 25 (19.5%) had one surgery prior to term-equivalent age, and 18 (14.1%) had ≥2. Children that required surgery before term-equivalent age were born at a younger gestational age, and had higher rates of complications of prematurity. After adjusting for multiple variables, ≥2 surgeries before term-equivalent age was associated with significantly reduced full-scale IQ (effect size: -18.4 points, 95% CI -29.8 to -9.3), performance IQ (effect size: -22.6 points, 95% CI -29.7 to -11.9), and verbal IQ (effect size: -9.8, 95% CI -29.8 to -0.4). The number of surgeries after term-equivalent age was not associated with cognitive outcome (all P > 0.2).

Conclusions: Two or more surgeries prior to term-equivalent age in premature newborns is independently associated with impaired cognitive performance.

Keywords: Neonatal Neurology

177. Serial Diffusion Imaging Reveals Tuber Evolution in Tuberous Sclerosis Complex
Peters JM, Prohl AK, Aymeric A, Thomas-Fernandez X, Scherrer B, Taquet M, Sablin M, Warfield SK (Boston, MA)

Objective: To describe the natural microstructural evolution of tubers, perituber tissue, and normal appearing white matter in Tuberous Sclerosis Complex using serial diffusion tensor imaging (DTI).

Figure 1. Microstructural Changes with Age. A generalized additive mixed model (GAMM) was inferred with the aim of predicting microstructural changes, assessed as the averaged fractional anisotropy (FA, top) and mean diffusivity (MD, bottom) in the different tissue types, while adjusting for age, lobe and segmented volume. The GAMM allowed accounting for and estimating the known non-linear relationship of MD and FA with age, and the intra- and inter-subject variability. Note that an equal volume is assumed for each tissue type and for each lobe, making comparison possible between lobes and tissue types. Controls: White matter in black (WM); patients: tubers in red (T), perituber rim in salmon (PT), normal appearing white matter in light blue (NAWM).
Methods: 3T structural and 35 direction diffusion magnetic resonance images (MRI) were automatically segmented based on a combined global-local intensity mixture model to define regions of tuber, an equal volume perituber rim, and the remaining normal appearing white matter (NAWM). A generalized additive mixed model (GAMM) was used to predict microstructural changes for each tissue type, assessed as the averaged mean diffusivity (MD) and fractional anisotropy (FA), adjusted for age, lobe and segmented volume.

Results: 25 patients, mean age 5.89 year (range 0.5–24.5 years) underwent 2–6 scans (total n = 70, average scan interval 1.1 years, range 0.9–7.9), and were compared to 73 scans of healthy controls. FA was lowest and MD was highest in tubers, next in perituber tissue, then in NAWM. In each scan, a smooth gradient was found of decreasing diffusion abnormality, from tuber, to perituber tissue, to NAWM. Longitudinal analysis using the GAMM showed a positive (FA) and negative (MD) correlation with age in tubers, perituber tissue and NAWM. All three tissue types followed a developmental trajectory similar to the white matter of controls.

Conclusions: Tubers, perituber tissue, and normal appearing white matter in Tuberous Sclerosis Complex are neither static nor discrete, and undergo microstructural evolution with age. The severity of diffusion abnormalities are a function of distance to the tuber, in line with known extent of histologic, immunohistochemical and molecular abnormalities.

Keywords: Neuroimaging
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