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 25.5 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, 2012.
PAST OFFICERS

President
Kenneth Swaiman 1972–73
Gerald Fenichel 1973–74
Manuel Gomez 1974–75
James Schwartz 1975–76
Richard Allen 1976–77
Bruce Berg 1977–78
N. Paul Rosman 1978–79
Arthur Prensky 1979–80
Paul Dyken 1980–81
Mary Anne Guggenheim 1981–82
Raymond Chun 1982–83
Robert Eiben 1983–85
David Stumpf 1985–87
Marvin Fishman 1980–82
Marvin Fishman 1980–82
Darryl C. De Vivo 1989–91
Joseph J. Volpe 1993–95
Michael E. Cohen 1995–97
Alan K. Percy 1997–99
Lawrence Lockman 1981–84
Robert Eiben 1978–81
Marvin Fishman 1984–86
Ira Lott 1986–89
Stephen Ashwal 2001–03
James Bale 2003–05
Ann Tilton 2005–07
John Bodensteiner 2007–09
Donna Ferriero 2009–11

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 1989–93
Stephen Ashwal 1993–97
Patricia Crumrine 1997–2002
Ann Tilton 2003–04
Nina Schor 2004–10
Harvey Singer 2010–

Councillor
Isabelle Rapin 1972–73
Manuel Gomez 1972–73
John Menkes 1972–74
James Schwartz 1972–74
Karin Nelson 1973–74
Raymond Chun 1973–75
Bruce Berg 1974–76
Paul Dyken 1974–76
Arthur Prensky 1975–77
N. Paul Rosman 1975–77
Jack Madsen 1976–78
Peggy Ferry 1976–78
Joseph French 1977–79
Francis Wright 1977–79
Mary Anne Guggenheim 1978–80
Gerald Golden 1978–80
Gerald Erenberg 1979–81
John Freeman 1979–81
Marvin Weil 1980–82

Marvin Fishman 1980–82
Peter Huttenlocher 1981–83
Michael Bresnan 1981–83
David Stumpf 1982–84
Gwendolyn Hogan 1982–84
Joseph Volpe 1983–85
Barry Russman 1983–85
Russell Snyder 1984–86
Ian Butler 1984–86
W. Edwin Dodson 1985–87
Michael Painter 1985–87
Robert Zeller 1986–88
Doris Trauner 1986–88
Darryl De Vivo 1987–88
Gary Goldstein 1987–89
Robert Vannucci 1988–89
Stephen Ashwal 1988–90
Jack Pellock 1988–90
Joseph Pasternak 1989–91
Patricia Duffner 1989–91
O. Carter Snead 1990–92
Edwin Meyer 1990–92
Israel Abroms 1991–93
William Logan 1991–93
Mary Johnson 1992–94
Alan Percy 1992–94
Phyllis Sher 1993–95
Gregory Holmes 1993–95
W. Donald Shields 1994–96
John Bodensteiner 1994–96
Patricia Crumrine 1995–97
James Bale 1995–97
Alan Hill 1996–98
Ann Tilton 1996–98
Edward Kovnar 1997–99
Richard Nordgren 1997–99
Michael Goldstein 1998–2000
Faye Silverstein 1999–01
Michael Johnston 1999–01
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
Sakkubai Naidu 2009–11
NATIONAL MEETINGS

Ann Arbor, Michigan 1972
Nashville, Tennessee 1973
Madison, Wisconsin 1974
Hamilton, Ontario, Canada 1975
Monterey, California 1976
Charlottesville, Virginia 1977
Keystone, Colorado 1978
Hanover, New Hampshire 1979
Savannah, Georgia 1980
Minneapolis, Minnesota 1981
Salt Lake City, Utah 1982
Williamsburg, Virginia 1983
Phoenix, Arizona 1984
Memphis, Tennessee 1985
Boston, Massachusetts 1986
San Diego, California 1987
Halifax, Nova Scotia, Canada 1988
San Antonio, Texas 1989
Atlanta, Georgia 1990
Portland, Oregon 1991
New Orleans, Louisiana 1992
Orlando, Florida 1993
San Francisco, California 1994
Baltimore, Maryland 1995
Minneapolis, Minnesota 1996
Phoenix, Arizona 1997
Montreal, Quebec, Canada 1998
Nashville, Tennessee 1999
St. Louis, Missouri 2000
Victoria, British Columbia, Canada 2001
Washington, DC 2002
Miami Beach, FL 2003
Ottawa, Ontario, Canada 2004
Los Angeles, CA 2005
Pittsburgh, PA 2006
Quebec City, QC, Canada 2007
Santa Clara, CA 2008
Louisville, KY 2009
Providence, RI 2010
Savannah, GA 2011
Huntington Beach, CA 2012
Hilton Austin, Austin, TX October 30–November 2, 2013
HOWER AWARD LECTURE RECIPIENTS

1974  Douglas Buchanan  Chicago
1975  Randolph K. Byers  Boston
1976  Sidney Carter  New York
1977  David B. Clark  Lexington
1978  Philip R. Dodge  St. Louis
1979  Paul I. Yakovlev  Boston
1980  John H. Menkes  Beverly Hills
1981  Kenneth F. Swaiman  Minneapolis
1982  Patrick F. Bray  Salt Lake City
1983  Betty Q. Banker  Cleveland
1984  Peter R. Huttenlocher  Chicago
1985  Raymond D. Adams  Boston
1986  Jean Aicardi  Paris
1987  Isabelle Rapin  Bronx
1988  Bruce Berg  San Francisco
1989  Manuel Gomez  Rochester
1990  Joseph J. Volpe  Boston
1991  Karin B. Nelson  Bethesda
1992  Darryl C. De Vivo  New York
1993  Bengt D. Hagberg  Goteborg
1994  Hugo Moser  Baltimore
1995  Salvatore DiMauro  New York
1996  William Bell  Iowa City
1997  Gerald Fenichel  Nashville
1998  N. Paul Rosman  Boston
1999  Marvin Fishman  Houston
2000  Arthur Prensky  St. Louis
2001  Charles Barlow  Boston
2002  Peter H. Berman  Philadelphia
2003  Michael E. Cohen  Buffalo
2004  John Freeman  Baltimore
2005  Alan Percy  Birmingham
2006  Michael Painter  Pittsburgh
2007  Robert S. Rust  Charlottesville
2008  Stephen Ashwal  Loma Linda
2009  Peter Camfield  Halifax
2010  Sakkubai Naidu  Baltimore
2011  Deborah Hirtz  Bethesda
2012  Ann Tilton  New Orleans
# INVITED SPEAKERS AND BERNARD SACHS LECTURERS

<table>
<thead>
<tr>
<th>Year</th>
<th>Speaker</th>
<th>City</th>
</tr>
</thead>
<tbody>
<tr>
<td>1977</td>
<td>George Cahill</td>
<td>Boston</td>
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<tr>
<td>1978</td>
<td>W. Maxwell Cowan</td>
<td>St. Louis</td>
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<tr>
<td>1979</td>
<td>Fred Plum</td>
<td>New York</td>
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<tr>
<td>1980</td>
<td>Dominick Purpura</td>
<td>New York</td>
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<tr>
<td>1981</td>
<td>Pasko Rakic</td>
<td>New Haven</td>
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<td>1982</td>
<td>John O'Brien</td>
<td>La Jolla</td>
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<td>1983</td>
<td>Roger N. Rosenberg</td>
<td>Dallas</td>
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<td>1984</td>
<td>William L. Nyhan</td>
<td>La Jolla</td>
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<td>1985</td>
<td>Patricia Goldman-Rakic</td>
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<td>1986</td>
<td>Louis Sokoloff</td>
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<td>1987</td>
<td>Hugo Moser</td>
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<td>1988</td>
<td>Victor Dubowitz</td>
<td>London</td>
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<td>Salvatore DiMauro</td>
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<td>1990</td>
<td>Roscoe O. Brady</td>
<td>Bethesda</td>
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<td>1991</td>
<td>Marcus E. Raichle</td>
<td>St. Louis</td>
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<tr>
<td>1992</td>
<td>Louis M. Kunkel</td>
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<td>1993</td>
<td>C. Thomas Caskey</td>
<td>Houston</td>
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<td>1994</td>
<td>David Prince</td>
<td>Stanford</td>
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<td>1995</td>
<td>Gerald D. Fischbach</td>
<td>Boston</td>
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<td>1996</td>
<td>Verne S. Caviness</td>
<td>Boston</td>
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<td>1997</td>
<td>Martha Bridge Denckla</td>
<td>Baltimore</td>
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<td>1998</td>
<td>Andrew Engel</td>
<td>Rochester</td>
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<td>1999</td>
<td>Carla Shatz</td>
<td>Berkeley</td>
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<td>2000</td>
<td>Joseph Volpe</td>
<td>Boston</td>
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<td>2001</td>
<td>Huda Zoghbi</td>
<td>Houston</td>
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<td>2002</td>
<td>Francis Collins</td>
<td>Bethesda</td>
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<tr>
<td>2003</td>
<td>Darryl C. De Vivo</td>
<td>New York</td>
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<td>2004</td>
<td>Karin Nelson</td>
<td>Bethesda</td>
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<td>2005</td>
<td>O. Carter Snead, III</td>
<td>Toronto</td>
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<td>2006</td>
<td>Donna Ferriero</td>
<td>San Francisco</td>
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<td>2007</td>
<td>Frederick Andermann</td>
<td>Montreal</td>
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<tr>
<td>2008</td>
<td>Michael Johnston</td>
<td>Baltimore</td>
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<tr>
<td>2009</td>
<td>Gregory Holmes</td>
<td>Lebanon, NH</td>
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<tr>
<td>2010</td>
<td>Thomas Jessell</td>
<td>New York</td>
</tr>
<tr>
<td>2011</td>
<td>Laura Ment</td>
<td>New Haven</td>
</tr>
<tr>
<td>2012</td>
<td>Roger Packer</td>
<td>Washington, DC</td>
</tr>
<tr>
<td>Year</td>
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<tr>
<td>1983</td>
<td>Michael Pranzatelli</td>
<td>Washington</td>
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<tr>
<td>1985</td>
<td>Richard J. Konkol</td>
<td>Milwaukee</td>
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<tr>
<td>1986</td>
<td>Faye S. Silverstein</td>
<td>Ann Arbor</td>
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<td>1987</td>
<td>Vinodh Narayanan</td>
<td>Pittsburgh</td>
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<tr>
<td>1988</td>
<td>Huda Zoghbi</td>
<td>Houston</td>
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<td>1989</td>
<td>Scott L. Pomeroy</td>
<td>St. Louis</td>
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<td>1990</td>
<td>Harris Gelbard</td>
<td>Rochester (NY)</td>
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<td></td>
<td>Evan Y. Snyder</td>
<td>Boston</td>
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<td>1991</td>
<td>Kenneth J. Mack</td>
<td>Madison</td>
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<tr>
<td>1992</td>
<td>Kelvin A. Yamada</td>
<td>St. Louis</td>
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<tr>
<td>1993</td>
<td>Jeffrey J. Neil</td>
<td>St. Louis</td>
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<tr>
<td>1994</td>
<td>Mia MacCollin</td>
<td>Boston</td>
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<tr>
<td>1995</td>
<td>Adre J. du Plessis</td>
<td>Boston</td>
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<tr>
<td>1996</td>
<td>Michael Rivkin</td>
<td>Boston</td>
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<tr>
<td>1997</td>
<td>William A. Weiss</td>
<td>San Francisco</td>
</tr>
<tr>
<td>1998</td>
<td>Joseph Gleeson</td>
<td>Boston</td>
</tr>
<tr>
<td>1999</td>
<td>Amy Brooks-Kayal</td>
<td>Philadelphia</td>
</tr>
<tr>
<td>2000</td>
<td>Stephen Back</td>
<td>Portland</td>
</tr>
<tr>
<td>2001</td>
<td>Daniel J. Bonthius</td>
<td>Iowa City</td>
</tr>
<tr>
<td>2002</td>
<td>Nigel Bamford</td>
<td>New York</td>
</tr>
<tr>
<td>2003</td>
<td>Bradley Schlaggar</td>
<td>St. Louis</td>
</tr>
<tr>
<td>2004</td>
<td>Terrie Inder</td>
<td>Melbourne</td>
</tr>
<tr>
<td>2005</td>
<td>Mustafa Sahin</td>
<td>Boston</td>
</tr>
<tr>
<td>2006</td>
<td>Elliott Sherr</td>
<td>San Francisco</td>
</tr>
<tr>
<td>2007</td>
<td>Mirjana Maletic-Savatic</td>
<td>Stony Brook</td>
</tr>
<tr>
<td>2008</td>
<td>Laura Jansen</td>
<td>Seattle</td>
</tr>
<tr>
<td>2009</td>
<td>Jeffrey Neul</td>
<td>Houston</td>
</tr>
<tr>
<td>2010</td>
<td>Stephen Maricich</td>
<td>Cleveland</td>
</tr>
<tr>
<td>2011</td>
<td>James Dowling</td>
<td>Ann Arbor</td>
</tr>
<tr>
<td>2012</td>
<td>Yoon-Jae Cho</td>
<td>Stanford</td>
</tr>
</tbody>
</table>
CNS LIFETIME ACHIEVEMENT AWARDS

2004 Jean Holowach Thurston
St. Louis, MO

2005 Robert Eiben
Cleveland, OH
Arnold Gold
New York, NY

2006 Raymond Chun
Madison, WI
Barry Russman
Portland, OR

2007 William Kennedy
Watertown, ME
Gordon Watters
Montreal, Quebec

2008 Cesare Lombroso
Boston, MA

2009 Mary Anne Guggenheim
Helena, MT

2010 Russell Snyder
Albuquerque, NM

2011 Warren Grover
Philadelphia, PA

2012 Bhuwan Garg
Indianapolis, IN

M. Richard Koenigsberger
Demarest, NJ

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

2010 Ruth D. Nass
New York, NY

2011 Shaul Harel
Tel Aviv, Israel

2012 Marvin Fishman
Houston, TX
<table>
<thead>
<tr>
<th>Year</th>
<th>Name</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>Meral Ozmen</td>
<td>Istanbul, Turkey</td>
</tr>
<tr>
<td>1990</td>
<td>Najoua Miladi</td>
<td>Tunis, Tunisia</td>
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<tr>
<td>1991</td>
<td>Sergio A. Antoniuk</td>
<td>Curitiba, Brazil</td>
</tr>
<tr>
<td>1992</td>
<td>Qin Jion</td>
<td>Beijing, China</td>
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<tr>
<td>1993</td>
<td>Anu Soot</td>
<td>Tartu, Estonia</td>
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<td>1994</td>
<td>Lai Choo Ong</td>
<td>Kuala Lampur, Malaysia</td>
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<td>1995</td>
<td>Nina Barisic</td>
<td>Zagreb, Croatia</td>
</tr>
<tr>
<td>1996</td>
<td>Shan Wei Song</td>
<td>Beijing, China</td>
</tr>
<tr>
<td>1997</td>
<td>Aleksandra Djukic</td>
<td>Belgrade, Yugoslavia</td>
</tr>
<tr>
<td>1998</td>
<td>Ana Keleme Novi Sad</td>
<td>Yugoslavia</td>
</tr>
<tr>
<td>1999</td>
<td>Magda L. Nunes</td>
<td>Porto Alegre, Brazil</td>
</tr>
<tr>
<td>2000</td>
<td>Brahim Tabarki-Melaiki</td>
<td>Brussels, Belgium</td>
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<tr>
<td>2001</td>
<td>Dimitrios Zafeiriou</td>
<td>Thessalonikki, Greece</td>
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<tr>
<td>2002</td>
<td>Vedrana Milic Rasic</td>
<td>Belgrade, Serbia</td>
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<tr>
<td>2003</td>
<td>David Chkhartishvili</td>
<td>Tbilisi, Georgia</td>
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<tr>
<td>2004</td>
<td>Natalia A. Yermolenko</td>
<td>Voronezh, Russia</td>
</tr>
<tr>
<td>2005</td>
<td>Lusine Kirakosyan</td>
<td>Yerevan, Armenia</td>
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<tr>
<td>2006</td>
<td>Gia Melikoshvili</td>
<td>Tbilisi, Georgia</td>
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<td>2007</td>
<td>David E. Kombo</td>
<td>Dars Es Salaam, Tanzania</td>
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<tr>
<td>2008</td>
<td>Ikeolu Lagunju</td>
<td>Ibadan, Nigeria</td>
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<tr>
<td>2009</td>
<td>Uduak Mayen Offiong</td>
<td>Abuja, Nigeria</td>
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<tr>
<td>2010</td>
<td>Parayil.S. Bindu</td>
<td>Bangalore, India</td>
</tr>
<tr>
<td>2011</td>
<td>Kyaw Linn</td>
<td>Myanmar</td>
</tr>
<tr>
<td>2012</td>
<td>Inga Talvik</td>
<td>Tartu, Estonia</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
- 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

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
- Jeffrey J. Gold
  University of California San Diego
- Gayatri Mainali
  Cleveland Clinic Foundation
- Christopher B. Oakley
  Johns Hopkins Medical Institute
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

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
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
THE CHILD NEUROLOGY SOCIETY GRATIFYINGLY ACKNOWLEDGES THE FINANCIAL SUPPORT OF

- Akron Children’s Hospital
- The Arnold P. Gold Foundation
- Eisai, Inc.
- GlaxoSmithKline
- Lundbeck Pharmaceuticals, Inc.
- The Nationwide Children’s Hospital
- Questcor Pharmaceuticals, Inc.
# 41st Annual Meeting of the Child Neurology Society Scientific Program

Huntington Beach, California  
October 31 – November 3, 2012  
E. Steve Roach, MD, President, CNS  
Mustafa Sahin, 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 25.5 AMA PRA Category 1 credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

## PROGRAM

### WEDNESDAY, OCTOBER 31

<table>
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<tr>
<th>Time</th>
<th>Session</th>
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<tr>
<td>7:30 AM</td>
<td><strong>Symposium I: Neurobiology of Disease in Children: Batten's Disease</strong></td>
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| 4:45 PM | Organizer: Bernie Maria, MD, MBA, Georgia Health Sciences University, Augusta, GA  
Supported by the National Institutes of Health (NIH grant 5R13NS040925-09), the Child Neurology Society and Batten’s Disease Support and Research Association |
| 7:30 AM | **Opening Comments**  
Bernard L. Maria, MD., MBA., Principal Investigator  
Georgia Health Sciences University, Augusta, Georgia  
Story Landis, PhD, Director of NINDS  
Bethesda, Maryland |
| 7:40 AM | **SESSION I: CLINICAL ASPECTS**  
Co-Director and Moderator: David Pearce, PhD  
Sanford Children’s Health Center, Sioux Falls, SD |
| 9:55 AM | **SESSION II: MOLECULAR MECHANISMS**  
Jonathan Mink, MD, PhD  
University of Rochester Medical Center, Rochester, NY |
| 9:55 AM | **SESSION II: MOLECULAR MECHANISMS**  
Jonathan Mink, MD, PhD  
University of Rochester Medical Center, Rochester, NY |
| 11:00 AM | **Neuroinflammation and Microglial Activation in JNCL**  
Tammy Kielian, PhD  
University of Nebraska Medical Center, Omaha, NE |
| 11:00 AM | **CLN3: What does it do?**  
David Pearce, PhD |
| 11:00 AM | **Neuronal Ceroid Lipofuscin: Marker or Cause of Disease?**  
David Palmer, PhD  
Lincoln University, Lincoln, Canterbury, New Zealand |
| 11:00 AM | **Question and Answer Session** |

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**8:30 AM – 8:55 AM**  
**Neurobehavioral Aspects of CLN3**  
Heather Adams, PhD  
University of Rochester School of Medicine, Rochester, NY

**8:55 AM – 9:20 AM**  
**Neuropathology of the NCLs**  
Jonathan Cooper, PhD  
Kings College London, London, UK

**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: MOLECULAR MECHANISMS**  
Jonathan Mink, MD, PhD  
University of Rochester Medical Center, Rochester, NY

**9:55 AM – 11:00 AM**  
**Neuroinflammation and Microglial Activation in JNCL**  
Tammy Kielian, PhD  
University of Nebraska Medical Center, Omaha, NE

**10:20 AM – 10:45 AM**  
**CLN3: What does it do?**  
David Pearce, PhD

**10:45 AM – 11:10 AM**  
**Neuronal Ceroid Lipofuscin: Marker or Cause of Disease?**  
David Palmer, PhD  
Lincoln University, Lincoln, Canterbury, New Zealand

**11:10 AM – 11:30 AM**  
**Question and Answer Session**
11:30 AM – 1:00 PM
Lunch and Presentation
by the Batten’s Disease Support and Research Association

1:00 PM – 2:40 PM
SESSION III: TRANSLATIONAL SCIENCE AND CLINICAL FRONTIERS
Co-Director and Moderator: Marc Patterson, MD
Mayo Clinic, Rochester, MN

1:00 PM – 1:25 PM
Gene Therapy and Enzyme Replacement
Beverly Davidson, PhD
University of Iowa, Iowa City, IA

1:25 PM – 1:50 PM
Combinational Therapies
Mark Sands, PhD
Washington University, St. Louis, MO

1:50 PM – 2:15 PM
Clinical Trials: Challenges and Opportunities
Erika Augustine, MD
University of Rochester Medical Center, Rochester, NY

2:15 PM – 2:40 PM
Question and Answer Session

2:40 PM – 3:00 PM
Coffee Break

3:00 PM – 3:30 PM
EXECUTIVE SUMMARY OF THE DAY
Jonathan Mink, MD, PhD
Mayo Clinic, Rochester, MN

3:30 PM – 4:10 PM
SESSION IV: FUTURE DIRECTIONS
PANEL DISCUSSION
Moderator: Danilo Tagle, PhD
NIH, Bethesda, MD
PANELISTS:
Gary Clark, MD;
Texas Children's Hospital, Houston, TX
Beverly Davidson, PhD;
University of Iowa, Iowa City, IA
Marc Patterson, MD;
Mayo Clinic, Rochester, MN
Anne Pariser, MD;
FDA, Silver Springs, MD
Robert Steiner, MD;
Oregon Health Science Center, Portland, OR

4:10 PM – 4:40 PM
Closing Comments and Thanks
Bernard L. Maria, M.D., MBA

6:00 PM – 8:00 PM
OPENING RECEPTION

8:00 PM – 10:00 PM
SIG Meetings (including Movement Disorders)

THURSDAY, NOVEMBER 1

7:00 AM – 8:15 AM
CONTINENTAL BREAKFAST AND SEMINARS

Breakfast Seminar 1: Childhood Encephalitis: Neuroradiographic, Electrodiagnostic, and Laboratory Crossroads
Organizer: John Crawford, MD MS; UCSD, San Diego, CA
Speakers: Carol Glaser, DVM, MPVM, MD UCSF, San Francisco, CA
Mark Nespeca, MD; UCSD, San Diego, CA
John Crawford, MD MS; UCSD, San Diego, CA

Breakfast Seminar 2: Ethical Issues Regarding Fetal MRI for Neurodevelopmental Disorders and Genetic Testing in Child Neurology Patients
Organizer: Leon Epstein, MD; Chicago Memorial Hospital, Chicago, IL
Speakers: William Graf, MD; Yale University School of Medicine, New Haven, CT
Jennifer Kwon, MD; University of Rochester School of Medicine, Rochester, NY
Edwin Trevathan, MD, MPH; St. Louis University, St. Louis, MO
Howard Schub, MD; Atlanta, GA

Breakfast Seminar 3: Recent Advances in Sturge-Weber Syndrome Pathophysiology, Diagnosis, and Treatment
Organizer: Anne Comi, MD, Kennedy Krieger Institute and Johns Hopkins Medicine
Speakers: Joshua Ewen, MD; Kennedy Krieger Institute and Johns Hopkins Medicine, Baltimore, MD
Csaba Juhasz, MD, PhD; Wayne State University School of Medicine, Detroit, MI

8:45 AM – 8:50 AM
Welcome/Opening Comments

8:50 AM – 9:05 AM
Lifetime Achievement Award:
M. Richard Koenigsberger, MD; Demarest, NJ

9:00 AM – 9:05 AM
Bernard D’Souza International Fellowship Award:
Inga Talvik, MD, PhD; Tartu, Estonia

9:05 AM – 12:00 PM
Symposium II: Presidential Symposium:
Mechanism Based Treatments in Neurodevelopmental Disorders
Organizer: Mustafa Sahin, MD, PhD;
Boston Children's Hospital, Boston, MA
Speakers:

Tuberous Sclerosis Complex
Mustafa Sahin, MD, PhD

Fragile X Syndrome
Elizabeth Berry-Kravis, MD, PhD
Rush University Medical Center, Chicago, IL

Down Syndrome
William Mobley, MD, PhD
UCSD, San Diego, CA

Rett Syndrome
Mriganka Sur, PhD
MIT, Cambridge, MA

Autism
Daniel Geschwind, MD, PhD
UCLA, Los Angeles, CA

Child Neuro News Break:
4:00 PM – 6:00 PM
Poster Review & Reception
Supported by a grant from Eisai, Inc.

Exhibitor Appreciation Reception
6:00 – 7:00 PM

FRIDAY, November 2

7:00 AM – 8:15 AM
CONTINENTAL BREAKFAST AND SEMINARS
Breakfast Seminar 4: NEURONEXT: Network for Excellence in Neuroscience Clinical Trials
Organizer: Bradley Schlaggar, MD, PhD; Washington University School of Medicine, St. Louis, MO
Speakers: Petra Kaufmann, MD, MSc; NIH, Bethesda, MD
Elizabeth McNeil, MD, MSc; NIH, Bethesda, MD
E. Steve Roach, MD; President, CNS; The Nationwide Children’s Hospital, Columbus, OH

Breakfast Seminar 5: Vaccines and Neurological Adverse Events: the Myth and the Reality
Organizer: Max Wiznitzer MD; Rainbow Babies & Children’s Hospital, Cleveland, OH
Speakers: Max Wiznitzer, MD

Breakfast Seminar 6: Beyond ADEM & MS: Alternative Diagnoses You Shouldn’t Miss during a Workup for Pediatric Demyelinating Disorders
Organizer: Keith Van Haren, MD, Lucile Packard Children’s Hospital/Stanford University, Stanford, CA
Speakers: Anita L. Belman, MD; School of Medicine, Stony Brook, NY
Teri L. Schreiner, MD, MPH; Children’s Hospital of Colorado, Denver, CO
Keith Van Haren, MD

Legislative Affairs Seminar: Advocacy 101 for Child Neurologists (NO CME Credit)
Organizer: Bennett Lavenstein, MD; Chair, CNS Legislative Affairs Committee; Children’s National Medical Center, Washington, DC
Supported by a grant from GlaxoSmithKline.
Speakers: Adam Chrisney, Powers Pyles Sutter and Verville, Esq. Washington, DC
Speakers: Joe Gagen; Legislative Grassroots Trainer, Austin, TX

8:30 AM – 10:15 AM

Platform Sessions 1 & 2:

Platform Session 1

1. Neurologic Sequelae in Long-Term Survivors of Childhood Brain Tumors: Childhood Cancer Survivor Study (CCSS)
   Wells EM (Washington, DC)

2. Synaptic Sequence in Human Fetal Cerebellar System
   Sarnat HB (Calgary, Alberta, Canada)

3. Hyperactivity Following Loss of mTORC2 Signaling in the Dorsal Cortex: An mTORC1 Independent TSC Phenotype?
   Carson R (Nashville, TN, USA)

4. An Array Tomographic Analysis of Excessive TrkB Mediated Signaling in Synapses in the Ts65Dn Mouse Model of Down Syndrome
   Nosheny RL (Stanford, CA)

5. En1 Directs Major Aspects of Superior Olivary Complex Development and Function
   Jalabi W (Cleveland, OH)
   (Presented by Maricich S)

6. GABA-A Receptor Phenotype of Premature Human Cortex
   Jansen LA (Seattle, WA)

7. ATP1A3 De Novo Mutations in Alternating Hemiplegia of Childhood
   Heinen EL (Durham, NC)

Platform Session 2

8. Newborn Screening for X-linked Adrenoleukodystrophy
   Tortorelli S (Rochester, MN)

9. Diurnal and Sleep/wake Patterns of Focal Seizures in Pediatric Patients
   Ramgopal S (Boston, MA)

10. Modified Pediatric ASPECTS Score Correlates with Infarct Volume in Childhood Arterial Ischemic Stroke
    Beslow LA (Philadelphia, PA)

11. Phase I Trial of Neonatal Erythropoietin in Perinatal Hypoxic-Ischemic Encephalopathy
    Wu YW (San Francisco, CA)

12. Low Palmitic Acid Levels Associated with Increased Risk for White Matter Injury in Preterm Newborns
    Tam EW (San Francisco, CA)

13. The Effect of Perinatal Infection on Neurodevelopmental Outcome in Newborns with Hypoxicischemic Encephalopathy
    Jenster M (Westerbork, Netherlands)

14. GABAA Receptor Imaging with Positron Emission Tomography in Human Newborn: A Unique Binding Pattern
    Chugani HT (Detroit, MI)

9:00 AM – 2:30 PM

Exhibits

10:45 AM – 10:50 AM

Child Neurology Foundation Awards

10:50 AM – 11:05 AM

Lifetime Achievement Award:
Presented Posthumously to family of Bhuwan Garg, MD; Indianapolis, IN

High School Neuroscience Prize Award: Vincent Shieh; Bronx, NY

11:05 AM – 11:35 AM

Philip R. Dodge Young Investigator Award Lecture: “Functional Annotations of the Medulloblastoma Genome”
Yoon-Jae Cho, MD; Stanford University School of Medicine, Stanford, CA [HRt] Supported by a grant from Questcor Pharmaceuticals, Inc.

11:35 – 12:15 PM

Bernard Sachs Lecture: “Medulloblastoma: Progress and the Challenges that Lie Ahead”
Roger Packer, MD; Children’s National Medical Center, Washington, DC

12:15 PM – 2:30 PM

Lunch & Poster/Exhibit Walkaround

12:45 PM – 2:15 PM

Moderated Poster Session

Moderators:
Bradley Schlaggar, MD, PhD, Washington University, St. Louis, MO; Janet Soul, MD; Boston Children’s Hospital, Boston, MA

15. Cooling in the Real World: A Comparative Study of Therapeutic Hypothermia in Hypoxic-Ischemic Encephalopathy
    Garfinkle JS (Montreal, Quebec Canada)

16. The Role of Continuous EEG Monitoring in Childhood Encephalitis
    Gold JJ (San Diego, CA)

17. Head-shaking Stereotypies in Rhombencephalosynapsis: an Important Diagnostic Clue to an Underrecognized Cerebellar Malformation
    Tully HM (Seattle, WA)
18. Variant Innervations of EDB in Children
Ahsan N (Los Angeles, CA)

19. Prevalence of Intraventricular Hemorrhage in Preterm Neonates: the Twins and the Singles
Mainali G (Cleveland, Ohio)

20. Diagnostic Criteria of Rasmussen Encephalitis Compared to Pathology
Olson HE (Boston, MA)

21. Pediatric Myasthenia: Results of the Canadian Paediatric Surveillance Program (CPSP)
VanderPluym J (Edmonton, AB)

22. Correlation of Cognitive Performance with White Matter Microstructure in Adolescents Treated in Early Infancy for d-TGA
Rollins CK (Boston, MA)

23. Use of a Standard Protocol to Reduce the Time to Treatment of Seizure Emergencies on a Neuroscience Floor in a Large Urban Pediatric Hospital
Xie Y (Memphis, TN)

24. Anti-NMDA Receptor Encephalitis: Case Series at the University Pediatric Hospital in Puerto Rico
Sanchez LG (San Juan, Puerto Rico)

2:30 – 4:45 PM

Symposium IV: Novel Therapies for Pediatric Epilepsy
Organizer: Mary L. Zupanc, MD; University of California Irvine, Irvine, CA

Speakers: The Protean Nature of Epilepsy: Beyond Seizures
Rod C. Scott, MD; Dartmouth-Hitchcock Medical Center, Durham, NH

The Newly Described Pediatric Epilepsy Syndromes: From the Channelopathies to Autoimmune Epilepsy
Susan Koh, MD; Children’s Hospital of Colorado, Denver, CO

Current State of the Art Therapeutic Approaches to Pediatric Epilepsy
Mary Zupanc, MD

Re-engineering the Epileptic Developing Brain: Future Approaches to Therapy
Tallie Z. Baram, MD, PhD; University of California Irvine, Irvine, CA

4:45 – 6:00 PM

Junior Member Career Seminars:
1. Academic/Research
2. Private Practice
Organizer: Renee Shellhaas, MD; University of Michigan, Ann Arbor, MI

7:00 – 9:00 PM

CLOSING RECEPTION

SUNDAY, NOVEMBER 4

7:00 – 10:00 PM

CNS ALUMNI RECEPTION

SATURDAY, NOVEMBER 3

7:00 – 8:15 AM

Continental Breakfast and Seminars
Organizer: Doris Trauner, MD; UCSD, San Diego, CA

Speakers:
- Harley Kornblum, MD, PhD; UCLA, Los Angeles, CA
- William Gaillard, MD; Children’s National Medical Center, Washington, DC
- Donna Ferriero, MD; UCSF, San Francisco, CA

Breakfast Seminar 7: Plasticity in the Developing Brain
Organizer: Bruce Cohen, MD, Chair; CNS Practice Committee; Children’s Hospital of Akron, Akron, OH

Speakers:
- Jeffrey Buchhalter, MD, PhD; Alberta Children's Hospital, Calgary, AB, CA
- Deborah Hirtz, MD; NINDS, Bethesda, MD

Breakfast Seminar 8: 2012 Update for CPT, ICD-10-CM, PQRS and Guidelines: Sit at the Table or be Served as the Meal
Organizer: Jennifer Friedman, MD; Rady Children's Hospital, UCSD, San Diego, CA

Speakers:
- Terence D. Sanger, MD, PhD; Sanger Lab, USC, Los Angeles, CA
- Kathryn J. Swoboda, MD, FACMG; Primary Children's Hospital, University of Utah, Salt Lake City, UT

8:45 AM – 8:55 AM

Arnold P. Gold Foundation Humanism in Medicine Award at the Child Neurology Society Annual Meeting
Marvin Fishman, MD; Houston, TX
Supported by a grant from The Arnold P. Gold Foundation

9:00 – 9:45 AM

Hower Award Lecture: “The Power of Belief”
Ann Tilton, MD; Children’s Hospital of Louisiana, New Orleans, LA [HRt]
Supported by a grant from Akron Children’s Hospital
10:00 AM – 12:15 PM
Symposium V: Mitochondria: So Many Diseases, So Little Cross-sectional Area
Organizer: Nina Schor, MD, PhD; University of Rochester School of Medicine and Dentistry, Rochester, NY

Speakers: Conventional Mitochondrial Disease: New Approaches to Diagnosis and Classification
Amy Goldstein, MD; Children’s Hospital of Pittsburgh, Pittsburgh, PA

Conventional Mitochondrial Disease: Not-so-conventional Treatment
Sumit Parikh, MD; Cleveland Clinic Foundation, Cleveland, OH

Unconventional Roles for Mitochondria: They’re Not Just Little Fuel Cells
George Porter, MD, PhD; University of Rochester School of Medicine and Dentistry, Rochester, NY

From Neurodevelopmental Disorders to Neurodegenerative Disease: It’s All Mitochondria!
Nina Schor, MD, PhD
Agenda for 2012 ACNN CONFERENCE PROGRAM
Huntington Beach Resort, Huntington Beach, CA
October 30–November 2, 2012

Tuesday October 30, 2012
7:00 pm–9:00 pm  ACNN Welcome Reception (Nurses only)

Wednesday October 31, 2012
7:00 am–8:00 am  Registration and Continental Breakfast
8:00 am–8:15 am  Welcome and Introduction
8:15 am–9:00 am  Janet Brucker Keynote Address:
  Accidental Leadership: A Result of Intentional Engagement?
  Linda R. Littlejohns RN, MSN, FAAN
9:00 am–10:00 am  Case Studies: Neurogenetic and Metabolic Disorders Identified in a
  Neurology/Neurogenetics Collaborative Practice.
  Marian J Kolodgie MSN, CPNP
10:00 am–10:15 am  Break
10:15 am–10:45 am  Pediatric Neurology: The Role of Genetic Testing.
  Dona Clarin MSN, FNP
10:45 am–11:30 pm  Independent NP/PA practice Model as a method for improving new patient
  access within an academic pediatric neurology clinic.
  Scott Turner MSN, FNP
11:30 am–12:00 pm  Awards Presentation and Business Meeting
12:00 pm–1:00 pm  Lunch
1:00 pm–1:30 pm  Innovative Practice Award Presentation Parenting with Parents:
  A recipe for success. Claire Chee RN, BS
1:30 pm–2:30 pm  “Handle with Care” Dealing with Dravet Syndrome.
  Deborah A. Gardner, RNC, BSN
2:30 pm–2:45 pm  Break
2:45 pm–3:45 pm  Implementing Evidence Based Nursing Practice in Pediatric Neurology.
  Ruth Rosenblum DNP, RN, PNP-BC
3:45 pm–4:15 pm  Cyclic Vomiting Syndrome: Assessment, Diagnosis and Management.
  Cynthia B. tenHoopen MS, RN, CPNP
4:15 pm–4:30 pm  Wrap up

Thursday, November 1, 2012
12:00 pm–12:45 pm  Lunch
12:45 pm–1:15 pm  Special Interest Groups Table Discussions
1:15 pm–1:45 pm  Epilepsy at a glance-Health Information Transfer.
  Melissa Reider-Demer DNP, CPNP
4:30 pm  5K Run/Walk fundraiser for ACNN/CNF Nursing Research Grant.

Friday, November 2, 2012
12:00 pm–12:30 pm  Lunch
12:30 pm–1:00 pm  Diagnosing MLD: A case Presentation.
  Cleo Park RN, MSN, CPNP
1. Neurologic Sequelae in Long-Term Survivors of Childhood Brain Tumors: Childhood Cancer Survivor Study (CCSS)

Wells EM (Washington, DC), Ullrich NJ (Boston, MA), Seidel K, Leisenring W (Seattle, WA), Armstrong G (Memphis, TN), Diller L (Boston, MA), King A (St. Louis, MO), Krull KR (Memphis, TN), Neglia J (Minneapolis, MN), Robison LL (Memphis, TN), Sovall M (Houston, TX), Whelan KF (Tuscaloosa, AL), Sklar C (New York, NY), Packer RJ (Washington, DC)

Objective: Determine the incidence and risk factors for adverse neurologic outcomes in survivors of childhood brain tumors.


Results: Of survivors, 34% were diagnosed when<5, 30% when 5-9, and 36% when 9 years old. Tumors were 66% astroglial, 20% primitive neuroectodermal, 9% ependymoma, 5% other. Treatments included 23% surgery, 37% surgery + radiation, 25% surgery + radiation + chemotherapy. Median follow-up 23 years (range 5-39). Cumulative incidence curves showed 5/15/30 year percentages of 50/57/61 for coordination/balance problems, 27/35/41 seizures, 21/28/35 motor problems, 9/15/23 hearing loss, 14/16/18 legal blindness. In multivariable analyses, relapse increased risk of all neurologic sequelae (RRs 2.2-4.8, all p-values <0.001). Hearing loss was increased by dose-dependent radiation to posterior fossa (RR 2.1, p<0.01 for <50Gy; RR 2.9, p<0.0001 for 50+Gy) and temporal lobe (RR 2.8, p<0.0001 50+Gy). Seizures increased with radiation to temporal (RR 1.8, p<0.05 <50Gy; RR 2.1, p<0.005 50+Gy) and frontal (RR 1.8, p<0.05 50+Gy) lobes and with secondary malignancies (RR 2.9, p<0.05). Coordination or balance problems increased with brain radiation regardless of location or dose (RR 1.9, p<0.01) and with secondary malignancies (RR 4.4, p<0.005). Motor problems increased with high-dose radiation to temporal (RR 1.6, p<0.05) and parietal (RR 2.0, p<0.01) lobes.

Conclusions: Cumulative incidence curves demonstrate continuing risk of new onset neurologic deficits in survivors of childhood brain tumors up to 30 years after diagnosis. Cranial radiation and tumor relapse are the strongest predictors of increased risk.

2. Synaptic Sequence in Human Fetal Cerebellar System

Sarnat HB, Florea-Sarnat L (Calgary, AB, CA), Auer RN (Montreal, QC, CA)

Background: Precise temporal and spatial sequences of synaptogenesis in the cerebellar system can be demonstrated by immunoreactivity to synaptophysin, a synaptic vesicular wall protein within axonal terminals at all synapses, regardless of site, function or transmitter.

Methods: Synaptophysin immunoreactivity was studied prospectively in postmortem tissue sections of 172 human fetuses and neonates: Guillain-Mollaret triangle (dentato-olivo-rubro-cerebellar circuit), fastigial and interpositus nuclei, pontine nuclei, cerebellar cortex.

Results: Synaptophysin demonstrates not only progressive increase in the number of synaptic vesicles in each structure, but also the maturation of shape of inferior olivary and all deep cerebellar nuclei from amorphous globular neuronal aggregates. Intensity of synaptophysin becomes strong before the mature shape of these nuclei is achieved. The dorsal blade forms earlier than the ventral, initially peripherally and later centrally. Dorsal and medial accessory olives show strong reactivity earlier than the principal olives; accessory cerebellar nuclei are earlier than the dentate. Development of both shape and reactivity follows caudorostral and dorsorostral gradients in the axes of the brainstem. Pontine nuclei exhibit reactivity from 15wk, forming a patchy pattern reminiscent of the fetal corpus striatum and becoming uniformly intense by 34wk. Morphogenesis and synaptophysin reactivity mature earlier in the vermis than the cerebellar hemispheres, beginning around Purkinje cells and in the molecular zone. Initiation is at 13wk in the inferior olive, 16wk in the dentate, 13wk in the red nucleus, 15wk in the vermis and 17wk in the hemisphere.

Conclusions: This study of normal fetal synaptic neuroanatomy provides a basis for interpreting aberrations in timing and sequences of synaptogenesis in malformations involving the cerebellar system, genetic and metabolic disorders, and associated with acquired insults to the fetal brain.

3. Hyperactivity Following Loss of mTORC2 Signaling in the Dorsal Cortex: An mTORC1 Independent TSC Phenotype

Carson R, Fu C, Winzenburger P, Es S (Nashville, TN)

Objectives: Tuberculous sclerosis complex (TSC) is a multisystem genetic disorder with symptoms including epilepsy, autism spectrum disorder and attention deficit/hyperactivity. The mammalian target of rapamycin (mTOR) kinase is the best understood downstream effector of the TSC complex and exists within two functionally distinct signaling complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). As a key regulator of cell growth and protein translation, mTORC1 is better studied than the two complexes and much of the TSC phenotype has been attributed to hyperactivation of mTORC1. Regulation of the mTORC2 pathway is not as well characterized as mTORC1, but there is evidence for decreased mTORC2 function in TSC that is not expected to respond to rapamycin. We hypothesize that decreased mTORC2 activity in TSC contributes to disease pathogenesis requiring additional considerations for targeted therapy.

Methods: To study the role of the mTORC2 complex in neurodevelopment we generated mice expressing a floxed allele of Rictor, a critical mTORC2 subunit, with Emx1-Cre mice to conditionally inactivate Rictor in dorsal neural progenitor cells (Rictor CKO).

Results: Rictor CKO mice had increased locomotor activity and decreased anxiety related traits relative to littermate controls. These behavioral abnormalities were associated with abnormal expression of central myelin markers as well as increased levels of cortical monoamines.

Conclusions: The hyperactive behavior and central myelin anomalies observed in Rictor CKO mice recapitulate a subset of the clinical manifestations in human TSC suggesting that this may be a useful model for studying mTORC1-independent complications of TSC.

4. An Array Tomographic Analysis of Excessive TrkB-mediated Signaling in Synapses in the Ts65Dn Mouse Model of Down Syndrome

Noveny RL (Stanford, CA), Belichenko PV (La Jolla, CA), Bause B (Houston, TX), Salehi A, Dang V (Palo Alto, CA), Smith SJ (Stanford, CA), Mobley WC (La Jolla, CA)

Objectives: Down Syndrome (DS) (trisomy 21) is characterized by learning and memory deficits, the development of...
Alzheimer’s disease (AD) neuropathology, and progressive cognitive decline. Ts65Dn mice, which are trisomic for 140 mouse genes orthologous to those on human chromosome 21, model DS. The objective of this research was to identify changes in neurotrophic factor signaling in Ts65Dn mice, and to analyze the affect of such changes on synaptic function.

Methods: We use biochemical methods and array tomography to identify TrkB-mediated signaling abnormalities in the cerebral cortex of Ts65Dn mice, uncover the sub-cellular location of these abnormalities, and identify affected synapse subtypes.

Results: Ts65Dn mice have increased overall levels and activation of the BDNF receptor TrkB and associated downstream signaling proteins, blunted response to BDNF, and decreased BDNF surface binding. Using array tomography, we found a specific increase in pTrkB colocalization with the signaling-endosome related proteins Rab5, pERK, and pAKT in synapses in Ts65Dn mice. Automated classification of synapse subtypes revealed an increase in the number of GABAergic synapses and a decrease in then number of glutamatergic and cholinergic synapses. Proteomic analysis at the single synapse level of resolution demonstrated that increased TrkB signaling is specific to both the pre- and postsynaptic sites at GABAergic synapses, as well as the postsynaptic densities of glutamatergic synapses.

Conclusions: These findings demonstrate that TrkB-mediated signaling is abnormal in the cortex of Down syndrome model mice, a phenomenon which may contribute to the pathogenesis underlying cognitive deficits in Down syndrome and Alzheimer’s disease.

5. En1 Directs Major Aspects of Superior Olivary Complex Development and Function

Objective: Neuronal loss in and aberrant connectivity of auditory brainstem nuclei occur in diverse neurological conditions including autism, central auditory processing disorders and tinnitus. Unfortunately, genetic pathways that control specification and differentiation of the involved neurons are poorly characterized, limiting understanding of underlying pathogenesis. We discovered that the homeobox transcription factor En1 is expressed by neurons in several regions of the developing and adult superior olivary complex (SOC), a group of nuclei critical for sound localization and efferent auditory control. Our objective was to determine En1’s role in the development and survival of these neurons.

Methods: We used Cre-loxP technology to conditionally delete En1 in the developing murine SOC; immunohistochemistry and in situ hybridization for qualitative and quantitative analyses; lipophilic dye placement to study afferent and efferent connectivity; and in vitro slice preparations and auditory brainstem evoked responses (ABRs) to study auditory brainstem function.

Results: Neurons in the medial and ventral nuclei of the trapezoid body (MNTB and VNTB) were completely absent in Egr2+/−; En1−/− mice, while other SOC neurons were unaffected. Intrinsic glycinergic innervation of the SOC, thought to arise from MNTB projections, was (unexpectedly) only modestly decreased. Cochlear nucleus neurons that target the SOC formed novel, aberrant projections. In vitro electrophysiology and ABRs demonstrated significant abnormalities.

Conclusions: Our data suggest that functionally-relevant central circuit reorganization occurred in Egr2+/−; En1−/− mice. Our findings reveal the importance of En1 in the specification and development of SOC neurons, and how disruptions of these neurons detrimentally affect auditory system function and connectivity.

6. GABA-A Receptor Phenotype of Premature Human Cortex

Jansen LA, Roden WH, Siebert JR (Seattle, WA)

Objective: GABAergic medications are often used in preterm infants for sedation and treatment of seizures. In this study, we analyzed GABA-A receptor composition and pharmacology in premature infant cortex to identify divergence from properties of mature cortex.

Methods: Frozen postmortem cortical tissue from 20-40 week EGA infants was subjected to Western blot analysis using GABA-A receptor subunit antibodies. Tissue membrane fractions were injected into Xenopus oocytes, resulting in incorporation of the brain membrane vesicles with their associated receptors into the oocyte cellular membrane. Two-electrode voltage clamp analysis of GABA-A receptor currents was then performed. Formalin-fixed, paraffin-embedded sections were used for fluorescence immunohistochemistry studies.

Results: Cortical GABA-A receptor subunit expression and GABAergic currents were detectable at all gestational ages. However, subunit predominance and receptor pharmacologic properties differed between preterm infants, term infants, and older children. GABA-A 21 subunits, which are the most abundant alpha subtype in mature cortex, were the least abundant in premature cortex. This corresponded with low current responses to the z1-selective agonist zolpidem. The expression patterns of α2, α3, and α5 subunits were highly correlated, and peaked in the early third trimester. Expression of the α4 subunit was biphasic, with peaks at the earliest gestational ages and again at term. GABA-A delta subunits were nearly undetectable in premature cortex.

Conclusions: Although GABA-A receptor subunits and currents are present in preterm infant cortex, receptor composition and pharmacologic responses differ from that in mature brain. These findings suggest that treatment of premature infants with GABAergic drugs may produce unanticipated effects.

7. ATP1A3 De Novo Mutations in Alternating Hemiplegia of Childhood

Heinzen EL (Durham, NC), Swoboda KJ (Salt Lake City, UT), Hitomi Y (Durham NC), Carrière P (Rome, Italy), Nicole S (Paris, France), Vries BD (The Netherlands), Tiziano D (Rome, Italy), Fontaine B (Paris, France), Walley NM (Durham, NC), Heinav S (Melbourne, Australia), Panagiotakaki E (Lyons, France), European AHC Genetics Consortium, I.B.AHC Consortium, ENRAH for SME

Objective: Neuronal loss in and aberrant connectivity of auditory brainstem nuclei occur in diverse neurological conditions including autism, central auditory processing disorders and tinnitus. Unfortunately, genetic pathways that control specification and differentiation of the involved neurons are poorly characterized, limiting understanding of underlying pathogenesis. We discovered that the homeobox transcription factor En1 is expressed by neurons in several regions of the developing and adult superior olivary complex (SOC), a group of nuclei critical for sound localization and efferent auditory control. Our objective was to determine En1’s role in the development and survival of these neurons.

Methods: We used Cre-loxP technology to conditionally delete En1 in the developing murine SOC; immunohistochemistry and in situ hybridization for qualitative and quantitative analyses; lipophilic dye placement to study afferent and efferent connectivity; and in vitro slice preparations and auditory brainstem evoked responses (ABRs) to study auditory brainstem function.

Results: Neurons in the medial and ventral nuclei of the trapezoid body (MNTB and VNTB) were completely absent in Egr2+/−; En1−/− mice, while other SOC neurons were unaffected. Intrinsic glycinergic innervation of the SOC, thought to arise from MNTB projections, was (unexpectedly) only modestly decreased. Cochlear nucleus neurons that target the SOC formed novel, aberrant projections. In vitro electrophysiology and ABRs demonstrated significant abnormalities.

Conclusions: Our data suggest that functionally-relevant central circuit reorganization occurred in Egr2+/−; En1−/− mice. Our findings reveal the importance of En1 in the specification and development of SOC neurons, and how disruptions of these neurons detrimentally affect auditory system function and connectivity.

6. GABA-A Receptor Phenotype of Premature Human Cortex

Jansen LA, Roden WH, Siebert JR (Seattle, WA)

Objective: GABAergic medications are often used in preterm infants for sedation and treatment of seizures. In this study, we analyzed GABA-A receptor composition and pharmacology in premature infant cortex to identify divergence from properties of mature cortex.

Methods: Frozen postmortem cortical tissue from 20-40 week EGA infants was subjected to Western blot analysis using GABA-A receptor subunit antibodies. Tissue membrane fractions were injected into Xenopus oocytes, resulting in incorporation of the brain membrane vesicles with their associated receptors into the oocyte cellular membrane. Two-electrode voltage clamp analysis of GABA-A receptor currents was then performed. Formalin-fixed, paraffin-embedded sections were used for fluorescence immunohistochemistry studies.

Results: Cortical GABA-A receptor subunit expression and GABAergic currents were detectable at all gestational ages. However, subunit predominance and receptor pharmacologic properties differed between preterm infants, term infants, and older children. GABA-A α1 subunits, which are the most abundant alpha subtype in mature cortex, were the least abundant in premature cortex. This corresponded with low current responses to the α1-selective agonist zolpidem. The expression patterns of α2, α3, and α5 subunits were highly correlated, and peaked in the early third trimester. Expression of the α4 subunit was biphasic, with peaks at the earliest gestational ages and again at term. GABA-A delta subunits were nearly undetectable in premature cortex.

Conclusions: Although GABA-A receptor subunits and currents are present in preterm infant cortex, receptor composition and pharmacologic responses differ from that in mature brain. These findings suggest that treatment of premature infants with GABAergic drugs may produce unanticipated effects.
and characterized by recurrent hemiplegic episodes and a distinct constellation of neurologic manifestations. AHC is usually a sporadic disorder with unknown etiology.

**Methods:** The exomes of seven patients with AHC, and unaffected parents, were sequenced using next-generation sequencing and scanned for causal mutations. Three additional patients were whole-genome sequenced. In a follow-up study, ninety-one additional AHC patients were screened for causal mutations in \( ATP1A3 \). Disease-causing mutations in \( ATP1A3 \) were evaluated for their effects on protein expression and ATPase activity in vitro.

**Results:** We initially identified de novo nonsynonymous mutations in \( ATP1A3 \) in seven AHC patients. Subsequent sequencing of \( ATP1A3 \) exons in ninety-one additional patients revealed that approximately 66% of AHC cases have \( ATP1A3 \) mutations, including one inherited mutation in a family with autosomal dominant AHC. The causal mutations cluster in or near transmembrane domain; remarkably, two recurrent mutations (D801N and E815K) explain 45% of cases. Comparing the in vitro functional effects of AHC-causing \( ATP1A3 \) mutations to those that cause rapid-onset dystonia-parkinsonism (DYT12) revealed consistent reductions in ATPase activity in both conditions; however, only DYT12 mutations were associated with reduced protein expression. This suggests that AHC mutations may alter the intrinsic activity, as opposed to reducing the amount, of \( \text{Na}^+/\text{K}^+ \)-ATPase.

**Conclusions:** This work identifies \( ATP1A3 \) as a key AHC gene explaining the majority of cases. These findings offer insight into AHC pathophysiology, suggest a direction for drug-discovery, and offer a valuable tool for confirming the AHC diagnosis.
Platform Session 2: (#8–14)

8. Newborn Screening for X-linked Adrenoleukodystrophy
Tortorelli S, Turgeon C, Magera M (Rochester, MN), Moer AR (Baltimore, MD), Lorry P (Richmond, CA), Rinaldi P, Matern D (Rochester, MN)

Objective: X-ALD is the most common peroxisomal disorder (incidence 1:21,000 males). It is a progressive and fatal disorder that affects nervous system, adrenal cortex and testis. Adrenal insufficiency is totally prevented by presymptomatic therapy, while the cerebral phenotype, affecting 40% of all male patients, can be prevented by hematopoietic cell transplantation. However, this intervention has a narrow window of opportunity to be effective. The ability to identify presymptomatic patients is of paramount importance for a better outcome. Lysophosphatidylcholine species (lyso-PC) on blood spots have been shown to be abnormally elevated in newborns affected with X-ALD and peroxisomal biogenesis disorders (PBD).

Methods: Using a flow injection analysis MS/MS (FIA-MS/MS) method, we have measured lyso-PC species (C26:0) on dried blood spots from 16 male patients with X-ALD (12 adults and 4 newborns), 12 XALD adult heterozygotes, and 6 patients with PBD (4 adults and 2 newborns). Data were compared with 340 controls (NBS dried blood spots).

Results: Concentrations of lyso-PC fraction containing hexacosanoic acid (C26:0) were distributed as follows:

<table>
<thead>
<tr>
<th>C26 (µg/ml)</th>
<th>1 percentile</th>
<th>99 percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>XALD (16)</td>
<td>0.28</td>
<td>0.75</td>
</tr>
<tr>
<td>XALD H (12)</td>
<td>0.15</td>
<td>0.51</td>
</tr>
<tr>
<td>PBD (6)</td>
<td>0.25</td>
<td>1.06</td>
</tr>
<tr>
<td>Controls (340)</td>
<td>0.07</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Conclusions: The data of the present study strongly indicate that our method is analytically suitable as a screening tool for X-ALD. Patients affected with peroxisomal biogenesis disorders and 70 – 85% of XALD female carriers will be detected by this assay.

9. Diurnal and Sleep/wake Patterns of Focal Seizures in Pediatric Patients
Ramgopal S, Shab A (Boston, MA), Zarowski M (Poznan, Poland), Vendrame M (Boston, MA), Alexopoulos AV (Cleveland, OH), Rotenberg A, Kothare SV, Loddenkemper T (Boston, MA)

Objective: To study the diurnal and sleep/wake variations of focal seizures in children.

Methods: Charts of 281 pediatric patients with focal epilepsy undergoing video-EEG were reviewed for seizure occurrence in 3-hour time blocks and out of wakefulness/sleep. Diurnal patterns of seizures based on ictal EEG onset and clinical presentation were assessed using binomial calculations and odds ratios.

Results: Two-hundred-and-eighty-one patients (138 girls, mean age: 10.2±5.9 years) had 1,264 seizures. Sixty-two patients had 271 temporal-lobe seizures, 41 patients had 184 frontal-lobe seizures, 11 patients had 50 parietal-lobe seizures, 2 patients had 13 occipital-lobe seizures, and 165 patients had 746 multilobar seizures. Frontal-lobe seizures occurred more during sleep (p<0.001) whereas temporal (p<0.0001) and occipital-lobe (p<0.001) seizures occurred more during wakefulness. Temporal-lobe seizures occurred more frequently during wakefulness compared to all extra-temporal seizures (odds ratio: 1.40, 95% confidence interval: 1.07-1.83) and specifically compared to frontal-lobe seizures (odds ratio: 2.61, 95% confidence interval: 1.76-3.84).

In frontal-lobe seizures, motor seizures (tonic, clonic, tonic-clonic, hypermotor, automotisms, myoclonic, versive, gelastic and complex motor seizures) occurred most frequently during wakefulness (p<0.05). In temporal-lobe seizures, auras occurred most between 12PM-3PM (p<0.01) and during wakefulness (p<0.0001).

Conclusions: Seizures occur in diurnal and sleep/wake patterns that relate to underlying EEG localization. These data may assist in the prediction of seizure risk in relation to time of day and may assist in the design of individualized therapeutic paradigms where patients are treated preferentially at times of highest seizure susceptibility.

10. Modified Pediatric ASPECTS Score Correlates with Infarct Volume in Childhood Arterial Ischemic Stroke

Objective: The Alberta Stroke Programme Early CT Score (ASPECTS) predicts functional outcome and symptomatic hemorrhagic transformation for adult arterial ischemic stroke. In children, stroke volume ≥50% of supratentorial brain volume (SBV) predicts poor outcome and hemorrhagic transformation. In neonates, higher modified pediatric ASPECTS (modASPECTS) on diffusion-weighted imaging (DWI) predicts seizure recurrence. Objectives were to develop the relationship of the modASPECTS to infarct volume and to assess the interrater reliability of the score.

Methods: Thirty neonates (≥37 weeks gestation, ≤28 days) and 38 children (>28 days-19 years) with supratentorial arterial ischemic stroke were identified from a tertiary care center stroke registry. Infarct volume on DWI was expressed as a percent of supratentorial brain volume (SBV) using computer-assisted manual segmentation tracings. Three independent raters performed modASPECTS on diffusion-weighted imaging (DWI) to assess interrater reliability. Objectives were to evaluate the relationship of the modASPECTS to infarct volume and to assess the interrater reliability of the score.

Results: Thirty neonates (≥37 weeks gestation, ≤28 days) and 38 children (>28 days-19 years) with supratentorial arterial ischemic stroke were identified from a tertiary care center stroke registry. Infarct volume on DWI was expressed as a percent of supratentorial brain volume (SBV) using computer-assisted manual segmentation tracings. Three independent raters performed modASPECTS on DWI. ModASPECTS were compared among raters and to infarct volume as a percent of SBV.

Results: ModASPECTS correlates well with infarct volume, with Spearman rank correlation coefficients of 0.87 for the perinatal group (p<0.001) and 0.80 for the childhood group (p<0.001). The intraclass correlation coefficients among the 3 raters for the perinatal and childhood groups were 0.93 [95% confidence interval (CI) 0.89-0.97, p<0.001] and 0.94 (95% CI 0.91-0.97, p<0.001), respectively. The sensitivity and specificity of a modified pediatric ASPECTS of ≥5 for predicting a childhood stroke ≥50% SBV were 80% (95% CI 65.4%-90.4%) and 87% (95% CI 76.7%-93.9%), respectively.

Conclusions: Modified pediatric ASPECTS can be used to estimate stroke volume as a percent of SBV with a high degree of validity and interrater reliability.
11. Phase I Trial of Neonatal Erythropoietin in Perinatal Hypoxia-Ischemic Encephalopathy

Wu YW, Ballard RA (San Francisco, CA), Bauer LA (Seattle, WA), Ferriero DM, Glidden DV (San Francisco, CA), Chang T (Washington DC), Glass HC (San Francisco, CA), Mayock DE (Seattle, WA), Durand DJ (Oakland, CA), Bonifacio S, Gonzalez FF (San Francisco, CA), Song D (San Jose, CA), Juul SE (Seattle, WA)

Objective: Hypothermia improves outcome of hypoxic-ischemic encephalopathy (HIE), a cause of neonatal encephalopathy; yet > 40% of cooled infants die or exhibit moderate-severe disability. Preclinical studies suggest high-dose erythropoietin (Epo) is neuroprotective in models of hypoxia-ischemia. In addition to reducing apoptosis, inflammation and accumulation of oxygen free radicals, Epo also enhances long-term neuronal regeneration and repair. Benefit is achieved in animals who achieve plasma Epo concentrations of 6,000-15,000 mU/mL. We aimed to examine the safety and pharmacokinetics of high-dose Epo in term infants undergoing hypothermia for HIE.

Methods: In this multicenter dose-escalation open-label study, we gave Epo 250 (N = 3), 500 (N = 6), 1000 (N = 7) and 2500 U/kg/dose (N = 8) IV to 24 infants receiving hypothermia for HIE. Infants received up to 6 total doses of Epo, administered QOD starting at < 24h of age. We measured serum Epo levels, and monitored safety until hospital discharge.

Results: Patients received an average of 4.8 ± 1.2 doses. Although Epo followed nonlinear pharmacokinetics, excessive accumulation did not occur during multiple dosing (Figure). At 500, 1000 and 2500 U/kg Epo, half-life was 7.2, 15.0 and 18.7 hours; Cmax was 7,046, 13,780 and 33,316 U/L. Drug clearance at a given dose was slower than expected; severe, a 1% decrease in palmitic acid was associated with 1.55-fold increased odds of WMI (95% CI 1.04-2.31, P = 0.033). No other fatty acid was associated (P > 0.12). Categorizing WMI into none, mild, and moderate-severe, a 1% decrease in palmitic acid was associated with 1.55-fold increased odds of higher severity of WMI (95% CI 1.04-2.31, P = 0.033).

Conclusions: Low palmitic acid levels are associated with higher risk for WMI. More studies are required to assess whether modulation of preterm nutritional exposures can decrease this risk.

12. Low Palmitic Acid Levels Associated with Increased Risk for White Matter Injury in Preterm Newborns

Tam EW (San Francisco, CA), Chau V (Vancouver, BC, CA), Barkovich AJ (San Francisco, CA), Poolek KJ (Vancouver, BC, CA), Ferriero DM (San Francisco, CA), Miller SP, Innis SM (Vancouver, BC, CA)

Objective: Fatty acids are important components of white matter, and infant exposure changes dramatically when born preterm. To determine if early postnatal red blood cell (RBC) fatty acid levels are associated with white matter injury (WMI) on MRI studies in preterm newborns.

Methods: A prospective cohort of preterm newborns (born 24-32 weeks gestational age) was assessed using serial MRI studies soon after birth and near term-equivalent age for WMI. Blood samples were obtained within 7 days of the first MRI to analyze for RBC fatty acid composition via gas chromatography-flame ionization detector. To study the association between each fatty acid level and WMI, ordered logistic regression analysis was used to adjust for other clinical risk factors for WMI including chorioamnionitis, antenatal betamethasone exposure, 5-minute Apgar score, patent ductus arteriosus, hypotension, intubation, and neonatal sepsis.

Results: Sixty subjects were enrolled, 7 (12%) with mild WMI and 9 (15%) with moderate-severe WMI. Adjusting for clinical factors, a 1% decrease in palmitic acid was associated with 1.55-fold increased odds of WMI (95% CI 1.04-2.31, P = 0.033). No other fatty acid was associated (P > 0.12). No deaths or serious adverse effects were seen.

Conclusions: Epo 1000 U/kg/dose IV given with hypothermia is well tolerated, and produces plasma concentrations that are neuroprotective in animals. A large efficacy trial is needed to determine whether Epo further improves outcome in infants undergoing hypothermia for HIE.

13. The Effect of Perinatal Infection on Neurodevelopmental Outcome in Newborns with Hypoxic-ischemic Encephalopathy

Jenster M (Westerbork, Netherlands), Bonifacio SL, Ruel T, Rogers EE, Tam EW, Barkovich AJ, Ferriero DM, Glass HC (San Francisco, CA)

Objective: Studies of preterm neonates suggest that infection may potentiate hypoxic-ischemic (HI) brain injury. In term neonates, infection is a known risk factor for encephalopathy and cerebral palsy, however whether it potentiates the risk of brain injury and adverse outcome in the setting of hypoxic-ischemic encephalopathy (HIE) is not clear.

Methods: The charts of 257 term newborns with HIE were reviewed for signs of maternal and infant infection, including chorioamnionitis and proven or suspected sepsis. Multivariate logistic regression was used to assess the effect of infection on severity of brain injury as seen on a neonatal MRI (normal-mild vs. moderate-severe), and on risk of adverse neurodevelopment at 30 months in a subset of subjects (neuromotor score, NMS ≥ 2, or Bayley Scales of Infant Development II or III MDI < 70 or cognitive score < 85).

Results: Chorioamnionitis (42 subjects) was associated with a lower risk of moderate-severe brain injury (OR 0.3; 95%CI 0.1-0.7; p = 0.003), and trended toward lower risk of adverse neurodevelopment. Infant infection (32 subjects) trended toward association with moderate-severe injury (OR 1.6; 95%CI 0.8-3.5; p = 0.2), and was significantly associated with an abnormal NMS (OR 3.4; 95%CI 1.2-10.2; p = 0.03) but not cognitive outcome. After adjusting for hypothermia and severity of encephalopathy, maternal infection remained associated with a lower risk of brain injury, whereas the association between infant infection and NMS was no longer significant.

Conclusions: These preliminary results are in keeping with animal studies that suggest that the timing of an
inflammatory signal may determine whether infection is injurious or protective.

14. GABA<sub>A</sub> Receptor Imaging with Positron Emission Tomography in Human Newborn: A Unique Binding Pattern
Chugani HT, Kumar A, Muzik O (Detroit, MI)

Objective: Flumazenil (FMZ) is a specific, reversibly bound antagonist at benzodiazepine binding sites of GABA<sub>A</sub> receptors and, using positron emission tomography (PET) with <sup>11</sup>C-FMZ, these binding sites can be imaged/quantified. We have previously reported an exponential decline of FMZ volume of distribution (which is proportional to the receptor binding) of GABA<sub>A</sub> receptors between 2 and 17 years of age.

Methods: A total of six newborns (age: 33.3 to 46.7 weeks, post-conception) were studied. All subjects had experienced epileptic seizures and underwent 60-min dynamic <sup>11</sup>C-FMZ-PET scanning (WSU/IRB-approved) in 3-D list-mode, after injection of 0.4 mCi/kg of <sup>11</sup>C-FMZ (maximum 2.5 mCi). Infants were fed 2 hours prior to the scanning and were scanned during their natural sleep in the Neonatal Intensive Care Unit using a microPET-Focus-220 scanner. Subsequently, binding potential (FMZ-receptor binding) was calculated using logan-plot analysis.

Results: Visual and quantitative analysis showed highest receptor binding in amygdala-hippocampus, sensory-motor cortex, thalamus, brainstem and basal ganglia, in that order (Figure & Table). Cerebellum and most of cerebral cortex showed relatively low binding. However, older babies (even preemies) showed binding in auditory and visual cortices, reflecting environment-dependent development/modulation of GABA<sub>A</sub> receptors.

Conclusion: This is the first demonstration of GABA<sub>A</sub> receptor binding in human neonates; the pattern is strikingly different from that seen in older children/adults and shows a programmed pattern of ontogeny, possibly modulated by external factors/interactions.
MODERATED POSTER SESSION

15. Cooling in the Real World: A Comparative Study of Therapeutic Hypothermia in Hypoxic-Ischemic Encephalopathy
Garfinkle JS, Guilherme Mendes S, Nabeel A, Morneault L, Locas L, Shevell M (Montreal, QC, CA)

Objective: To compare the neurodevelopmental outcomes of neonates with hypoxic-ischemic encephalopathy (HIE) before and after the implementation of a whole-body therapeutic hypothermia protocol.

Methods: In this single-center retrospective study we collected and compared data of (1) neonates born between October 2008 – June 2010 who were consecutively cooled and (2) non-cooled term neonates born between March 1999 – September 2008 with HIE who were consecutively followed in the institution's neonatal neurology clinic. Outcome measures were dichotomously defined as: normal and adverse, which included cerebral palsy (CP), global developmental delay (GDD), and epilepsy. Neonates submitted to withdrawal of care or followed for less than 12 months were excluded.

Results: 30 term neonates received therapeutic hypothermia and 27 were adequately followed. 30 infants were included in the non-cooled group. 3/27 (11%) cooled neonates had an adverse outcome (3 had both CP and GDD compared to 19/30 (63%) of the non-cooled neonates (14 neonates had an adverse outcome (3 had both CP and GDD) included in the non-cooled group. 3/27 (11%) cooled neonates had an adverse outcome (3 had both CP and GDD) compared to 19/30 (63%) of the non-cooled neonates (14 had CP, 18 had GDD, and 12 had epilepsy) (P<0.001). The incidences of clinically apparent seizures and maternal distress, sentinel events, and cesarean section.

Conclusions: These results validate the reduced risk of eventual neurodevelopmental disability in neonates treated with therapeutic hypothermia outside of a clinical trial. Also, therapeutic hypothermia was associated with fewer neonatal seizures.

16. The Role of Continuous EEG Monitoring in Childhood Encephalitis
Gold JJ, Crawford JR, Bykowski J (San Diego, CA), Glaser C (San Francisco, CA), Kruk P, Mower A (San Diego, CA), Sheriff H (San Francisco, CA), Wang S, Nespeca M (San Diego, CA)

Objective: To investigate the utility of continuous EEG in a single institutional series of children with newly diagnosed encephalitis.

Methods: Retrospective review of consecutive children presenting to Rady Children's Hospital San Diego with a diagnosis of encephalitis from 2006-2012 who had routine and/or continuous EEG performed. All received lumbar puncture and etiologic testing through the California Department of Public Health’s California Encephalitis Project.

Results: Sixty-five percent (112/172) of children (50% boys, age range 0-17 years, mean 8.1 years) had EEG studies during hospitalization. Continuous EEG was performed in 40% children (45/112). EEG was abnormal in 81% of children (72% diffuse cortical dysfunction, 48% focal abnormality, 46% epileptiform discharges). Sixty-four percent of children had clinical seizures during continuous EEG and 53% (25/45) had subclinical seizures. Eight percent had clinical signs suspicious of seizures without EEG correlate. An abnormal EEG was strongly correlated with an abnormality on MRI (p<0.01). An etiologic agent was identified by laboratory testing in 50% of children with encephalitis. There was no distinction between those children with and without an identifiable pathogen with regards to number of abnormal EEGs, electrographic seizures or subclinical seizures (p>0.1). Patients without an identified agent were more likely to have abnormal movements without an EEG correlate (p<0.01).

Conclusions: Subclinical seizures were present in greater than half of children receiving continuous EEGs in our series. Our findings support expanding the use of continuous EEG monitoring for all children with newly diagnosed encephalitis.

17. Head-shaking Stereotypies in Rhombencephalosynapsis: an Important Diagnostic Clue to an Under-Recognized Cerebellar Malformation
Tally HM, Phillips JO, Weiss AH, Ishak GE, Dempsey JC, Doherty D, Dobyns WB (Seattle, WA)

Objective: Head-shaking stereotypies have occasionally been described in patients with brain malformations. We noted an unusual preponderance of these movements in our cohort of patients with rhombencephalosynapsis (RES), a cerebellar malformation characterized by absent vermis and fusion of hemispheres across the midline. We sought to delineate the movements and determine whether oculomotor and vestibular testing could reveal their cause.

Methods: Information was collected from direct observation, video review and parental questionnaire. Quantitative oculomotor and vestibular testing was performed in a dedicated laboratory.

Results: 37 of 45 patients with RES had strikingly similar, high-amplitude horizontal or figure-8 head-shaking stereotypies that occurred most frequently during times of fatigue, excitement, or reduced visual attentiveness. These movements were often observed months to years before the underlying cerebellar malformation was recognized. Oculomotor and vestibular testing was performed in several patients and revealed abnormal gaze-holding, smooth pursuit, and vestibulo-ocular reflex function.

Conclusions: Head-shaking stereotypies are very common in RES and are associated with decreased vestibular function. These movements may provide somatosensory input about head position, especially at times when visual input is reduced. They may also reduce the duration of locked gaze in extreme eccentric positions. These distinctive stereotypies should alert clinicians to the possible presence of RES, a cerebellar malformation that is under-recognized both clinically and radiographically.

18. Variant Innervations of EDB in Children
Ahlan N, Ramos-Platt I (Los Angeles, CA)

Background: EDB (Extensor Digitorum Brevis) causes extension of digits 2-4 in dorsiflexion. EDB is usually innervated with Deep Peroneal Nerve but in 21-28% of adults it was found to have innervations from Accessory deep peroneal nerve and Tibial nerves. The aim of our study is to identify the percentage of children with the variant innervations of EDB.

Methods: We did a retrospective review of 161 patients who came for EMG/NCV at Children's Hospital Los Angeles Neurology department for various other reasons. The nerve conduction was performed on a Sierra Wave, by a fellowship trained boarded neurophysiologist. The protocol used favored doing a tibial nerve first as sedation was
not used. If there was reasonable response at the typical location (distal ankle), no further conduction was done. If there was not a reasonable response the lateral malleolus was checked, if that did not give a reasonable response the lateral malleolus was checked.

**Result:** The mean age of the patients was 10.16yrs. Of the 161 patients reviewed 13(8.07%) were found to have a variant innervations. Out of these 5 were female (38%), 8 Male (61%). On further evaluation of race, 11 (84%) were Hispanics and 2 (15.3%) were Caucasians.

**Conclusion:** The presence of variant innervations of EDB in children is 8%, of these 84% were hispanics. Awareness of these variations is important for correct diagnosis, interpreting EMG/Nerve findings and avoiding erroneous diagnosis of Deep Peroneal nerve pathology.

**References**


19. Prevalence of Intraventricular Hemorrhage in Preterm Neonates: the Twins and the Singletons

Mainali G (Cleveland, OH), Rao KJ (Buffalo, NY), Kim R, Sokal M (Brooklyn, NY)

**Objective:** Intraventricular hemorrhage (IVH) is among the leading causes of death and morbidity among preterm infants. In previous studies, twins are found to have more complications than singletons. The aim of our study is to compare prevalence of IVH between preterm twins and singletons over 5 year period.

**Methods:** Retrospective charts of all preterm very low birth weight neonates (VLBW<1500gm) admitted in our center in 2005-2009 were reviewed. IVH was determined by cranial ultrasound. Triplets, higher order multiple births and neonates with major congenital anomalies were excluded.

**Results:** Of 213 VLBW neonates, 175 were singletons and 38 were twins. Mean gestational age 26 weeks, 121 males. Extremely low birth weight (<1000gms) were 123 and 90 were 1001-1500gms. The mean gestational age, gender, mode of delivery, birth weight, exposure to antenatal steroid, sepsis, initial temperature, surfactant use and mechanical ventilation were similar in singletons and twins. Thirty seven of total 213 (17.3%) neonates had IVH. Twenty five of 175 (14.3%) were singletons and 12 of 38 (31.5%) were twins. Twins had statistically significant IVH rate, suggesting preterm twin gestation is independent risk factor of IVH.

**Conclusions:** Compared to singletons, higher rates of IVH in preterm twins may be due to difficult cardiopulmonary transition, intrauterine crowding, unequal sharing of placental mass and placental insufficiency.

20. Diagnostic Criteria of Rasmussen Encephalitis Compared to Pathology

Olsen HE, Gorman MP, Letchpammer M, Ciarni R, Prabhu S, Poduri A, Gregas M, Luddenkemper T (Boston, MA)

**Objective:** The 2005 diagnostic criteria for Rasmussen Encephalitis (RE) (Bien et al., 2005) are based on seizures, clinical deficits, EEG, neuroimaging, and pathology. We applied these criteria to patients evaluated for RE and epilepsy surgery controls to determine the sensitivity, specificity, and positive and negative predictive values using pathology as the gold standard.

**Methods:** We identified patients evaluated for RE based on medical records from 1994-2010 using the search term “Rasmussen.” Fifty-two control patients with refractory epilepsy, unilateral MRI changes and biopsies were selected from an epilepsy surgery database from matching years. Patients meeting 3 of 3 group A and/or 2 of 3 group B criteria were classified as meeting full criteria (positive); those not meeting full criteria were classified as negative. Biopsies were re-reviewed when available.

**Results:** RE was considered in the differential diagnosis for 82 patients, of whom 36 had biopsies. Twenty patients met full criteria (positive), including 6 for whom biopsy was required to meet criteria. Thirty-seven met partial criteria (negative), of whom 15 had another etiology identified. Twenty-five met no criteria (negative). The diagnostic criteria had a sensitivity of 80% with 4 false negatives (criteria-negative, biopsy-positive) and specificity of 94% with 4 false positives. The false positives all had another etiology identified. The positive predictive value of the diagnostic criteria was 80% and the negative predictive value was 94%.

**Conclusion:** The 2005 Bien clinical diagnostic criteria for RE have reasonably high sensitivity and specificity and good clinical-pathologic correlation in most cases.

21. Pediatric Myasthenia: Results of the Canadian Paediatric Surveillance Program (CPSP)

VanderPluym J, Kolksi H (Edmonton, AB, CA), Mah J (Calgary, AB, CA), Grenier D (Ottawa, ON, CA), Vajsar J (Toronto, ON, CA)

**Objective:** Evaluate the incidence, clinical features and treatment trends of pediatric myasthenia (PM) in Canada.

**Methods:** Through established CPSP methodology, pediatric specialists were anonymously surveyed on a monthly basis for cases of PM using a standardized clinical questionnaire containing de-identified data. Inclusion criteria were: Any child less than 18 years old with at least one of the following: a) fluctuating ptosis or extraocular weakness; b) skeletal muscle weakness or fatigue AND c) any of the following supportive tests: clinical response to acetylcholines- terase inhibitor, positive acetylcholine receptor or musclespecific kinase antibodies, abnormal slow repetitive nerve stimulation or single fiber EMG.

**Results:** In two years of surveillance, 57 confirmed cases were reported. There were 33 generalized and 19 ocular reports of acquired PM plus 5 congenital myasthenic syndrome cases. There were 14 incident cases in 2010 and 6 in 2011: generalized (n=13) and ocular (n=7). Age of onset ranged from birth to 17 (median = 9) years for the generalized form compared to 18 months to 12.5 (median=4) years for the ocular subtype. Positive acetylcholine receptor titres were found in 21/33 (64%) generalized cases and 9/ 19 (47%) ocular patients. Of patients started on pyridostigmine, improvement was noted in 31/32 (97%) generalized cases and 16/18 (89%) ocular cases.

**Conclusions:** This study represents the largest descriptive series of PM in North America and provides valuable information about clinical characteristics. A high index of suspicion is important, even in seronegative patients, for this treatable disease. Children generally respond promptly to readily available therapies.
22. Correlation of Cognitive Performance with White Matter Microstructure in Adolescents Treated in Early Infancy for d-TGA
Rollins CK, Watson CG, Scoppetoala LA, Wypij D, Bellinger DC, Newburger JW, Rikvink MJ (Boston, MA)

Objective: We have identified widely distributed reduction of fractional anisotropy (FA) in brain deep white matter in adolescents treated for d-transposition of the great arteries (d-TGA) during infancy as compared to controls. In addition, we have observed that adolescents with d-TGA perform significantly more poorly than normative populations on neuropsychological tests of reading, mathematics, visuospatial skills, executive function, and attention. Here, we report correlations between neuropsychological outcomes and regional white matter microstructure as measured by FA in adolescents treated for d-TGA as infants.

Methods: 49 patients with d-TGA and 29 controls underwent brain MRI diffusion tensor imaging (DTI) and standardized neuropsychological testing. Using whole brain DTI, 18 regions of reduced FA were found in d-TGA compared to controls.

Results: Mathematics achievement scores correlated with left parietal FA (R = 0.34, p = 0.006); executive function correlated with right and left parietal FAs (right R = 0.28, p = 0.018; left R = 0.34, p = 0.018); and attention correlated broadly with FA across several regions including left parietal (R = 0.34, p = 0.007), right anterior cingulate (R = 0.30, p = 0.007), and right precentral gyrus (R = 0.2, p = 0.030). In left parietal lobe an interaction between group and education was identified.

Conclusions: White matter microstructure correlates with cognitive performance in several domains among adolescents treated for d-TGA. Cognitive functions which rely on widely distributed networks, such as attention, correlate broadly with FA across multiple regions.

Reference

23. Use of a Standard Protocol to Reduce the Time to Treatment of Seizure Emergencies on a Neuroscience Floor in a Large Urban Pediatric Hospital

Objective: To evaluate the use of a standard seizure emergency protocol to decrease the time to treatment of inpatients with seizures and improve the outcome of patients who develop status epilepticus.

Methods: The charts of inpatients who developed seizures on the neuroscience floor of a large urban children's hospital were reviewed. Time to treatment with anti-epileptic medication was calculated from the time when the nurse first noted the seizure to when medications were administered on the floor. Factors interfering with emergency anti-epileptic drug administration were identified. A standardized treatment strategy was developed and implemented. The efficacy of this strategy was analyzed.

Results: In 2008, prior to use of this standard protocol, 20 inpatients had a total of 46 seizure emergencies. Twenty-eight (61%) of these seizures needed to be treated with anti-epileptic medication; however, none were treated with 1st line of anti-epileptic drugs in less than 5 minutes. Nine seizures (20%) required 2nd line anti-epileptic drugs, but none were treated in less than 15 minutes. Causes of delayed treatment were identified and corrected when possible. A standardized protocol for treating seizures was initiated. After implementation of our project, the mean time to treatment with 1st line anti-epileptic drugs was 3 minutes, a reduction by 62.5%; the mean time to treatment with 2nd line anti-epileptic drugs was 27 minutes, a reduction by 50%.

Conclusion: We produced an effective model for reducing the time to treatment of seizure emergencies on a neuroscience floor that may be useful to similar institutions.

24. Anti-NMDA Receptor Encephalitis: Case Series at the University Pediatric Hospital in Puerto Rico
Sánchez IG, González J, Montalvo J, Vázquez M, Fernández-Sein A, Arroyo I, Dávila M (San Juan, Puerto Rico)

Objective: To describe the first three cases of anti-NMDA (N-methyl D-aspartate) receptor encephalitis at the main tertiary referral center for pediatric patients in Puerto Rico.

Methods: A retrospective medical record review of all three patients was performed.

Results: Three cases of anti-NMDA receptor encephalitis have been diagnosed and treated at our institution, including two males and one female, between 9 and 17 years old. Clinical presentation occurred in a multistage manner, including a combination of seizures, behavioral changes, movement disorders, psychiatric symptoms and language disturbances. Two of our patients developed marked dysautonomia during the course of illness requiring pediatric intensive care unit admission. Specific antibody CSF analysis confirmed the diagnosis. Initial neuromaging was normal in all patients and two of them had nonspecific slowing on the electroencephalogram. Work up for malignancy was negative in all cases. Modalities of treatment included the use of intravenous immunoglobulins, intravenous steroids, plasmapheresis and immunomodulator therapy. Two of the patients were started on treatment months after symptom onset and have begun showing clinical improvement, but baseline neurologic status has not been reached. The other patient was started on treatment two weeks after symptom onset and has already achieved complete clinical recovery.

Conclusions: Non paraneoplastic anti-NMDAR encephalitis is an increasingly recognized disorder in the pediatric population and should be considered in the differential diagnosis of encephalitis of unknown origin. Early identification and institution of treatment is associated with faster recovery and better prognosis, for which physicians must recognize and be aware of this type of encephalitis.
POSTERS: Brain Tumors/Oncology

B-1. KIDINS220: A Regulator of Neuroblastoma Cell Differentiation
Rogers D, Schor NF (Rochester, NY)

Objective: KIDINS220 is a protein substrate for phosphorylation by TrkA and TrkB receptors. After phosphorylation, KIDINS220 acts as a scaffold for the MAPK signaling cascade. Neuroblastoma is a peripheral nervous system tumor that originates from the neural crest. Aggressive neuroblastomas often have amplifications of chromosome 2p in the region encoding KIDINS220. Because KIDINS220 can affect the signaling of neurotrophic receptors and is encoded on chromosome 2p, we tested the hypothesis that KIDINS220 could function to alter the proliferation, differentiation, and/or survival of neuroblastoma cells.

Methods: Six different neuroblastoma cell lines (2 neural type; 1 Schwann cell-type; 2 intermediate type; 1 mixed differentiation, and/or survival of neuroblastoma cells. KIDINS220 expression construct.

Results: All of the cell lines express KIDINS220. Transfection of neural-type cells with KIDINS220 siRNA causes downregulation of KIDINS220 protein and curtailment of the phosphorylation of ERK at 30 min exposure to neurotrophin. Scrambled siRNA-transfected cells have sustained phosphorylation of ERK. Neural cells with KIDINS220 downregulation become Schwann cell-like and have reduced expression of doublecortin, a protein found only in neuroblasts and immature neurons. Transfection of KIDINS220-downregulated cells with an expression construct for full-length KIDINS220 reversion to the neural-type morphology.

Conclusion: KIDINS220 expression is necessary and sufficient for interconversion of neuroblastoma cells from Schwann cell-type to neural-type.

B-2. p75NTR Potentiation of Fenretinide Efficacy against Neuroblastoma
Ganeshan V, Schor NF (Rochester, NY)

Objective: The retinoic acid analogue, fenretinide, has been shown to cause apoptosis by increasing generation of reactive oxygen species in cancer cells. Minimal residual disease after treatment of neuroblastoma is often refractory to chemotherapy. Fenretinide has variable efficacy against neuroblastoma. We tested the hypothesis that expression of the p75 neurotrophin receptor (p75NTR), a redox-active protein, enhances neuroblastoma responsiveness to fenretinide.

Methods: Neuroblastoma cell lines derived from minimal residual disease were used to determine the effect of p75NTR signaling on susceptibility to fenretinide-induced apoptosis. Changes in oxidative stress as a result of fenretinide treatment were determined using redox-active dye staining and site-specific antioxidants.

Results: Fenretinide reduces cell viability in all neuroblastoma cell lines tested for 24 (15%)-72 (40%) hrs. p75NTR expression is pro-apoptotic and sensitizes neuroblastoma cells to fenretinide-induced apoptosis. Treatment of SH-EP1 neuroblastoma cells with fenretinide for 72 hrs revealed no change in production of cellular hydroxyl radical or cytosolic superoxide, but a sharp increase was observed in mitochondrial superoxide production. Downregulation of p75NTR with shRNA attenuated superoxide production. Mitochondria-specific oxygen radical scavengers or inhibitors of mitochondrial complex II diminish the efficacy of fenretinide. Akt signaling is enhanced in SH-EP1 cells treated with p75shRNA compared to scrambled shRNA-treated cells.

Conclusions: Fenretinide anti-neuroblastoma efficacy is enhanced by p75NTR expression. Mitochondrial oxidative stress and suppression of Akt signaling are responsible for this potentiation. p75NTR is a biomarker for likely efficacy of fenretinide against neuroblastoma.

B-3. Neurological Manifestations Determine the Outcome of Hemophagocytic Lymphohistiocytosis
Myung-Mi Kim, Mi-Sun Yum, Hae-Won Choi, Tae-Sung Ko, Ho Joon Im, Jong-Jin Seo, Kyung-Nam Koh, Seoul, Korea

Objective: Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder characterized by nonmalignant diffuse infiltration of multiple organs by lymphocytes and histiocytes. We compared the clinical characteristics, treatment, and prognosis of patients with HLH according to central nervous system (CNS) involvement.

Methods: Clinical data of 50 patients diagnosed with HLH and treated at Asan Medical Center between January 1995 and August 2011 were retrospectively reviewed and analyzed. CNS involvement was defined as presence of neurological symptoms or elevated white blood cell count (WBC) in the cerebrospinal fluid (CSF).

Results: Of the 50 patients, 23 developed CNS disease. Fourteen patients had evidence of CNS involvement at diagnosis, and nine developed CNS disease during treatment. Among patients with CNS disease, 19 (82.6%) had neurological symptoms, including seizures (n=15), altered consciousness (n=4), facial palsy (n=2), dysarthria and dysphagia (n=1). Four patients (17.4%) had elevated CSF WBC counts without neurological symptoms. Patients with CNS disease had lower ferritin (7814.7 ± 14603.2 ng/mL vs. 28092.6 ± 46948.5 ng/mL; p=0.049), aspartate aminotransferase (399.5 ± 667.4 IU/L vs. 1269.8 ± 2295.2 IU/L; p=0.026), and alanine aminotransferase (193.1 ± 283.1 IU/L vs. 541.2 ± 844.6 IU/L; p=0.011); and showed worse survival (p=0.006) than those without CNS disease.

Conclusions: CNS involvement is common among patients with HLH. Patients with CNS disease show poor outcomes than patients without CNS involvement. To improve outcomes, careful monitoring of neurological manifestations in patients with HLH and appropriate intensified chemotherapy in patients with CNS disease are needed.

B-4. Psychiatric Symptoms in Survivors of Childhood Germ Cell Tumors
Campsen Cf (Palo Alto, CA); Ashby D (Portland, OR); Fisher PG, Monje M (Palo Alto, CA)

Objective: Cranial irradiation disturbs cell production in the hippocampus and white matter tracts of the developing frontal lobe, areas critical for memory, learning, and behavior. Furthermore, the germ cell tumor (GCT) predilection for midline, subcortical structures may disrupt frontal-basalganglionic-subcortical circuitry and thalamo-cortices thought to be involved in psychiatric disease.

Methods: Included patients were identified via the LPCH Pediatric Brain Tumor Database, diagnosed between 1/1/1997-6/1/2011, and aged birth-30 years at the time of their incident CNS GCT diagnosis.

Results: GCTs were identified in 28 patients (germinoma: 21, nongerminomatous germ cell tumor (NGGCT): 7), in
whom 11 (39.2%) had psychiatric symptoms, including hallucinations: 4 (14.3%), and mood/anxiety disorders: 7 (25.0%). Neither gender (p = 0.70) nor age (p = 0.69) predicted development of psychiatric symptoms. Median time to first mood/psychotic symptom was 18.5 and 32 months, respectively. Higher radiation dosage predicted psychiatric symptoms (median with psychiatric symptoms: 50.4 Gy vs. 30.6 Gy [without], p = 0.0001), as did receiving more chemotherapy (median with psychiatric symptoms: 4 vs. 2 [without], p = 0.0043).

Conclusions: Psychiatric sequelae of brain-tumor therapy are under-recognized and poorly understood. We note that patients with GCTs have a high risk for late psychiatric, particularly psychotic disorders, with risk factors including higher radiation and chemotherapy doses. The delay in symptomatology suggests the underlying etiology may be one of disrupted brain development. Understanding the mechanism of the psychiatric sequelae of midline brain tumor therapy will be critical for patients requiring such therapy, and may help to elucidate the pathophysiology and neural substrate for psychotic disorders in general.

B-5. Rates and Risk Factors of Intracerebral Cavernous Malformation in Pediatric Cancer Survivors Treated with Cranial Radiation Therapy
Gastelum ET, Sear K, Chettout N, Hills N, Hess C, Fullerton HJ, Mueller SC (San Francisco, CA)

Objective: To assess the incidence of Intracerebral Cavernous Malformation (ICM) in pediatric cancer survivors who received Cranial Radiation Therapy (CRT) and examine other risk factors as predictors of ICM.

Methods: Pediatric patients who received CRT between 1980 and 2009 were retrospectively analyzed (n = 325) and cumulative incidence after radiation was determined using Kaplan-Meier techniques whereas potential predictors of ICM were determined using logistic regression.

Results: Of 325 patients, ten (initial diagnosis of high grade glioma (n = 5), medulloblastoma (n = 2), germ cell tumor (n = 1), Burkitt’s lymphoma (n = 1), carcinoma (n = 1)) developed ICM at a median time of 11.5 years after CRT (range 1-24 years). Median age of onset for ICM was 21.4 years (IQR 15-28). Of those who developed ICM, 80% were male (n = 8). All ICM patients received CRT doses >5000 cGy (range 5400-6600 cGy) at a median age of 9.7 years (range 6-16), with 30% receiving CRT > 12 years old (n = 3), and 70% receiving CRT ≤ 12 years old (n = 7). The overall rate of ICM was 322 (95% CI 288-359) per 100,000 person years. The cumulative incidence of ICM was 0.4%, 2%, and 8% at 5, 10, and 20 years respectively. Three patients had a surgical resection for their ICM.

Conclusion: Survivors of childhood cancer who receive CRT are at high risk for ICM. Larger studies are needed to find clear risk factors that lead to ICM and recurrent ICM.
POSTERS: Case Studies

CS-1. Autosomal Dominant Familial Chorea Arising from a Novel Deletion of Chromosome 14q13.3
Bhutia P; Coffman K (Pittsburgh, PA)

Objective: To report a family with a dominantly inherited, progressive chorea that arises from a previously unreported deletion of chromosome 14q13.3, in close proximity to NKX2-1, a gene associated with benign hereditary chorea.

Methods: Three patients, a mother and her two children, were identified from the Movement Disorders Clinic at Children's Hospital of Pittsburgh of UPMC based on a similar phenotype and an identical 117kb deletion of chromosome 14q13.3. Retrospective review of clinic notes and diagnostic testing was obtained to compare the phenotypes.

Results: The mother has a phenotype characterized by mild static chorea and no psychiatric disease. Conversely, her children have a severe, progressive phenotype, characterized by a mixed hyperkinetic movement disorder, with chorea, dystonia, spasticity, and tics as well as comorbid cognitive dysfunction and psychiatric disease. All three have an identical 117 kb deletion of chromosome 14q13.3. Interestingly, the mother also has a copy gain in 14q13.3 proximal to and which does not overlap the deletion she and her children share. All other genetic and metabolic testing was unremarkable.

Conclusion: We present a family with a dominantly inherited neurologic disorder resulting from a novel deletion on chromosome 14q13.3. The mother, who has a mild phenotype, also has a copy gain on 14q13.3 that does not overlap this deletion. The deletion seen in this family does not involve the gene NKX2-1, which is associated with benign familial chorea. These results suggest that deletions of chromosome 14q13.3 may be a genetic cause of a severe familial chorea.

CS-2. Complications of Intrathecal Baclofen Pump in Children: the Past and the Present
Mainali G, Ghosh D, Luciano M (Cleveland, OH)

Objective: Intrathecal baclofen (ITB) therapy is very useful in treating spasticity and dystonia but it has many complications. The aim of this study was to establish the spectrum of abnormalities in individuals with ITB identified on fetal MRI.

Methods: We retrospectively identified a series of fetuses with T21 diagnosed pre or postnatally referred to Advanced Fetal Care Center at Children's Hospital Boston between 2003 and 2011 who underwent fetal MRI.

Results: A total of 115 fetuses with T21 were evaluated at the Advanced Fetal Care Center (Children Hospital Boston), with 17 pregnancies, and 18 fetuses (1 twin pregnancy) undergoing a total of 23 fetal MRI studies. Five fetuses underwent second imaging studies. In total 12 fetuses were male, and 6 were female. Of the 17 pregnancies 12 were continued, and 5 were terminated, resulting in 13 live births. The average gestational age at the time of first imaging assessment was 24+0 weeks (+/5+5). The average gestational age at the time of repeat imaging study (n=5) was 29+5 weeks. In total 14 fetuses had CNS abnormalities identified: the most prevalent being ventriculomegaly (n=9), followed by cerebellar hypoplasia (n=6) and partial agenesis of the corpus callosum (n=4).

Conclusion: The spectrum of congenital cerebral malformation in fetuses with T21 includes ventriculomegaly, partial ACC and cerebellar hypoplasia.

CS-3. Spectrum of Cerebral Malformation in Fetuses with Trisomy 21
Jacob FD, Grant PE, Khwaja OS (Boston, MA)

Objective: Trisomy 21 (T21) has become recognized as the most common viable trisomy. Even though it is invariably associated with mild to severe developmental delay and mental retardation, no gross central nervous system (CNS) malformation has been consistently identified in individuals with T21. The aim of this study was to establish the spectrum of abnormalities in individuals with T21 identified on fetal MRI.

Methods: We retrospectively identified a series of fetuses with T21 diagnosed pre or postnatally referred to Advanced Fetal Care Center at Children's Hospital Boston between 2003 and 2011 who underwent fetal MRI. We also collected data from a previous study which included fetal MRI of 29 cases.

Results: A total of 115 fetuses with T21 were evaluated at the Advanced Fetal Care Center (Children Hospital Boston) with 17 pregnancies, and 18 fetuses (1 twin pregnancy) undergoing a total of 23 fetal MRI studies. Five fetuses underwent second imaging studies. In total 12 fetuses were male, and 6 were female. Of the 17 pregnancies 12 were continued, and 5 were terminated, resulting in 13 live births. The average gestational age at the time of first imaging assessment was 24+0 weeks (+/5+5). The average gestational age at the time of repeat imaging study (n=5) was 29+5 weeks. In total 14 fetuses had CNS abnormalities identified: the most prevalent being ventriculomegaly (n=9), followed by cerebellar hypoplasia (n=6) and partial agenesis of the corpus callosum (n=4).

Conclusion: The spectrum of congenital cerebral malformation in fetuses with T21 includes ventriculomegaly, partial ACC and cerebellar hypoplasia.

CS-4. Idiopathic Basal Ganglia Calcification: Pediatric Presentation of a Rare Neurodegenerative Disorder
Singhal NS, Hess CP (San Francisco, CA), VanHarten K (Stanford, CA), Toro C (Washington, DC), Kilbane C, Wu Y (San Francisco, CA)

Objective: Idiopathic basal ganglia calcification (IBGC), also called Fahr’s disease, is a rare progressive neurodegenerative disorder in adults characterized by a progressive movement disorder and psychiatric symptoms. The underlying etiology is unknown. Diagnosis is clinical, based on characteristic imaging findings and excluding systemic causes of secondary basal ganglia calcification. Few reports describe IBGC in pediatric patients. We report the first case series of pediatric IBGC.

Methods: We present three adolescents with IBGC.

Results: Case one. A 14 year old girl presented with two years of progressive dystonia, poor balance, bradykinesia, aggression and impulsivity. MRI showed changes in bilateral globus pallidi. CT confirmed mineralization within globus pallidi consistent with calcium. Family history was non-contributory. Case two. A 14 year old boy presented with 2 years of motor tics, progressive anxiety and difficulty with social interactions. CT showed bilateral calcifications in the globus pallidi, thalamus and white matter. MRI confirmed mineralization. Family history was non-contributory. Case three. A 14 year old boy with learning disability and ADHD presents with a 4-year history of complex visual hallucinations and 3 (8.1%) infective. Group B had statistically significant lower complication rate.

Conclusion: Significant reduction in complication (both mechanical and infective) with time may be due to advanced technology of the catheter system, surgical experience, and better asepsis during surgery and refill procedure.
focal hand dystonia. MRI demonstrated mineralization within bilateral globus pallidi. CT scan confirmed calcification. Family history was notable for an asymptomatic brother with incidentally-discovered basal ganglia mineralization.

Systemic causes of secondary basal ganglia calcification were ruled out in all cases.

Conclusions: IBGC has rarely been described in children. We present three adolescents with classic features of this disease. Children with a movement disorder and psychiatric symptoms should be evaluated for IBGC.

CS-5. Cross-sectional Study of Neurological Outcome in HIV Infected Children at One HIV Centre in London


Background: Neurological complications of paediatric HIV disease present multidisciplinary challenges since HIV became a chronic treatable condition. There is limited published data regarding neurological manifestations in HIV infected children.

Methods: We reviewed local and Collaborative HIV Paediatric Study data on patients diagnosed since March 1996 seen at our centre. All available neuroimaging was reviewed by a paediatric neuroradiologist. Screening for additional neurological complications employed a parental questionnaire.

Results: 51 HIV infected children (28 girls) were evaluated comprising 3.4% of the UK cohort. 10/51 had clinical focal neurological and cognitive deficits (20%, median age 13.6 years range 6.5-19.3 years); 6/10 following neonatal HIV encephalopathy. 2/6 had bilateral watershed infarcts. Of the remaining 4/10 children with acute neurological events, one was diagnosed with antiviral toxicity progressing to encephalitis lethargica, one had three episodes of recurrent alternating Bell’s palsy associated with white matter changes and enhancement of the facial nerve, and two had acute encephalopathic episodes. 47/51(92%) completed the screening questionnaire. Of those without known acute neurological events, schooling difficulties were revealed in further 8/37(22%) and 7/37 (19%) reported headaches.

Conclusion: Neurological sequelae of paediatric HIV disease are heterogeneous and under-recognised. We propose that the prevalence of schooling difficulties in this cohort supports implementation of systematic neuropsychological assessments. The majority presented with acute encephalopathy that associated gray and white matter injury on MRI but also co-existent cerebral vasculopathy, hypoperfusion injury and neuritis could be seen. Greater understanding of neurological injury is required to guide investigations and management at the time of presentation.

CS-6. Brainbook: A Statewide Pilot for Educating High School Athletes About Concussion


Objective: Through legislative and administrative channels we developed an effective online educational module and tested its efficacy to educate student-athletes in the state of Arizona about mild traumatic brain injury.

Methods: We designed a comprehensive, age-appropriate e-learning module called Brainbook. This educational program was deployed along with a 10 item pre and post test based on four educational objectives. Additionally, a 12-item questionnaire was used to determine prior attitudes/awareness about concussions. Post-attitude survey was administered to determine if participation in this module influenced attitudes and awareness.

Results: During 2011-2012 academic year, a total of 80,250 participants (45,876 male (57%) and 34,374 female (43%) enrolled in the Brainbook e-module on concussion education. The participants were between the ages of 13-19. Out of 26 possible points, the average pre- and post-test scores were 16.9 and 18, respectively. Using a Wilk’s lambda analysis, this was noted to be a significant result. Moreover, participants reported increased awareness and attitudes emphasizing the seriousness of concussion.

Conclusions: Despite a small effect size, the Brainbook e-learning module had a significant impact on teaching student-athletes in the state of Arizona about concussion. Our results suggest that the students have a fair baseline awareness of mTBI, but that this and similar learning modules can enhance the education and prevention of mTBI in this high-risk group.

CS-7. What is the Worst Thing about Having Epilepsy? A Child and Parent Perspective

Ng YT, Van Stratten A, Oklahoma City, OK.

Objective: The psychosocial burden on children with epilepsy and their families has been documented although often without specific reasons why epilepsy is so bad and the effects of the disease on the child and the parent can be vastly different. Do children and parents view epilepsy similarly?

Methods: Children with epilepsy who attended a one-week summer camp specifically for children with epilepsy and their parents were asked to participate in a voluntary survey (formal questionnaire). Full parental consent was obtained.

Results: Twenty campers, aged 9 to 15 years, and their parents responded. Thirty-eight percent of campers and 30% of parents chose being thought of as different or being teased as the worst thing about having epilepsy whereas only 37% and 33% respectively, chose the actual seizures themselves. Over half of children and parents would want to have fewer or no seizures if they could change one thing. The majority of children and parents, 65% and 93%, agree that epilepsy camp is fun while the other third of children cite it as a place where they feel normal.

Conclusion: Overall, children with epilepsy and their parents tend to view the burdens of epilepsy the same. We believe that it is dramatic that despite the morbidities and potential risks of the seizures and treatments themselves, the majority of children are most concerned about the stigma attached to having epilepsy! Epilepsy camps and similar activities are beneficial for the children and their families to feel better, normal and be more independent with their diagnosis.

CS-8. Longitudinal Measurements of Anti-Neuronal Biomarkers for Sydenham’s Chorea in Children with Acute Exacerbations of Tic and Obsessive Compulsive Symptoms following a Streptococcal Infection

Singer, HS, Morris-Berry, CM, Pollard M (Baltimore, MD), Mascaro-Blanco A, Alvarez K (Oklahoma City, OK), Kaplan E (Minneapolis, MN), The Tourette Syndrome Study Group, Cunningham MW (Oklahoma City, OK)

Objective: PANDAS (pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection), modeled upon Sydenham’s chorea (SC), is proposed to be an autoimmune disorder. If, as postulated, a clinical exacerbation is triggered by a streptococcal antibody cross-reactive against neuronal tissue, then a prospective longitudinal analysis might be expected to identify a temporal correlation between symptoms and autoimmune markers.

Methods: Serial serum samples from twelve children in a prospective blinded study: two samples before, one during, and two after a documented clinical exacerbation. Six
subjects had well-defined clinical worsening temporally associated with a Group A streptococcal infection (ExWS) and six without an infection (ExWOS). Samples were assayed for autoantibodies (IgG binding activity) against markers reported to be abnormal in SC (tubulin, lysoganglioside GM1, D1 and D2 dopamine receptor, and calcium calmodulin dependent protein kinase II (CaMKII) antibody signaling activity).

**Results:** Changes between pre-exacerbation and clinical exacerbation time-points for all assays showed little increase and did not correlate with the rise in anti-streptococcal (ASO, anti-DNase B) titers. However, in several subjects, values for anti-lysoganglioside and anti-D1 receptor antibodies as well as antibody activated CaMKII signaling were greater than those identified in a small number of provided control values.

**Conclusions:** Results from this longitudinal study raise questions about the definition and etiology of PANDAS and emphasizes the need for further autoimmune related investigations. Additional longitudinal evaluations on well-characterized controls are required to interpret the meaning of elevated individual single-point measurements.

**CS-9. An Evidence-Based, Open-Database Approach to Pediatric Neurologic Diagnostic Decision Support**

**Reduces Errors in Diagnosis and Testing**

Segal MM (Chestnut Hill, MA), Williams MS (Daville, PA), Gropman AL (Washington, DC), Torres AR (Boston, MA), Forryth R (Newcastle upon Tyne, UK), Connolly AM (St. Louis, MO), El-Hattab AW (Columbia, MO), Perlmann SJ (St. Louis, MO), Samanta D (Charlotteville, VA), Parikh S (Cleveland, OH), Pavlakis SG (Brooklyn, NY), Betensky RA (Boston, MA), Gospe SM Jr. (Seattle, WA)

**Objective:** To test the diagnostic and workup advice of diagnostic decision support and improbability of the underlying database.

**Method:** Using the SimulConsult diagnostic decision support program, we evaluated the changes in diagnosis and workup lists of 16 pediatric neurologists (11 junior, 5 senior) who worked through 40 real case vignettes with known diagnoses. Two assessments were used: a baseline in which testers could use any resources other than SimulConsult (for average of 27 minutes), followed by a second assessment in which using SimulConsult was allowed. We tested both the existing SimulConsult database and a database refined using a two-step process of disease-based and case-based modification of evidence-based information.

**Results:** Diagnostic error, defined as the diagnosis being absent from the differential diagnosis, dropped from a baseline of 36% down to 18% using SimulConsult. Among junior clinicians who used the refined or unrefined database randomly for each case, error dropped from 37% to 23% with the unrefined database and from 36% to 9% with the refined database (p <0.002). Using the software resulted in a 6% drop in workup items (p = 0.001) accompanied by a 34% increase in relevance of listed items compared to the “gold standard” (p <0.001). Workup errors dropped from 38% to 26% for the unrefined database and 41% to 18% for the refined (p <0.002).

**Conclusions:** Using the diagnostic software on challenging cases produced highly significant reductions in diagnostic and workup error compared to a baseline allowing all other resources. The improvement was most notable after the 2-step database refinement process.

**CS-10. Prevalence and Characteristics of Severe Sensory Impairment in a Population-Based Cohort of Children with Cerebral Palsy**

Dufresne D, Dagenais L, REFACTQ Consortium, Shelleb M (Montreal, QC, CA)

**Objective:** To ascertain the prevalence of severe sensory (visual and auditory) impairment in a cohort of children with cerebral palsy, as well as characteristics correlating with such impairment.

**Method:** The Quebec Cerebral Palsy Registry was used to identify children with cerebral palsy over a 4-year birth interval (1999-2002), covering approximately half of the province’s population. The prevalence of severe visual and hearing impairment were evaluated, and correlated with demographic and clinical characteristics pertaining to etiology, outcome and investigations.

**Results:** Data was available for 212 children with cerebral palsy. Prevalence of severe hearing loss in our cohort was, at 2.8% (n=6), in line with data from previously published cohorts. Severe visual loss was found in 9.9% (n=21) of our cohort. Both outcomes correlated strongly with a Gross Motor Function Classification System (GMFCS) score of IV or V, as well as with spastic quadriplegia, dyskinetic cerebral palsy or cognitive impairment. Being born at term and the presence of seizure in the year prior to enrolment was correlated with the presence of severe visual loss, whereas hyperbilirubinemia requiring exchange transfusion was associated with severe hearing loss.

**Conclusions:** Severity and the topographical distribution of motor impairment remain the strongest predictors of either visual or hearing impairment. Comorbid conditions also significantly correlated together.

**CS-11. Atomoxetine “Treatment Failures” Usually Respond to Dosing Changes**

Unson DK (Boston, MA)

**Objectives:** Atomoxetine is second-line treatment for ADHD. It has been disappointing, and several authors have reported that is fundamentally inefficacious. This study evaluates an experience with patients referred for treatment “failure” with atomoxetine.

**Method:** Referrals to a tertiary-hospital clinic for treatment failure in children with ADHD between the 6.0 and 18.11 years in the years 2009–2011 were reviewed. 173 children were referred for treatment failure with atomoxetine.

**Results:** 173 children (mean 10.4 years; 35 females and 138 males) met criteria. All had failed to tolerate and/or respond to at least one stimulant and had been placed on once-daily atomoxetine by referring providers. 147 patients had failed to respond to atomoxetine, 17 failed to tolerate, and 9 had both. All who failed to respond were placed on divided dose atomoxetine, as were 12/17 who failed to tolerate and 5/9 who failed to respond and tolerate. Of the non-responders, 110 (75%) responded adequately when dose was divided. 7/12 who failed to tolerate, and 3/5 who...
both failed to tolerate and respond to once-daily dosing, responded to BID treatment (roughly 60% in each instance).

Conclusions: All four investigations that demonstrated efficacy of atomoxetine as therapy for children who could not tolerate or failed to respond to stimulants used BID dosing schedules. The agent was nonetheless approved for use as once-daily dosing. Our sample shows that the majority of children who failed to respond and/or tolerate atomoxetine once daily did well when changed to a BID dosing

CS-12. Neurodevelopmental Evaluations of Children with Sickle Cell Disease: A Case Series
Lance EL, Comi AC, Shapiro BK (Baltimore, MD)
Objective: Sickle cell disease (SCD) is a hemoglobinopathy with severe neurocognitive complications in children, including stroke, seizures, and headaches. SCD patients with and without prior stroke also have an increased rate of neuropsychological testing abnormalities; however, there are only few studies relating those findings to increased incidence of neurodevelopmental disabilities in the population. This case series reviews the neurodevelopmental profiles of SCD children with and without a history of stroke.

Methods: Subjects with diagnoses of SCD who had neurodevelopmental evaluations done at Kennedy Krieger Institute between 2002 and 2012 were selected for a retrospective chart review. Charts were evaluated for multiple neurodevelopmental diagnoses, including attention deficit hyperactivity disorder, autism spectrum disorder, intellectual disability, language disorder, and cerebral palsy. Charts were also evaluated for diagnostic materials utilized, neurological examination findings in patients, and stimulant medication efficacy and safety.

Results: Subjects with and without prior stroke were found to have a variety of neurodevelopmental diagnoses, including attention deficit hyperactivity disorder, intellectual disability, and specific learning disabilities in math and reading. Commonly used developmental standardized testing measures (WRAT-4, Conners-3) showed diagnostic sensitivity in the SCD population. Stimulant medication was utilized in some subjects with minor side effects and varying efficacy.

Conclusion: This study reviews the neurodevelopmental evaluations of children with SCD seen at a large tertiary care center. Subjects represented the full spectrum of neurodevelopmental disabilities seen across motor, cognitive, language, and behavioral domains. Future studies will prospectively evaluate the specific developmental profiles of the neurodevelopmental disabilities as seen in SCD.

CS-13. Everolimus Decreased Frequency of Self-Injurious Behavior and Seizure Severity in an Adolescent With Tuberous Sclerosis
Gregory ML, Gipson TT, Wachtel LE, Jennett HK, Johnston MV (Baltimore, MD)
Objective: Tuberous sclerosis complex (TSC) is a genetic disorder that is characterized by hamartomas in multiple organs, including the brain, resulting in neurodevelopmental disorders such as intellectual disability, epilepsy, and behavioral and psychiatric disorders. Recent research has indicated a potential site for targeted therapy of TSC, inhibition of mTOR. Immunomodulators such as everolimus (Afinitor,) inhibit mTOR and show promise for treating hamartomas. Animal models have suggested potential benefits of the medication for TSC-associated neurodevelopmental disorders. Study of these benefits in humans has been limited by the difficulty of accurately and consistently measuring these behaviors. We report a case of an adolescent with TSC manifested by intellectual disability, refractory epilepsy, and severe aggression and self-injury who was treated with a 6-month course of everolimus during a long-term inpatient hospitalization in a neurobehavioral unit.

Methods: During the patient’s inpatient hospitalization he was continuously monitored with measurement by trained staff of multiple neurodevelopmental parameters, including levels of aggressive and self-injurious behaviors, quantitative and qualitative measurement of seizures, and overall functional analysis. Daily measurements of these parameters were compared from three time-points: before starting everolimus, during medication trial, and after discontinuation of everolimus.

Results: Prolonged seizures (requiring treatment by rectal diazepam) were significantly decreased during the trial of everolimus. The degree of self-injurious behavior was also significantly lowered. Additionally, the appearance of cutaneous angiofibromas was improved.

Conclusions: A significant decrease in seizure severity and self-injurious behavior was documented following initiation of everolimus.

CS-14. Developmental Fine Motor Incoordination: Associated Developmental and Psychiatric Disorders from Primary School to High School Age
Pokrajac NA, Mirtzbuehni AA, Divito BD, Koch HA, Schilling AR, Duane DD, Institute for Developmental Behavioral Neurology/Arizona State University, Scottsdale/(Tempe, AZ)
Objective: To evaluate the differential frequency of developmental learning disorders (LD) including AD(H)D and frequency of comorbid psychiatric disorders in children with Developmental Fine Motor Incoordination Disorder (DFMD) from primary through high school age.

Method: Retrospective chart analysis of referred children, each evaluated similarly, including a quantitative neuropsychological examination, which included a timed writing sample (Denckla, 1985) with a diagnosis of DFMD for the frequency of other developmental disorders – LD and AD(H)D and psychiatric disorders, contrasting 5-8 year olds with 8-18 year olds. Excluded were mental retardation and Pervasive Developmental Disorder.

Results:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>5–8 y/o</th>
<th>8–18 y/o</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>78</td>
<td>132</td>
</tr>
<tr>
<td>Male Sex</td>
<td>77%</td>
<td>81%</td>
</tr>
<tr>
<td>Age Range</td>
<td>5 3/12–7</td>
<td>8 1/12–17</td>
</tr>
<tr>
<td></td>
<td>11/12</td>
<td>9/12</td>
</tr>
<tr>
<td>3 diagnoses</td>
<td>31%</td>
<td>23%</td>
</tr>
<tr>
<td>≥4 diagnoses</td>
<td>46%</td>
<td>52%</td>
</tr>
<tr>
<td>Oral Language Disorder</td>
<td>40%</td>
<td>26%</td>
</tr>
<tr>
<td>Dyslexia</td>
<td>30%</td>
<td>16%</td>
</tr>
<tr>
<td>Dyscalculia</td>
<td>21%</td>
<td>25%</td>
</tr>
<tr>
<td>ADD</td>
<td>32%</td>
<td>46%</td>
</tr>
<tr>
<td>ADHD</td>
<td>44%</td>
<td>31%</td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>40%</td>
<td>39%</td>
</tr>
<tr>
<td>OCD</td>
<td>37%</td>
<td>47%</td>
</tr>
<tr>
<td>Major Depression</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Grade II or III (Mayo)</td>
<td>21%</td>
<td>20%</td>
</tr>
<tr>
<td>EEG Abnormality</td>
<td>12%</td>
<td>13%</td>
</tr>
</tbody>
</table>
**Conclusion:** The majority of referred students with DFMID have multiple additional developmental disorders at early and later age. The most common at all ages is an attention disorder. Oral Language Disorder and Dyslexia are more common in early age. Dyscalculia remains at about a fourth at all ages. Psychiatric co-morbidity, perhaps because of AD(H)D includes high rates of anxiety but a surprising rate of Obsessive-Compulsive Disorder symptoms.

**CS-15. Deep Brain Stimulation for Pediatric Onset Secondary Dystonias**

*Marks W, Bailey L, Reed M, Acosta F, Honecutt J (Fort Worth, TX)*

Deep brain stimulation of the globus pallidus (GPi) is accepted as a treatment for primary dystonias. Typically, these patients have preserved basal ganglia anatomy. There is less experience with pallidal stimulation in secondary dystonias. Secondary dystonias may arise from genetic disorders, or from an acquired injury to the brain. Since 2007, fifty-six patients (median age 13; range 7-26 years) have undergone primary implant of deep brain stimulation electrodes in the GPi for dystonia. Forty (median age 15 years) of these patients have pediatric onset secondary dystonias. Cerebral palsy is the most common etiology, accounting for twenty five of our patients (62.5%). Other external injuries account for an additional 7 patients. Three patients with strokes have been implanted in the GPI unilaterally; two of these patients had supplemental leads in the subthalamic nucleus or ventral-intermediate nucleus of the thalamus. Only 8 patients had genetic disorders that resulted in a dystonic state, and all had preserved basal ganglia anatomy. There is less experience needed to help refine patient selection, lead placement, and stimulation parameters. Anatomic placement is difficult when anatomy is distorted by gliosis, atrophy, or mineral deposition, but that alone does not negate response to pallidal stimulation.

**CS-16. Non-Autistic Complex Motor Stereotypies in 40 Older Children and Adolescents: Clinical Features and Longitudinal Follow-Up**

*Oakley CB, Morris-Berry CM, French BM, Singer HS (Baltimore, MD)*

**Objective:** Complex motor stereotypies (CMS), once believed to only occur in children with autistic spectrum disorders, have been well established in otherwise normal children. Despite recent gains regarding their clinical presentation and phenotype, there remains a lack of knowledge regarding etiology, co-morbidities, and long-term outcome.

**Methods:** Children over the age of 9 years with the diagnosis of primary (non-autistic) CMS were identified either in the pediatric neurology movement disorders clinic at the Johns Hopkins Hospital or by video and parent interview (including a formal screen for autistic symptoms) by knowledgeable personnel. Families of the identified study subjects were then contacted by telephone and interviewed using a structured questionnaire.

**Results:** Forty healthy individuals (15 girls, 25 boys; 38 families), aged 9 to 19 years, with primary CMS were identified. Onset was prior to age 3 years in 98%. Family history of CMS was identified in 38% with 73% of those being a first-degree relative. In all, movements stopped with distraction and were never noted during sleep. Triggers included excitement 90%, engrossment 67%, anxiety 69%, fatigue 33%, and boredom 26%. At time of follow-up 98% reported their stereotypies persisted, and one stopped at age 15.

**Conclusions:** Accurate knowledge about the clinical features and long term co-morbidities affecting individuals with primary (non-autistic) complex motor stereotypies will enable more appropriate diagnoses, treatment, counseling, and future expectations.


*Kumar A, Muzik O, Behen M, Chakrabarty P, Chugani HT, Chugani DC (Detroit, MI)*

**Objective:** Several post-mortem studies show neuroinflammation in patients with autism spectrum disorders (ASD); however, it is difficult to control for brain inflammation related to the immediate cause of death in postmortem studies. Therefore, we evaluated neuroinflammation in ASD patients in vivo with PET using the tracer [11C]-[R]-PK-11195 (PK), as PK binds to the 1kD translocator protein (TSPO) expressed by activated microglia.

**Methods:** Three boys (aged 7.5, 8.3 and 9.2 years) and one adult male (age: 22.3 years) with ASD and 10 pediatric controls (mean age: 8.8±5.2 years; 5 males), in whom suspicion of neuroinflammation was eventually ruled out based on negative PK binding were studied.

**Results:** Mean ± SD PET binding was recorded in the brain structures and compared with age-matched controls. Using a novel approach to identifying PK binding, we identified PK binding in the thalamus, temporal lobe, and cerebellum of the ASD patients and non-autistic stereotypic children (mean age: 7.5±3 years; 5 males).

**Conclusion:** Our findings indicate that neuroinflammation is present in young children with ASD and non-autistic stereotypies. Further studies are needed to determine the impact of neuroinflammation on the clinical course and outcome of these patients.
on available clinical, biochemical and radiological data, and 15 normal healthy adult controls (mean age: 29.0 ± 8.5 years; 7 males), underwent dynamic PK PET scanning. The PET images were evaluated visually, as well as by calculating standardized uptake value (PK uptake) and binding potential (PK receptor binding).

Results: The PK binding was increased in cerebellum, occipital cortex, basal ganglia and thalamus in children with ASD and in basal ganglia, thalamus and fronto-parietal cortex in the adult with ASD, both visually and quantitatively (Table), suggesting underlying neuroinflammation in these regions. The whole brain PK uptake was also found to be increased in one child with ASD.

Conclusion: This pilot study shows neuroinflammation in vivo in subjects with ASD, consistent with the postmortem studies. In vivo imaging of neuroinflammation with PET may be useful in elucidating the pathophysiology of ASD and may guide therapeutics aimed at the inflammatory process.

CS-18. WITHDRAWN

CS-19. Neurologic Complications Following Pediatric Renal Transplant
Ghosh PS, Kwon C, Klein M, Corder J, Ghosh D (Cleveland, OH)

Objective: We studied neurological complications (NCs) after renal transplantation (RT) in children.

Methods: Retrospective chart-review of RT patients ≤ 21 years during a 20-year period (1990–2010). NCs were classified as early (within 3 months post-RT) and delayed (beyond 3 months).

Results: Of 115 children with RT, 10 (8.7%) had NCs; 5 were boys, mean age was 15.3 ± 3.6 years. Early NCs were found in 4.35% (5/115) patients: seizures in 4 (posterior reversible leukoencephalopathy syndrome (PRES) due to immunosuppressant toxicity — 2, sepsis/meningitis-1, and indeterminate-1) and headache in 1 (chronic daily headache). Neurological examination was non-focal in all, abnormal neuroimaging findings were PRES in 2 patients. On follow-up, there was 1 death (unrelated to NC). Two patients with seizures were treated with anti-epileptics for 6 months; one with headache was on amitryptiline prophylaxis for 1 year. Late NCs were found in 4.35% (5/115) patients: seizures in 3 [PRES due to hypertension-2, indeterminate-1], headache in 3 [migraine-2, PRES-1], and tremors in 1. Two had both seizures and headache. Neurological examination was non-focal in all; abnormal neuroimaging findings were PRES (1), non-specific white matter changes in magnetic resonance imaging (1). On follow-up, there was 1 death (unrelated to NC). Two patients with seizures were treated with anti-epileptics for 1–2 years; one with migraine was treated with cyproheptadine for 6 months.

Conclusions: NCs develop in children after RT (both early and delayed). Seizure is the commonest complication, PRES being the most common etiology. Early detection and appropriate management of NC is important.

CS-20. Levetiracetam vs. (fos)Phenytoin for Seizure Prophylaxis in the Pediatric Intensive Care Unit
Banial S, Carpenter JL, Dean N, Kebede T (Washington, DC)

Objective: In the PICU, children with acute supratentorial intracranial hemorrhage (ICH) are commonly placed on antiepileptic medication (AED) for seizure prophylaxis. (Fos)phenytoin has traditionally been used, but levetiracetam is increasingly provided as an alternative due to its favourable side effect profile and pharmacokinetics.

Methods: A prospective NeuroICU database identified 166 children admitted with acute ICH from September 2008 to February 2012, of which 127 received seizure prophylaxis. Patients with a prior history of seizure(s) were excluded. AEDs were chosen according to physician discretion.

Results: Seizure prophylaxis was provided with levetiracetam in 58 children, (fos)phenytoin in 32 children and both drugs in 28 patients. Twelve patients who received levetiracetam had subsequent seizures during hospitalization, 46 patients did not. Seven patients who received (fos)phenytoin had seizures while 25 did not. Of the 28 patients who received both drugs, 25 remained seizure-free, while three required additional AEDs for breakthrough seizure. Nine patients were provided seizure prophylaxis with an AED other than (fos)phenytoin or levetiracetam; of these, three had seizures during hospitalization.

Adverse drug reaction prompted one patient to be switched from (fos)phenytoin to levetiracetam (rash). The same switch was made pre-emptively for a second patient due to a concern for cardiac side effects.

Conclusion: Neither levetiracetam nor (fos)phenytoin appeared acutely superior in this study. Levetiracetam and (fos)phenytoin are well tolerated in this population. Future studies are needed to determine if seizure prophylaxis for patients with acute ICH improves outcome and if levetiracetam is the preferred AED.

CS-21. Glut-1 Transporter Deficiency Syndrome Presenting as Ataxic Cerebral Palsy Without Intractable Epilepsy
Collins A, Stence N, Bernard T, Benke T (Aurora, CO)

Objective: Glut-1 transporter deficiency syndrome is a rare disorder of brain energy failure due to insufficient transport of glucose across the blood-brain barrier via the Glut-1 transporter. Classically, it presents with acquired microcephaly, infantile-onset intractable epilepsy, global developmental delays, ataxia and spasticity. Additional phenotypes have been described including a late-onset classical phenotype with intractable epilepsy onset after 2 years, and non-classical phenotypes with movement disorders but without epilepsy. We describe a series of 7 patients, 6 of which had ataxic cerebral palsy and medically-controlled or no epilepsy.

Methods: Case series of consecutively diagnosed patients at our institution over 3 years.

Results: All 7 patients had non-progressive congenital ataxia with mild (2) to moderate (5) global developmental delay. Pyramidal signs were present in 4, but 3 were hypotonic with decreased reflexes. Microcephaly was only present in 1. Five had epilepsy, but 4 were controlled on medications. CSF glucose ranged from 24 to 37 mg/dL, with CSF:serum glucose ratios of 0.32 to 0.46. Sequencing of the SLC2A1 gene found disease-causing mutations in 4/5 patients. Brain MRI scans were normal in 2, showed mild supratentorial volume loss in 2, mild-moderate global volume loss in 2, and enlarged extra-axial spaces in 1. Six had symptomatic improvement on the ketogenic diet with resolution of seizures, improved ataxia, stamina and developmental progress.

Conclusion: This series of 7 patients diagnosed in 3 years suggests that Glut-1 transporter deficiency syndrome is more common than previously thought and presents as ataxic cerebral palsy with well-controlled seizures.
CS-22. **Transient Ischemic Attack in Children**

*Lehman LL, Rivkin M (Boston, MA)*

**Objective:** Recent studies in adults show that 10-15% of patients with a transient ischemic attack (TIA) will have a stroke within 3 months of the episode. Among children, TIA has been poorly characterized. We present a consecutive case series of 50 children with TIA.

**Methods:** We searched the patient medical record database at Children's Hospital Boston using the search terms "transient ischemic attack" or "TIA". We examined cases of TIA in children 18 years of age or younger whose initial presentation occurred from 2009 to 2011. TIA was defined as a focal neurologic deficit that resolved completely.

**Results:** Our cohort comprised 44% females, 76% white, 10% black, 2% Asian, 10% other, and ranged in age from 2 to 18 years. Duration of the initial TIA ranged from 30 seconds to 36 hours. Recurrent TIAs occurred in 70% of our patients. Five of the 50 patients (10%) sustained a stroke following TIA. Collectively, these patients demonstrated established risk factors for stroke at the time of their TIA: moyamoya disease, sickle cell disease, autoimmune disease, congenital heart disease, oral contraceptive use, and cigarette use.

**Conclusion:** TIA occurs in children and appears to have a relationship to subsequent stroke. Children with TIA sustain subsequent stroke at a rate similar to that found in adults. Risk factors for stroke following TIA in children included those already associated with stroke in childhood but also some associated with adult stroke.


CS-23. **SCN1A Mutations Involving the Sodium Channel Pore Region Resulting in Intractable Seizures and Possible SUDEP (Sudden Unexplained Death in Epilepsy)**

*Sotero de Menezes MA, Saneto RP (Seattle, WA), Carmant L (Montreal, QC, CA), Simon E, Schoenfeld J, Doherty M (Seattle, WA)*

**Objective:** Delineate phenotypes associated with mutations in the pore region of the Nav1.1 (SCN1A) channel.

**Methods:** We describe the phenotypes of nine patients having mutations within the pore region of Nav1.1 (SCN1A). SCN1A analysis was performed using DHPLC and PCR amplification of highly purified genomic DNA. All 26 exons underwent unidirectional sequencing. Variants and abnormal patterns were confirmed by bidirectional sequencing. The patient’s charts were reviewed including the clinical data and EEG reports.

**Results:** The nine patients identified had severe epilepsy with either Dravet Syndrome or intractable focal seizures with onset in infancy and mutations within the pore region of SCN1A. EEG showed multifocal discharges in all cases. The children with the Dravet Syndrome phenotype also had generalized spike and wave discharges. Seizures in both populations were very difficult to control. Various combinations of seizure medications were used with only partial response. Although the best response was noted with the combination of stiripentol, clobazam, and valproic acid, none became seizure free on this regimen. One patient died of SUDEP even though she had a reduction in seizure frequency on medications. Several patients had Holter monitor findings of impaired beat-to-beat variation in heart rate.

**Conclusions:** SCN1A mutation phenotype-genotype correlations are challenging to define. Nonetheless, mutations that affect the most functional part of the protein had a more severe phenotype in our small cohort. In this group, medically refractory epilepsy is common and SUDEP remains possible even during brief periods of fair seizure control with antiepileptic therapy.

CS-24. **Twins With Novel AUTS2 Deletions and Autistic Disorder**

*Ho E, Montreau-Jacob F (Boston, MA), Shur N (Providence RI), Khwaja O (Boston, MA)*

**Objective:** To describe twin boys with a novel exon 19 deletion of isoform 3 in the AUTS2 gene with features of autistic disorder.

**Methods:** Clinical and genetic description of neurological and developmental symptoms and signs in monzygotic twin 3-year-old boys with deletions in 7q41.22 identified by chromosome microarray analysis.

**Results:** Chromosome microarray analysis identified a novel deletion in the AUTS2 gene approximately 57Kb in size. This deletion occurred in the last exon of isoform 3. Parents had normal testing indicating a de novo event. Other investigation including brain MRI was normal. Clinical features include global developmental delay, developmental regression, behavioral dysregulation, and complex partial seizures. Both boys meet clinical criteria for diagnosis of autistic disorder. They have impairment of social interaction, impairments in communication and restricted repetitive and stereotypical patterns of behavior.

**Conclusion:** Deletion in the last exon of isoform 3 of the AUTS2 gene is associated with features of autistic disorder.

CS-25. **MAO-A Promoter Polymorphisms: A Possible New Etiology of Dopamine and Serotonin-Responsive Neuropsychiatric Disorders**

*Rajan DC, Osorio MJ, Linday J, Coffman K (Pittsburgh, PA)*

**Objective:** To report a cohort of four patients with dystonia, dysautonomia, psychiatric symptoms, low cerebrospinal fluid (CSF) dopamine and serotonin metabolites that have a consistent MAO-A promoter variable number tandem repeat (VNTR) polymorphism.

**Methods:** Four patients were identified due to a similar clinical profile and low levels of dopamine and serotonin metabolites in the CSF. Gene sequencing for MAO-A revealed polymorphisms in the promoter sequence associated with increased MAO-A activity. A retrospective review of the clinical records and diagnostic testing was done to compare the phenotypes.

**Results:** Each patient presented with dystonia, dysautonomia and psychiatric symptoms. Initial laboratory evaluation and neuroimaging did not reveal a diagnosis. Evaluation of CSF neurotransmitters revealed low levels of 5- hydroxyindoleacetic acid and homovanillic acid. Other CSF assays, including 3-O-Methyldopa, 5-methyltetrahydrofolate, neopterin, and tetrahydrobiopterin were normal. Genetic evaluation for GTP cyclohydrolase, tyrosine hydroxylase, aromatic amino acid decarboxylase and vesicular monoamine transporter were normal. Genotyping of the MAO-A gene revealed polymorphisms in the MAO-A promoter (VNTR) that are associated with high MAO-A activity. All patients showed improvement after dopamine and/or serotonin replacement.
Conclusion: We present a possible new entity, characterized by dystonia, dysautonomia, psychiatric symptoms and decreased levels of dopamine and serotonin metabolites in the CSF. Each patient has a polymorphism in the MAO-A promoter region that is associated with increased MAO-A activity. These results suggest that alterations in MAO-A activity may cause a treatable neuropsychiatric disorder. A larger cohort of patients with a similar profile needs to be studied for better delineation of this entity.

CS-26. Retrospective Data Analysis of Neonatal Neurology Consults at the Miami Children's Hospital and Their Impact. Shubaither HH (Boston, MA), Alfonso I (Miami, FL)

Objective: This study compares the number of neonatal neurology consults and general pediatric consults done at Miami Children's Hospital from (2000-2010) and tabulates their diagnoses. Miami Children Hospital is a tertiary pediatric facility with no in-house deliveries. Miami Children's Hospital is a regional referral centre serving South Florida, South America, Central America and the Caribbean basin.

Method: Retrospective data analysis of inpatient requiring a neurological consultation. Neonates were identified as less than one month of age.

Results: Of 20,056 inpatient consultations, 3968 were neonatal neurology consults. Neonatal consultation represented 20% of all pediatric neurology consult in a 10 year period. Seizures and apnea were the most frequent diagnosis. Other condition encountered included hypoxic ischemic encephalopathy, cerebrovascular accidents, brain malformation, head trauma, facial palsy and brachial plexus palsy.

Conclusions: Neonatal neurology consultation was a significant percent of the total pediatric neurology consults at a tertiary pediatric facility. Pediatric neurology training programs should provide rotations to assure that trainees be proficient in neonatal neurology. Special neonatal neurology training and subspecialty board qualifications may be needed in the future to assure high quality care in this field.

CS-27. Hypomyelinating Leukodystrophy: Clinical, Electrophysiological and Neuroimaging Characterization Freitas MR, Kok E, Brenner C, Leite CC, Garzon E, Mangini NN, Amorim S (São Paulo, Brazil)

Objective: To describe clinical, electrophysiological and neuroimaging findings in patients with hypomyelinating leukodystrophies (HLD).

Method: Twenty-five patients with HLD were submitted to clinical evaluation, laboratory testing, electrophysiological studies (electroencephalogram, nerve conduction studies and multimodel evoked potentials) and magnetic resonance imaging of the brain (MRI). Age of disease onset, initial symptoms, clinical course and family history were obtained. Physical examination was performed: anthropometric data, particular non-neurological signs and neurological syndromes were determined. MRI included T1, T2 and FLAIR weighted images. Single voxel spectroscopy samples were collected in white and gray matter and displayed as metabolites ratios (NAA/CR, Cho/Cr and mI/Cr). The degree of myelination of selected brain structures was scored (0 to 2) and atrophy was rated (0 to 3) in supra and infratentorial structures.

Results: Twenty-five patients, aged 5-21 years, had clinical and/or molecular diagnosis of Pelizaeus-Merzbacher disease (n=5), Pelizaeus-Merzbacher-like disease (n=5), Cockayne syndrome (n=4), 18q- syndrome (n=1), hypomyelination with congenital cataract (n=1), hypomyelination with hypodontia and hypogonadotropic hypogonadism (n=5) or HLD of unknown origin (n=4). Clinical heterogeneity was observed. All patients displayed mild T2 hyperintensity and variable T1 signal (mildly hypointense, isointense or mildly hypointense) depending on the degree of myelination. Some entities shared common patterns of abnormalities.

Conclusion: Hypomyelination is a nonspecific neuroradiological pattern observed in a growing number of genetic disorders. HLD are a heterogeneous group of diseases. Although definite diagnosis requires molecular genetic testing for most of HLD, the combination of clinical data, laboratory/electrophysiological findings and MRI patterns may contribute to differential diagnosis of hypomyelinating disorders.

CS-28. Seizure and Developmental Outcomes in Patients With and Without Hemispherectomy for Hemimegalencephaly. Ostrander B, Candy M, VanOrman C (Salt Lake City, UT)

Objectives: Hemimegalencephaly is a congenital malformation of the brain that involves dysplastic enlargement of a cerebral hemisphere. We assessed seizure and developmental outcomes of those patients at our institution that did and did not undergo hemispherectomy.

Method: We retrospectively reviewed 13 patients with hemimegalencephaly followed from 1993-2011. We analyzed patient charts to assess age of onset and frequency of seizures, number of antiepileptic medications prescribed and developmental progress. We also reviewed the outcomes of patients who underwent hemispherectomy with regards to the impact on seizure frequency.

Results: Only 4/13 patients underwent hemispherectomy. Three developed infantile spasms necessitating surgery before 6 months of age. All patients who underwent surgery had a seizure free period of at least 18 months; however, all had recurrence of seizures though less frequent than prior. Of the patients that did not undergo hemispherectomy, 3/9 had seizure free periods of greater than 18 months while taking multiple antiepileptic medications. One of those patients has been seizure free for 4 years off medications. 5/13 did not have significant motor delays. Of 10 patients over 4 years of age, one has no significant cognitive impairment and is able to attend regular classes.

Conclusion: Both patient groups achieved seizure free periods. While global developmental retardation has been reported to be present in all children with early onset of neurological manifestations, our series found that one-third of patients did not have significant motor delays and one patient had no significant mild cognitive impairment.

CS-29. Asymptomatic Abnormalities in the White Matter of Patients with CMT-X. Robertschau Vieboever A, Schimmoeller L, Benzinger T, Mar S (St. Louis, MO)

Objective: X-linked Charcot-Marie-Tooth (CMT-X) is an X-linked dominant hereditary peripheral neuropathy caused by mutation in the GJB1 gene that codes for the connexin 32 protein which is highly expressed in Schwann cells as well as oligodendrocytes. Central nervous system involvement with white matter changes on magnetic resonance imaging (MRI) has been reported in this condition usually in children in the context of abnormal neurologic symptoms. We have initiated a study of CNS involvement in a large family with CMT-X to understand the relationship
between genotype and phenotype of CNS white matter involvement.

**Methods**: We collected structural brain MRI data from a large family with CMT-X. All participants had peripheral neuropathy and genetic confirmation of CMT-X. Only one subject, the 12 year old pro-band, had symptoms of CNS disease; the rest were asymptomatic.

**Results**: White matter signal changes were found in all cases of varying degrees of severity affecting the corpus callosum and periventricular areas with a posterior predominance similar to previous reported cases. In one case, there was profound multifocal white matter abnormalities.

**Conclusions**: There can be subclinical changes in the white matter of patients with CMT-X in absence of symptoms of CNS disease.

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**CS-30. Mass Psychogenic Illness in Leroy High School, New York**

**McVige JW, Fritz CL, Mchtler LL (Buffalo, NY)**

**Objective**: Present the clinical data from a unique case of Mass Psychogenic Illness (MPI) involving tic like movements in a high school population.

**Methods**: A retrospective study evaluated clinical histories, precipitating events, laboratory studies, treatment strategies, severity and duration of illness for patients seen at Dent Neurologic Institute (DNI). A timeline was developed to examine the evolution of the event and factors which may have precipitated and prolonged symptomatology.

**Results**: Nineteen teenagers reported prominent tic movements in the school. Two were known to have a pre-existing diagnosis of Simple Tic Disorder or Tourette Disorder, with exacerbated symptoms. The neurologic examination was unremarkable, except for findings consistent with conversion disorder. Fourteen teens (13 females and 1 male) ages 13-19 years were followed at DNI. Ten had significant life stressors. Six also developed syncope and psychogenic seizures. Nine had co-morbid migraines. Three were lost to follow up. Laboratory studies included ASO, ESR, CRP, TSH, heavy metals, tox screen, Ceruloplasmin, ANA, CBC, CMP, Lyme and Mycoplasma.

**Conclusions**: There were no consistent abnormalities to suggest a uniform organic (environmental, infectious or postvaccination) cause for the movement disorder. Treatments with behavioral modification techniques, psychologic support, education, pharmacotherapy, and removal from social setting were successful in allowing 5 teens to completely recover and 6 to improve by 85-97%. Notable exacerbation and prolongation of symptomatology was observed with increased media attention and psychosocial stressors.

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**CS-31. Successful Correction of Monozygotic Twin-Twin Transfusion Syndrome at 20 Weeks of Gestation Did Not Prevent Polymicrogyria.**

Azizi P, Clark G (Houston, TX)

**Objective**: While polymicrogyria in one of monozygotic twins owing to Twin-Twin Transfusion Syndrome (TTTS) has been reported, the timing of this presumed acquired lesion is unknown.

**Methods**: Case review.

**Results**: A twin pregnancy complicated by discordant sizes due to TTTS was diagnosed at 20 weeks of gestation and was repaired by intrauterine laser ablation without complications. The twins were followed by weekly ultrasounds and these demonstrated resumed growth (length, weight, FOC) of the donor twin. A successful, uncomplicated delivery via C/S at 37 weeks gestation was achieved. Donor twin was born first and weighed 2070 gram, with microcephaly while recipient twin was born second with a weight of 2623 gram and normal head size. While recipient twin had normal growth, development and a normal MRI of brain at 5 years of age, donor twin has had poor growth accompanied by a global developmental disorder and by intractable epilepsy. She has frontoparietal predominate polymicrogyria, and two subependymal heterotopia along the right lateral ventricle.

**Conclusions**: Polymicrogyria may be genetic or acquired, but the timing of this lesion, especially in acquired cases, is unknown. Whereas polymicrogyria has been reported in TTTS in monozygotic, presumably genetically identical twins, the timing of this acquired lesion is also unknown. This is the first reported case of TTTS successfully repaired at 20 weeks of gestation that still resulted in extensive polymicrogyria in the donor twin. This report gives evidence for a pathophysiologic mechanism prior to 20 weeks gestation resulting in polymicrogyria in TTTS.
POSTERS: Developmental/Degenerative Disorders

DD-1. Early Language Development After Perinatal Stroke
Eshagh K, Ballantyne A, Trauner D (La Jolla, CA)

Objective: To determine how language skills of children with perinatal stroke develop in the first 2 years, and whether longitudinal development differs among typically developing (TD) children, children with right hemisphere (RH) stroke, and left hemisphere (LH) stroke.

Methods: Subjects were infants with unilateral perinatal stroke and TD. (85 TD, 14 RH, 28 LH, at 10-13 months; 81 TD, 13 RH and 35 LH at 22-25 months). Parents completed the MacArthur Communication Development Inventory (CDI): Words & Gestures to 16 months, and the CDI: Words & Sentences after 16 months. Statistical analyses were performed using t-tests and correlation.

Results: At 12 months, children with RH lesions scored significantly lower than TD or LH children on Words Understood and Total Gestures. By 24 months, both lesion groups scored significantly lower than TD on word production and grammatical skills, but lesion groups did not differ from each other. Within the focal lesion group, expressive vocabulary declined significantly from 12 to 24 months. Only RH and TD groups showed a significant correlation between total gesture at 12 months and word production at 24 months. Neither lesion group demonstrated a correlation between expressive vocabulary at 12 months and expressive vocabulary at 24 months.

Conclusions: Brain reorganization for language after early unilateral injury takes a different course from that of typical language development. Side of the lesion does not predict language development. Early gestures do not predict future language development in LH children, suggesting a dissociation between language and gesture development in this population.

DD-2. Understanding Biochemical Alterations in Urea Cycle Disorders
Ellenhogen A (Charlottesville, VA), Ludwig W, Gropman A (Washington, DC)

Objective: Urea cycle disorders result in hyperammonemia. Ammonia is converted to glutamine in astrocytes. While this protects neurons from ammonia’s toxicity, glutamine, an osmolyte causes astrocytic edema and neurotoxicity. Current patient monitoring often include only measuring plasma ammonia/glutamine levels. Clinical manifestations of encephalopathy may occur in the absence of significantly increased plasma ammonia/glutamine. Furthermore, plasma glutamine is thought to rise before and remain elevated after ammonia levels have returned to normal, suggesting that neurotoxicity occurs for a longer period than what would be recognized. Additionally, compartmentalization imposed by the blood brain barrier, complicates the relationship between measurements of compounds in the plasma and the brain.

Methods: We evaluated 21 patients with OrnithineTranscarbamylase Deficiency (OTCD) and 17 age-matched controls. We measured plasma glutamine and ammonia levels;

Results: CNS glutamine and myoinositol values extracted from 1H MRS and DTI images of fiber tracts. Results: Plasma glutamine remained elevated after plasma ammonia levels returned to normal. Plasma glutamine and ammonia levels were not always correlated. Plasma ammonia levels weakly correlated to brain glutamine levels but not to brain myoinositol levels. Plasma glutamine and brain glutamine levels were not correlated. Significant inverse correlations existed between brain myoinositol and glutamine for OTCD subjects. Brain glutamine, but not myoinositol, is an index of neuronal cell deaths.

Conclusions: This data suggests a need to create and put into clinical practice a method to measure plasma and brain glutamine that matches the ease of that used to measure ammonia.

DD-3. FAST MRI in Pediatric Patients: A Safe, Quick Look to Answer the Question
Broomall EM, Niederhauser BD, Keating GE, Eckel LJ (Rochester, MN)

Objective: To describe the patient population in whom the use of fast MRI sequences have been found useful and effective in evaluation of hydrocephalus, eliminating radiation and sedation from other imaging procedures.

Methods: Review of medical records of all pediatric patients in the last three years who have fast MRI sequences, to determine the patient characteristics and diseases. In our institution we have labeled this our FAST (Fourier Acquisition Single-shot Technique) MRI.

Results: Over 500 MRIs were performed in approximately 350 patients ranging from age 0 to 14 years old, of varied developmental levels and underlying conditions, and in several clinical contexts, with demographic details to be further described. In every case, FAST MRI was able to answer the clinical question. No subsequent CT exams were needed, eliminating radiation in these patients. In addition, no diagnostic MRI was needed to further evaluate ventricular size, eliminating the need for sedation.

Conclusion: In evaluation of hydrocephalus in the pediatric population, regardless of neurological condition, developmental level or patient age, fast MRI sequences are safe, quick, and effective, obviating the need for sedated MRI and eliminating radiation exposure from CT.

DD-4. Mutations in Forkhead Transcription Factor Lead to Congenital Rett Syndrome, Memory Defects and Impaired Social Behavior
Rosenfelt C, Strautman J, Chambers DB, Bolduc FV (Edmonton, AB, CA)

Objective: The transcription factor forkhead box G1 (FOXG1) has has recently been associated with the congenital variant of Rett syndrome. Interestingly, forkhead was initially identified in Drosophila as a developmental gene. We therefore decided to study the role of forkhead in Drosophila memory and social interaction to gain a better understanding of the molecular basis underlying cognitive and social defects observed in patients with FOXG1 mutation.

Methods: The fruit fly Drosophila can be trained to associate an odor with a footshock. Fly memory is tested by measuring their avoidance to the odor paired with the shock compared to a neutral odor. Long-term memory (LTM) forms if repeated training sessions are separated by rest interval (spaced training). We used a mutant allele containing a P-element in the gene forkhead box o, foxo to test memory. Next we tested the social interaction of flies using a novel model. Statistical analysis was performed with T-test.

Results: Immediate learning is normal in foxo mutant flies (P=0.2551). In the other hand, we observed a significant defect in LTM when compared to controls (P=0.0007,
t test). Moreover, the mutant flies displayed an increased interfly distance compared to control flies.

**Conclusion:** Our findings of LTM defect in *Drosophila forhead* mutants suggest a role in transcription or translation dependent memory. This may also relate to abnormal brain development. In addition, our model reproduces some of the social interaction defects observed in patients with congenital Rett syndrome.

**DD-5. Gamma-Hydroxybutyric Acid Determination in Newborn Dried Blood Spots as a Biomarker for Succinic Semialdehyde Dehydrogenase Deficiency**

*Pearl PL (Washington, DC), Forni S (Dallas, TX), Gibson KM (Houghton, MI), Sweetman L (Dallas, TX)*

**Objective:** SSADH deficiency, an autosomal recessive disorder of GABA degradation, is characterized by elevated gamma-hydroxybutyric acid (GHB). Neurological outcomes may be improved with early intervention and anticipatory guidance. Morbidity has been compounded by complications, e.g. hypotonia and respiratory arrest, in undiagnosed infants with otherwise routine childhood illnesses. We report methodology to obtain newborn screening.

**Method:** Dried blood spots in affected patients were compared with controls. In this method three 1/8” dried blood spot punches are extracted with 200 µL methanol containing 500 ng/mL d6-GHB deuterium-labeled internal standard. The extract is dried, reconstituted, and analyzed via ultra-performance liquid-chromatography tandem mass spectrometry. GHB is completely separated from isomeric and isobaric interferences using a step gradient. Multiple selected reaction monitoring for d6-GHB is m/z 109→90 and for GHB 103→85. The same fragment is present in the spectra of the α-hydroxy and β-hydroxy isomers. Therefore major transitions for α-hydroxyisobutyric, α-hydroxybutyric, β-hydroxyisobutyric, and β-hydroxybutyric acids are monitored to verify separation from GHB.

**Results:** The above method was validated to meet satisfactory accuracy and reproducibility criteria, including intra-day precision and inter-day validation. Of 1,700 archival dried blood spots screened, GHB mean +/- S.D. was 8.2 ± 5.1 nM (99%-tile 63 nM). The measured concentrations in blood spots of four SSADH deficiency patients were 124, 271, 609 and 715 nM.

**Conclusions:** GHB concentration in all 1,700 dried blood spot cards was well below the lowest concentration of affected children. This shows validation of screening methodology for SSADH deficiency with applicability to newborn screening and enabling earlier diagnosis.

**DD-6. Social Communication Deficits Are Measurable in Very Young Infants At Risk For Autistic Spectrum Disorder (ASD)**

*Filipek PA (Houston, TX), Abdallah MM (Irvine, CA), Horner PL, Phan JT, Pham KL (Orange, CA)*

**Objective:** To identify differences in social communication in very young infants later classified as having an autism spectrum disorder (ASD+) or Non-Spectrum (N/S) by the Toddler-ADOS (ADOS-T).

**Methods:** Forty infants were enrolled by 2 months. At 3mo and 6mo, the toddlers were classified using the Rossetti Infant-Toddler Language Scales (RITLS) were performed. By ADOS-T at CA/NVMA ≥12mo, seventeen were ASD+ and 23 were N/S. RITLS subscale group differences were examined using Mann-Whitney analyses; individual item differences were evaluated by Chi-Square analyses.

**Results:** RITLS subscales: No significant differences were found at 3mo; at 6mo, ASD+ scored significantly lower than N/S in:

- Interaction-Attachment (z=-2.87/p=.034),
- Pragmatics (z=-2.94/p=.003),
- Language Comprehension (z=-2.92/p=.004), and
- Language Expression (z=-3.31/p=.001).

RITLS item analysis at 3-months revealed significant differences on:

- shows differing responses to vocalizations (χ²=6.01/p=.01),
- vocalizes to caregiver’s smile (χ²=4.39/p=.04),
- produces a hunger cry (χ²=6.01/p=.01), and
- vocalizes to express pleasure (χ²=4.39/p=.04); and at 6-months on:

- smiles spontaneously (χ²=4.34/p=.04),
- smiles when playing alone (χ²=6.01/p=.01),
- imitates facial expressions (χ²=9.63/p=.01),
- stops crying when spoken to (χ²=11.52/p=.001),
- discriminates between threatening/friendly voices (χ²=7.41/p=.01),
- vocalizes feelings through intonation (χ²=6.01/p=.01),
- takes turns vocalizing (χ²=11.47/p=.001),
- babbles (χ²=6.81/p=.01),
- stops babbling when another person vocalizes (χ²=3.87/p=.05),
- initiates “talking” (χ²=4.09/p=.04),
- demonstrates sound play (χ²=7.73/p=.005), and
- whines with a manipulative purpose (χ²=4.18/p=.04).

**Conclusions:** Social communication deficits are measurable with the RITLS as early as age 3mo in infants ultimately diagnosed with ASD. Identification of atypical development in very young infants at risk for autism is important for the earliest possible intervention. If replicated, these data may prove useful as a screening instrument for very young infants.

**DD-7. Directed Vocalizations and Smiles Can Differ as Early as 6 Months of Age in Infants at Risk for ASD**

*Filipek PA, Johns KM (Houston, TX), Abdallah MM (Irvine, CA), Pham KL, Horner PL, Phan JT (Orange, CA)*

**Objective:** To examine whether 6mo infants later classified with ASD (ASD+) differed from those later classified as NonSpectrum (N/S) in aspects of social interaction.

**Methods:** Twenty-seven infants were enrolled between birth-2mo (13 males, 63% Caucasian); they were followed with videotaped social interactions and psychometric instruments, including the Mullen Scales of Early Learning (MSEL) and the ADOS-Toddler Module (ADOS-T). At 6mo, infant-researcher interactions were videotaped with a fiberoptic eye-glass camera while the infant was seated in a car seat, during spontaneous infant-directed “motherese” paradigms, performed pre- (90sec) and post- (90sec) a Still Face maneuver (30sec).
At chronological and mental ages ≥12mo with independent ambulation, they were assessed with the ADOS-T for ASD classification. Videotapes were coded by blind research assistants for the following: direct eye contact; smiles: directed vs. undirected; and vocalizations: directed vs. undirected/ positive vs. negative.

Results: Eleven of the 27 infants met cutoff criteria for an ASD using the ADOS-T, 4 male and 7 female. Compared to N/S 6mo infants, ASD+ infants demonstrated:

- significantly lower rate (p<0.03) and proportion (p<0.04) of directed vocalizations throughout the entire Paradigm, particularly during the SF (p<0.02) and Post-SF (p<0.03) periods; and
- significantly briefer mean duration of directed smiles before the SF (p<0.002).

Conclusions: These data demonstrate further evidence that deficits in social interaction can be measured as early as at 6mo in at least some infants who are categorized as ASD+ in toddlerhood.

DD-8. Magnesium Role in Connectivity Changes Following Hypoxia
Doll E, Stevenson T, Bonkowsky J (Salt Lake City, UT)

Objectives: Hypoxic injury to the developing CNS is a frequent accompaniment of preterm birth, and is associated with elevated rates of adverse neurodevelopmental sequelae. Our goals were to develop a small vertebrate model for analyzing the molecular pathways of hypoxia on the development of CNS connectivity, and to determine whether the molecular pathways we identified are replicated in studies in human preterm infants.

Methods: We visualized connectivity in a novel zebrafish hypoxia model, examining effects both on axon pathfinding and synapse development, using novel transgenic lines. We examined the correlations between preterm birth, hypoxic injury, and adverse long-term neurodevelopmental outcomes using a well-defined cohort of 118 preterm infants (<1200 g, gestational age less than 27 weeks) with greater than two years of follow-up data.

Results: We have found that developmental hypoxic injury disrupts pathfinding of forebrain commissural axons in zebrafish, leading to errors in which commissural axons fail to cross the midline. We found that ephrinB2a is responsible for mediating these pathfinding errors from hypoxia, and that magnesium sulfate could protect against the pathfinding errors by preventing upregulation of ephrinB2a.

We analyzed the correlation between preterm birth, hypoxic injury, magnesium exposure and levels, and long-term outcomes including Bayley III scores, epilepsy, and autism. We found that magnesium levels or exposure correlated with improved outcomes.

Conclusions: Our results demonstrate that evolutionarily conserved genetic pathways regulate connectivity changes in the vertebrate CNS in response to hypoxia, and support a potential neuroprotective role for magnesium.

DD-9. Pursuit of Complementary and Alternative Medicine Treatments in Adolescents with Cerebral Palsy
Majnemer A, Shikako-Thomas K, Shevell M, Lach L, Law M, Schmitz N (Montreal, QC, CA)

Parents may seek Complementary and Alternative Medicine (CAM) treatments, with the expectation that these services will enhance their child’s functioning.

Objective: To determine the extent to which parents of adolescents with cerebral palsy (CP) seek CAM services and to identify factors associated with use.

Methods: As part of a study on quality of life, parents completed a questionnaire on demographic factors and services received. Parents were asked to identify services received over the past year from the following: acupuncture, chiropractic intervention, folk remedies, herbal therapy, high-dose vitamins, homeopathy, hyperbaric oxygen, hypnosis, massage therapy, osteopathy, reflexology, spiritual healing or other complementary services. Factors considered that may have mediated use were age, gender, socioeconomic status, family stress and functional limitations.

Results: A regional sample of 166 adolescents (15.3±2.2 years) with CP (GMFCS level I:31.4%, II-III:35.2%, IV-V:33.3%) were recruited. Most (73.2%) did not currently utilize any of the listed CAM services; 7.3% used two or more services. Most commonly used services were massage (15.4%), hyperbaric oxygen (9.6%) and osteopathy (5.7%). Youth with limited hand function were more likely (p<0.01) to undergo hyperbaric oxygen. Massage therapy services were more frequent in youth with greater activity limitations across domains (p<0.005). Socioeconomic factors were not predictive of use.

Conclusions: Approximately one quarter of families sought out CAM services for their adolescents with CP with hyperbaric oxygen and massage therapy most commonly used. These are expensive privately-funded treatments. Physicians should openly discuss these options with families, highlighting the current state of knowledge on their efficacy.

DD-10. Does Antenatal Tobacco or Alcohol Exposure Influence a Child’s Cerebral Palsy?
A Population-Based Study
Kyriakopoulos P, Oskoui M, Dagenais L, Shevell M (Montreal, QC, CA)

Introduction: Antenatal tobacco and alcohol exposure are established risk factors for premature birth, an independent risk factor for cerebral palsy (CP). In children with CP, it is not known whether such antenatal exposures are associated with a difference in clinical profile.

Objective: Compare the clinical profile of children with CP exposed or not to alcohol or tobacco in utero.

Methods: The Quebec Cerebral Palsy Registry was used to compare the neurologic subtype, gross motor functional impairment, and comorbidities in children with CP who were or were not prenatally exposed to alcohol or tobacco.

Results: In utero toxin exposure information was available on 249 children with CP born between 1999-2002, of which 77 were exposed to alcohol and 62 were exposed to tobacco in utero. No association was found between toxin exposure during pregnancy and neurologic subtype or GMFCS level. The mean number of comorbidities experienced did not differ significantly between groups. None of the five comorbidities explored was found to be associated with antenatal toxin exposure.

Conclusion: Adjusting for prematurity and low birth weight, exposure to tobacco or alcohol in utero does not appear to predict the diagnosis of a particular subtype of CP, severity of gross motor impairment or concurrent comorbidities.

DD-11. Stimulant Use in Patients with Sturge-Weber Syndrome: Safety and Efficacy
Lance EI, Lanier KE, Zabel TA, Comi AC (Baltimore, MD)

Objective: Sturge Weber Syndrome (SWS) is characterized by a facial port-wine birthmark, vascular eye abnormalities,
and a leptomeningeal angioma. Attention and behavioral issues are common in SWS; literature evidence for stimulant treatment is primarily derived from a previous survey. This study evaluates stimulant medication safety and efficacy in SWS patients.

**Methods:** The research database of the Hunter Nelson Sturge-Weber Center (n = 210 subjects with SWS brain involvement) was reviewed for stimulant use. Thirteen subjects (mean age 10.7 years, ages 4 to 21) on stimulants were seen between 2002 and 2012. A retrospective chart review obtained co-morbid diagnoses, stimulant type and dosage, medication side effects, vital signs, and medication efficacy.

**Results:** All thirteen subjects had brain involvement (unilateral - ten; bilateral – three). Subjects were diagnosed with attention issues by neurologist (six), neuropsychological testing (five), or had prior diagnoses (two). Additional co-morbidities included epilepsy (thirteen), hemi-paresis (nine), headaches (eight), and vision deficits (seven). Eight subjects reported side effects, primarily appetite suppression (four) and headaches (three). There were no statistically significant changes in weight or blood pressure six months after medication initiation. Medication efficacy was reported in twelve subjects. Eight patients remained on stimulants at their most recent follow up visit.

**Conclusions:** This study evaluates stimulant medication use in a group of SWS patients. Stimulants were tolerated and effective in most subjects. Side effects were mostly minor and medication did not negatively impact growth or vital signs. Stimulant medication may be a safe and effective intervention for SWS children with attention issues/ADHD.

**DD-12. Neurological Abnormalities among 16p11.2 Deletion and Duplication Carriers**

Steinman KJ (Seattle, WA), Ramocki MB (Houston, TX), Spence SJ (Boston, MA), Proud MB (Houston, TX), Kessler SK (Philadelphia, PA), Marco EF (San Francisco, CA), Simons VIP Consortium, Sherr EH (San Francisco, CA)

**Objective:** To characterize the neurological findings seen in a large cohort of individuals from the Simons Variation in Individuals Project with deletions and duplications of 16p11.2, recurrent genetic variations that increase the risk of autism spectrum and other neurodevelopmental disorders.

**Methods:** We performed neurologic examinations (including assessment for spinal and neurocutaneous abnormalities) on deletion carriers (del; n = 55) and duplication carriers (dup; n = 53) to define the range of findings in these groups. We used one-sample t-tests to assess whether head circumferences (percentile for age) differed significantly from the normal population.

**Results:** Head circumference was large for del (82.1 ± 22.3; p < 0.0001) and average for dup (44.9 ± 31.5; p = 0.3). Abnormalities of articulation (del 84%, dup 26%), deep tendon reflexes (67%, 35%), appendicular tone (63%, 54%), and casual gait (40%, 24%) were prominent among both groups. Both groups also exhibited numerous but varied neurocutaneous findings (56%, 51%) and spinal abnormalities (67%, 42%). Truncal ataxia was seen only in dup (10%) while abnormalities of heel walking were seen only in del (18%). Less common findings included facial tone and strength abnormalities (del 20%, dup 3%), truncal hypotonia (11%, 10%), and dysrhythmia (12%, 4%).

**Conclusions:** Deletions and duplications of 16p11.2 are associated with a variety of neurological abnormalities. While some are common in neurodevelopmental populations, others – such as articulation and spinal abnormalities – may be more specific to 16p11.2 copy-number variations. Identification of these neurological abnormalities serves an important role in understanding the protean clinical consequences of these recurrent variants and their role in common neurodevelopmental disorders.


McVicar K, Reiter L, Richie S, Ladd A, Jensen L (Memphis, TN)

**Objective:** Associations between autism spectrum disorders (ASD) and familial autoimmune disorders are described. Pooled IgG from mothers of autistic children known to be reactive against fetal brain tissue administered to rhesus macaques resulted in behaviors associated with autism compared to controls (1). This pilot data proposes to distinguish those with ASD with those without familial autoimmune history (FAIH).

**Methods:** Children with, 4, and without, 4, FAIH and ASD, per DSM IV criteria, were matched by gender and ethnicity. IQ testing and Childhood Autism Rating Scale was administered. Serum was collected and IgG levels tittered by fluorescent dot blot. Serum IgG levels were normalized to three previously collected typical control samples and hybridized to a human protein array containing >9,000 human proteins. Chips were scanned and data normalized to control proteins. All chips were analyzed for optimal Z-score prior to group comparative analysis. Data for each protein passing quality control was compared across each group to establish which proteins were IgG targets in FAIH and ASD serum at a significantly higher detection threshold.

**Results:** Forty-three proteins with elevated signals were more prevalent in autism with FAIH ($p_{val} = 1.43 \times 10^{-2}$). These included several unknown open reading frames (C20orf20, C8orf54 and C17orf44), two ubiquitin ligase related proteins (UBE2D3 and RN1F41) and several onco-genes (e.g. ABL1 and ERBB2).

**Conclusions:** Children with ASD and FAIH may share antibodies against proteins not present in those with ASD alone. Identification of these serum antibodies may provide an early biomarker and/or shed light on the etiologies of ASD.

**Reference**


**DD-14. White Matter Biomarker of Hereditary Spastic Paraplegia**

Delgado M, Smith L, Clegg N, Huang H (Dallas, TX)

**Objective:** To find an effective white matter biomarker of Hereditary Spastic Paraplegia (HSP) for early diagnosis with diffusion tensor imaging (DTI).

**Methods:** In this case controlled prospective study a convenient sample of 13 HSP children and 11 age matched controls were enrolled. High-resolution DTI data were acquired using a singleshot EPI with SENSE. DTI data with $2 	imes 2 	imes 2 \text{mm}^3$ resolution and b value 1000s/mm² was acquired. An atlas-based approach combined with tract-based spatial statistics (TBSS) of FSL was used for detecting the disrupted white matter.

**Results:** The disrupted tracts including one or multiple clusters with statistically significantly (FDR corrected) lower FA values were identified. Different colors indicate different
functions of the tracts. Multiple components of projection tracts directly related to motor function are shown. Detailed anatomical locations of disrupted clusters in projection tracts are also displayed.

**Conclusions:** DTI is sensitive to subtle white matter structural changes that play essential roles in motor dysfunction of children with HSP. Disruption among and within affected white matter tracts is inhomogeneous and a specific region of the tract is more severely disrupted by HSP than other regions of the same tract.


Mahone EM, Ryan M, Ferenc L, Morris-Berry CM, Singer HS (Baltimore, MD)

**Objective:** Complex motor stereotypies (CMS) are patterned, repetitive, rhythmic, involuntary movements that stop with distraction and persist over time. Stereotypies are grouped into "primary" (otherwise normal) and "secondary" (e.g., associated with autism, intellectual disability, sensory deficits) categories. Although occurring in normal individuals, a careful analysis of the underlying neuropsychological correlates of primary CMS has not been performed.

**Methods:** Thirty-seven children with primary CMS (verified by observation or video and screening for autistic spectrum disorders; ages 4-12 years) and 37 typically developing controls (matched on age, sex, handedness, and race) completed neuropsychological assessments including IQ, language, motor, attention, and executive functions. Stereotypy severity was rated by parents of children in the CMS group.

**Results:** Compared to controls, children with primary CMS were rated by parents as having significantly more problems with attention, hyperactivity/impulsivity, and executive dysfunction (all p<.01). The primary CMS group performed significantly worse than controls on motor speed, and inhibition of motor overflow (p<.05), but not on core language skills. Identified deficits in motor speed and overflow persisted after controlling for IQ and ADHD symptoms. Within the primary CMS group, none of the neuropsychological variables significantly correlated with parent report of stereotypy frequency or severity.

**Conclusions:** Despite having age-appropriate core language and IQ, children with primary CMS manifest neurobehavioral deficits in executive and motor control. Recognition of these deficits is important, since they could potentially affect communication and social skills. Parent report of the frequency and intensity of stereotypies does not appear to be a marker for neuropsychological dysfunction.

**DD-16. Visual Attention and Recognition Memory in Girls with Rett Syndrome**

Djukic A, Rose SA, Jankowski JJ, Feldman JF, Valicenti McDermott M (Bronx, NY), Rishman I (New York, NY)

**Objective:** Rett syndrome, a genetically based transmitted neurodevelopmental disorder, affecting about 1/10,000 girls, is associated with a wide range of neurodevelopmental disabilities. Assessing cognitive skills has been difficult because these girls have severe deficits in purposeful hand use and expressive language. The present study sought to bypass these difficulties by using nonverbal measures of attention and visual recognition memory originally developed for preverbal infants.

**Method.** 57 subjects were tested (29 controls; 28 Rett; aged 2-26 years) on 9 problems (5 Face, 4 Abstract Patterns), using a TX 300 eye-tracker. Each problem consisted of a familiarization phase (3-5s), followed by a test phase (10s), where the familiar target was paired with a novel one. Recognition was measured by the Novelty Score (% test time looking to novel target), attention by looking time/fixation duration. Analyses controlled for age and total look duration.

**Results.** Rett girls were able to discriminate and recognize the stimuli, with novelty scores significantly greater than chance (50%) for Patterns and marginally so for faces. However, compared to controls, their memory performance was significantly poorer.

**Conclusions:** Despite having age-appropriate core language and IQ, children with primary CMS manifest neurobehavioral deficits in executive and motor control. Recognition of these deficits is important, since they could potentially affect communication and social skills. Parent report of the frequency and intensity of stereotypies does not appear to be a marker for neuropsychological dysfunction.
than nose or mouth; for patterns, both distributed their looks equally across the four quadrants.

Conclusions. Girls with Rett syndrome are able to discriminate and recognize patterns and faces, but show poorer recognition and poorer attention than controls.


Objectives: To systematically review the diagnostic value of chromosomal microarray testing in child neurology practice.

Methods: In the setting of a regional children's hospital-based general child neurology clinic, we retrospectively reviewed medical records of 500 consecutive patients who had high-resolution chromosomal microarray (a.k.a. array comparative genomic hybridization or aCGH) testing in the diagnostic evaluation of a presumed primary neurodevelopmental disorder. Additionally, we sub-categorized pertinent clinical findings (microcephaly, intellectual disability, sensory or behavior dysfunction, motor impairment, dysmorphic features, EEG findings, and neuroimaging abnormalities). Multiple regression analysis was used to assess possible predictive variables.

Results: 80 patients (16%) had an abnormal microarray, while 20 (4%) had no variant of unknown significance. Individual categorical variables did not predict positive microarray results (e.g. 14% of patients with microcephaly and 18% with intellectual disability had an abnormal microarray). In the multiple regression analysis, dysmorphic features was the only clinical variable that showed significantly increased abnormal microarray test results (odds ratio between 2-4 depending on the first clinical feature analyzed).

Conclusions: The diagnostic yield of microarray in this study is higher than previously reported test results in other clinical settings. Except for dysmorphic features, individual clinical findings did not predict a significantly higher positive microarray test result. Chromosomal microarray testing is a clinically useful technology in the evaluation of child neurology patients with the major finding of primary "developmental delay", intellectual disability, autism and other abnormalities such as microcephaly.

DD-18. Behavioral Phenotype in Down Syndrome With Autism: Differences From Autism Alone Doran E, O'ann K, Spence MA, Fiodman P, Lor T (Irvine, CA)

Objective: Recent studies have suggested that 6-7% of children with Down syndrome (DS) have a co-morbid diagnosis of autistic disorder (AD); 10 times as common as in the general population. The objective of the study was to compare cognitive and behavioral profiles of children with DS+AD to children with AD alone.

Methods: Fourteen children with DS+AD were compared to 98 children with idiopathic AD. Stanford-Binet Intelligence Test or the Mullen Scales of Early Learning were used to evaluate intellectual functioning. Symptoms of autism were measured by the Autism Diagnostic Interview-Revised (ADI), and the Autism Diagnostic Observation Schedule-General (ADOS). Multivariate analysis of variance was used to compare domain scores and their components between AD and DS+AD.

Results: Children with DS+AD had significantly lower IQ scores than children with AD alone. After adjustment for age and IQ differences, children with DS+AD had significantly lower scores (less abnormal) for nonverbal communication (pointing and gesturing) on both the ADOS and ADI. Scores were also significantly lower (less impaired) for overall quality of social rapport in children with DS+AD compared to AD alone.

Conclusions: While similar to children with AD in the core features of autism, children with DS+AD showed a greater degree of cognitive impairment, yet in spite of their low intellectual function, were less impaired in the use of non-verbal communication and had better social behaviors. These findings suggest that children with DS+AD may have a distinct behavioral phenotype and provide a foundation for the further study of children with the dual diagnosis.

DD-19. Anatomical Alterations of Neurogenesis in Offspring of Mice Prenatally Exposed to IgG From Mothers of Children With Autistic Disorder Kadam SD, French BM, Kim S-T, Morris-Berry CM, Blue ME, Singer HS (Baltimore, MD)

Objective: Autoantibodies found in mothers of children with autistic disorder (MCAO) when passively transferred to pregnant mice cause behavioral alterations in juvenile and adult offspring (Singer et al 2009). The goal of this study was to identify whether the intraperitoneal injection of MCAO-IgG during gestation affects perinatal neurogenesis and cell survival in P7 offspring.

Methods: Pooled MCAO-IgG or IgG from mothers of unaffected children (MUC) or phosphate buffered saline (PBS) was injected daily into C57BL/J6 pregnant dams (gestational days E13-E18). On postnatal day 1 (P1) or P7, pups received single intraperitoneal injections of BrdU (30mg/kg) to label proliferating neural stem cells. P1 injected pups were sacrificed on P7 to determine new-cell fate whereas P7-injected pups were sacrificed 2h later to investigate stem cell proliferation. Fixed coronal brain sections were stained for BrdU, NeuN, Iba-1 and Aldh1-L1 to identify newborn cells, neurons, microglia and astrocytes, respectively.

Results: MCAD-IgG exposure produced significant increases in stem cell proliferation in the SVZ and SGZ at 2h. In contrast, cell densities in frontal and parietal sensorimotor cortices of MCAO mice were reduced compared to those in MUC and PBS-injected mice at both survival times. New-cell survival was significantly lower in the MCAO than MUC group in layers 2-4 of frontal sensorimotor and parietal sensory cortices. At 7 days of survival, microglial activation was detected both in MUC and MCAO mice.

Conclusions: Increased stem-cell proliferation at P7, poor new-cell 7-day-survival and increased microglial activation indicates an ongoing inflammatory pathogenesis in neonatal MCAO offspring.


Objective: Complex motor stereotypes (CMS; patterned, purposeless, rhythmic, repetitive, involuntary movements, which stop with distraction) occur in children with autism and in those who are otherwise typically developing. The underlying pathophysiologic mechanism for CMS in either group is poorly understood, with proposed hypotheses ranging from psychological to neurobiological abnormalities. This neuroimaging study compared children with CMS, with and without autism.
Methods: High-resolution anatomical (MPRAGE) images, acquired at 3.0T, were analyzed in 36 children ages 8-12 years (12 with primary [non-autistic] CMS; 12 high-functioning autism [HFA], and 12 controls—matched on age, sex, handedness, and IQ). Cortical regions were delineated and measured using automated methods in Free-surfacer; basal ganglia structures (caudate, putamen, globus pallidus) were manually delineated.

Results: The HFA group had significantly increased total cerebral volume (TCV), and increased gray matter volume in frontal, temporal, parietal and occipital lobes bilaterally (all p<.05), compared to both CMS and control groups (the latter did not differ from one another). Primary CMS group had significantly reduced gray and white matter volumes (compared to controls) in the right occipital lobe. There were no significant differences in basal ganglia volumes among the three groups.

Conclusions: Increased cortical and gray matter volumes distinguish children with HFA from those with primary CMS. Findings of altered cortical white matter in primary CMS (compared to controls) supports prior findings (Kates et al., 2005) and lends support to an underlying neurobiological etiology. Further neuroimaging studies in primary CMS are indicated to help define the underlying mechanism in complex stereotypic movements.

Vallicenti-McDermott MR (Bronx, NY)

Objective: The classical presentation of Rett Syndrome includes developmental regression with the loss of acquired skills, specifically hand use and communication skills, at around 18 months. Prior to the regression, there is variability in the early presentation of Rett Syndrome. The objective of this study is to examine early developmental history in girls with Rett Syndrome.

Methods: Review of medical records of girls diagnosed with Rett Syndrome who attended a Rett Center from 2008 until 2011. Information included developmental milestones (sitting, crawling, walking, presence of pincer grasp) and age at regression. Statistical analysis included chi-square, t test and non-parametrics.

Results: Ninety-four girls were identified. The mean age at regression was 19±13 months, 26 (28%) regressed before 12 months. In terms of motor milestones, 59% sat, 44% crawled and 57% walked, and 23% had a pincer grasp. Girls who walked were more likely to have a history of crawling (83% vs. 31% p<0.001), achieving this milestone (crawling) at an earlier age (12±5m. vs. 17±10m. p=0.04), and to experiment developmental regression at a later age (21±11 m. vs. 16±15 m. p=0.009). Girls who crawled were also more likely to regress later (22±15 m. vs. 13±9 m. p=0.01).

Conclusions: Early presentation of Rett Syndrome is variable. Girls who achieved motor milestones such as crawling and walking are more likely to regress at a later age. Girls with history of crawling are more likely to walk.

DD-22. Dopamine-dependent Behaviors are Generated through Striatal Tonically-active Interneurons that Promote Long-lasting Plasticity at Striatal Synapses
Bamford NS, Storey GP, Wang W (Seattle, WA)

Objective: Behavioral adaptations to novel experience are encoded in basal ganglia circuits via dopamine and play an important role in disorders of movement and attention. Emerging evidence suggests that basal ganglia plasticity is maintained through tonically-active acetylcholine-releasing interneurons. However, the mechanisms underlying striatal plasticity remain unclear.

Methods: Locomotor sensitization was produced in adolescent C57BL6 mice following repeated evoked dopamine via amphetamine (2 mg/kg/d, i.p.) for 5 days. Behaviors were monitored and striatal activity was measured 10 days later in brain slices by optical recordings of glutamate release, cell-attached recordings of cholinergic interneurons and whole-cell recordings of striatal output neurons.

Results: Repeated amphetamine produced a long-lasting plasticity in behavior and at excitatory striatal synapses, characterized by a dopamine D2-receptor-dependent chronic presynaptic depression (CPD) in striatal glutamate release and a D1-receptor-dependent paradoxical presynaptic potentiation (PPP) in glutamate following amphetamine reinstatement. Both CPD and PPP were produced by dopamine-dependent plasticity registered at tonically-active cholinergic interneurons, since interneuron firing rates decreased in response to repeated amphetamine, increased following amphetamine reinstatement, and cholinergic activity promoted reciprocal changes in corticostriatal activity.

Conclusions: Dopamine released in response to novel stimulation or following psychostimulants promotes enduring plasticity at striatal synapses that is encoded in acetylcholine-releasing striatal interneurons. Results suggest that repeated dopamine perturbs the balance between excitatory D1- and inhibitory D2- dopamine receptor modulation of these interneurons. Cholinergic output may then be maintained at a specified level via muscarinic M4 and nicotinic autoreceptors, providing novel targets for pharmacological treatment of movement disorders and abnormal behaviors.

DD-23. GPR88 Regulates Medium Spiny Neuron Activity and Motor- and Cue-dependent Behaviors
Bamford NS, Quintana A, Wang W, Storey GP, Palminter RD (Seattle, WA)

Objective: The striatum regulates motor control, reward and learning. Abnormal function of striatal GABAergic medium spiny neurons (MSNs) is believed to contribute to the deficits observed in many neuropsychiatric diseases. Orphan G-protein-coupled receptor (GPCR) GPR88 is robustly expressed in MSNs and regulated by neuropharmacological drugs, but its contribution to MSN physiology and behavior is unclear.

Methods: To evaluate the role of Gpr88 in MSN physiology, we generated animals homozygous for the targeted allele (Gpr88<sup>KO</sup>) that lack endogenous Gpr88 expression (KO mice). Motor-coordination and cue-based learning were assessed using a battery of behavioral tests. MSN physiology was assessed using in vivo extracellular and in vitro whole-cell electrophysiological techniques in wild-type and KO mice.

Results: In the absence of GPR88, MSNs have increased glutamatergic excitation, reduced GABAergic inhibition, and enhanced firing rates in vivo, resulting in hyperactivity, poor motor-coordination and impaired cue-based learning. Targeted viral restoration of GPR88 expression normalizes these behaviors. Additionally, we found alterations in glutamate receptor phosphorylation and GABA-A receptor composition potentially caused by decreased Rgs4 expression, a GTPase-activating protein involved in the regulation of Gz1 and Gz4 GPCRs, in KO mice.

Conclusions: Our results describe a novel role for GPR88 in MSN function. We propose that the absence of GPR88 alters MSN intracellular signaling through reduced

Munian Govindan R, Tiwari VN, Behen ME, Gjolaj N, Chugani DC (Detroit, MI)

Objective: Alteration of cortical connectivity has been hypothesized to be present in children with autism spectrum disorder (ASD). We used a surface-based cortical parcellation method and probabilistic tractography to study the thalamocortical connection pattern in ASD children compared to typically developing children.

Methods: Diffusion and structural MRI were obtained in 19 children with ASD (age [years]: mean = 5.8 ± 2.4 (SD); range = [3.8–12.5]) and 20 typically developing children (age [years]: mean = 7.6 ± 2.2 (SD); range = [4.3–12.2]). In each child, thalamic and cortical regions was segmented using the structural MRI and used as a seed and target regions, respectively for probabilistic tractography. Mean connectivity (MC) values from the thalamus to the ipsilateral cortical regions were calculated.

Results: In the ASD group, the MC of the thalamus to the frontal pole (26.2 ± 5.3 (SE) vs. 7.5 ± 5.1 (SE); p = 0.02) was higher, whereas the MC of the thalamus to the fusiform (25.3 ± 8.9 vs. 55.1 ± 8.1; p = 0.028), precuneus (20.6 ± 8.2 vs. 54 ± 8; p = 0.008), paracentral (30.8 ± 12 vs. 70.6 ± 11; p = 0.029) and superior-parietal gyrus (82 ± 16 vs. 137 ± 16; p = 0.03) were lower compared to the healthy children. The MC of the thalamus to the precentral (350 ± 42 vs. 359 ± 6; p = 0.03) and the postcentral (162 ± 24 vs. 221 ± 24;1; p = 0.1) gyrus showed no significant differences between the groups.

Conclusions: This objective analysis demonstrates the presence of lower thalamocortical connectivity to visual (fusiform, precuneus) and somatosensory (paracentral and superior-parietal) processing cortical regions in children with ASD. Thalamocortical connectivity is regulated by serotonin during development, and these results may be related to our previous finding of altered serotonin synthesis of the dentatothalamicortical pathway in children with ASD.


Bonithius DJ, Rahe G, Klein H, Karacay B (Iowa City, IA)

Objective: We examined whether congenital LCMV infection can disturb neuronal migration in humans and utilized a rat model to study its mechanisms.

Methods: 21 human infants with congenital LCMV underwent MR brain scans and were clinically followed. As an animal model of congenital infection, neonatal rats were inoculated with LCMV. To determine the pathogenic role of immune mechanisms, wild type rats were compared with congenitally athymic (nude) rats. To determine the specific role of lymphocytes, adoptive transfer experiments were performed in which lymphocytes from LCMV-exposed rats were administered to infected athymic rats.

Results: Ten congenitally infected infants had radiologic evidence of neuronal migration disturbances, including gyral malformations or lissencephaly. These infants presented as newborns with microcephaly or abnormal tone and had long-term cognitive deficits and seizures. In rats, LCMV specifically and heavily infected cerebellar glial cells, granule neurons, and Purkinje cells. Within the cerebellum, infected wild type rats had neuronal migration disturbances, consisting of clusters of granule neurons ectopically located within the molecular layer, where granule cells do not normally reside. The structure of Bergman glia, which granule cells utilize to guide their migration, was severely corrupted. In contrast, nude rats had no neuronal migration defects or abnormal Bergman glia. However, adoptive transfer of LCMV-sensitive lymphocytes into nude rats altered Bergman glia structure and induced neuronal migration defects.

Conclusions: Congenital LCMV infection can disturb neuronal migration in humans. These migration defects are immune-mediated and specifically depend upon the action of lymphocytes. Support: NIH, March of Dimes and John Martin Fund.

DD-26. Filling a GAP: A Domain Specific Conditional Allele of Tsc2

Fu C, Es KC (Nashville, TN)

Background: Tuberous sclerosis complex (TSC) is an autosomal dominant hamartomatic disease with severe neurological manifestations. Loss of function mutations of either TSC1 or TSC2 cause disease with TSC2 mutations being associated with greater severity. Dysregulation of mTORC1 as a result of tuberin-GAP deficiency is presumed to underlie much of the disease pathogenesis in TSC. Recent evidence supports GAP domain independent functions of tuberin leading us to hypothesize that GAP domain restricted mutations contribute differentially to TSC disease pathogenesis. To test this hypothesis in mice we have generated a conditional “floxed” allele of Tsc2 creating an in-frame deletion within the GAP domain.

Methods: The Tsc2 gene targeting vector with LoxP sites flanking exons 36 and 37 was generated using recombination based methods. A germline flippase mouse strain was used to remove the FRT flanked selection cassette from the knockin allele yielding the final “floxed” Tsc2 allele (Tsc2f/f). We generated mice with conditional gene deletion in dorsal neural progenitors using Emx1-Cre mice.

Results: Tsc2f/f mice are born in Mendelian proportions and are phenotypically identical to wildtype littermates. Tsc2-GAP conditional knockout mice have complete mortality by postnatal day 19 and increased mTORC1 activity in the brain with wildtype levels of Tsc2 mRNA.

Conclusions: We have generated a conditional allele of Tsc2 specifically targeting GAP domain exons. Preliminary evidence indicates a stable mRNA transcript with dysregulated mTORC1 signaling. Additional analyses of the mutant protein are ongoing. Using this novel reagent, the specific role of the tuberin GAP in TSC pathogenesis can be further dissected.

DD-27. Angiogenesis Factors as Urine Biomarkers in Sturge-Weber Syndrome

Sreenivasan A (Baltimore, MD), Caratolo A, Conners S, Moses MA (Boston, MA), Comi AM (Baltimore, MD)

Objective: Sturge-Weber Syndrome (SWS) is a rare neurocutaneous disorder characterized by vascular anomalies, suggesting that one underlying cause is abnormal angiogenesis. We hypothesized that angiogenesis factors in the urine of SWS subjects might be clinically useful for monitoring disease severity and treatment response.
**DD-28. Structural Brain Characteristics of Adolescents with d-Transposition of the Great Arteries Identified using Volumetric MRI and Brain Parcellation.**

Watson CG, Scoppettuolo LA, Wypij D, Newburger JW, Rivkin MJ (Boston, MA)

**Objective:** To investigate structural brain characteristics of adolescents treated in early infancy for d-Transposition of the Great Arteries (d-TGA) using volumetric magnetic resonance imaging (MRI).

**Methods:** Ninety-two d-TGA patients and 49 control subjects were scanned using a 1.5-Tesla MRI system. Subcortical and cortical gyral volumes and cortical gyral thicknesses were measured using Freesurfer. Groups were compared using a multiple linear regression model.

**Results:** TGA patients demonstrated significantly reduced volumes in several subcortical structures: bilateral caudate (p = 0.019, p = 0.049), bilateral pallidum (p = 0.011, p = 0.006), and bilateral nucleus accumbens (p = 0.033, p = 0.025). Cortical regions in the left hemisphere demonstrating reduced volumes included: caudal anterior cingulate (p = 0.014), inferior parietal lobule (p = 0.007), paracentral gyrus (p = 0.003), posterior cingulate gyrus (p = 0.001), rostral middle frontal gyrus (p = 0.009), superior parietal lobule (p = 0.046), and temporal pole (p = 0.009); and in the right hemisphere: fusiform gyrus (p = 0.014), inferior parietal lobule (p = 0.002), lateral orbitofrontal gyrus (p = 0.048), and superior temporal gyrus (p = 0.039). d-TGA adolescents displayed altered cortical thickness in the left hemisphere including: entorhinal cortex (p = 0.008), inferior parietal lobule (p = 0.01), pericarcarine cortex (p = 0.004), rostral anterior cingulate (p = 0.002), supramarginal gyrus (p = 0.005), and temporal pole (p = 0.002); and in the right hemisphere: fusiform gyrus (p = 0.043), inferior parietal lobule (p = 0.01), rostral anterior cingulate (p = 0.001), and supramarginal gyrus (p = 0.002).

**Conclusions:** Adolescents born with and treated for d-Transposition of the Great Arteries exhibit widespread differences in gray matter volumes and thicknesses, particularly in parietal, midline, and subcortical brain regions. These structural features are likely to be related to the cognitive characteristics recently identified in this adolescent cohort.1

Results: There was a reproducible increase in EDA during periods of emotional arousal. Invasive clinical evaluations produced a higher DA response than noninvasive procedures.

Conclusion: Measurement of EDA is a potential method of quantifying painful response in girls with Rett syndrome.

DD-31. Metabolic and Growth Deficits in Down Syndrome Lymphoblastoid Cells
Caskun PE, Thomas J, Nematinejad Z, Doran E, Buciglio J, Lott IT (Irvine, CA)

Objective: Individuals with Down syndrome (DS) develop progressive Alzheimer disease (AD) neuropathology in which a prominent feature is mitochondrial dysfunction. In order to study potential oxidative differences in mitochondria, we compared lymphoblastoid cell lines (LCLs) from individuals with DS, DS with AD (DSAD), sporadic AD and age matched controls.

Methods: The growth rate of each LCL group (n=12 lines/group, 48 lines, 50% male, 50% female) was evaluated under glycolytic and oxidative conditions. We assessed short term (7 days) and long term (21 days) time epochs. Separate analysis was performed for male and female lines.

Results: DSAD and DS LCLs showed significantly slower long term growth rate compared to control and AD LCLs under both glycolytic and oxidative conditions. Specifically, both DS and DSAD growth pace is affected significantly after 10 days of cell survival. Specifically, no growth increase is detected in DSAD and DS LCLs whereas control lines exhibited a doubling every 24 hours for the 21 day observation period. The growth rate was particularly affected under oxidative conditions. Interestingly, male LCLs were more sensitive to oxidative conditions than female LCLs.

Conclusions: Here, we show that DS LCLs exhibit traceable metabolic defects which could be particularly useful as markers of disease progression and/or treatment outcomes.

DD-32. Risk of Autism in Children Exposed to Early Psychosocial Deprivation
Levin AR (Boston, MA), Zeannah CH (New Orleans, LA), Fox NA (College Park, MD), Nelson CA (Boston, MA)

Objective: To determine risk factors for autism, both genetic and environmental factors must be evaluated. Psychosocial deprivation early in life leads to atypical development in multiple domains also affected in autism. We examined effects of institutionalization and foster care placement on risk of meeting criteria for autism.

Methods: Through the Bucharest Early Intervention Project, children abandoned at birth were randomly assigned to care as usual in the institution (CAUG) or family centered foster care (FCG). The average age of placement into foster care was approximately 22 months. At age 8, the Social Communication Questionnaire (SCQ) screened for symptoms of autism in children in both groups, and in a never-institutionalized group (NIG) from the Romanian community. Children scoring high on the SCQ, and those in whom staff/caregivers raised concern for autism, were evaluated clinically using DSM IV criteria at age 12.

Results: No children in the NIG met criteria for autism. Children with any history of institutionalization had an increased risk of meeting DSM IV criteria for autism (4.3%, p<0.05), with no significant difference in autism risk between the CAUG (5.3%) and FCG (3.4%).

Conclusions: Risk for the autism phenotype, which is associated with institutional rearing, is not lessened by foster care placement. Further studies are needed to determine whether genetic predisposition or prenatal experience may account for the increased risk, whether postnatal deprivation accounts for symptoms of autism, and whether earlier foster care placement would have mitigated the risk of autism.

DD-33. Neurodevelopmental and Behavioral Outcomes of Late Preterm Hispanic Infants
Bolo MM, Negrin G (San Juan, PR)

Objective: Since late-preterm infants (34-36 6/7 weeks’ gestation) have been recognized as a high risk group compared to term infants for mortality and morbidities, interest to study this population has emerged. Given that late-preterm infants are born before their nervous systems have fully developed, large population studies that evaluate long-term neurodevelopmental and behavioral outcomes of these patients are needed to determine its prevalence rates. Few studies had evaluated these, but none in a solely Hispanic population or including all the aspects of child development. Therefore, we compared late-preterm and term (37-41 weeks’ gestation) Hispanic infants based upon longstanding neurodevelopmental and behavioral morbidities.

Method: A retrospective study of 406 medical records of patients aged 1 month-17 years old followed in Neurodevelopmental clinics at San Juan City Hospital, Puerto Rico from January 2007 to February 2012. Diagnosis were given by same neuropsychologist pediatrician based on CAT-CLAMS, WRAT-R, Gesell figures, DSM IV criteria, extended neurologic exam, among others.

Results: From a total of 406 revised medical records, 300 were included in this study with 64 (21.3%) patients born late-preterm and 236 (78.7%) born term. Language, visomotor, neuromotor and behavioral abnormalities were the most frequent long-term neurodevelopmental morbidities in late-preterm and term groups with higher rates in late-preterm group. Statistical analysis will be described on poster presentation.

Conclusions: Hispanic infants born late-preterm are at a significantly higher risk of long-term neurodevelopmental and behavioral disabilities compared to those born at term. Language, visomotor, neuromotor and behavioral morbidities being the most frequent disabilities.

DD-34. Resting State Cortical Connectivity in Tuberous Sclerosis Complex
Peters JM, Taquet M, Sanchez-Fernandez I (Boston, MA), Tan J (Amsterdam, Netherlands), Sahin M, Wartfield SK (Boston, MA)

Objective: Diffusion tensor imaging (DTI) in patients with Tuberous Sclerosis Complex (TSC) reveals microstructural white matter abnormalities, which may relate to autism. To study if these structural changes have a functional correlate, we examined resting state EEG cortical connectivity.

Methods: EEG segments of 3 – 20 minutes with limited muscle artifact of 43 patients with TSC, 16 patients with an absent corpus callosum (ACC), and 13 controls were analyzed. Eye-movements were removed using ICA decomposition. The magnitude squared coherence (MSC) was calculated and averaged in the alpha band (8-12 Hz) for each subject. A weighted undirected graph was built using the electrodes as nodes and the MSC as a connectivity measure. The global efficiency of the resulting weighted network was computed as a measure of short-range connectivity, and the characteristic path length was computed.
as a measure of long-range connectivity. A one-way ANOVA with age as a covariate was carried out to test for group differences.

**Results:** TSC patients had less cortico-cortical connectivity than controls at both a short-range ($d_f=53, F=8.0, p<0.007$) and at long-range ($d_f=53, F=7.0, p<0.02$) scales. ACC patients also had less connectivity than controls at both a short-range ($d_f=26, F=6.7, p<0.02$) and at long-range ($d_f=26, F=4.8, p<0.04$) scales. No difference was found between TSC and ACC patients.

**Conclusions:** Macrostructural abnormalities in ACC and microstructural changes in TSC result in a similar functional disconnection. In TSC, structure (DTI) and function (EEG) are inextricably linked. Aberrant structural and functional connectivity may play a pathogenic role in autism in TSC.

**DD-35. Adolescents with D- Transposition of the Great Arteries Reaired in Early Infancy Demonstrate Reduced White Matter Microstructure Associated with Clinical Risk Factors**

Riskin MJ, Watson CG, Scoppettuolo LA, Wijpp J, Vajapeyan S, Bellinger DC, DeMazo DR, Robertson RL, Newburger JW (Boston, MA)

**Objective:** Whole brain diffusion tensor imaging (DTI) was performed in adolescents with d-transposition of the great arteries (d-TGA) who underwent the arterial switch operation as infants. Additionally, we explored patient and medical risk factors for abnormalities of white matter assessed by regional fractional anisotropy (FA) values.

**Methods:** Magnetic resonance imaging (MRI) data, including whole brain DTI and conventional anatomic MRI, were acquired from 49 adolescents with d-TGA and 29 control adolescents. Each subject's data were analyzed using a random effects analysis to evaluate for regional white matter differences in FA between d-TGA and control adolescents.

**Results:** While multifocal punctate MRI hyperintensities suggestive of mineralization were found, other evidence of gross white matter injury was absent. Eighteen discrete regions of significantly reduced FA in d-TGA adolescents as compared to controls were observed in deep white matter of both cerebral hemispheres, cerebellum, and midbrain. Among d-TGA adolescents, lower FA was associated with younger gestational age, shorter duration of intraoperative cooling during the arterial switch operation, longer intensive care unit length of stay after repair and a greater total number of open heart operations.

**Conclusions:** Despite the absence of white matter injury on conventional brain MRI, adolescents with d-TGA repaired in infancy demonstrate striking white matter FA reduction that is likely related to their reported neurocognitive deficits. The severity of white matter abnormalities is associated with patient and perioperative factors, some of which are modifiable.

**DD-36. Neurocognitive Performance of Young Children Following Concussion**

Burton VJ, Risen SR, Suskauer SJ, Lam JC, Kramer ME, Slomine BS, Reeman JH (Baltimore, MD)

**Objective:** Despite increasing awareness of concussion in the pediatric population, little is reported regarding neurocognitive manifestations in younger children. We describe the performance of children younger than 13 years on standardized, normed measures of verbal memory, attention, response speed, and executive functioning.

**Methods:** Retrospective chart review of initial and follow-up concussion clinic visits for patients aged 6–12 years from 2010-2012.

**Results:** L 51 patients aged 6-8 (n=12) and 9-12 (n=39) years presented within 50 days of concussion. At initial evaluation, 50% of patients endorsed at least one cognitive symptom. 64% had missed at least one day and 34% had missed a week or more of school. On measures of initial and delayed verbal memory scores (WRAML-2 Verbal Learning Immediate and Delayed; Recognition), response speed (W-J-III Math Fluency), and executive functioning (ACT Total Score; Letter Fluency), mean scores for the sample fell within the average range for age, although some individual patients displayed clinically significant deficits.

**Conclusions:** Neurocognitive testing indicated that as a group, these patients displayed average range performance. Despite these findings, they struggled with school attendance and presented as largely symptomatic at initial clinic visit. These results highlight the importance of multi-disciplinary management of young patients with concussion, examining both neurocognitive functioning and symptom presentation in order to understand cognitive complaints. Future research is needed to better delineate the specific neurocognitive deficits profiles underlying the clinical presentation and to examine predictors of recovery in order to guide treating clinicians in the management of concussion in this younger population.


Zaki MS, Sahar S (Cairo, Egypt), Dobyns WB (Seattle, WA), Barkovich AJ (San Francisco, CA), Bartsch H, Dale A (San Diego, CA), Ashari M (Philadelphia, PA), Akizu N, Grjiafa-Perez AM, Gleeson J (San Diego, CA)

**Objective:** Characterizing six cases from three unrelated consanguineous Egyptian families with a novel characteristic brain malformation at the level of the diencephalic-mesencephalic junction (DMJ).

**Methods:** The patients were enrolled in the Neurogenetics Clinic at the National Research Centre (NRC), Cairo, Egypt, between December 2010 and November 2011. Diffusion tensor imaging and surface reconstruction of the brain, brain stem and ventricles was analyzed. Homozygosity mapping was performed.

**Results:** Brain MRI demonstrated a dysplasia of the DMJ with a characteristic “butterfly”-like contour of the midbrain on axial sections. Additional imaging features included variable degrees of supratentorial ventricular dilation and hypoplasia to complete agenesis of the corpus callosum. Diffusion tensor imaging showed diffuse hypomyelination and lack of an identifiable corticospinal tract. All patients displayed severe cognitive impairment, postnatal progressive microcephaly, axial hypotonia, spastic quadriparesis and seizures. Autistic features were noted in older cases. Talipes equinovarus, non-obstructive cardiomyopathy and persistent hyperplastic primary vitreous were additional findings in two families. One of the patients required shunting for hydrocephalus, however, this yielded no change in ventricular size suggestive of dysplasia rather than obstruction.

**Conclusions:** We propose the term diencephalic-mesencephalic junction dysplasia (DMJD) to characterize this novel autosomal recessive malformation. Homozygosity mapping has revealed some potential chromosomal regions of interest in one of the affected families.
DD-38. Effects of Atomoxetine on Reading Abilities in Children with Dyslexia and Children with Attention Deficit/Hyperactivity Disorder and Comorbid Dyslexia

Shaywitz SE, Shaywitz BA (New Haven, CT), Wietecha LA (Indianapolis, IN), Wigal SB (Irvine, CA), McBurnett K (San Francisco, CA), Williams DW, Kronenberger WG (Indianapolis, IN), Hooper SR, (Chapel Hill, NC)

Objective: To evaluate atomoxetine treatment in pediatric patients with dyslexia only and attention-deficit/hyperactivity disorder (ADHD) and comorbid dyslexia.

Methods: Pediatric patients (10 - 16 years) with dyslexia only (n=58), ADHD + dyslexia (ADHD+D, n=124), or ADHD only (n=27) were treated with atomoxetine (1.0-1.4 mg/kg/day) or placebo (not ADHD-only patients) in a 16-week, randomized, double-blind trial with a 16-week open-label extension phase. Assessed were changes from baseline to Weeks 16 and 32 on Woodcock Johnson III (WJ III), Comprehensive Test of Phonological Processing (CTOPP), Gray Oral Reading Test-4 (GORT-4), Test of Word Reading Efficiency (TOWRE), Kiddie Sluggish Cognitive Tempo Interview (K-SCT), and ADHD Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv). Between- and within-treatment or diagnosis comparisons were conducted using ANCOVA with effects for treatment or diagnosis, investigator, gender, age.

Results: Dyslexia-only patients had a significantly (p < .05) greater score increase on WJ III Basic Reading Skills, Reading Vocabulary, and Word Attack scores compared to placebo at 16 weeks and within-group changes on CTOPP and GORT-4 subscale scores at 32 weeks. After 16 Weeks, atomoxetine treatment resulted in significant (p < .05) improvement in patients with ADHD+D compared with placebo for CTOPP Elision score, K-SCT Teacher subscale, and ADHDRS-Parent:Inv total and subscales. Scores on several WJ III, CTOPP, GORT-4 and TOWRE subscales had significant within-group changes for the ADHD+D group at 16 weeks with improvement on additional measures, including WJ III Basic Reading Skills, Reading Fluency and Word Attack subscales, at 32 weeks.

Conclusions: Atomoxetine treatment improved reading scores in patients with dyslexia only and ADHD+D.
POSTERS: Demyelinating Disease

DM-1. NG2 Expressed by Macrophages and Oligodendrocyte Precursor Cells Increases at the Leading Edge of Cerebral X-linked Adrenoleukodystrophy Lesions
Muolo In P, Suter T, Aziz-Bose R, Dietrich J, Caviness VS, Eichler FS (Boston, MA)

Objectives: Cerebral X-linked Adrenoleukodystrophy (CALD) is a genetic disorder resulting from a mutation in ABCD1 that leads to accumulation of very long chain fatty acids. Some children will develop devastating CNS demyelination. The presence of a prominent mononuclear perivascular infiltrate at the leading edge of the lesion strongly suggests that disruption of the neurovascular unit (NVU) is a determinant of the phenotypic conversion. We investigated the anatomy of different elements of the NVU in children with CALD.

Methods: Immunofluorescence of IBA-1, VWF, GFAP, MBP, CD45, CD68, SMA and NG2 were performed in frozen 14 μm brain autopsy sections of 6 children with CALD and 2 controls. Confocal microscopy was used for co-localization. Quantification and statistical analysis was performed using an Image J protocol and two-way ANOVA.

Results: NG2 expression was increased 30-60% at the inflammatory edge and perilesional white matter compared to cortex in all 6 CALD cases. There was no significant difference of NG2 expression between cortex and white matter in controls. Co-staining of NG2 with MBP, CD45 and CD68 showed that MBP+ myelinating cells account for a large proportion of NG2 staining in CALD and most perivascular CD68+ macrophages co-expressed NG2.

Conclusions: Our data suggests that NG2+ perivascular cells originate from hematopoetic cells. The dramatic increase in NG2 expression at the active demyelinating edge appears to be at the expense of early myelinating oligodendrocytes. Our data suggest that NG2 cells play an important role in the pathophysiology of inflammatory demyelination in ALD and partially originate from the bone marrow.

DM-2. Characteristic Brain Magnetic Resonance Imaging Pattern in PTEN Associated Disorders
Tonduti D (Pavia, Italy), Kahn L, Schmidt J (Washington, DC), Waldman AT, Medne L (Philadelphia, PA), Martin J, Chapman K, Gropman A, Lanpher B (Washington, DC), Lourenco C (Sao Paulo, Brazil), Orceci S (Pavia, Italy), Bonnemann C (Bethesda, MD), van der Knaap MS (Amsterdam, Netherlands), Vandeveer A (Washington, DC)

Objective: Recently, PTEN tumor suppressor gene mutations have been identified in children with isolated macrocephaly in the context of developmental delay. However, these features, even in association, are highly non-specific. The identification of a suggestive MRI pattern could help narrow diagnostic testing when pathognomonic clinical features in childhood (such as pigmented speckled macules of the glans penis) are not present.

Methods: Twelve patients were identified and consented to Institutional Review Board approved biorepositories. All patients were referred for developmental delay and/or autistic spectrum disorders and macrocephaly, but also had abnormal neuroimaging. Patients demonstrated mutations in the PTEN gene. Review of clinical histories and laboratory testing excluded other diagnoses.

Results: On MRI, all twelve patients, with genetically proven PTEN mutations, demonstrated static white matter multifocal abnormalities hyperintense on T2W and FLAIR images and hypointense on T1W images in association with enlarged perivascular spaces.

Conclusion: PTEN spectrum disorders may be associated with an MRI pattern characterized by multifocal white matter abnormalities and enlarged perivascular spaces. This pattern is not specific and is also seen in other diseases such as mucopolysaccharidoses and Oculocerebrorenal syndrome of Lowe. The frequency of this pattern in the overall PTEN hamartoma tumor syndrome population is unknown. However, we propose that the presence of this MRI pattern in a patient with macrocephaly and developmental delay or autistic spectrum disorders should prompt PTEN sequencing. Appropriate recognition can avoid extensive diagnostic testing for heritable disorders of the white matter and result in appropriate referral to specialized centers for cancer monitoring.

DM-3. Spectrum of Pediatric Neuromyelitis Optica
Moodley M, Hong SB (Cleveland, OH)

Background: Neuromyelitis optica (NMO) is a severe autoimmune demyelinating disorder of the CNS characterized by either monophasic or recurrent optic neuritis and acute myelitis and commonly sparing the brain in the early stages. There are few published reports of NMO in children and NMO IGG seropositive patients are rare.

Objective: To describe the clinical, radiological, laboratory features, management and outcome of children with NMO spectrum disorder in order to raise awareness and provide a fuller understanding of pediatric NMO.

Methods: Retrospective chart review of all patients ≤18 with NMO (2002-2012)

Results: 10 patients had NMO: 8 female; 5 were black, 4 white and 1 other. Median age at onset was 10 years (range 7-15). Median disease duration was 6 years (range 3-17). Median interval between 1st and 2nd attack was 4 months (range 1 month-8 years). Black females experience higher attack rates. 8 patients had optic neuritis and transverse myelitis, 2 had only 1 symptom. Vomiting was present in 8 children, intractable vomiting in 3 (all black); 1 had persistent hiccup and another vomiting and hypersomnolence; 7 had longitudinally extensive transverse myelitis. All patients had brain lesions-brainstem and periventricular). NMO antibody was positive in 5 patients. 6 patients had residual visual impairment.

Conclusion: NMO is a devastating demyelinating disorder in children. Apart from the defining features of optic neuritis and transverse myelitis, awareness of unusual symptoms like persistent vomiting, hiccup and hypersonomolence should help in the early diagnosis of this condition and allow appropriate and effective therapeutic measures.
POSTERS: Epilepsy

E-1. Vigabatrin in the Treatment of Pediatric Refractory Epilepsy
Manhant A, Chadehumbe M (Grand Rapids, MI)

Objective: Vigabatrin is an anti-epileptic medication recently approved by the Food and Drug Administration (FDA). The most concerning side effect of vigabatrin is peripheral vision loss. This review was done at our center to establish the relevance of this concern.

Methods: We conducted a retrospective cohort review of all patients receiving vigabatrin at the Helen DeVos Children’s Hospital Neurology Clinic from 1997 to 2011. Demographics, dosing information, seizure type, benefits, side effects, and ophthalmologic examinations were abstracted.

Results: Thirty-four patients accumulated 164 person-years on vigabatrin. Treatment duration ranged from 5 months to 14 years with an average of 58 months. Partial seizures alone (55.9%) or in combination with a history of infantile spasms (41.2%) were the most frequent indication for vigabatrin use. Ninety-seven percent of our patients had some neurological impairment at baseline. Eighty-five percent of patients experienced fewer seizures with vigabatrin therapy. The etiology of seizures showed no significant difference in the median dose required for seizure control. Somnolence was the most common reported adverse effect, occurring in 14.7% of patients. Twenty-seven patients (79.4%) underwent ophthalmologic assessments during the review period, with none found to have any measurable vision loss associated with vigabatrin therapy.

Conclusions: Vigabatrin was generally effective for partial seizures and infantile spasms, and was not associated with clinically detectable peripheral vision loss. In the pediatric population, we argue that unless validated and feasible ophthalmologic assessments are developed, the current recommendation by the FDA for biannual vision testing may be excessive.

E-2. Quality Measures for Epilepsy Care at a Tertiary Care Pediatric Epilepsy Center
Veeravigrom M, French BC, Sivaswamy L (Detroit, MI)

Objective: Epilepsy is a commonly encountered condition in pediatric neurology clinics. The American Academy of Neurology (AAN) has developed and published quality measures for epilepsy care in 2011. The purpose of this evaluation was to evaluate compliance of child neurologists and mid level providers including nurse practitioners, in implementing the AAN guidelines in the care of children with epilepsy.

Methods: Eight quality measures were assessed: Clinic records and electronic charts of 120 children with an established diagnosis of epilepsy, who follow up in the pediatric neurology clinics at Children Hospital of Michigan for at least 1 year since the initial diagnosis of epilepsy were reviewed.

Results: Seizure type was addressed in 101 patients (83.3%). Seizure frequency was documented in 119 patients (99.2%). Etiology of epilepsy was documented in 65 patients (54.2%). EEG was documented in all patients. MRI or PET scan was documented in 101 patients (88.4%). AED side effects were addressed in 101 patients (84.2%). Surgical therapy referral was addressed in 20 of 26 intractable epilepsy patients (76.9%). Counseling for females of child bearing age was documented in 1 of 15 patients (6.7%). Counseling about epilepsy safety issues was documented in 66 patients (55%).

Conclusions: Child neurologists are unlikely to counsel families regarding teratogenic effects of antiepileptic drugs and do not routinely discuss safety issues in children with a known diagnosis of epilepsy. Computerized pre formatted templates may encourage greater adherence to these recommendations and ensure superior patient care.

E-3. Epilepsy at a Glance (EAG)
Reider-Demer M (Los Angeles, CA)

Objective: Transfer of health information among facilities is a challenge in healthcare delivery. Information transfer is inefficient, fragmenting care and causing duplicate interventions. We conducted a randomized control study to determine if supplying records on a USB memory (EAG) would expedite causing sharing of information among providers.

Methods: We enrolled 30 subjects, 15 each in experimental and comparison groups. The experimental group received the EAG; the comparison group received usual care and a medical alert bracelet at the end at study end. Parents were surveyed at beginning and end of the study regarding contact with other providers for epilepsy care. The experimental group was also surveyed at follow-up clinical visits to determine the feasibility and impact of the EAG device.

Results: In the EAG group, the device was brought to >90% of outside care encounters; >80% of primary care, 68% of urgent care, and 100% of emergency room providers viewed the EAG at the point of care. No outside provider who viewed the EAG performed duplicative testing or inappropriately altered the long term plan of care. Patients and outside providers were enthusiastic about the value of the EAG.

Conclusions: This pilot study demonstrated the feasibility of EAG usage by patients and medical providers, and suggests that the EAG is usable for medical information transfer. Future studies should be performed with larger groups using EAG or alternative devices to document improved care and reduction in test duplication.

E-4. Modifiable Factors Contribute to Treatment Adherence Among Adolescents with Epilepsy
Carbone LA, Zebrack BJ, Plegue MA, Joshi SM, Shellhaas RA (Ann Arbor, MI)

Objective: Although critical for transition to independent self-management, treatment adherence is often suboptimal among adolescents with epilepsy. Knowledge is lacking regarding factors that affect adherence. We assessed self-management skills, self-concept, and sense of control among adolescents with epilepsy, and their parent, and analyzed these factors’ impact on adherence to treatment.

Methods: In a cross-sectional clinic-based study, 12-to-17-year-olds with epilepsy, whose cognitive abilities allowed independent completion of questionnaires, and their parent, completed surveys independently on adherence, treatment knowledge/expectations, barriers to care, beliefs about medication efficacy, sense of control, and self-efficacy. Medical records were reviewed for epilepsy type, treatments, and missed appointments. Data were analyzed using stepwise regression models.

Results: 88 adolescent/parent pairs completed surveys (N=42 Males; mean age 14.4 ± SD 2 years). Fifty percent had generalized and 50% had focal epilepsies. Multiple regression, adjusting for sociodemographic variables, demonstrated that for adolescents, higher epilepsy knowledge/expectations scores (p<0.0001) and stronger belief about medication efficacy (p=0.005) correlated with improved adherence, while discordance between parent and adolescent responses (p=0.027), and having siblings with epilepsy...
(p=0.019) correlated with decreased adherence. For parents, better epilepsy knowledge score (p<0.0001) and increasing numbers of medications (p=0.042) correlated with better reported adherence, while discordance between parent and adolescent responses correlated with worsening adherence (p<0.0001).

Conclusions: Several modifiable factors contribute to treatment adherence among adolescents with epilepsy. Treatment adherence could be improved by directly addressing the adolescent’s knowledge of epilepsy and their treatment plan, beliefs about their medication, and facilitating agreement between the adolescent and their parent.

E-5. A Feasibility Study of Prospectively Recording Cardiopulmonary Disturbances in Association with Epileptic Seizures in Children: A Prelude to Understanding Sudden Unexpected Death in Epilepsy Patients
Singh K (Lexington, MA), Zarowski M, Loddenkemper T, Katz E, Koibare SV (Boston, MA)
Objective: Sudden Unexpected Death in Epilepsy Patients (SUDEP) is an important cause of death in children with epilepsy. We assessed cardio-pulmonary abnormalities associated with epileptic seizures in children, with the long-term goal of identifying potential mechanisms of SUDEP.

Methods: We prospectively assessed pulse-oximetry, EKG, and respiratory-inductance-plethysmography (RIP) belts to determine cardio-pulmonary abnormalities in children with epilepsy. Association with patient-characteristics was further done by logistic regression.

Results: One-hundred-and-one seizures in 26 children (age 1-20 years, average 10.7 years) were captured. Respiratory belts provided data in 78% and pulse oximetry in 63% seizures. Ictal-apneas were observed more in younger age (p=0.01), temporal-lobe-onset (p<0.001) left-sided (p<0.01), longer-duration seizures (p<0.001), desaturation (p<0.0001), ictal-bradycardia (p=0.02), and more antiepileptic-drugs (AEDs) (p<0.01). Ictal-apneas were less likely to occur in frontal-lobe seizures (p<0.01). Ictal-bradypnea occurred more in left-sided compared to right-sided seizures (p=0.04). Ictal-tachypnea occurred more in older (p=0.01) females (p=0.05), frontal-lobe-onset (p=0.01) right-sided (p<0.001) seizures, and decreased with more AEDs (p<0.01). Ictal-bradycardia occurred more in females (p=0.028), longer-duration seizures (p=0.03), desaturation (p<0.001), and more AEDs (p=0.045), and decreased with frontal-lobe seizures (p=0.01). Ictal and post-ictal-bradycardia were directly associated (p=0.026). Ictal-tachycardia occurred more in females (p=0.001), and decreased with more AEDs (p=0.016). Desaturation was more likely to occur with longer-duration seizures (p<0.0001), ictal-apnea (p<0.0001), ictal-bradycardia (p=0.001), and more AEDs (p<0.001).

Conclusions: Children present with a specific and predictable pattern of patient characteristics with cardio-pulmonary abnormalities during seizures. Further insight into these may assist in the identification of children at risk of SUDEP.

E-6. Efficacy and Tolerability of Levetiracetam in the Treatment of Neonatal Seizures
Objective: To evaluate the efficacy and tolerability of levetiracetam (LEV) in the treatment of neonatal seizures.

Methods: We retrospectively reviewed the records of neonates with electrographically confirmed seizures treated with LEV at our institution between 2006 and 2012. The following data were collected: gender, weight, gestational age, seizure type and etiology, age at initiation of LEV treatment, prior AEDs used, LEV dose, treatment response, and adverse events.

Results: Twenty-two children were identified (mean gestational age 35.3 weeks, range: 23-41 weeks). Median age at onset of seizures was 2 days. Etiology of seizures was hypoxic ischemic encephalopathy (5), infection (8), cortical malformation (5), cryptogenic (2), inborn error of metabolism (1), and CNS tumor (1). LEV was used as adjunctive therapy in all patients. Mean number of AEDs tried prior to LEV was 1.4; all children had been treated with at least phenobarbital (PB) prior to adding LEV. Mean starting dose of LEV was 27.9 mg/kg/day, and mean maintenance dose was 47.3 mg/kg/day. Eleven (50%) patients had a mean decrease in seizure frequency of >50% with 10 of them becoming seizure free. Seven of the 11 patients who didn’t respond to LEV died before discharge due to underlying complications of illness not related to seizure or LEV. Fifteen neonates were discharged home, 2 on no AEDs, 5 on LEV, 4 on PB, and 4 on both. There were no adverse events noted.

Conclusion: LEV is effective and well tolerated as adjunctive therapy in the treatment of neonatal seizures.

E-7. Both Epilepsy-related and Psychosocial Factors Affect Ketogenic Diet Success
McNamara NA, Carbone LA, Shellhaas RA (Ann Arbor, MI)
Objective: The ketogenic diet can improve seizure control among some children with epilepsy. This diet has important impacts on families, which could affect successful treatment. We aimed to assess psychosocial factors associated with successful ketogenic diet treatment.

Methods: The family of every child currently or previously treated with the ketogenic diet at our center received a questionnaire, including inquiries about challenges to successful dietary treatments, the Factors for Parent Response to Child Illness Scale and the General Functioning Scale of the McMaster Family Assessment Device. Descriptive and univariate logistic regression analyses were employed.

Results: Twenty-three families completed questionnaires (28% response). Fourteen were boys (mean 5±4.4 years at ketogenic diet initiation). Fourteen were considered successful (diet discontinued once the child was seizure-free or continued as clinically indicated). Family-identified challenges were time to prepare foods (n=11) and that the diet was too restrictive (n=11). Reduction in seizure frequency (n=12) and the feeling that there were no other treatment choices (n=11) were the most commonly cited motivating factors. Lower seizure frequency prior to diet initiation (p=0.019), post-diet seizure improvement (p=0.014), and parent’s condition management score (assessing confidence in managing the child’s epilepsy; p=0.034) were associated with increased odds of successful treatment. Neither Medicaid insurance nor family functioning scale scores were significantly associated with success on the ketogenic diet.

Conclusions: Successful ketogenic diet treatment is dictated both by epilepsy-related and psychosocial influences. Some factors are modifiable, others are not. Understanding these issues may help to improve families’ experiences and success with the ketogenic diet.
E-8. Antiepileptic Prescription Adherence in a Large Population of Individuals with Intellectual Disability
Horn C, Nguyen VQ, Toucheze P, Plon L, Fernandez G, Tournay A, Lott IT (Orange, CA)

Background: Antiepileptic drugs (AED) are used for seizure control and/or mood stabilization in individuals with Intellectual Disability (ID). Failure to take prescribed medication can increase morbidity in this population but little is known about factors influencing AED adherence.

Methods: Closed pharmacy billing records were obtained over a 30 month consecutive period for 734 individuals with ID managed by a State agency in California. Adherence was determined by a formula based upon number of days without access to medication arising from not filling prescriptions over an extended period (>6 month) and was defined as 75% or greater. Logistic regression was used to estimate the adjusted odds ratio of non-adherence for individuals living semi-independently or in a Community Care Facility (CCF). Robust standard errors were used for inference, and Holm’s method was used to account for multiple comparisons. We declared that an odds ratio is significantly different than 1 at the 0.05 level if the adjusted p-values is less than 0.05.

Results: Among those with the same age and gender, individuals living semi-independently showed a 4.23-fold increase (95% CI: 2.76—6.49) in the odds of AED non-adherence compared to those living in a CCF. This odds ratio is statistically different than 1 at the 0.05 level if the adjusted p-values is less than 0.05.

Conclusion: Individuals with ID who live semi-independently are at a greatly increased risk of non-adherence to AEDs compared to those who live in a CCF where medications are monitored. This finding should inform policy for the management of community-based individuals with ID who receive AEDs.


Objective: To evaluate the influence of time of day and sleep/wake state on the clinical evolution of seizures.

Methods: We included patients (0-21 years) undergoing Video-EEG from 2002 to 2010. Clinical evolution of seizures was characterized according to the 2001 ILAE terminology. Generalized linear mixed models using a Poisson distribution were used to test the main effects (time of day in 3-hour bins and wakefulness/sleep) and potential confounders. This finding should inform policy for the management of community-based individuals with ID who receive AEDs.

Results: Among those with the same age and gender, individuals living semi-independently showed a 4.23-fold increase (95% CI: 2.76—6.49) in the odds of AED non-adherence compared to those living in a CCF. This odds ratio is statistically different than 1 at the 0.05 level if the adjusted p-values is less than 0.05.

Conclusion: Individuals with ID who live semi-independently are at a greatly increased risk of non-adherence to AEDs compared to those who live in a CCF where medications are monitored. This finding should inform policy for the management of community-based individuals with ID who receive AEDs.

E-10. The Neuroprotective Effects of the Trk Inhibitor CEP-701 in the Hypoxic Seizure Model
Obeid M, Jensen FE (Boston, MA)

Objective: Tyrosine kinase B receptor phosphorylation at Y816 (p-TrkB) has been implicated in epileptogenesis (He XR J Neurosci 2010). We investigated p-TrkB levels and potential neuroprotection by the Trk receptor inhibitor, CEP-701, following hypoxic seizures (HS) in postnatal day 10 (P10) pups.

Methods: P10 Long–Evans male rat pups were divided into 3 groups. The Tx group received 2 doses of CEP-701 intraperitoneally (i.p.). 3 mg/kg/dose, immediately after, and 12 hours after HS (induced by 15 min of graded exposure to 7-4% O2). The Hx group received vehicle after HS. Controls were manipulated under normoxic conditions (Nx). Pups were sacrificed at 6, 12, or 24 hours post-HS to assess hippocampal p-TrkB levels by western blotting. Parallel groups received 2.5 mg/kg of kainic acid (KA) i.p. at P14, and behavioral seizure severity was assessed. Results are reported as percent of Nx.

Results: Western immunoblot analysis revealed a statistically significant 1.5-fold increase in hippocampal p-TrkB 12 hours after HS in the Hx group (153.8%±10.6%, n=6, p<0.01) but not in the Tx group (109.6%±8.2%, n=11; p>0.05). The severity of KA-induced seizures in Tx (97.9%±12.6%, n=12) was comparable to Nx (p>0.05), and both were significantly lower than Hx (156.7%±17.9%, n=9; p<0.05).

Conclusions: Post-HS treatment with CEP-701 attenuates the increase in TrkB phosphorylation and the enhanced seizure susceptibility observed at P14. These data suggest that TrkB receptor blockade may be a therapeutic strategy to prevent epileptogenesis in the immature brain.

E-11. Juvenile Spasms in Tuberous Sclerosis Complex
Hsieh DT, Jennesson MM, Thiele EA (Boston, MA)

Purpose: To characterize juvenile spasms (JS) – epileptic spasms occurring after the age of two-years-old – in patients with tuberous sclerosis complex (TSC), particularly treatment response to vigabatrin (VGB), which is extremely effective for infantile spasms (IS) in TSC.

Methods: The authors retrospectively reviewed 19 patients with TSC and JS. Medical records were assessed for clinical and treatment data, neurocognitive, EEG, and MRI data, and genetic analyses.

Results: Of 391 patients with TSC, 19 (4.8%) had JS. Of those with detailed clinical data, six had infantile spasms that persisted after age two-years-old, six returned later (range 2 to 24-years-old) after an initial remission of infantile spasms, and four occurred de novo over the age of two-years-old (range 2 to 20-years-old). All concurrently had other seizure types. One had hypsarrhythmia on EEG. All had brain MRI stigmata typical of TSC. Thirteen had a mutation in TSC2, and one in TSC1. Six patients became spasms-free with medication treatment, to include four with VGB, one with VGB in combination with the low glycemic index diet, and one with felbamate. Five became
spasm-free after epilepsy surgery. VGB was not effective for eight patients. The majority continued to have refractory epilepsy.

Conclusions: JS are not uncommon in patients with TSC, especially TSC2. JS in TSC occur in the setting of other seizure types and refractory epilepsy. Hypearsarrhythmia is rare. VGB can be effective, but the success of VGB for JS in TSC is not equivalent to that of IS in TSC.

E-12. The Extent and Types of Behavioral Problems in an Urban Hispanic Pediatric Epilepsy Cohort

Winkle JK, Stewart SB, Sandoval A, Ter-Zakarian A, Aldinger K, Lane CJ, Partikian A (Los Angeles, CA)

Objective: Data from the National Survey of Children With Special Health Care Needs indicate that parents of Hispanic children from predominantly Spanish-speaking households report more global developmental and functional limitations but lower rates of diagnosed ADHD. To better understand the extent and types of behavioral problems noted by parents of Hispanic children with epilepsy, we have been conducting an observational study at the Pediatric Neurology Clinic of Los Angeles County + University of Southern California Medical Center.

Methods: We recruited subjects between 2 to 18 years of age clinically diagnosed with epilepsy. Sociodemographic and epilepsy information were collected, and caregivers completed the Short Acculturation Scale for Hispanics and developmentally and language appropriate versions of the Child Behavior Checklist (CBCL).

Results: We have enrolled 114 subjects with an age of 10.4 ± 4.7 years (mean ± standard deviation), with 55% being males. 90% of the subjects identified themselves as Hispanic or Latino, with a relatively low acculturation score of 1.8 ± 1.1 (mean ± standard deviation). In a subset of 98 children with adequate data, we found that 48% versus 41% score in the borderline/clinically significant range for internalizing versus externalizing behavioral problems, respectively, with 27% having significant behavioral dysfunction in both domains. We found no correlation between clinically-significant CBCL T-scores and age, gender, seizure characteristics (etiopath, frequency, number of anticonvulsant medications), or acculturation.

Conclusions: There exist high rates of behavioral problems in urban Hispanic children with epilepsy that appear to be independent of obvious seizure-related or sociodemographic factors.


Moosa NVA, Jeel L, Marashly A, Cosmo G, Lachhwani D, Wyllie E, Kotagal E, Bingeman W, Gupta A (Cleveland, OH)

Objective: We examined the long-term functional outcome-ambulation, language, reading and behavior- and their predictors in a cohort of 115 children who had hemispherectomy for refractory epilepsy.

Methods: Of 186 children who had hemispherectomy (1997-2009), 125 families completed a structured questionnaire to assess functional and seizure outcome. Prognostic predictors were examined using a multivariate regression analysis.

Results: At a mean follow-up of 6.05 years after hemispherectomy, 70 (56%) patients were seizure-free and 45 (36%) had seizure recurrence; 10 (8%) had new onset non-epileptic spells and were excluded from analysis. At follow-up (mean age 12.7 years), 96 (83%) patients walked independently, 10 (8.7%) walked with assistance, and 9 (7.8%) were unable to walk. Significant behavioral problems were reported in 30 (27%), 35 (30%) had poor language abilities and 61/105 (58%) school age children had poor reading skills. 28 patients (24%) reported new visual symptoms. Multivariate logistic regression analysis identified the following as independently associated with poor outcome: seizure recurrence affected all functional outcome measures (p < 0.05); contralateral hemisphere abnormalities on MRI (p < 0.05) and pre-existing quadriparesis (p < 0.01) correlated with poor motor outcome; contralateral multilobar abnormalities on MRI [Odds ratio (OR) = 13.9, p = 0.001] and young infants (<18 months) with uncertain pre-operative language development at surgery (OR = 11.1, p = 0.01) predicted poor language outcome. Younger age at seizure onset (p = 0.01) correlated with poor reading skills.

Conclusion: Seizure recurrence after hemispherectomy negatively influences all domains of functional outcome and development. Identification of factors affecting motor, language, and reading outcomes in this study will help in pre-surgical counseling.

E-14. Early Efficacy of the Ketogenic Diet is not Affected by Initial Body Mass Index Percentile

Shull SE, Diaz-Medina GE, Wong-Kötöl LC, Eckert SK, Nickels KC, Wirrell EC (Rochester, MN)

Objective: Does body mass index (BMI) and weight percentile impact efficacy of the traditional ketogenic diet (KD) in children initiating therapy for intractable epilepsy?

Methods: Charts of all children initiating the KD at Mayo Clinic Rochester from 01/2001-12/2010 were reviewed. Patients were included if they were followed for ≥1 month after initiation with documented BMI (for subjects ≥2 years of age) or weight percentile (<2 years of age) and seizure frequency at baseline and after 1 month on diet. Reduction in seizure frequency was calculated as a percentile and responders were defined as achieving a >50% seizure reduction from baseline.

Results: Of 72 charts reviewed, 24 were excluded (20 lacked BMI and 4 lacked seizure data). Our cohort (N=48) consisted of 20 males (42%). At diet onset, median BMI-for-age percentile (≥2 years of age) was 62.5 (25th-75th percentile, 26.8-86.0) and median weight-for-age percentile (<2 years of age) was 63.0 (25th-75th percentile, 4.8-92.3). Median seizure frequency change was a 60% reduction (25th-75th percentile, 87.8-0.0) and 52% of children were responders. There was no significant correlation between initial BMI or weight percentile and seizure frequency reduction at one month (p=0.72 and p=0.91) or between BMI or weight percentile quartile and responder rates (p=0.21 and p=0.57). Children considered overweight or obese at diet initiation (BMI or weight percentile ≥85) did not have lower responder rates than those with BMI or weight-for-age percentiles <85 (6/14 vs. 19/34, p=0.41).

Conclusions: Higher BMI and weight-for-age percentiles do not adversely affect the efficacy of the ketogenic diet.

E-15. Lacosamide for the Treatment of Children with Primary Generalized Epilepsy

Carvalho KS, Yorns WR, Kshetra DS, Valencia I, Hardison HH, Melvin JF, Legido A (Philadelphia, PA)

Objective: LAC is a new antiepileptic drug (AED) approved as adjunctive therapy in adults with partial-onset epilepsy (PE). Small case series have suggested that LAC is safe and effective in children. There is no data on using LAC for treatment of primary generalized epilepsy (PGE) in
children. The objective of this study was to evaluate the efficacy and tolerability of LAC in pediatric PGE.

Methods: We retrospectively reviewed the records of children with PGE treated with LAC in our institution during 2009-2012. Data collected included age, gender, seizure type, prior AEDs, LAC dosage, follow-up duration, treatment response, and adverse effects.

Results: Nine patients (4 M, 5 F) were identified (mean age at follow-up 12.8 years, range 5.4-17.8). Eight (89%) patients had failed 2 or more AEDs. LAC was used as monotherapy in 2 (22%) patients, and as adjunctive therapy in 75 (78%). Starting dose was 100 mg/day in all patients (mean dose 22.1 mg/kg/day). Mean follow-up period was 5 months (range 0.6-13.8). Four (44%) patients were non responders, 2 (22%) had 50-74% improvement, and 3 (33%) became seizure free. Three (33%) patients had LAC discontinued due to lack of efficacy in 2 and adverse effects in 1. The latter were reported in 4 (44%) patients, including weight loss, tremor, memory problems, and nausea/dizziness in one each.

Conclusion: In this small study, LAC was well tolerated and showed a good response (>50%) in 55.5% of children with PGE. A larger randomized, prospective study is necessary to establish the effectiveness of LAC in children with PGE.

E-16. Overall and Disease-related Healthcare Utilization and Costs in Children with Stable and Uncontrolled Epilepsy

Cramer JA (Houston, TX), Wang Z (Woodcliff Lake, NJ), Chang E (Beverly Hills, CA), Powers A, Copher R (Woodcliff Lake, NJ), Cherepanov D, Broder M (Beverly Hills, CA)

Objective: Epilepsy affects over 300,000 children in the U.S. and more than 90,000 have seizures not adequately controlled. We examined healthcare utilization and costs in children with epilepsy treated with antiepileptic drugs (AEDs).

Methods: Pediatric patients (<12 years) with epilepsy (ICD-9-CM 345.xx or 780.39) in 2008 were identified from MarketScan claims database 2007-2009. Patients were defined as stable (on the same AED for ≥12 months) or uncontrolled (added additional AED). Index date was date of additional AED start for uncontrolled patients and random date from AED fills for stable patients. Epilepsy-related utilization included medical services with 345.xx or 780.39 in any position and AED fills. Logistic regression and analysis of covariance were used to adjust for baseline differences.

Results: Over 2,000 patients were identified (mean: 7.5 years; 45.3% female; Charlson comorbidity-index: 0.3; 422 uncontrolled and 1,748 stable patients. Uncontrolled patients had significantly more hospitalizations (30.1% vs. 12.0%), greater overall healthcare costs per patient-year (PPY) ($30,343 vs. $18,206) and epilepsy-related costs PPY ($16,894 vs. $7,979), of which $12,926 vs. $5,524 were medical costs and $3,968 vs. $2,456 for AEDs (p < .001). After adjusting for demographics, region, usual-care physician specialty, and risk factors, the odds of hospitalization (OR: 2.5; 95% CI: 1.9-3.3), overall ($3,908) and epilepsy-related costs ($5,744) were greater in uncontrolled patients (p < .001).

Conclusions: Compared to stable children, those with uncontrolled epilepsy incur significantly more healthcare resource use and economic burden despite treatment. Comorbidity conditions are likely high as epilepsy comprised only half of overall costs. More effective AEDs are needed for difficult-to-treat epilepsy and reducing economic burden.

E-17. The Current Treatment of Infantile Spasms Among Members of the Child Neurology Society

Mietinger J (Charlestown, VA), Joshi SM (Ann Arbor, MI), Pediatric Epilepsy Research Consortium

Objective: Infantile spasms (IS) are age-specific seizures commonly associated with an epileptic encephalopathy. The approach to IS varies among clinicians. The aim of this survey was to assess how clinicians currently evaluate and treat infantile spasms.

Methods: To determine common practice among clinicians who treat infantile spasms, a survey was distributed via the Child Neurology Society to its members. Anonymous responses were collected over a two week period.

Results: The response rate was 18.5% with 222 responses. Ninety-four percent of respondents were from the United States. Seventy percent of responders reported seeing 10 or fewer new-onset cases of IS annually. The most commonly used first-line treatments for IS due to an unknown etiology were adrenocorticotropic hormone (ACTH) (67%), oral corticosteroids (15%), and vigabatr (9%). The most commonly used first-line treatments for IS due to a structural/metabolic etiology (excluding tuberous sclerosis [TS]) were ACTH (44%), oral corticosteroids (23%), vigabatr (14%), and topiramate (12%). Most responders (86%) use vigabatr as the first-line treatment for IS due to TS. We found that the diagnostic evaluation of IS varied among clinicians.

Conclusions: While ACTH is still the most commonly used first-line treatment for IS not due to TS, there is significant variation among clinicians in both first-line treatments as well as initial evaluation of IS. Infantile spasms are relatively uncommon. Therefore future clinical trials will require multicenter collaboration. An important first step in such collaboration is the standardization of the evaluation and treatment practices within and between participating centers.

E-18. Efficacy and Safety of Adjunctive Perampanel in the Subgroup of Adolescent Patients With Refractory Partial Onset Seizures Included in the 3 Double-Blind, Placebo-Controlled Phase III Clinical Trials

Rosenfeld W (St. Louis, MO), Rozenthal G (Riga, Latvia), Yang H, Squillacote D, Rain R, Kumar D, Laurenza A, Williams B (Woodcliff Lake, NJ)

Objective: Compare efficacy and safety of adjunctive perampanel in adolescents to previously published data in overall population (≥12 years) from 3 Phase III trials.

Methods: 143 adolescent patients (12-17 years, receiving 1-3 AEDs) were enrolled. Dose response for perampanel 2-8mg/day was analyzed from Study 306 alone (placebo N=14, 2mg N=21, 4mg N=13, 8mg N=12) while data for comparison of 8 and 12mg/day was pooled from all 3 studies (placebo N=45, 8mg N=44, 12mg N=20). Study endpoints included change from baseline in seizure frequency/28 days, population PK, PK/PD, and safety.

Results: Population PK showed no age effects on exposure. The relationship between exposure and seizure frequency in adolescents was comparable to the overall study population. Median change in seizure frequency was 4.6%, 12.8%, −23.9%, and −34.6% for placebo, 2, 4 and 8mg groups in Study 306, consistent with the overall population indicating 4mg as the minimal effective dose. Median change in seizure frequency from baseline was −18%, −34.8%, and −35.6% for pooled placebo, perampanel 8, and 12mg groups.

AEs occurring at >5% in the total perampanel group and twice placebo included dizziness (20.4% vs 8.9%), somnolence (15.3% vs 6.7%), aggression (8.2% vs 0%),
decreased appetite (6.1% vs 2.2%), and rhinitis (5.1% vs 2.2%). There were no deaths. AE-induced discontinuation was higher with placebo (6.7%) than perampanel (2.0%). AE-induced dose interruption/reduction in >5% of patients included dizziness (5.1%) and somnolence (5.1%).

Conclusions: Safety and efficacy of perampanel 4, 8, and 12 mg/day in adolescents with POS is comparable to the overall population.


Objective: To evaluate the efficacy and safety of adjunctive perampanel, a novel antiepileptic drug, in adolescents during the open-label extension phase of the Phase III trials.

Methods: 122 adolescents (12-17 years) with refractory partial seizures were included in the analysis. The ongoing study includes a 16-week blinded conversion, 256-week maintenance, and 4-week follow-up period. Both DB-placebo and DB-perampanel patients were up-titrated to maximum tolerated dose (<12 mg/day) from 2 mg/day and last received dose, respectively. An analysis was performed after the last patient from the DB-studies rolled over into this study. The parameters included reduction in seizure frequency/28 days, 50% responder rate, and safety.

Results: 92.6% patients took 10 or 12 mg/day dose of perampanel. Median reduction in seizure frequency relative to the pre-perampanel baseline was 30.7% (n=122, weeks 1-13); 33.1% (n=109, weeks 14-26); 44.8% (n=97, weeks 27-39); and 41.7% (n=77, weeks 40-52). The corresponding 50% responder rates were 29.5%, 36.7%, 45.4%, and 39.0%, respectively. Adverse events (AEs) leading to discontinuation included subject choice (12.4%), AEs occurring in >5% of patients included dizziness, somnolence, headache, aggression, convulsion, irritability, fatigue, and decreased appetite. Primary reasons for study discontinuation included subject choice (12.4%), AEs (11.6%), and inadequate efficacy (6.6%). AEs leading to study discontinuation in >2 patients included dizziness (n=3), somnolence (n=3), and aggression (n=3). There were no deaths.

Conclusions: Long-term treatment with perampanel demonstrated a favorable risk/benefit ratio in this population of adolescents with refractory partial seizures. There was a 41.7% median reduction in seizure frequency with low rates of AE-related discontinuation.

E-20. Nonepileptic Events Following Traumatic Brain Injury: Comparison of Two Pediatric Cohorts

Matsumoto JH, Kaplan R, McArthur DL, Forsey MJ, Giza CC (Los Angeles, CA)

Objective: To compare the characteristics of children presenting with epileptic vs. nonepileptic “spells” following traumatic brain injury (TBI).

Methods: Two cohorts evaluated at a pediatric TBI center for spells of epileptic or uncertain nature were compared. One cohort was retrospective from 2002-2005, and the other was prospective from 2005-2010. Five spell types were classified: 1) Post-traumatic Epilepsy (PTE), 2) Epilepsy with other potential etiologies (cortical dysplasia, primary generalized), 3) Psychopathology (nonepileptic seizures, panic attacks), 4) Misinterpreted behavior (tantrums, attentional lapses), and 5) Other neurologic events (posturing, dysautonomia, syncope). Injury severity and gender were compared by Chi-square or Fisher’s exact tests, and injury age by t-test and analysis of variance.

Results: The two cohorts were similar in age, gender and spell type distribution. Injury severity was milder in the retrospective group (p=0.035). Due to prominent similarities, the cohorts were combined for subsequent analyses. Overall, PTE comprised 44% of spells, epilepsy with other etiologies 15%, psychopathology 19%, other neurologic events 25%, and misinterpreted behavior 8%. PTE was associated with severe TBI (p=0.001), and psychopathology (p=0.014) and epilepsy with other etiologies (p=0.006) with milder TBI. PTE (p=0.002) and misinterpreted behavior (p=0.049) were associated with younger injury age, while psychopathology (p=0.021) and other neurologic events (p=0.002) were associated with older age.

Conclusion: Less than half of children with “spells” following TBI had PTE. Given the negative medical, psychiatric, and psychosocial implications of misdiagnosis and treatment, clinicians should maintain a broad differential when evaluating possible PTE, particularly with mild TBI sustained at an older age.

E-21. Abnormal White Matter Microstructure in Infantile Spasms Identified with Tract Based Spatial Statistics (TBSS)

Tiwari VN, Kumar A, Chugani HT (Detroit, MI)

Objective: We sought to determine whether diffusion tensor imaging (DTI) is useful in evaluating brain white matter pathways and seizure propagation in children with cryptogenic infantile spasms (IS).

Methods: Tract based spatial statistics (TBSS), an objective and sensitive technique, was used to evaluate brain white matter integrity in children with IS (n=11; mean fractional anisotropy (Mean ± SD)

<table>
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<tr>
<th>Cluster-regions</th>
<th>Side</th>
<th>Infantile spasms Controls</th>
<th>%difference</th>
<th>p-value</th>
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<tr>
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<td></td>
<td>0.55 ± 0.07</td>
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age = 20.4 ± 7.1 months) as compared with age-matched epilepsy controls (n = 11; mean age = 20.1 ± 6.9 months). All IS children showed hypsarrhythmic pattern on EEG at the time of DTI scan. Fractional anisotropy (FA) maps were used for TBSS analysis.

**Results:** Children with IS had significantly lower FA than the control group in 7 brain regions including bilateral occipital and temporal lobes regions, right frontal lobe, brainstem and corpus callosum (Figure). On average, the mean FA was decreased by 22.9% in these regions in the IS group compared to control group, with maximum decrease of 25.8% observed in the right occipital region (Table).

**Conclusions:** IS children showed disturbances of brain white matter integrity different from that of non-spasms epileptic controls, thus supporting different seizure propagation pathways in these conditions. Furthermore, our findings are consistent with the notion that interaction between cortical and sub-cortical structures plays an important role in the pathophysiology of IS.


**Objective:** To study the cost-effectiveness of seizure evaluation of children with epilepsy in the ED.

**Methods:** We reviewed the database of epilepsy patients seen at our institution’s ED from 1/01/2010 to 12/31/2010. The following data were gathered: gender, age, ethnicity, blood, urine, CSF and neuroimaging studies results, treatment, disposition, and usefulness of the visit, defined as dictating the need for hospitalization or improving the clinical status of the patient.

**Results:** We identified 330 patient-visits, 187 M and 143 F, ages 25 days-21 years, 84% of them African American or Hispanic. 190 (58%) had blood tests, 45 (24%) urine analysis, 2 (1%) CSF testing, 42 brain CTs and 2 MRIs. The tests’ positive yield was 41%, 11%, 0% and 4.5%, respectively. 122 (37%) patients were treated with antiepileptic drugs, most frequently levetiracetam (39%) and benzodiazepines (27%). Other therapies, including antipyretics, anti-inflammatories, rehydration, and antiemetics, were administered to 44 (15%) patients. 118 (36%) patients were admitted to our hospital, 4 (1%) were transferred to another institution, and 208 (63%) were discharged. The total number of useful visits was 208 (63%), including 118 patients admitted to our hospital, 4 transferred, and 86 discharged who received some therapeutic intervention.

**Conclusion:** About 1/3rd of the visits did not provide useful patient care. Approximately 60% of patients had some test performed, the median of positive yield being 8%. Therefore, these visits are expensive and not very cost-effective. Investment in education of epileptic patients about seizure management could decrease unnecessary visits to the ED.

**E-24. Comprehensive Molecular Diagnostic Testing Using a Next-generation Sequencing Panel and Exon-level Array CGH Identifies Mutations in a Broad Spectrum of Epilepsy Phenotypes**

**Aradhya S, Baker E, McKnight D, Rubenstein R, Hruska K, Gabriele R (Gaithersburg, MD)**

**Objective.** Epilepsy affects 1% of the population. Current molecular testing is costly and limited to a few genes. We validated a sequencing and deletion/duplication test for 53 genes associated with major primary and syndromic forms of epilepsy, including infantile epileptic encephalopathy, BFNS, GEFS+, JME, PME, neuronal ceroid lipofuscinosis, glucose transporter deficiency, Rett, Angelman, Mowar-Wilson syndromes and others.

**Methods.** More than 700 coding exons and their splice junctions were evaluated by exon array and by microdroplet multiplex-PCR followed by next-generation sequencing. Individuals were tested for the full panel or a subpanel based on the age of epilepsy onset.

**Results.** In 64 unrelated clinical cases we reported 50 sequence variants and one exon deletion. Twelve individuals (19%) received a conclusive molecular diagnosis and five (8%) had a likely mutation. In twelve individuals (19%), the detected variants were of unclear significance (VUS) and parental testing was recommended. 29% (5/17) of known or predicted mutations were in sodium channel genes and the remaining were in genes associated with Ohtahara syndrome, GLUT1 deficiency, Rett syndrome, POLG- or CDKL5-related epileptic encephalopathy, and vitamin-responsive epilepsy. In five cases the results had immediate treatment implications. Six individuals had a variant of definite or possible clinical relevance in >1 gene. The VUS were distributed almost exclusively in non-ion channel genes.

**Conclusions.** Our comprehensive sequencing and exon array approach identified known or predicted mutations in 27% of individuals with a range of epilepsy phenotypes. This testing provided a molecular diagnosis in patients with non-specific clinical presentations, including unexpected rare disorders.

**E-25. Cyclic Anticonvulsant Therapy: An Alternative for Refractory Epilepsy in Children and Adolescents?**

**Vasconcelos MM, Azevedo LG, Brito A, Herdy GVH (Rio de Janeiro, Brazil)**

**Objective:** This is a pilot study to assess effectiveness of an alternative scheme for refractory epilepsy: Anticonvulsant Therapy in Rapidly Alternating Cycles throughout Time (ATRACT). It was designed in an effort to circumvent the persistent cerebral tendency to develop tolerance to antiepileptic drugs when they are used continuously.

**Methods:** Three antiepileptic drugs were successively added to the patient’s therapy, and each drug was used for a period of ten days, after which another drug was substituted for the previous one, so that consecutive use of the three drugs constituted one cycle spanning 30 days, after which...
another cycle was initiated. Side effects were monitored through frequent clinic visits; weekly in the first month, every two weeks in the 2nd-3rd months, then monthly thereafter. When appropriate, laboratory tests were ordered. Seizure frequency was based upon parental report.

**Results:** Two boys and two girls were recruited. Average age was 14.4 years (range, 13-16 yr.). The only observed side effect was somnolence. One patient left the study due to excessive sleepiness and low compliance. After an average duration of 10.6 months of cyclic therapy, three out of four patients benefited from a greater than 90% reduction in seizure frequency. In addition, a significant improvement in cognition and activity level was reported by their parents.

**Conclusions:** ATRACT was effective in three out of four subjects in this small pilot study. It seems appropriate to extend this study to a larger number of epileptic patients in order to assess its safety and effectiveness.


**Objective:**

In children with unilateral Sturge-Weber Syndrome: A Longitudinal Study

**Methods:** Following baseline, patients were randomized to once-daily placebo, perampanel 2, 4, 8, 12 mg. Endpoints included percent change in CPS+SGS and SGS across Phase III studies according to actual doses of perampanel achieved. The randomized population, with prespecified endpoints, will be presented in the poster.

**Results:**

Overall, 442, 180, 172, 431, and 254 patients were randomized to placebo, perampanel 2, 4, 8, 12 mg, respectively; 1264 patients completed the studies. The numbers of patients achieving each actual dose were: 348, 161, 159, 46, 287, 14, and 114 for placebo, perampanel 2, 4, 6, 8, 10, 12 mg.

Median percent changes in CPS+SGS frequency were −14.6% (n=319), −26.6% (n=150), −35.6% (n=145), −35.9% (n=267), −30.3% (n=104) for placebo, perampanel 2, 4, 8, 12 mg actual doses. Responder rates were 21.9%, 29.3%, 37.9%, 40.1%, and 39.4%.

**Conclusions:** In this sensitivity/subgroup analysis, we summarized the efficacy of perampanel in both complex partial plus secondarily generalized seizures (CPS+SGS) and SGS across Phase III studies according to actual doses of perampanel achieved. The randomized population, with prespecified endpoints, will be presented in the poster.

E-27. Predictors of Verbal-cognitive Outcome Patterns in Children with Unilateral Left-sided Sturge-Weber Syndrome

**Objective:**

A significant proportion of children with unilateral left hemispheric Sturge-Weber Syndrome (SWS) demonstrate preservation of verbal-cognitive functions, which may involve reorganization of neural substrates. We evaluated predictors of cognitive outcome patterns in children with unilateral left-sided SWS.

**Methods:**

Twenty-four children (mean age=61 months; age range=28-153 months) with unilateral left-sided SWS underwent neurocognitive assessment, MRI and interictal glucose PET. Linear discriminant function analysis (LDFA) was used to evaluate demographic (age, gender), seizure (age of onset, frequency), and lesion (extent of severe cortical hypometabolism on PET; frontal lobe involvement) variables as predictors of cognitive outcome patterns.

**Results:**

Three patterns were identified: reorganized (preserved VIQ, VIQ > PIQ, n=14); traditional (reduced VIQ, preserved PIQ, n=5); and bilateral (both VIQ and PIQ reduced, n=5). Two functions significantly differentiated the groups (p=0.001; p=0.004). The first primarily reflected lesion variables; the second seizure variables. Group loadings on the functions indicated that the reorganized pattern was negatively associated with extent of severe hypometabolism and positively associated with global intellect; the bilateral pattern positively associated with extent of severe hypometabolism and negatively with global intellect. The traditional pattern was associated with earlier seizure onset and high seizure frequency. LDFA correctly classified 83.3% of the sample.

**Conclusion:** These data support that early seizure onset and high seizure frequency hinder reorganization of verbal functions in children with left-sided SWS. On imaging, extensive hypometabolism is also associated with poor verbal outcomes, with the exception of a few cases where early severe hemispheric damage was associated with functional reorganization in the unaffected hemisphere.


**Objective:**

In children with unilateral Sturge-Weber Syndrome, hypometabolism affects cognitive outcome. In this prospective, longitudinal study, we evaluated the relationship between extent of hypometabolism and verbal-cognitive outcome (VIQ) over time in this patient population.

**Methods:**

Fourteen children with unilateral (left n=8; right, n=6) SWS underwent neurocognitive assessment, MRI and PET, at baseline (mean age=27 months) and at follow-up (mean age=55 months). Repeated-measures ANOVA with time as the within subjects variable and lobes involved (4 groups: 1-4 lobes) as the between-subjects variable was used to evaluate the relationship between number of affected lobes on PET and VIQ over time.

**Results:**

While there was a general inverse association with baseline VIQ, and significantly predicted VIQ over time (p=0.014). While there was a general improvement of VIQ across groups, the number of abnormal lobes predicted the rate of improvement. Children with three or four affected lobes on baseline imaging demonstrated a more rapid rate of improvement of VIQ (from 91 to 104 and from 79 to 92, respectively), while those with one or two lobes affected demonstrated a slower rate of improvement (112 to 116 and 96 to 100, respectively).

**Conclusion:** Extensive hypometabolism, affecting at least three lobes at the early stage of unilateral SWS is associated with a lower initial VIQ but a higher rate of improvement at follow-up. This finding indicates that even children with
extensive unilateral hemispheric damage have the capacity to recover and approach normal verbal functioning.

E-29. A Retrospective Analysis of the Usefulness of Pediatric Emergent Computed Tomography and Risk Classification after an Afzebile Seizure
Berry SL, Culleton, WV, Taravath S, Tad Welch, C, McJunkin J (Charleston, WV)

Objective: Concern of possible overutilization of ionizing radiation, particularly computed-tomography (CT), in the pediatric population is growing. We investigated the possible overutilization of emergent CT (ECT) scanning and the potential usefulness of risk-classification after an afzebile seizure (ASZ) in children.

Methods: We reviewed 383 cases of ASZ evaluated in the emergency department at a tertiary care children's hospital. Patients were classified as high or standard-risk as defined by Sharma et al (2003), and ECT findings were classified as normal, clinically insignificant abnormal, or clinically significant abnormal. Clinical significance was defined as requiring further intervention, transfer, or further studies.

Results: Forty-five percent of patients (95% confidence interval (CI) 40.4-50.4; 174/383) with ASZ had ECT. Risk-classification demonstrated 8.6% of patients (95% CI 5.8-11.4; 33/383) were high-risk, and 91% (95% CI 88.6-94.2; 350/383) were standard risk. Thus, 63.6% (21/33) of high-risk patients, and 43.7% (153/350) of standard-risk patients received ECT (p = 0.013) with 52.4% (11/21) of high-risk patients and 1.9% (3/153) of standard-risk patients having abnormalities on ECT (p = <0.0001); only 2/11 and 1/3 had clinically significant abnormalities, respectively.

Conclusions: Our retrospective analysis of ECT, demonstrated clinically significant abnormalities at a low frequency, with more in the high-risk group. Abnormalities that altered the course of treatment were uncommon in both groups. Patients with known hydrocephalus comprised the largest group of high-risk patients with positive findings, but none required further intervention. Future studies may reveal a need to change the risk classification, evaluate alternate methods of imaging in known hydrocephalus, and a potential cost-savings by using risk-classification scheme.

E-30. Utilization of Medical Media in Child Neurology Practice
Sahebkar F, Kuch O, Connv M (San Francisco, CA)

Objective: An effective triage system is an integral part of scheduling patients in pediatric neurology practices. Referrals accompanied by video documentation augments the traditional triage system, allowing more effective use of limited resources for patients with suspected paroxysmal disorders.

Methods: For the purpose of triage, patients were twice dichotomized into urgent vs. non-urgent groups. A child neurologist reviewed primary medical doctor (PMD) referrals and medical records without, and subsequently with, videos of 19 children between the ages of 6 months to 7 years. CaptureProof™ was the medical media platform used to organize and review the videos. Following a comprehensive history and physical exam a diagnosis was made.

Results: Review of PMD referrals and medical record without video resulted in 1 non-urgent patient referred for tics, 18 urgent patients referred to rule out seizures, and 18 pre-appointment EEGs scheduled. The review of medical records with videos resulted in 15 non-urgent patients: (4) gratification disorder, (2) paroxysmal tonic upgaze (PTU), (6) stereotypes, (1) staring, (2) tics; 4 urgent patients: (1) absence seizure, (2) infantile spasms, (1) unclear, and 4 pre-appointment EEGs scheduled.

Conclusion: This study demonstrates the usefulness of media when triaging patients in child neurology practices with suspected paroxysmal disorders. It led to better triage and can avoid unnecessary costly tests prior to appointment. Additionally, at the patient's visit, this media platform aids in the differential diagnosis, by allowing observation of these events, as most patients do not have an episode in the office.

E-31. Post-traumatic Seizures in Children with Traumatic Brain Injury Admitted to the Pediatric ICU: A Role for Continuous EEG Monitoring
Leung M, Zsiga C, Van Hintum-Dat M (Los Angeles, CA), Brooks-Kayal A (Denver, CO), Sankar R, Giza CC (Los Angeles, CA)

Objective: In children, the #1 cause of morbidity and mortality is traumatic brain injury (TBI). Clinical and subclinical early post-traumatic seizures (EPTS) have been documented in up to 22% of patients admitted to the adult ICU. The incidence and risk factors for EPTS in ICU-hospitalized children have not been determined in an unsolicited cohort.

Methods: Continuous video EEG monitoring (cEEG) was performed on all consecutive TBI patients admitted to two pediatric ICUs. Demographic data, imaging results and global outcomes were also collected.

Results: 92 patients were consented and enrolled over a 3-year period. The average age at the time of injury was 6.4±0.6 years. Injury severity included: 8 mild, 51 moderate and 33 severe. Injury mechanism included falls (41%), abusive head trauma (20%), blunt trauma (7%) and bicycle accident (7%). EPTS of any type were seen in 34 (37.0%) patients, clinical seizures in 28 (30.4%), subclinical seizures in 14 (15.2%) and 6 (6.5%) patients had subclinical-only seizures. TBI severity (p <0.05) and injury mechanism (p <0.02) were risk factors for any clinical seizure. Subclinical seizures were strongly associated with younger age (p <0.001), injury mechanism (p <0.001) or any intra-axial bleed (p <0.005).

Conclusions: Given the significant incidence of subclinical EPTS and in particular subclinical-only EPTS, cEEG monitoring should be strongly considered for pediatric TBI patients admitted to ICUs. The greatest risk factors for subclinical seizures were younger age, abusive head trauma and intra-axial bleeding, and thus identify a group after pediatric TBI that may benefit the most from monitoring.

E-32. Seizures, Encephalopathy, and Vaccines: Experience in the National Vaccine Injury Compensation Program (NVICP)
Lateef TM, Johann-Liang R, Kaul Hasun N, Nelson KB (Washington, DC)

Background: The delivery of the DPT (Diphtheria Pertussis Tetanus) vaccine has been plagued by concerns about a causal link to epilepsy and encephalopathy. The NVICP is a national effort within the Department of Health and Human Services to compensate children who develop neurologic problems within 72 hours of immunization.

Objective: To describe clinical characteristics of children alleging seizure disorder as an injury due to vaccination.

Results: NVICP retrieved 242 cases alleging seizure disorder as vaccine injury. Of 96 cases reviewed thus far, 71 were filed in 1995-6, 10 in 1997-2002. Half were male. Vaccines implicated (sometimes multiple) were DPT 75, MMR 17, Hib and DT 2 each, DTaP and OPV one each. Less than half (42%) had a seizure within 72 hours of vaccination. There was a history of seizure before the alleged vaccine injury in 18%, abnormal neurological examination before the alleged vaccine injury in 13%. A definite diagnosis of pre-existing abnormality (tuberous sclerosis, epilepsy, congenital malformations, developmental delay) was given in 11%. Chronic myoclonic epilepsy developed in a quarter of the children.

Conclusion: A significant number of children with alleged vaccine induced seizure disorders had pre-existing neurological or neurodevelopmental abnormalities. Among those developing chronic epilepsy, many had clinical features suggesting genetically determined epilepsy. Future studies of these children, including genotyping, may allow more specific therapy and prognostication and may have implications for public confidence in vaccination.
POSTERS: Genetics

G-1. Fiber Tracts in the Corpus Callosum Correlate with Glutamine Levels and Neurobehavioral Measures in Patients with Ornithine Transcarbamylase Deficiency (OTC)


Objective: OTCD, an X-linked disorder of ureagenesis present a phenotypic spectrum from no deficits to significant deficits in attention and working memory. We used DTI and MRS to correlate structural and biochemical findings in white matter with clinical and functional deficits.

Methods: 20 control subjects, 21 subjects with OTCD - 8 asymptomatic, 13 symptomatic underwent MR imaging using 3T MRI, Siemens Tim Trio. Diffusion tensor was calculated using singular value decomposition. Regions of interest included the corpus callosum which was determined and normalized using Talairach atlas. Characteristics of fiber bundles were calculated using DTI studio version 2. H MRD was obtained using a 8cm³ voxel placed in the posterior cingulate gray matter and parietal white matter and quantitated with LCModel. Cognitive tests included Color Stroop, a test of cognitive flexibility and the TRAILS, a test of cognitive processing speed.

Results: Asymptomatic individuals had more fibers in corpus callosum than symptomatic individuals. In symptomatic subjects the number of fibers correlated with performance on the TRAILS. Individuals with OTCD performed more poorly on the TRAILS test than did controls or asymptomatic subjects. In symptomatic subjects there was a correlation between fiber track count/length and levels of glutamine.

Conclusions: The data suggest microstructural changes in the white matter of the corpus callosum of patients with symptomatic OTCD that correlate with scores on the TRAILS and STROOP task as well as glutamate levels in the brain. These microstructural changes are likely caused by clinical and/or subclinical hyponnemonic episodes

G-2. MAPK Levels as a Biomarker of Cognitive Deficits in Neurofibromatosis Type 1

Rosser T, Lee YS, Enrique N, Silva A, Bearden C (Los Angeles, CA)

In the NF1 mouse model, the loss of neurofibromin regulation leads to increased Ras/MAPK signaling which causes deficits in working and long-term spatial memory. Similar mechanisms may be responsible for the deficits seen in the NF1 human population but have not been thoroughly investigated.

Objective: We hypothesized that higher MAPK blood levels would correlate with poorer cognitive function.

Methods: Phosphorylated MAPK (p-MAPK) Western blots were performed on blood samples from 14 patients with NF1. Protein concentration was measured by performing BCA protein assay. After electrophoresis, protein was transferred to nitrocellulose membrane followed by blocking with 5% BSA. After incubation and washing with TBS-T, the membrane was incubated with an HRP-conjugated secondary antibody. The signal was detected with chemiluminescence. Blood MAPK levels were then correlated with patients’ frontally-mediated cognitive tasks.

Results: Strong correlations were observed between MAPK levels and multiple cognitive measures. Pearson correlations (r) of blood MAPK values for the cognitive tasks were as follows: Vocabulary = −0.73; Response inhibition/attention (Cancellation) = −0.37; Working memory (Letter number sequencing) = −0.33; Set switching (Verbal fluency-switching condition) = −0.64. All of the relationships were negative as would be predicted given that mutations in the NF1 gene lead to pathologically elevated Ras activity.

Conclusions: Poorer performance on several neurocognitive assessments correlated with elevated peripheral blood MAPK levels. If these methodologies are validated, the use of peripheral MAPK levels as a biomarker for cognitive dysfunction in NF1 would serve as a powerful, non-invasive tool for determining prognosis.

G-3. Triheptanoin Therapy for Inherited Disorders of Fatty Acid Oxidation

Goldstein A, Barone A, DeWard S, Payne N, Vockley J (Pittsburgh, PA)

Background: Fatty acid oxidation (FAO) disorders result in inadequate energy production from fatty acids during fasting and stress. Deficiencies of long chain FAO share many clinical features such as episodes of recurrent hypoglycemia and rhabdomyolysis, myopathy, and cardiomyopathy. Treatment generally consists of medium chain triglycerides (MCT), but is only partially effective. In contrast, the seven-carbon MCT heptanoate results in production of the three carbon TCA cycle precursor propionyl-CoA (C3) in addition to acetyl-CoA that can replenish odd carbon intermediates, improving production of reducing equivalents for ATP synthesis by the respiratory chain.

Methods: 22 patients are currently enrolled in a compassionate use trial of triheptanoin at Children’s Hospital of Pittsburgh were reviewed. Diagnoses included deficiencies of VLCAD (11 patients), LCHAD (5 patients), TFP (2 patients), CPT (3 patients) II, and CACT (1 patient). Patients received 1-2 g/kg/day of triheptanoin. Metabolic and nutritional parameters were collected upon study entry and at 2 months, 6 months, and every 6 months after that.

Results: Of the 20 patients who have participated at least 12 months in the study, there were on average 0.6 hospitalizations per year per person, decreased by report compared to prior to starting triheptanoin therapy. Two patients demonstrated the often dramatic effect of triheptanoin therapy.

Conclusions: Triheptanoin oil is a well-tolerated alternative to MCT oil in patients with long chain FAO disorders, and has led to marked clinical improvement in some patients. A double blind FDA Phase II is currently underway to directly compare the safety and efficacy of these therapies.

G-4. Computerized Cognitive Training for Children with Neurofibromatosis Type 1 (NF1): A Pilot Neuropsychological and Resting State Functional Connectivity (r-fMRI) Study

Hardy K (Washington, DC), Castellanos FX, Chabernaud C (New York, NY), Walsh KS (Washington, DC), Harel BT (New Haven, CT), Hostetter SA, Kadom N, Packer RJ, Acosta MT (Washington, DC)

Objectives: Among the cognitive domains affected in Neurofibromatosis type 1 (NF1), deficits in attention and executive function are increasingly appreciated. We assess the feasibility of a home-based, and web-based computerized working memory training program (Cogmed®) for children with NF1 and working memory deficits while examining potential changes in resting-state functional connectivity (FC) in the frontoparietal intrinsic connectivity network.
Methods: This prospective, single-arm trial (target n=20) includes pre- and post-intervention neuropsychological assessment and resting-fMRI. Eligible children undergo 9 weeks (25 sessions) training with web-based CogniFit® with phone-based coaching support. Primary outcomes include change in attention ratings and working memory function. We also collected 6-minute EPI scans pre- and post-treatment (TR=3000ms; 39 slices, voxels= 3x3x3mm). We conducted whole-brain corrected FC voxel-wise analyses using 11 frontoparietal regions-of-interest (Dosenbach et al., 2007).

Results: Ten participants (4 male; mean age=10.6) to date have completed >92% of training sessions without adverse events. Attention and executive function measures improved after computerized cognitive training; children reported enjoying the intervention, and 90% of parents indicated satisfaction with the study. Frontoparietal FC also changed significantly; e.g., positive FC between right precuneus and supramarginal gyrus was significantly greater pre- vs. post-intervention. NF1 participants also showed less negative FC post-treatment between left precuneus and (1) fusiform gyrus and (2) thalamus.

Conclusion: Our preliminary results suggest that computerized working memory training is well tolerated. Attention and working memory measurements improved after treatment and is accompanied by changes in FC in the frontoparietal network that underlies attention and working memory processes.

G-5. Novel Critical Region Implicated in Microcephaly and Neurodevelopmental Delay in 2q37 Microdeletion Syndrome


Objective: Primary microcephaly is associated with alteration of neural progenitor cell genes leading to mental retardation. 2q37 microdeletion syndrome is associated with loss of approximately 100 genes. Identification of the precise set of genes responsible for the neurodevelopmental phenotype requires the identification of smaller interstitial deletions. A novel 496 kb deletion was discovered in a patient who fulfilled the criteria for 2q37 microdeletion syndrome. The 5 year-old female patient presented with microcephaly, stereotypic, wringing hand movements, toe walking, poor attention span, self-injurious behavior, speech delay and learning disability. The patient also had epilepsy with EEG showing generalized spike and waves. MRI revealed microcephaly but no other cortical malformation.

Methods: Genomic DNA was isolated from blood for whole genome array CGH; the microdeletion was confirmed by FISH. Genomic analysis was done by using the UCSC genome browser; ingenuity pathway was used for network analysis.

Results: Chromosome analysis revealed a 46XX karyotype with normal G-banding patterns. MECP2 and Fragile X genes were normal. Whole genome array CGH using 3063 probes revealed an interstitial deletion of 496 kb at band 2q37.3. The abnormal segment contains 10 genes based on UCSC 2006 hg18. The genes within the deleted region are evolutionarily conserved including SEPT2,-FARP2,HDLBP,PASK. Pathway analysis of these genes revealed links to neural development, ciliogenesis and interaction with genes associated with neural function.

Conclusions: Our report narrows the genomic region for 2q37 microcephaly and developmental delay to 10 candidate genes and suggests that haploinsufficiency in this critical region may lead to human microcephaly and neurodevelopmental delay.

G-6. Chromosomal Microarray in Children with Neuromuscular Disorders


Objective: To demonstrate the usefulness of chromosomal microarray (CMA) in the diagnosis of children with neuromuscular disorders.

Methods: We used CMA, both SNP microarray and array comparative genomic hybridization, to evaluate 12 children with neuromuscular disorders.

Results: In seven patients CMA was the confirming diagnostic test. Six children with findings compatible with Charcot-Marie-Tooth (CMT) were diagnosed with CMT1A. A 14-year-old girl with a family history of HNPP and a radial neuropathy, was diagnosed with HNPP. In three children the diagnosis was unexpectedly made with CMA. Two children, one with developmental delay (DD) and one with autism, were unexpectedly found to have HNPP. An 8-year-old girl with autism and two brothers with Duchenne muscular dystrophy (DMD) was found to have a dystrophin gene deletion. In 2 children the diagnosis was unexpectedly made with CMA and confirmed after further testing. A 26-month-old boy with global DD demonstrated a deletion within the dystrophin gene. Follow-up testing showed CK of 30,825 U/L and a deletion of exons 7-25 of the dystrophin gene. An 8-year-old boy with kyphoscoliosis and congenital hypotonia/ weakness demonstrated a 76 kb deletion at 21q22.3 which included COL6A2 gene (Ullrich congenital MD).

Conclusion: CMA provides an alternative test to make the diagnosis of CMT1A (30-40% of CMT) and HNPP. CMA is a first tier diagnostic test in children with DD, autism, and multiple congenital anomalies. In these children, diagnosis of an unsuspected neuromuscular disorder will result in genetic counseling, prevention of additional familial cases, and early implementation of preventive treatment.

G-7. Intrachromosomal Variation of Symptom Severity in Collagen VI (COL6) Myopathy

Dicarlo SM, Lotze TE, Adesina AM, Warringer MF (Houston, TX), Bonnemann CG (Bethesda, MD)

Objective: To discuss genotype and phenotypic variation in collagen VI myopathy as demonstrated by a sibling pair with a novel COL6 splice-site mutation.

Methods: A brother and sister with known COL6 myopathy were both compared in regards to their phenotypic features, muscle biopsy results, and COL6 gene analysis.

Results: The female patient, currently age 12, presented at age 8 with symptoms of elevated CK as well as minimal fatigue with prolonged exercise. Her muscle biopsy results showed variable and mildly decreased expression of COL6. Her brother, currently age 15, was referred 2 years later at age 12 due to symptoms of incoordination and progressive muscular weakness. A muscle biopsy was performed and he was found to have severely decreased expression of COL6. Genetic testing sent on both siblings revealed a c.1957-5C>T (IVS30-5C>T) nucleotide change in COL6A1 resulting in a missense mutation in intron 30. The female patient is heterozygous for this mutation while the male is homozygous.

Conclusion: COL6 myopathies are under recognized in pediatric neuromuscular populations secondary to a widely
variable phenotype that overlaps with other myopathies. This sibling pair raises the question of whether or not collagen VI myopathies may exhibit variable expression of symptoms depending on patient’s genotype. Further genetic studies are underway to determine whether the finding is related to the phenotype and muscle biopsy results.

G-8. Mutations in ADD3 Lead to Inherited Forms of Spastic Diplegia and Spastic Quadriplegia
Cerebral palsy is estimated to affect nearly 1 in 500 children, and a significant proportion of cases are believed to be genetic. Previous studies have identified mutations in ankyrin and components of the adaptor protein complex in forms of inherited cerebral palsy, suggesting a role for components of the dynamic cytoskeleton in the genesis of the disease. In the present study, we identified a mutation in ADD3, encoding gamma adducin, in a multiplex consanguineous Jordanian family by exome sequencing. In vitro studies in patient fibroblasts found that the p.G367D mutation, which occurs within the putative oligomerization critical region, impairs the ability of gamma adducin to associate with the alpha subunit. Knockdown studies of the drosophila adducin homolog hs confirmed a critical role for adducin function in locomotion. Our findings are consistent with a critical role for adducins in normal neuromotor activity, and indicate that impaired adducin function may lead to inherited neuromotor disability.

G-9. Segmental Neurofibromatosis in Children and Adolescents
Shlomit J, Moodley S, Moodley M, Rothner AD (Cleveland, OH)
Objective: To study clinical features, improve recognition and discuss genetic and prognostic implications of SNF.

Background: SNF is characterized by cafe-au-lait macules (CALM) and/or neurofibromas limited to one region of the body. It is thought to be a post-zygotic mutation in the NF-1 gene leading to localized mosaicism. Features are limited from a single dermatome to one quadrant or one half of the body. Prevalence is 1 in 36000. We report 82 children with SNF. We suggest further studies to better define the entity.

Design/Methods: A retrospective chart review. IRB approval was obtained. Eligible subjects met two criteria: segmental expression of NF-1 and age under 18. Anthropometric, medical history, location and manifestations were noted. Further evaluations: ophthalmology, cardiology, genetics and MRI were recorded.

Results: Eighty-two patients with SNF were identified. Mean age was 7.83 years. Eighty patients had unilateral distribution of NF-1, two patients had bilateral features. The trunk was affected in 74(89%), upper limb in 31(37%), lower limb in 31(37%). Some had contiguous lesions affecting more than one part the body. Most were pigmented skin lesions 80(97%). Three (3.6%) had neurofibromas and plexiform neurofibromas; two had involvement of half their body, one had unilateral internal involvement resulting in pain and atrophy. Seven patients had segmental CALM in a limited dermatomal distribution only. Thirty-four (41%) had MRI and 44(53%) eye exam: none showed findings related to NF-1. No patients showed hereditary disposition.

Conclusions: In our clinic SNF is more common than NF-2. The genetic risks seem limited. Our patients lacked: optic gliomas, dystrophic scoliosis, psuedoarthrosis, lisch nodules and a 1” relative. The patients with deep NF had pain, weakness and atrophy. Further DNA studies of typical cases including blood, skin of affected and unaffected areas are needed.

G-10. The 14q32 Deletion Syndrome: Narrowing the Critical Locus for Intellectual Disability
Holder JL, Lotze TE, Bacin C, Cheung SW (Houston, TX)
Objective: Terminal and interstitial deletions involving chromosome 14q32 are rare with only fifteen cases reported. Individuals harboring such deletions have similar phenotypes including facial dysmorphisms, moderate intellectual disability and epilepsy. Because of the rarity of such deletions, the genes that contribute to this phenotype are unknown. Our objective is to determine what genes are critical for the intellectual disability phenotype of 14q32 deletions.

Methods: A search of the Baylor College of Medicine’s Medical General Laboratory clinical chromosomal microarray database revealed a child with global developmental delay, greatest in language development, with a 14q32 deletion.

Results: Array CGH analysis revealed a 14q32.33 deletion with a maximum size of 0.305Mb which includes NUDT14, BRF1, BTB6, PACS2 and MTA1. FISH confirmed the same deletion to be present in our patient’s father who also has intellectual disability. A comprehensive literature search for individuals with deletions encompassing 14q32.3 was performed. The results indicate a common phenotype involving facial dysmorphisms, intellectual disability and epilepsy.

Among the genes identified to be deleted in our patient, several are known to be expressed in the developing central nervous system; however, none have previously been linked to intellectual disability. Interestingly, deficiency of BTBD6 orthologues in animal models disrupts normal CNS development.

Conclusions: We have identified a patient with the smallest 14q32 deletion ever reported with a similar phenotype as individuals with much larger deletions. We propose that within this small deletion lies a gene that significantly contributes to the 14q32 deletion phenotype, especially with regard to intellectual disability.

G-11. Disruption of Antiquitin (ALDH7A1) Function in Astrocytes is Associated with Neuronal Migration Defects in Pyridoxine-Dependent Epilepsy
Jansen LA, Hiner RE, Roden WH, Haliv S, Jung S, Gospe SM (Seattle, WA)
Objective: Structural brain abnormalities, including cortical dysplasia and neuronal heterotopias, have been reported in individuals with pyridoxine-dependent epilepsy (PDE). PDE is caused by mutations in ALDH7A1, also known as antiquitin. How antiquitin dysfunction leads to neuronal migration defects is unknown. In this study, we analyzed control brain tissue and tissue from a child with PDE to determine the normal distribution of antiquitin expression, its distribution in PDE, and associated structural abnormalities.

Methods: Formalin-fixed human brain sections were subjected to routine histopathology as well as fluorescence immunohistochemistry studies. Brain tissue frozen at autopsy was utilized for measurement of PDE-associated metabolites and Western blot analysis. Comparative studies
of antiquitin distribution were performed in mouse brain sections.

Results: Histologic analysis of PDE cortex revealed areas of abnormal tangential neuronal organization consistent with type Ia focal cortical dysplasia. Neuronal heterotopias were identified in subcortical white matter, as well as cortical astrogliosis, hippocampal sclerosis, and patchy gliosis of the basal ganglia. Highly elevated levels of AASA, piperidine-6-carboxylate, and pipecolic acid were measured in PDE cortex. Interneuron density in PDE cortex was not reduced, although total GAD-67 expression was. In control human and mouse cortex, cytoplasmic antiquitin immunofluorescence was identified in astrocytes, ependyma, and choroid plexus. In PDE cortex, antiquitin immunofluorescence was greatly attenuated, with perinuclear accumulation in astrocytes.

Conclusions: Antiquitin is expressed within neuroglial cells in the brain, and its dysfunction in PDE is associated with neuronal migration defects. These structural brain abnormalities likely persist despite postnatal pyridoxine supplementation and may contribute to neurodevelopmental impairments.

G-12. Confirmation in a Second Dataset of a Maternally Acting Gene Allele (MAGA) for Autism in a Small Region of Chromosome 3p24.3
Johnson WG, Buyske S, Stenroos ES (Piscataway, NJ)

Objective: Maternally-acting gene alleles, MAGAs, act in mothers prenatally to alter fetal environment and affect offspring phenotype, independently of any inheritance by the fetus. Evidence of MAGAs has previously been found by candidate gene approaches. Earlier, we reported the first, to our knowledge, genome-wide association study (GWAS) for MAGAs, that implicated a small region of chromosome 3p24.3 for autism. We now attempted to replicate this in a second dataset.

Methods: We used the Weinberg log-linear method to analyze GWAS data from the Autism Genome Project (AGP) genotyped on the Illumina 1M array in 1366 families.

Results: In our earlier analysis, SNP rs12487874 (intronic in the RFTN1 gene) showed genome-wide significance (p = 8.61E-11) with no evidence of child effect. The AGP dataset showed genome-wide significance (p = 1.83E-19) for SNP rs12636481, located near rs12487874 and not in the earlier dataset. SNP rs12487874 was not part of the AGP dataset. Both SNPs showed a marked asymmetry in parents in both studies, where the mothers identified were homozygotes for the minor allele.

Conclusions: Since this study confirmed the action of a MAGA for autism in a small region of chromosome 3p24.3, we are now testing the hypothesis that a structural DNA variant in this region is responsible for the observed effect. We expect these studies will lead to understanding its mode of action in contributing to autism, to approaches to identifying risk of autism prenatally or even before pregnancy begins, and perhaps to methods of preventing or treating autism at a very early stage.

Caruso P (Boston, MA), Loes D (Minneapolis, MN), Pan J, Eichler FS (Boston, MA)

Objective: GM2 gangliosidoses are autosomal recessive disorders caused by deficiency of β-hexosaminidase. The deficiency results in excess accumulation of glycolipids in the lysosomes of neuronal cells and leads to neurodegeneration. We hypothesized that MRI brain abnormalities in GM2 could be quantified along a scale.

Methods: Brain MRIs of GM2 gangliosidoses patients were collected by the National Tay Sachs and Allied Diseases Association (NTSAD). Nineteen brain MRIs from 11 patients with infantile and 7 patients with juvenile GM2 were reviewed for global disease burden. A visual scoring method was based on a point system derived from the location of gray and white matter changes and the presence of brain atrophy.

Results: The age range of the late infantile patients was from 3 to 19 months (mean 12.7 months); that of juvenile patients was from 2 years to 4 years and 3 months (mean 34.3 months). All infantile patients displayed hypomyelination while juvenile patients had isolated focal white matter abnormalities. Most infantile patients had hypertensities in the caudate and putamen on T2-weighted images, with several displaying distinct striations in the thalamus. A minority of patients displayed subtle cerebellar white matter abnormalities as well. No atrophy or ventricular enlargement was present.

Conclusion: We find hypomyelination and grey and white matter changes in specific structures on the brain MRIs of childhood GM2 patients. We propose a MRI scoring system based on these abnormalities with the goal to evaluate the progression in GM2 gangliosidoses patients.
POSTERS: History/Teaching of Child Neurology

HI-1. Mapping the Literature: Palliative Care Within Child Neurology
Dallara A, Saroyan J (New York, NY)

Objectives: This review assesses the existing evidence base regarding practice of palliative care in child neurology. Previous studies have shown shortfalls in usage of palliative care in patients with long-term neurological conditions. Objectives of this review were to examine definitions and background of pediatric palliative care, as well as address whether there is an increased need for palliative care education amongst child neurologists. The review also explores what literature exists regarding palliative care within the field of child neurology, including the prevalence and management of symptoms in children living with different life-threatening neurological illnesses.

Methods: A comprehensive literature review was conducted examining use of palliative care within child neurology. Over 30 articles and textbooks were retrieved and reviewed.

Results: Expert guidelines stress the importance of expertise in palliative care amongst neurologists. Subspecialties written about in child neurology include that of neuromuscular disease, metabolic disorders, and neonatal neurology. Early initiation of palliative care has been shown to result in better patient outcomes.

Conclusions: Palliative care is a vital component to the care of any child with a potentially life-threatening condition. Key to its effectiveness is instituting it at the child’s time of diagnosis. Child neurology is one of the subpopulations in greatest need of pediatric palliative care services.

HI-2. Children with Neurological Conditions Report Low Rates of Influenza Vaccination

Objective: Recent studies suggest that school-age children have the highest incidence of influenza; however, rates of influenza immunization in the pediatric population remain low. Children with neurological conditions often require more healthcare resources than their unaffected peers, and thus may have increased opportunities for vaccination annually. Our objective was to describe influenza vaccination rates among children with various neurological conditions.

Methods: We analyzed data from the 9,417 children in the United States whose health-status information was collected in the 2007 National Health Interview Survey (NHIS) data, including influenza vaccination status within the past 12 months and neurological diagnoses.

Results: As a whole, children with neurological conditions had annual influenza vaccination rates equal to those of the general pediatric population (21.0% vs 21.1%). Rates were similar among children who reported use of Complementary and Alternative Medicine. Within the subgroup of children with neurological conditions, those with developmental delay had the highest rate of vaccination (28.2%), while those with non-migraine headache had the lowest rate (17.6%).

Conclusions: Despite the increased importance of influenza prevention in children with neurological conditions, the frequency of immunization in this group is not greater than that of the general pediatric population. Pediatric Neurologists can influence the rate of vaccination in their patients by being mindful of influenza vaccine recommendations.

HI-3. Survey of Recently Certified Child Neurologists about Education and Practice Needs
Gilbert DL (Cincinnati, OH), Ridel KR (Carmel, IN), Reynolds TQ (Scarborough ME), Patterson MC (Rochester, MN), Valencia I (Philadelphia, PA)

Objective: To obtain information about utility of child neurology residency training from recent graduates in order to improve residency education.

Methods: We used Survey Monkey and to query 437 child neurologists first certified in “Neurology with Special Qualification in Child Neurology” by the American Board of Psychiatry and Neurology (ABPN) between 2001 and 2010.

Results: Our response rate was 41% (56% male; 70% white). 59% completed two years of pediatrics; >50% completed adult neurology primarily in-hospital in one large block; 58% completed fellowships. Current practice location is hospital based for 85%; academic for 79%. 67% provide no adult services; 3% provide general adult neurology services. Most considered all types of child neurology rotations clinically useful on a daily basis. Most types of adult rotations and experiences were viewed clinically useful on a monthly basis. Respondents desired more child neurology training, especially in genetics, behavior and development, neonatology, and sleep. Overall, residency with more child and fewer adult neurology months was considered clinically optimal by 55% for common and 69% for rare disorders (see figure).

Conclusions: In this survey of recently certified child neurologists, respondents were divided about the value and purpose of adult training. A minority provides clinical services to adults, primarily within subspecialties. Otherwise, most reported infrequent use of adult training knowledge. These results support child neurology training reform, flexibility within the current training model, and reduction in adult neurology training.
POSTERS: Headache/Migraine

HM-1. Life-style Behaviors in Children and Adolescents with Recurrent Headache

Objectives: Assess life-style behaviors in children and adolescents with recurrent headache.

Methods: We conducted a retrospective chart review of all new patients seen at Children's Hospital Colorado Headache Clinics referred from primary care providers and neurologists from January 1, 2011 to April 1, 2012. Patients completed an intake headache questionnaire which included information about life-style habits and behaviors: fluids intake, nutrition, exercise, electronic use, and sleep. Individuals were excluded if they had chronic daily headache. Correlations were performed using simple linear regression.

Results: Of 87 new patients seen, 51 (58.6%) were included with a mean age of 14.3 years (SD 3.2) and 66% female. Forty-nine (96.1%) patients had primary headache diagnosis of migraine. On average, patients consumed four glasses of fluids per day with 71% of patients reporting caffeine intake and 43% skipping meals. Patients exercised an average of 3.6 hours per week. Average electronics use was 6.4 hours a day with 3.7 hours texting or talking on phone, 1.9 hours on TV and 0.8 hours surfing computer. Patients averaged 7.8 hours of sleep per night with 45% reporting difficulty falling asleep and taking 45 minutes on average to fall asleep. Caffeine use (r = 0.240; p = 0.09), time on phone texting or talking (r = 0.266; p = 0.059), total electronic use (r = 0.258; p = 0.07), and sleep duration (r = 0.257, p = 0.07) were the most highly correlated with headache frequency.

Conclusions: Behavioral modification may be promising in reducing headache frequency in the pediatric headache population. Specifically, management may focus on caffeine use, phone and electronic use, and sleep hygiene.

HM-2. Headache Drawings in Primary Pediatric Headaches: Experience From a Developing Nation
Javarayee PM, Ray M, Malhi P, Singh PD (Chandigarh, India)

Objectives: To evaluate the usefulness of drawings in diagnosing Primary headaches (PH) in children of developing country.

Methods: Children were asked to draw a picture to depict their headaches felt. Later a clinical diagnosis was made based on International Headache Society criteria. Each child had two headache diagnoses, one based on clinical diagnosis and other based on drawing. Drawings were classified either as migraine or non-migraine based on blind analysis of the headache drawing by the psychologist and pediatric neurologist. The clinical diagnosis was considered the 'gold standard' to which the headache drawing diagnosis was compared.

Results: The mean age of the children was 10.3 ± 2.0 years and 52.5% were boys. Of the 50 children, 43 were clinically diagnosed with migraine (86%), 6 with tension-type headache (12%) and one with somatisation disorder. Drawings had a sensitivity of 88.37% and a specificity of 57.14% when compared with the clinical diagnosis. The positive and negative predictive values were 92.68% and 44.44%, respectively. Drawings of focal neurological defects, phonophobia, photophobia and unilaterality predicted clinical migraine in all cases. Depictions of sleep, recumbency, nausea, vomiting and severe pain correlate closely with a migraine clinical diagnosis, with PPVs exceeding 90%.

Conclusions: Our study highlights usefulness of drawings in diagnosing headache in children of developing nation. This potential usefulness this diagnostic tool is important given its low cost, ease of implementation and lack of invasiveness makes it a valuable tool in economically challenged regions.

HM-3. Acute Presentations of Stroke and Stroke Mimics in Children: A Prospective Observational Study of Brain Attacks in the Emergency Department

Objectives: To determine signs, symptoms and etiology of children presenting to emergency departments (ED) with stroke and stroke mimics as a key step for developing a brain attack pathway.

Methods: Prospective observational study at a large tertiary ED of children 1 month-18 years with brain attacks (focal brain dysfunction of apparently abrupt onset) with ongoing symptoms or sign on arrival. Exclusion criteria included known epilepsy, hydrocephalus, head trauma and isolated headache.

Results: There were 292 children with 306 consecutive presentations over 18 months. Median age was 9.4 years. 35% arrived by ambulance. Median symptom duration prior to arrival was 6 hrs and median time from triage to medical assessment was 22 mins. Symptoms included headache (56%), vomiting (36%), focal weakness (35%) or numbness (25%), visual disturbance (23%), dizziness (21%), seizures (20%), altered consciousness (20%), speech disturbance (17%), ataxia (15%) and syncope (11%). Signs included focal weakness (31%) or numbness (13%), ataxia (11%), speech (8%) or visual disturbance (7%). Diagnoses were migraine (27%), seizures (15%), Bell's Palsy (9%),
cerebrovascular disorders—ischemic or hemorrhagic—(7%), conversion disorders (6%), syncope (5%), non-specific headache (4%), demyelination, methotrexate encephalopathy, post-infectious cerebellitis (all 3%), malignancy, CNS infections (both 2%) and drug intoxication (1%).

Conclusions: In this first prospective study of acute presentations of brain attacks in children stroke was the fourth most common cause. Etiology, presentation and EMS utilization in children differ from adult brain attack data. These findings will be the basis for the development of tools and ED pathways for pediatric brain attacks.

HM-4. Successful Treatment of Childhood Migraines with a Conservative Approach - A Retrospective Study
Gutu STH, Johnson MI, Erickson TC (Albuquerque, NM)

Objective: Migraines in children are common, affect quality of life and are often due to identifiable risk factors. We document here a successful conservative, non-pharmacological approach.

Methods: A retrospective chart review of children with headaches, aged 4-18 years, seen and followed in our Child Neurology Clinic, was conducted. The study included children with normal neurological exams and diagnosis of migraines at initial visit (V1) and with one follow up visit (V2). A checklist of modifiable risk factors was used at both visits. Our conservative approach addressed these risk factors with in depth discussion and recommendations to improve sleep hygiene, increase daily water intake, recognize and avoid dietary/environmental triggers, reduce stress and withdraw daily medications. Frequency, severity and duration of the headaches were documented at V1 and V2. Patients were classified as completely compliant (CC), partially compliant (PC) or non-compliant (NC).

Results: Sixty patients met criteria: 37 females and 23 males. Mean age was 11.95 years; age of onset, 3.27 years, and mean time to V2, 3.62 months. There were 32 CC patients, 15 PC, and 13 NC. Headache frequency (days/month) was reduced in CC patients (14.06, V1 and 0.541, V2, p<0.001) and in PC patients (20.4, V1 and 8.8, V2, p<0.001). Similar decreases were seen in headache duration and severity. NC patients showed no improvement (10.818, V1 and 11.182, V2, p=0.827).

Conclusions: Migraine headaches are decreased in completely or partially compliant children with a conservative approach to reducing risk factors without daily use of pharmacological agents.

HM-5. Clinical Presentation of Concussion in Young Children in a Multidisciplinary Concussion Clinic
Rien SR, Bougrab NM, Reesman J, Kramer ME, Lam JC, Slomine BS, Suskauer SJ (Baltimore, MD)

Objective: Pediatric concussion is an increasingly recognized public health concern. Less is known about the presentation of concussion in younger children as compared to teenagers.

We describe the experience with children 6-12 years old in a pediatric concussion clinic staffed by neurology, physical medicine and rehabilitation, and neuropsychology.

Methods: We completed a retrospective chart review of all visits for patients aged 6-12 years seen from 2010-2012. Data were extracted from initial and follow-up visits.

Results: 51 patients aged 6-8 (n=12) and 9-12 (n=39) years presented within 50 days of concussion. 65% were male (n=33). Average time from injury to initial clinic presentation was 19 days (range 4 to 48 days). 48% of concussions occurred during sport (n=24). 17 patients reported suspected or confirmed loss of consciousness; 18 reported prior concussion. At initial evaluation, physical symptoms were most commonly endorsed (average 2 symptoms per child), followed by cognitive, sleep, then emotional symptoms. Average number of school days missed by initial evaluation was 4.8 (range 0-35). Patients were followed until symptom-free; 82% were followed beyond 2 weeks post-injury and 50% were followed beyond 1 month. Number of symptoms at initial visit was highly correlated with time to discharge from clinic (r = .992, p = .000).

Conclusions: In these younger children, physical and cognitive symptoms predominate, and school attendance is adversely impacted. Number of symptoms at the first visit was associated with need for ongoing follow up. Data suggests that clinical care needs to address management of physical symptoms and accommodations in school.

HM-6. Validation of a Headache Interview for Children and Adolescents

Objective: To date there are no structured interviews to ascertain the diagnostic criteria for headache in children. The objective of this study is to assess the validity of the Diagnostic Interview of Headache Syndromes – Child Version (DIHS-C) developed at the National Institute of Mental Health for a community based family study of headache syndromes and comorbid disorders.

Methods: The DIHS-C is a fully structured diagnostic interview comprised of an open-ended clinical history, modules with key symptoms for each of the major headache subtypes, and associated impairment, duration, frequency, course, and treatment. This report presents the validation of the interview in a sample of 104 children evaluated as part of a community based family study of migraine.

Results: Sensitivity of interview diagnosis compared with expert neurologist diagnosis of migraine was 98%, and specificity was 60%. Similar levels of sensitivity and specificity were found by sex and age of the children.

Conclusion: The DIHS-C provides a new tool that can enhance the reliability of pediatric diagnosis in both clinical and community settings.
POSTERS: Infectious Disease

I-1. Serum Soluble CD163 Levels in Patients with Influenza-associated Encephalopathy
Takahisa Ichiyama, Shunji Hasegawa, Takehi Matsushige, Madoka Kajimoto, Hirofumi Inoue, Seigo Okada, Midori Takahara (Ube, Japan)

Objective: Influenza-associated encephalopathy (IAE) is a severe neurologic complication of influenza, which is characterized by an abrupt onset of seizures and coma within a few days of developing a high-grade fever. We previously reported hypercytokinemia was related to the poor outcome of IAE. However, it is still unclear which cells produce proinflammatory cytokines in IAE. To investigate activations of monocytes in the peripheral blood, serum soluble CD163 levels were determined in patients with IAE.

Methods: Serum samples were obtained from 35 IAE patients (21 males and 14 females, aged from 11 months to 30 years; median, 6.1 years) admitted to our hospital and 16 collaborating research hospitals in Japan, from January 2007 to March 2011. Three patients died and four had severe neurological sequelae. Sixty-nine patients were enrolled with uncomplicated influenza (43 males and 26 females, aged from 1 month to 15 years; median, 5.3 years). The control group comprised 63 healthy children (30 males and 33 females, aged from 2 days to 17 years; median, 6.8 years). The serum concentrations of soluble CD163 were determined with sandwich-type ELISA kits (R&D Systems, USA).

Results: The serum levels of soluble CD163 in IAE patients with a poor outcome (n = 7) were significantly higher than those in IAE patients without neurological sequelae (n = 28), in patients with uncomplicated influenza, and in the control group (p = 0.023, p < 0.001, and p < 0.001, respectively).

Conclusions: Our results suggest that activations of monocytes in peripheral blood are related to poor outcome in IAE.

I-2. Using Laboratory and Seasonal Differences in Retinopathy Negative versus Positive Cerebral Malaria to Improve the Understanding of Disease Pathophysiology
Potels, DG, Birbeck, GL, Valin C (Boston, MA), Mannor KM (East Lansing, MI)

Objective: Children with cerebral malaria (CM) can be categorized by the presence or absence of malaria retinopathy. We compared admission laboratory, demographic, and seasonal data between children admitted with retinopathy positive versus negative CM and used these comparisons to gain insight into the underlying pathophysiology of retinopathy negative CM.

Methods: We retrospectively reviewed admission laboratory and clinical parameters and the seasonal pattern of disease presentation in patients admitted with CM in Blantyre, Malawi from 1997–2010 and compared these data across retinopathy status.

Results: Patients with retinopathy negative CM had higher glucose concentrations, hematocrits, platelet counts, and lower lactate concentrations and peripheral parasite counts than those with retinopathy positive CM. Children with retinopathy negative CM were more likely to be in deeper coma upon admission than those with malaria retinopathy. The seasonal pattern of disease presentation also varied by retinopathy status.

Conclusions: Taken together, these findings support the hypothesis that these conditions have different underlying etiologies. Acute Plasmodium falciparum infection is not sufficient to produce the retinopathy negative CM syndrome.

I-3. Clinical and Laboratory Features of Childhood Encephalitis Using a Standardized Diagnostic Algorithm
Shieh A, Gold J, Bykowski J, Kruk P, Leake J, Bradley J (San Diego, CA), Sheriff H, Glaser C (San Francisco), Crawford J (San Diego, CA)

Objective: To determine the clinical features and pathogenic etiologies of a prospective single institutional series of childhood encephalitis using a standardized diagnostic algorithm.

Methods: Prospective cohort of children diagnosed with encephalitis at Rady Children's Hospital, San Diego from 2005-2011 was evaluated by the California Department of Public Health's California Encephalitis Project as part of routine diagnostic workup. Clinical and laboratory features were evaluated for identifiable pathogens.

Results: One hundred forty three consecutive children (82 boys, average 8.2 years, range 2 days-19 years) diagnosed with encephalitis were available for review. Twenty three percent of children had a single seizure and 3% (5/143) had status epilepticus as a presenting feature. Workup included viral respiratory screening (38/143), MRI (65/127 abnormal), CT (24/114 abnormal) EEG (69/90 abnormal), and CSF/Serum Testing for potential pathogens (68/143 positive). The average length of hospitalization was 14.4 days, 31% had repeat hospitalization, and there were 6 deaths. A pathogen was identified in 68/143 cases (18/143 confirmed, 50/143 probable). Most commonly detected pathogens included Mycoplasma sp. (35%), Rhinovirus (15%), Enterovirus (11%) and Human herpesvirus-6 (5%). There was no distinction between clinical, radiographic, EEG features, or outcome among those patients with and without an identified pathogen. However, children positive for a pathogen had a significantly longer hospital course (20 vs 9.4 days, p = 0.008).

Conclusions: Childhood encephalitis remains a diagnostic challenge and is associated with prolonged hospitalization and significant morbidity. A standardized laboratory encephalitis workup is associated with increased number of identifiable pathogens compared to historical controls and worthy of further study.
POSTERS: Neuroimaging

NI-1. Resting State Functional Connectivity in Children with Neurofibromatosis Type 1
Rosser T, Karlsgodt K, Schreiner M, Enrique N, McGough J, Silva A, Bearden C (Los Angeles, CA)

Resting-state functional MRI (rs-fMRI) is a noninvasive means of assessing the brain’s intrinsic functional architecture. Research has demonstrated that NF1 patients frequently have deficits in frontal lobe functioning and a markedly increased incidence of ADHD.

**Objective:** We hypothesized that patients with NF1 would have poorly synchronized long distance connectivity between the frontal cortex and other brain systems and that this disruption plays an important role in cognitive dysfunction.

**Methods:** Resting-state fMRI was performed on 8 children with NF1 ages 10-15 years and 23 age-matched typically developing controls (mean age = 12.5 years). First level analysis modeled the global signal and 6 motion parameters. The time series for a seed within the posterior cingulate gyrus (PCC), a key node within the default mode network, was extracted from the original residuals files. Subject-wise correlation models were run, generating contrasts corresponding to the partial correlation estimate with the PCC seed voxel entered as an explanatory variable.

**Results:** The group-level analysis produced the following threshold z-score maps: 1) Maps of significant frontal connectivity off the PCC across the NF1 sample; and 2) Maps of PCC connectivity in relation to ADHD-RS scores. Within the NF1 group, a significant inverse correlation with ADHD severity was seen, indicating increased frontal-PCC resting functional connectivity in NF1 children with fewer ADHD symptoms.

**Conclusions:** Decreased long-range connectivity within the default mode network is related to attentional symptomatology in NF1 patients, suggesting a biological basis for these deficits.

NI-2. Corpus Callosum Integrity in Acute and Chronic Traumatic Brain Injury Mapped with Diffusion Tensor Imaging
Villalon J, Zhan L, Prasad G, Babikian T, Molina L, Asarnow R, Thompson P (Los Angeles, CA)

**Objective:** Diffuse axonal injury is widely reported in patients with traumatic brain injury (TBI), but white matter abnormalities are not always evident in standard clinical brain scans. As the major system for interhemispheric information transfer, the corpus callosum (CC) is particularly vulnerable to the effects of TBI, and patients commonly show signs of impaired interhemispheric communication. Here we analyzed tract-based statistics from the corpus callosum, based on diffusion tensor images collected in the post-acute and chronic phases of TBI.

**Methods:** 3D whole-brain diffusion tensor images were acquired from 36 TBI patients in the post-acute phase, and 15 age-matched controls (38 males, 13 females, mean age: 14.6±3.1). 18 chronic TBI patients and 10 age-matched controls were also scanned (21 males, 7 females, mean age: 16.8±1.9). We computed fractional anisotropy (FA) maps and performed whole-brain tractography on each subject, to map the integrity of neural pathways. CC fibers were extracted and bundled into 12 different tracts using a method developed in-house to cluster fibers based on the JHU atlas (http://cmrm.med.jhmi.edu). Group differences in FA between patient and relevant control groups were computed pointwise along the 12 extracted tracts.

**Results:** We mapped significant FA differences in the fibers of the body of the corpus callosum. These differences were more extensive in the chronic phase of the disease.

**Conclusions:** We were able to successfully extract CC fiber bundles and calculate FA differences between patients and controls at two different stages of TBI.

NI-3. A Longitudinal Analysis of Metabolic Abnormalities, and Their Structural and Neurobehavioral Correlates Following Moderate to Severe Pediatric TBI
Babikian T, Alger JR, Marion S, Kernoan C, Giza CC, Yudovin S (Los Angeles, CA), Mink R (Torrance, CA), Asarnow RF (Los Angeles, CA)

**Objective:** Diffuse axonal injury secondary to traumatic brain injury (TBI) plays a significant role in the long-term functional morbidity following TBI, particularly in brain structures rich in white matter that are particularly vulnerable to this type of injury.

**Methods:** Whole brain Magnetic Resonance Spectroscopic Imaging (MRS/MRSI) was used to characterize the metabolic status of white matter structures and their structural (DTI) and neurobehavioral (bimanual coordination, general neurocognitive functioning, and interhemispheric transfer time [IHTT] from an ERP paradigm) correlates. Children and adolescents (age range 10-18) with moderate/severe TBI were studied post-acerually (2-5 months post-injury) and chronically (9-14 months post-injury), and compared to a group of healthy controls.

**Results:** Markers of energy metabolism (creatine), cell degeneration/inflammation (choline), and neuronal functioning (NAA) were quantified in targeted white matter structures for both the post-acute and the chronic period post injury, with significant group differences observed (p < .05). Changes in these metabolic markers were correlated with recovery in neurobehavioral functioning supported by the structures evaluated and changes in the structural integrity of the targeted regions of interest using DTI FA.

**Conclusions:** Multimodal longitudinal studies of distinct time points are necessary to delineate the course of the degenerative and reparative processes following a brain injury in childhood. These studies will allow testing of specific hypotheses about the nature and course of neural mechanisms underlying functional morbidity and help guide the future development of targeted therapeutic agents.
POSTERS: Neonatal Neurology

NN-1. Cerebral Oxygen Metabolism in Critically Ill Neonates Varies with Sleep-wake Cycling
Shellhaas RA, Burns JW, Wiggins SA, Christensen MK, Barks JDE, Chervin RD (Ann Arbor, MI)

Objective: In adults, wakefulness and rapid eye movement (REM) sleep, compared to non-REM sleep, require higher overall brain metabolism, but in neonates analogous data are not available. Higher metabolic demand during some sleep-wake states could in theory increase vulnerability to hypoperfusion or hypoxia. We used cerebral oximetry (rSO2), measured by near-infrared spectroscopy (NIRS), and simultaneous polysomnography (PSG) to evaluate whether cerebral oxygen metabolism varies by sleep-wake state among critically ill newborn infants.

Methods: Newborn infants (gestational age >35 weeks) judged clinically to be at risk for seizures were enrolled prospectively. NIRS recording from bilateral parietal-occipital regions was synchronized with PSG. NIRS-derived rSO2 and fractional tissue oxygen extraction (FTOE) were analyzed during PSG-defined wakefulness, quiet, and active sleep. Kruskal-Wallis and Mann-Whitney U-tests were used to compare rSO2 and FTOE across behavioral states.

Results: For each of ten infants, sleep-wake cycling was detected by PSG, and cerebral rSO2 or FTOE varied in a highly significant manner (p<0.0001) across behavioral states. However, patterns varied between subjects: cerebral FTOE was higher during wakefulness than during active or quiet sleep in 4 subjects (p<0.003), lower in another 4 (p<0.0001), and not different in 2.

Conclusions: Cerebral oxygen metabolism varies with sleep-wake states among critically ill newborn infants. The direction and degree of these changes are variable and subject-specific in this initial sample. However, such changes could reflect or possibly affect brain injury and vulnerability.

NN-2. Intraparenchymal Hemorrhage in a Neonate with Cleidocranial Dysostosis
Gardner MA, Li BC, Slavotinek AM, Wu YW (San Francisco, CA)

Objective: We present a case of intraparenchymal hemorrhage in a neonate with cleidocranial dysostosis, a skeletal dysplasia that leads to delayed skull ossification. The hemorrhage occurred beneath an area with no protective skull, suggesting a probable traumatic mechanism of injury.

Methods: The case is described in detail, including neuroimaging, photographs of the classic dysmorphic features, and genetic testing.

Results: Following a spontaneous vaginal birth, the patient was hypotonic and encephalopathic with unusually large and boggy fontanelles. He had no palpable bone overlying his bilateral temporal lobes. He had multiple dysmorphic facial features (Figure 1). The patient's father had similar facial features and congenital absence of the right clavicle, suggestive of cleidocranial dysostosis. A head ultrasound at 2 days of age was concerning for hemorrhage. MRI at four days of age confirmed a large right temporal lobe IPH, with extensive subarachnoid hemorrhage overlying both temporal and parietal lobes (Figure 2). A skeletal survey revealed decreased ossification of the calvarium.

FIGURE: Substantially increased rSO2 (decreased metabolic demand) during quiet sleep, compared to wakefulness and active sleep, in one representative subject (p<0.0001).

FIGURE 1: Patient's dysmorphic facial features.
marked dysplasia of the scapulae bilaterally, and diminutive cervical vertebral bodies. A clinical diagnosis of cleidocranial dysostosis was confirmed by genetic testing of the RUNX2 gene, which revealed a novel sequence alteration that is predicted to be disease-causing.

Conclusions: Given that there was no palpable bone overlying the location of brain hemorrhage, and no other cause for hemorrhage was identified, we speculate that the temporal lobe hemorrhage in this case was due to birth trauma.

NN-3. Inflammation and Newborn Brain Injury in Pregnancies Complicated by Preterm Premature Rupture of Membranes
Armstrong-Wells J, Post MD, Donnelly M, Manco-Johnson MJ, Winn VD (Aurora, CO)

Objective: Preterm premature rupture of membranes (PPROM) is associated with chorioamnionitis (CA), a risk factor for poor newborn neurologic outcome. PPROM may give insight into mechanisms of newborn brain injury.

Methods: Pregnant women with PPROM (n=22) were enrolled in our pilot prospective cohort study from 01/01/2010-06/30/2011. Fetal cord blood IL-1β, IL-6, IL-8 and TNF-α was measured. Placenta underwent pathological analysis for fetal (funisitis or chorionic plate vasculitis) or maternal-side inflammation. Newborn cranial ultrasounds (CUS) and standardized neurological exams at 38-42 weeks corrected gestational age were performed. Disability was quantified as none, mild, moderate or severe.

Results: Median gestational age at rupture was 29 6/7 weeks (range 25 3/7 – 33 4/7). Over 50% of placentas had histologic CA (n=14). Funisitis and chorionic plate vasculitis was often present (41% and 36%, respectively), frequently with CA (57% and 100%, respectively). Maternal-side inflammation was uncommon (n=3; 14%). There was no significant difference in mean rupture length with CA or fetal-side inflammation. Newborn cranial ultrasounds (CUS) and standardized neurological exams at 38-42 weeks corrected gestational age were performed. Disability was quantified as none, mild, moderate or severe.

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NN-6. Diffusion Tensor Imaging (DTI) White Matter Changes in Infants with Neonatal Encephalopathy (NE) Subjected to Therapeutic Hypothermia (TH) is an Early Predictor of Neurocognitive (NC) Outcome

Purpose: The ability to predict NC outcome in infants with NE subjected to TH is most consistently associated with basal ganglia (BG) changes. DTI is more sensitive to white matter (WM) changes than conventional MRI (cMRI). In the current study, we use DTI to evaluate WM integrity (WMI) in a priori selected regions to predict NC outcome.

Methods: Eighty-eight neonates born at 24-32 weeks gestational age, treated with TH, were enrolled in this study. All underwent MRI between 8-10 days and were subsequently evaluated with Bayley Scales-III at 18–24 months. All underwent cMRI, including DTI sequence, at 18–24 months. DTI imaging was performed using a 1.5 T MRI GE Scanner using a 33 gradient direction sequence. Fractional anisotropy (FA) was measured within specific WM tract regions of interest and was correlated with cognitive scores (CS), receptive language (RL) and expressive language (EL) scores.

Results: FA of right forceps major (FM) was lower in those cases with abnormal cMRI BG injury (p=0.0001). No other region of interest was different. Only right FM (p=0.002) predicted NC outcome; a trend with left FM (p=0.07), splenium (p=0.06) was noted; but not with anterior or posterior limbs of the internal capsule bilaterally (p > 0.10). FA of right FM correlated with CS (r = 0.25, p=0.04), RL (r = 0.26, p=0.03), EL (r = 0.27, p=0.03) and left FM with CS (r = 0.26, p=0.04) EL (r = 0.24, p=0.04).

Conclusion: DTI is sensitive to subtle microstructural changes overlooked by cMRI. Variations in WMI in specific pathways (bilateral FM) can predict early CS including RL and EL in infants with NE treated with TH.

NN-7. Magnetic Resonance Imaging (MRI) Changes, Neurocognitive Outcome of Term Infants (TI) with Neonatal Encephalopathy (NE) Subjected to Selective Head Cooling (SHC)
Ross G, Kasdorf E, Engel M, Perlman J (New York, NY)

Objective: Determine factors contributing to unfavorable outcome in TI with NE treated with SHC.

Methods: Study population included term infant ≥36 weeks (n=37) treated with SHC and subsequently evaluated between 18–24 months with the Bayley Scales-III. All underwent MRI between 8-10 days.

Results: Infants were of mean BW 3960g, GA 39 wks. Cord arterial pH was 6.80±0.18, BD 20±6, initial post-natal pH 7.01±0.22. Encephalopathy was moderate (ME) (n=24), severe (SE) (n=13) (Sarnat). MRI findings included normal (n=16), Basal ganglia injury (BG) (n=9), Focal (n=4), Hippocampal only (n=3) and Intracranial Hemorrhage (ICH) (n=4). There was no relationship between NE and MRI changes. There was a significant relationship between postnatal pH and Cognitive scores (CS) (r=0.36, p=0.0006), but not cord pH. For a postnatal pH < 7.00 vs ≥7.00 the CS were lower 74±21 vs 94±11, receptive language (RL) 69±17 vs 89±17, expressive language (EL) 68±19 vs 89±15 and more BG injury i.e. 6/12 vs 2/16 respectively.

Conclusions: A postnatal pH < 7.00 is an early biomarker identifying infants with NE at risk for BG injury and adverse neurocognitive outcome. Importantly the extent of NE cannot consistently be attributed to underlying MRI changes. The potential neuroprotective effects of hypothermia are least likely followed prolonged and/or pronounced intrapartum hypoxia-ischemia (prolonged acidosis). Such infants should become candidates for early targeted adjunctive therapy in addition to hypothermia.
NN-09. Morphine Exposure is Associated with Altered Cerebellar Growth in Premature Newborns
Zwicker JG, Miller SP, Grunau RE, Chau V, Synnes A, Pockitt KJ (Vancouver, BC, CA) Tam EWY (San Francisco, CA)

Objective: Altered cerebellar development is an important cause of neurodevelopmental disability in premature infants. Morphine, a commonly used medication to manage neonatal pain, has been associated with impaired cerebellar development in animal models. Our objective was to examine the relationship between morphine exposure and cerebellar development in premature newborns.

Methods: 76 premature newborns born at 24-32 weeks gestation (median:27.3 weeks; IQR:25.9-29.7) were serially scanned with MRI near birth and at term-equivalent age. Measured cerebellar volumes and microstructural diffusion parameters [fractional anisotropy (FA) and mean diffusivity (MD)] of the middle cerebellar peduncle (MCP) were used as markers of cerebellar development. Generalized estimating equations examined the relationship between morphine exposure, cerebellar volume, and MD and FA of the MCP. Factors associated with poor cerebellar development [early illness severity, intraventricular hemorrhage (IVH), cerebellar hemorrhage, infection, intubation, hypotension, patent ductus arteriosus (PDA), dexamethasone, hydrocortisone] were adjusted for and retained if significant at p<0.1.

Results: 52/76 (68%) infants received morphine (median cumulative dose:0.23mg; IQR:0-3.93). Significant interaction between morphine dose and age at MRI was detected (p<0.001); higher morphine exposure was associated with reduced cerebellar growth. This interaction remained significant after adjusting for IVH, infection, PDA, and glucocorticoids (p<0.001). Morphine exposure was not associated with FA of the MCP (p=0.11), but was associated with higher MD (p=0.007); significance was attenuated by adjusting for confounders (p=0.06).

Conclusions: Higher morphine dose is associated with impaired growth of the cerebellum in premature infants. Follow-up of this cohort will determine if morphine exposure is associated with poorer long-term neurodevelopmental outcome.

NN-10. Cerebral Near Infrared Spectroscopy does not Predict Short-term Outcome after Therapeutic Hypothermia for Neonatal Hypoxic Ischemic Encelopathy
Shellhaas RA, Thelen BJ, Burns JW, Barks JDE (Ann Arbor, MI)

Objective: Neonatal hypoxic ischemic encephalopathy (HIE) is now treated with therapeutic hypothermia, yet adverse outcomes remain common. Multimodality neuro-monitoring, with amplitude-integrated EEG (aEEG) and rSO2 measured by near infrared spectroscopy (NIRS) might allow predictive models to identify high risk infants who could benefit from additional interventions. We evaluated which combination of parameters is the most instructive for neonates with HIE.

Methods: Neonates with HIE were monitored with bilateral cerebral and unilateral systemic NIRS, as well as dual channel aEEG, throughout cooling and rewarming. Short-term outcome scores were derived as a composite of neurological examination scores and 7-10 day brain MRI scores. Multiple regression models were developed to assess NIRS and aEEG recorded during the 6-hours prior to rewarming as predictors of short-term outcome.

Results: 21 infants, mean gestational age 38.8±1.6 weeks, median 10-minute Apgar score 4 (range 0-8), and mean initial pH 6.93±0.19, were enrolled. The most parsimonious model, which best predicted short-term outcome, included 4 parameters (adjusted R²=0.59; p=0.006): lower values of systemic rSO2 variability (p=0.004), aEEG band width variability (p=0.019), and mean upper margin of the aEEG (p=0.006), combined with higher mean aEEG band width (worse discontinuity; p=0.013) predicted worse short-term outcome. Cerebral NIRS data did not contribute to the model.

Conclusions: During day 3 of cooling, loss of physiologic variability (by systemic NIRS) and invariant, discontinuous aEEG patterns, predict poor short-term outcome among neonates with HIE. These parameters, but not cerebral NIRS, might identify subjects suitable for studies which modify the duration of cooling and/or rewarming
Methods: Cre-lox recombination system is used to yield transgenic mice with conditional ablation of β1-integrin within astrocytes (cKO). Animals undergo unilateral HI injury using the Rice-Vannucci method or sham surgery at postnatal day 8. Animals are sacrificed one week post-injury. For in vitro studies, astrocytes are harvested and cultured from these transgenic animals. Astrocytes are treated with BMP4 +/- BMP4 inhibitor Noggin. Tissue and cells are examined for astrocyte markers (e.g. GFAP) and BMP and β1-itg targets.

Results: There is no difference in astrocyte morphology between cKO and control animals in un-injured animals. However, following HI injury, there is enhanced astrocytosis in cKO animals in cortical hemispheres both ipsi-and contralateral to injury. Cell culture studies confirm enhanced astrocytosis following ablation of β1-integrin in astrocytes and interactions between BMP and β1-itg signaling pathways are present.

Conclusions: β1-itg regulates astrocytosis following HI injury in the perinatal brain in a cell-autonomous manner that involves the BMP signaling pathway.

Objective: We compared outcomes after neonatal brain injury in offspring of rat dams fed low fat (LF,14%) or high fat (HF,34%) chow from day 7 of pregnancy and postnatally. The HF diet replicates the typical dietary fat composition of US women of child-bearing age.

Methods: Paired pregnant dams received each diet. On post-natal day 7 (P7), pups underwent right carotid artery ligation, followed by 60, 75, or 90 minute 8% oxygen exposure (N=16-32/group) (brain damage increases with increasing hypoxia duration). Sensorimotor function and brain damage were compared 1 week later.

Results: P7 weights did not differ. All pups developed left forepaw sensorimotor deficits. Vibrissae-stimulated placement (normal:10/10) was worse in each HF group (60 min: 5.8/10±2.0 vs. 8.5/10±1.3; 75 min 3/10±1.6 vs. 7/10±0.9; 90 min 2.7/10±1.6 vs. 7.4/10±1.4, p<0.001, ANOVA); severity of right cerebral hemisphere damage increased with increasing duration of HI, but did not differ between diet groups. Serum omega-3 fatty acids were lower (4.9±1.3% vs. 10.2 ±1.5%, p<0.001) and blood glucose was higher (120±29 vs. 88±26 mg/dl, p<0.001) in HF pups.

Conclusion: Maternal dietary fat composition during pregnancy and lactation markedly influences functional outcome after neonatal HI brain injury. We speculate that the HF diet disrupts plasticity mechanisms; alternatively, LF diet may enhance recovery. These findings have significant implications, both for refinement of neonatal brain injury models and for understanding the impact of maternal diet on neonatal outcomes.
**POSTERS: Neuromuscular Disease**

**NM-1. Metformin Reduces Weight and BMI in Duchenne Muscular Dystrophy Patients on Long Term Glucocorticoid Therapy**

*Weatherspoon SE, Wong BL, Sucharew H, Rybalsky I, Collins J, Rose SR, Rutter MM (Cincinnati, OH)*

**Objective:** Obesity is a significant problem in Duchenne muscular dystrophy (DMD) due to glucocorticoid (GC) therapy and motor decline. Excessive weight gain can further impair mobility, increase risk for diabetes and cardiovascular disease, and affect quality of life. Metformin improves weight and insulin resistance in obesity and type 2 diabetes. The purpose of this study was to determine if metformin reduces weight and BMI in DMD patients on long term GC who have excessive weight gain and insulin resistance.

**Methods:** This was a retrospective case series of DMD boys on daily GC therapy who were treated with metformin for excessive weight gain and insulin resistance. Primary outcomes were rate of weight gain and BMI pre and post starting metformin. Weight and BMI measurements were collected 1 year prior, at initiation of metformin, and 6 and 12 months post. Generalized linear models for the vector of outcomes were rate of weight gain and BMI pre and post starting metformin. Weight and BMI measurements were fit using generalized estimating equations.

**Results:** Forty-five DMD patients (mean age 12.7 ± 3.1 y) were studied. Mean rate (±SE) of weight gain decreased from 7.5 ± 1.0 pre to −0.2 ± 1.7 kg/y (p < 0.001) post. In non-ambulatory boys (N=29), rate of weight gain decreased from 8.3 ± 1.5 pre to −0.6 ± 2.5 kg/y post (p < 0.001). In ambulatory boys (N=16), rate of weight gain decreased from 6.1 ± 0.7 pre to 1.0 ± 1.3 kg/y post (p < 0.001), and rate of BMI gain decreased from 2.8 ± 0.4 pre to 0.1 ± 0.7 kg/m²/y post (p < 0.001).

**Conclusion:** Metformin reduced weight and BMI in DMD patients on daily GC therapy with excessive weight gain.

**NM-2. A Protein-Based Assay for Population Screening and Therapeutic Drug Discovery for Friedreich Ataxia**

*Ogledree D, Krull C, Galbi O (Rochester, MN), Sellberg J (Minneapolis, MN), Deutsch E, Lynch D (Philadelphia, PA), Raymond K, Gavrilov D, Tortorelli S, Rinaldo P, Matern D (Rochester, MN), Hook D (Minneapolis, MN), Isaya G (Rochester, MN)*

**Objective:** Friedreich ataxia (FRDA) is a neurodegenerative disease characterized by progressive ataxia and cardiomyopathy with an incidence of 1:50,000. FRDA is typically diagnosed by detecting GAA-repeat expansions, or mutations, in *FXN* that reduce frataxin expression. Current diagnostic methods are unapplicable to population screening or therapeutic monitoring.

**Methods:** We describe a high-throughput immunoassay to measure frataxin in whole blood (WB) and dried blood spots (DBS) for population screening and therapeutic monitoring. In addition we adapted this assay to a MesoScale Discovery platform and completed an initial screen of a Library of Pharmacologically Active Compounds (LOPAC 1280) in FRDA patient cells.

**Results:** Recovery for frataxin is 99% from WB and DBS. Intra-assay imprecision is 4.9-13% CV and inter-assay imprecision is 9.8-15.8% CV. The LOD is 0.07 ng/mL and reportable range is 2-200 ng/mL. The reference range for adult and pediatric normals is 15-82 ng/mL (median: 33) for DBS and WB. FRDA carriers (n=30) have frataxin levels of 12-30 ng/mL (median: 18) and FRDA patients (n=82) of <26 ng/mL (median: 6). Frataxin was stable for over 6 months at 22°C, 4°C and −70°C. A screen of LOPAC 1280 did not uncover a positive hit but it has provided evidence that some commercial forms of EPO can enhance frataxin expression by 20% as observed by others in different experimental settings.

**Conclusions:** We validated a high-throughput assay for frataxin that is applicable to diagnosis and population screening and modified the method for FRDA drug discovery. Ongoing work includes expanding the drug screen beyond LOPAC 1280.

**NM-3. Fractures, Functional Status, and Health-related Quality of Life in Duchenne Muscular Dystrophy (DMD)**

*Riss VJ, Finanger EL, Russman BS (Portland, OR)*

**Objective:** The literature on long bone fractures in boys with DMD suggests that those with greater function and on steroids are at higher risk for fracture. We studied the functional status and health-related quality of life (QOL) of those DMD boys who experienced fracture with DMD boys of similar function who had not experienced fracture.

**Methods:** A cross-sectional study was conducted with chart review and parent interviews on 25 subjects with DMD (7-22 years, mean 12.4 years) regarding fracture occurrence, disease progression, use of steroid medication, and a validated pediatric QOL survey. (Still in progress)

**Results:** Using a modified Brooks Scale (MBS), 3 of 25 respondents were MBS 1 (could climb stairs), 8 of 25 were MBS 2 (could walk but could not climb stairs), 14 of 25 were MBS 3 (non-ambulatory). 9 of 25 subjects had at least 1 fracture. 7 of 9 fractures occurred in children who were MBS 1 or 2 at time of fracture, 4 of 9 occurred in children taking steroids.

Mean QOL score in subjects with MBS 1 or 2 was 56.2 in subjects who had not experienced a fracture versus 74.5 in those who had. Mean QOL in subjects with MBS 3 was 75.0 with no fractures vs. 85.5 with fractures (lower scores indicate better QOL).

**Conclusions:** In our population, more fractures occurred in patients with DMD with MBS 1-2. Additionally, QOL was better in patients with comparable MBS scores who did not have a history of fracture.
POSTERS: Stroke

S-1. Long-term Outcomes of Pediatric Ischemic Stroke in Adulthood
Elbers J, deVeber G, Pontigon AM, Moharir M (Toronto, ON, CA)

Objective: Childhood stroke is considered to cause significant long-term disability. However, outcomes are understudied, with available reports limited to relatively short follow-up times and pediatric ages. Our objective was to assess the long-term impact of childhood stroke on function and independence in young adults.

Methods: Children (birth-18 years) with arterial ischemic stroke (AIS) and cerebral sinus venous thrombosis (CSVT) diagnosed from 1994-2010 in the Toronto Children’s Stroke Registry were followed prospectively to age 18. We conducted a cross-sectional outcome study of these patients after age 18 during 2010. Outcomes included neurologic impairment, activities of daily living, depression and a standardized independence questionnaire.

Results: We studied 26 patients: 21 AIS, 5 CSVT. Mean age at stroke was 12.1 years. Mean follow-up interval was 11.4 years. By modified Rankin Scale outcomes were 37% normal, 42% mild, 8% moderate, and 15% severe deficits. Mortality (77-84%) was independent of driving, relationships and employment. Stroke recurrent in 4/26 (15%), prior to age 18. Depression was present in 30%. Risk factors for poor outcome included: AIS stroke-type, arteriopathy, and 1-year post-stroke Pediatric Stroke Outcome Measure (PSOM) score (p<0.05 univariate). One-year PSOM remained independently predictive (p<0.0001 multivariate).

Conclusions: In this adult cohort surviving childhood stroke, 80% had full recovery or mild deficits, and showed high levels of independence in driving, relationships, education and employment. Most childhood stroke survivors are independent by young adulthood. Functional status at one-year post-stroke strongly predicts long-term outcome. Depression in one-quarter of young adults surviving childhood stroke represents an important direction for research.

S-2. The Presence of Epilepsy Adversely Affects Behavioral Outcomes in Perinatal Stroke
Harbert M (San Diego, CA), Nass R (New York, NY), Trauner D (San Diego, CA)

Objective: The goal of the study was to study behavioral outcome in children with perinatal stroke.

Methods: In a prospective cohort study of subjects with perinatal stroke, parents of 79 subjects completed the Achenbach Child Behavior Checklist, which yields nine T-scores. Higher scores reflect greater abnormality of behavior. Outcomes were T-scores for total score, attention problems, social problems and thought problems. Outcomes were correlated with multiple variables, including the presence of epilepsy, lesion location, lesion severity, lobar involvement and the presence of hemiparesis.

Results: The presence of epilepsy was associated with increased thought problem scores (p=0.05) and increased attention problem scores (p=0.004). Temporal lobe involvement was associated with increased social problem scores (p=0.048). Lesion severity, lesion side and the presence of hemiparesis were not associated with increased T-scores. Involvement of frontal, parietal or occipital lobes were not associated with increased T-scores.

Conclusions: In children with perinatal stroke, epilepsy appears to produce an additional cognitive and behavioral burden on the developing brain. Temporal lobe lesions may have more detrimental effects on behavior than lesions in other brain locations. This is consistent with previous studies in which temporal lobe lesions have been associated with abnormal social behavior in both human and animal models, though this is the first study to demonstrate this association in perinatal stroke.

S-3. Middle and Anterior Cerebral Arteries Vasculitis Induced by Maternal Exposure to E. Coli Components: a New Preclinical Model of Neonatal Stroke Pathophysiology
Brochu ME, Garant JM, Guiraut C, Tasen K, Girard S, Sebire G (Sherbrooke, QC, CA)

Objectives: Perinatal arterial strokes result from defects of arterial blood flow mainly located at internal carotid bifurcations. The pathophysiological mechanisms leading to arterial occlusions remain relatively obscure. Gestational inflammation is an established risk factor of perinatal stroke. Our hypothesis is that pathogen-induced maternalfetal inflammation triggers a vasculitis specifically affecting the arterial walls of the carotid bifurcations. Our aims are to compare in a preclinical rat model the induction of inflammatory response and susceptibility to thrombosis between carotid versus posterior cerebral arterial walls from fetuses exposed or unexposed to gestational inflammation induced by lipopolysaccharide (LPS) from E. Coli.

Methods: Gestational Lewis rat were injected i.p. with LPS (200µg/kg/12h) or saline from gestational day (G) 21 to birth (G23). Cytokines and infiltrating immune cells were detected in arterial walls at post-natal day 1 (P1) by IHC.

Results: IL-1β and TNFα were significantly up-regulated within the arterial wall of the anterior cerebral artery system from pups exposed to prenatal LPS compared to arterial walls of posterior cerebral arteries, and to control pups. The density of Iba-1+ macrophages was increased within P1 pups anterior and middle cerebral arteries’ wall by maternal LPS exposure. This inflammatory response might activate locally the coagulation cascades and lead to focal occlusions and strokes.

Conclusion: We detected a highest inflammatory response to maternal LPS exposure within the arterial wall of the carotid bifurcation compared to vessels from the posterior circulation and to extracerebral arteries. This might reflect variations of macrophage distribution within arterial walls.

S-4. Is D-dimer Useful in the Management of Cerebral Sinovenous Thrombosis in Children?
Lagman-Barolome AM, Brandao L, Moharir M (Toronto, ON, CA)

Background: Clinical and radiological diagnosis of Pediatric Cerebral sinovenous thrombosis (CSVT) is challenging. Biomarkers to quantify CSVT severity and/or prognosis are lacking. Utility of D-dimer (DD) assay has been studied in adult CSVT, but not in children.

Objectives:
1) To determine the frequency of elevated D-dimer levels in pediatric CSVT
2) To determine correlation of D-dimer levels with clot burden, risk factors and clot recanalization.

Methodology: Subjects were identified from the Stroke Registry at the Hospital for Sick Children, Toronto from Sept/1999-Dec/2009. Children >1 month-18 years with CSVT and D-dimer assay done within 7-days before and
30-days after CSVT diagnosis were studied. Investigators reviewed neuroimaging to determine clot burden (multiple sinus involvement, occlusive clots, hemorrhage). Risk factors and D-dimer levels were extracted from health records. D-dimer levels were presented as means (±SD). Distributions of D-dimer test results and patient characteristics were analyzed by Fisher’s exact or Chi-Square analysis.

**Results:** Three-hundred and five subjects with CSVT were identified. Ninety-three (30%) were included for analysis (55% males, range: 31d-18yrs; median: 6.5 yrs). Main risk factors were infection (41%), prothrombotic disorder (18%) and trauma (17%). Eighty-four percent had high clot burden. 59% had D-dimer levels 4-days before and 27-days after diagnosis (median: 2 days ± 6.19). 71% had elevated D-dimer levels. High clot burden showed a trend toward abnormal D-dimer levels (p=0.06).

**Conclusion:** Majority of children with CSVT have elevated D-dimer levels at diagnosis, which appear to be associated with high clot burden. D-dimer could potentially be useful in determining childhood CSVT severity.
POSTERS: Translational Research

T-1. Dosage Considerations for Transcranial Direct Current Stimulation in Children: a Computational Modeling Study


Objective: Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method which uses weak electric currents applied on the scalp to modulate activity of underlying brain tissue. TDCS is a tool for neurophysiologic investigation, and has therapeutic potential in epilepsy, post-stroke rehabilitation, and other neurologic disorders. Though the safety and tolerability of tDCS in adults is well-established, safety information on tDCS in children is lacking. This study aimed to present computational models of tDCS current flow in pediatric subjects.

Methods: High resolution MRI images of two healthy children, ages 8 and 12 years, and one healthy adult, were semi-manually segmented into skin, bone, air, eyes, CSF, gray and white matter. A volumetric mesh was generated and overlaid with digitally simulated stimulation electrodes. The electrical properties of the tissues were assigned average isotropic conductivity values. Using finite-element modeling, cortical electrical field maps were generated for 3 stimulation intensities and 5 electrode configurations.

Results: The peak electrical fields for a given stimulus intensity were 2 to 4 times higher in the pediatric brains compared to the adult brain, depending on the electrode montage used. For example, 2 mA stimulation over motor cortex (anode) and contralateral forehead (cathode) produced peak electric fields of 1.01 V/m for the 8 year old, 1.04 V/m for the 12 year old and 0.35 V/m for the adult.

Conclusions: Acceptable tDCS stimulation parameters may be different in children compared to adults. Further studies are needed to help guide decisions about applied current intensity.
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