Child Neurology Society

Presented at
The Duke Energy Convention Center
Cincinnati, OH
October 12 – October 15, 2022
CME Joint Sponsorship Provided by Minnesota Medical Association and the Child Neurology Society

Fifty-First National Meeting of the Child Neurology Society

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Matthew Elrick	Baltimore, MD	Christopher Smyser	St. Louis, MO
Grace Gombolay	Atlanta, GA	Liu Lin Thio	St. Louis, MO
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Ajay Gupta	Cleveland OH	Jennifer Vermilion	Rochester, NY
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Wilfreda Lindsey	Houston, TX		

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Kathy Pavel, Office Administrator
Emily McConnell, Professional Development Manager

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Cincinnati, OH
October 12-15, 2022

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The Minnesota Medical Association designates this live activity for a maximum of 30.75 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Past Officers

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Gerald Fenichel 1973-74
Manuel Gomez 1974-75
James Schwartz 1975-76
Richard Allen 1976-77
Bruce Berg 1977-78
N. Paul Rosman 1978-79
Arthur Prensky 1979-80
Paul Dyken 1980-81
Mary Anne Guggenheim 1981-82
Raymond Chun 1982-83
Robert Eiben 1983-85
David Stumpf 1985-87
Marvin Fishman 1987-89
Darryl C. De Vivo 1989-91
Peter H. Berman 1991-93
Joseph J. Volpe 1993-95
Michael E. Cohen 1995-97
Alan K. Percy 1997-99
Michael J. Painter 1999-2001
Stephen Ashwal 2001-2003
James Bale 2003-2005
Ann Tilton 2005-2007
John Bodensteiner 2007-2009
Donna Ferriero 2009-2011
E. Steve Roach 2011-2013
Nina F. Schor 2013-2015
Kenneth Mack 2015-2017
Jonathan Mink 2017-2019
Phillip Pearl 2019-2021
Bruce Cohen 2021-

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Patricia Crumrine 1997-2002
Ann Tilton 2003-2004
Nina Schor 2004-2010
Harvey Singer 2010-2015
Bruce Cohen 2015-2020
Lori Jordan 2020-

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 Copple (Ferry) 1976-78
Joseph French 1977-79
Francis Wright 1977-79
Mary Anne Guggenheim 1978-80
Gerald Golden 1978-80
Gerald Erenberg 1979-81
John Freeman 1979-81
Marvin Weil 1980-82
Marvin Fishman 1980-82
Peter Huttenlocher 1981-83
Michael Bresnan 1981-83
David Stumpf 1982-84
Gwendolyn Hogan 1982-84
Joseph Volpe 1983-85
Barry Russman 1983-85
Russell Snyder 1984-86
Ian Butler 1984-86
W. Edwin Dodson 1985-87
Michael Painter 1985-87
Robert Zeller 1986-88
Doris Trauner 1986-88
Darryl De Vivo 1987-88
Gary Goldstein 1987-89
Robert Vannucci 1988-89
Stephen Ashwal 1988-90
Jack Pellock 1988-90
Joseph Pasternak 1989-91
Patricia Duffner 1989-91
O. Carter Snead 1990-92
Edwin Meyer 1990-92
Israel Abroms 1991-93
William Logan 1991-93
Mary Johnson 1992-94
Alan Percy 1992-94
Phyllis Sher 1993-95
Gregory Holmes 1993-95
W. Donald Shields 1994-96
John Bodensteiner 1994-96
Patricia Crumrine 1995-97
James Bale 1995-97
Alan Hill 1996-98
Ann Tilton 1996-98
Edward Kovnar 1997-99
Richard Nordgren 1997-99
Michael Goldstein 1998-2000
E. Steve Roach 1998-2000
Faye Silverstein 1999-2001
Michael Johnston 1999-2001
Carmela Tardo 2000-02
Pauline Filipek 2000-02
Michael Noetzel 2001-03
Carl Crosley 2001-03
Julie Parke 2002-04
Roy Elterman 2002-04
Marc Patterson 2003-05
Douglas Nordli 2003-05
Donna Ferriero 2004-06
Leon Dure 2004-06
Kenneth Mack 2005-07
Laura Ment 2005-07
Leslie Morrison 2006-08
Anne Anderson 2006-08
Steven Leber 2007-09
Jonathan Mink 2007-09
Robert Rust 2008-10
Wendy Mitchell 2008-10
Warren Lo 2009-11
Sakkubai Naidu 2009-11
Gary Clark 2010-12
Sidney Gospe 2010-12
Barry Kosofsky 2011-13
Suresh Kotagal 2011-13
Vinodh Narayanan 2012-14
Jayne Ness 2012-14
Bruce Cohen 2013-15
Roger Packer 2013-15
Kevin Ess 2014-16
Kara Lewis 2014-16
Phillip Pearl 2015-17
Renee Shellhaas 2015-17
Peter B. Kang 2016-18
Mary Zupanc 2016-18
Donald Gilbert 2017-2019
Michael Shevell 2017-2019
Lori Jordan 2018-2020
Mark Wainwright 2018-2020
Nigel Bamford 2019-2021
Nancy Bass 2019-2021
Audrey Brumback 2020-2022
Sonia Partap 2020-2022
Sucheta Joshi 2021-
Janet Soul 2021-

Annual Meetings

2025
October 8-11
Charlotte, NC

2024
November 11-14
San Diego, California

2023
October 4-7
Vancouver, BC Canada

2022
October 12-15
Cincinnati, Ohio

2021
Boston, Massachusetts

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

2019
Charlotte, North Carolina

2018
Chicago, Illinois

2017
Kansas City, Missouri

2016
Vancouver, British Columbia, Canada

2015
Washington, DC

2014
Columbus, Ohio

2013
Austin, Texas

2012
Huntington Beach, California

2011
Savannah, Georgia

2010
Providence, Rhode Island

2009
Louisville, Kentucky

2008
Santa Clara, California

2007
Quebec City, PQ, Canada

2006
Pittsburgh, Pennsylvania

2005
Los Angeles, California

2004
Ottawa, Ontario, Canada

2003
Miami Beach, Florida

2002
Washington, DC

2001
Victoria, British Columbia, Canada

2000
St. Louis, Missouri

1999
Nashville, Tennessee

1998
Montreal, Quebec, Canada

1997
Phoenix, Arizona

1996
Minneapolis, Minnesota

1995
Baltimore, Maryland

1994
San Francisco, California

1993
Orlando, Florida

1992
New Orleans, Louisiana

1991
Portland, Oregon

1990
Atlanta, Georgia

1989
San Antonio, Texas

1988
Halifax, Nova Scotia, Canada

1987
San Diego, California

1986
Boston, Massachusetts

1985
Memphis, Tennessee

1984
Phoenix, Arizona

1983
Williamsburg, Virginia

1982
Salt Lake City, Utah

1981
Minneapolis, Minnesota

1980
Savannah, Georgia

1979
Hanover, New Hampshire

1978
Keystone, Colorado

1977
Charlottesville, Virginia

1976
Monterey, California

1975
Hamilton, Ontario, Canada

1974
Madison, Wisconsin

1973
Nashville, Tennessee

1972
Ann Arbor, Michigan

CNS Hower Award Recipients

2022
Leon G. Epstein
Chicago, IL

2021
Jonathan W. Mink
Rochester, NY

2020
Kenneth J. Mack
Rochester, MN

2019
James F. Bale, Jr.
Salt Lake City

2018
Bernard L. Maria
Morristown, NJ

2017
Nina F. Schor
Rochester, NY

2016
Harvey Singer
Baltimore

2015
E. Steve Roach
Columbus

2014
Michael Shevell
Montreal

2013
John Bodensteiner
Rochester, MN

2012
Ann Tilton
New Orleans

2011
Deborah Hirtz
Bethesda

2010
Sakkubai Naidu
Baltimore

2009
Peter Camfield
Halifax

2008
Stephen Ashwal
Loma Linda

2007
Robert S. Rust
Charlottesville

2006
Michael Painter
Pittsburgh

2005
Alan Percy
Birmingham

2004
John Freeman
Baltimore

2003
Michael E. Cohen
Buffalo

2002
Peter H. Berman
Philadelphia

2001
Charles Barlow
Boston

2000
Arthur Prensky
St. Louis

1999
Marvin Fishman
Houston

1998
N. Paul Rosman
Boston

1997
Gerald Fenichel
Nashville

1996
William Bell
Iowa City

1995
Salvatore DiMauro
New York

1994
Hugo Moser
Baltimore

1993
Bengt D. Hagberg
Goteborg

1992
Darryl C. De Vivo
New York

1991
Karin B. Nelson
Bethesda

1990
Joseph J. Volpw
Boston

1989
Manuel Gomez
Rochester

1988
Bruce Berg
San Francisco

1987
Isabelle Rapin
Bronx

1986
Jean Aicardi
Paris

1985
RaymondD.Adams
Boston

1984
Peter Huttenlocher
Chicago

1983
Betty Q. Banker
Cleveland

1982
Patrick F. Bray
Salt Lake City

1981
Kenneth F.Swaiman
Minneapolis

1980
John H. Menkes
Beverly Hills

1979
Paul I. Yakovlev
Boston

1978
Philip R. Dodge
St. Louis

1977
David B. Clark
Lexington

1976
Sidney Carter
New York

1975
Randolph K. Byers
Boston

1974
Douglas Buchanan
Chicago

Bernard Sachs Lecturers Recipients

2022
Steven Paul Miller
Vancouver, BC, Canada

2021
Jerry Mendell
Columbus, OH

2020
Joseph Gleeson
San Diego

2019
Scott Pomeroy
Boston

2018
William B. Dobyns
Seattle

2017
Solomon Moshé
Bronx, NY

2016
Harvey Sarnat
Calgary

2015
Harry T. Chugani
Detroit

2014
Gabrielle deVeber
Toronto

2013
Tallie Z. Baram
Irvine

2012
Roger Packer
Washington, DC

2011
Laura Ment
New Haven

2010
Thomas Jessell
New York

2009
Gregory Holmes
Lebanon, NH

2008
Michael Johnston
Baltimore

2007
Frederick Andermann
Montreal

2006
Donna Ferriero
San Francisco

2005
O. Carter Snead III
Toronto

2004
Karin Nelson
Bethesda

2003
Darryl C. De Vivo
New York

2002
Francis Collins
Bethesda

2001
Huda Zoghbi
Houston

2000
Joseph Volpe
Boston

1999
Carla Shatz
Berkeley

1998
Andrew Engel
Rochester

1997
Martha Bridge Denckla
Baltimore

1996
Verne S. Caviness
Boston

1995
Gerald D. Fischbach
Boston

1994
David Prince
Stanford

1993
C. Thomas Caskey
Houston

1992
Louis M. Kunkel
Boston

1991
Marcus E. Raichle
St. Louis

1990
Roscoe O. Brady
Bethesda

1989
Salvatore DiMauro
New York

1988
Victor Dubowitz
London

1987
Hugo Moser
Baltimore

1986
Louis Sokoloff
Bethesda

1985
Patricia Goldman-Rakic
New Haven

1984
William L. Nyhan
La Jolla

1983
Roger N. Rosenberg
Dallas

1982
John O'Brien
La Jolla

1981
Pasko Rakic
New Haven

1980
Dominick Purpura
New York

1979
Fred Plum
New York

1978
W. Maxwell Cowan
St. Louis

1977
George Cahill
Boston

Philip R. Dodge Young Investigator Award Recipients

2022
Bhooma Aravamuthan
St. Louis, MO

2021
Monica Lemmon
Durham, NC

2020
Hsiao-Tuan Chao
Houston

2019
Louis Dang
Ann Arbor

2018
Christopher Elitt
Boston

2017
Audrey C. Brumback
Austin

2016
Diana Bharucha-Goebel
Bethesda

2015
Jimmy Holder, Jr.
Houston

2014
Christopher Smyser
St. Louis

2013
Peter Tsai
Boston

2012
Yoon Jae-Cho
Stanford

2011
James Dowling
Ann Arbor

2010
Stephen Maricich
Cleveland

2009
Jeffrey Neul
Houston

2008
Laura Jansen
Seattle

2007
Mirjana Maletic-Savatic
Stony Brook

2006
Elliott Sherr
San Francisco

2005
Mustafa Sahin
Boston

2004
Terri Inder
Melbourne

2003
Bradley Schlaggar
St. Louis

2002
Nigel Bamford
New York

2001
Daniel J. Bonthius
Iowa City

2000
Stephen Back
Portland

1999
Amy Brooks-Kayal
Philadelphia

1998
Joseph Gleeson
Boston

1997
William A. Weiss
San Francisco

1996
Michael Rivkin
Boston

1995
Adre J. du Plessis
Boston

1994
Mia MacCollin
Boston

1993
Jeffrey J. Neil
St. Louis

1992
Kelvin A. Yamada
St. Louis

1991
Kenneth J. Mack
Madison

1990
Evan Y. Snyder
Boston

Harris Gelbard
Rochester, NY

1989
Scott L. Pomeroy
St. Louis

1988
Huda Zoghbi
Houston

1987
Vinodh Narayanan
Pittsburgh

1986
Faye S. Silverstein
Ann Arbor

1985
Richard J. Konkol
Milwaukee

1983
Michael Pranzatelli
Washington

Roger and Mary Brumback Lifetime Achievement Award Recipients

2022
Jeff Buchhalter
Calgary, AB, Canada

Roger Larson
St. Paul, MN

Michael Noetzel
St. Louis, MO

2021
Robert Baumann
Lexington, KY

Sidney Gospe, Jr
Seattle, WA

2019
Carol Camfield
Halifax, Nova Scotia

W. Edwin Dodson
St. Louis, MO

2018
Gerald Erenberg
Cleveland, OH

William Logan
Toronto, Ontario

Alfred Spiro
Bronx, NY

2017
Abe Chutorian
New York, NY

W. Donald Shields
Los Angeles, CA

2016
Kalpathy Krishnamoorthy
Boston, MA

Doris Trauner
La Jolla, CA

2015
Pat Crumrine
Pittsburgh, PA

Suresh Kotagal
Rochester, MN

2014
G. Robert De Long
Durham, NC

2013
Arthur Rose
Brooklyn, NY

A. David Rothner
Cleveland, OH

2012
Bhuwan Garg
Indianapolis, IN

M. Richard Koenigsberger
Demarest, NJ

2011
Warren Grover
Philadelphia, PA

2010
Russell Snyder
Albuquerque, NM

2009
Mary Anne Guggenheim
Helena, MT

G Dean Timmons
Akron, OH

2008
Cesare Lombroso
Boston, MA

Niels Lowe
Tenafly, NJ

2007
William Kennedy
Watertown, ME

Gordon Watters
Montreal, Quebec

2006
Raymond Chun
Madison, WI

Barry Russman
Portland, OR

2005
Robert Eiben
Cleveland, OH

Arnold Gold
New York, NY

2004
Jean Holowach Thurston
St. Louis, MO

Arnold P. Gold Foundation Humanism in Medicine Award Recipients

2022
Jorge Vidaurre
Columbus, OH

2021
Mary Zupanc
Irvine, CA

2019
H. Terry Hutchison
Fresno, CA

2018
Audrey Foster-Barber
San Francisco, CA

2017
David Coulter
Boston, MA

2016
Oscar Papazian
Miami, FL

2015
Robert Zeller
Houston, TX

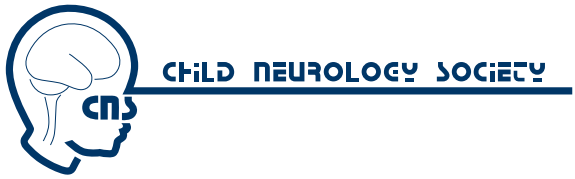
2014
Kenton Holden
Mt. Pleasant, SC

2013
Douglas Postels
East Lansing, MI

2012
Marvin Fishman
Houston, TX

2011
Shaul Harel
Tel Aviv, Israel

2010
Ruth Ness
New York, NY



Martha Bridge Denckla Award Recipients

2022
Michael Shevell
Montreal, QC, Canada

2021
Elizabeth Berry-Kravis
Chicago, IL

Bernard D'Souza International Fellowship Award

2022
Robert K. Sebunya
Kampala, Uganda

Paulina C. Tejada
Santiago, Chile

2019
Nicolás Garófalo Gómez
Havana, Cuba

Jitendra Kumar Sahu
Chandigarh, India

2018
Suvasini Sharma
New Delhi, India

2017
Charles Hammond
Kumasi, Ghana

Aye Mya Min Aye
Yangon, Myanmar

2016
Arushi Gahlot Saini
Chandigarh, Indian

Tipu Sultan
Lahore, Pakistan

2015
Edward Kija
Tanzania

2014
Jithangi Wanigasinghe
Dehiwela, Sri Lanka

2013
Samson Gwer
Nairobi, Kenya

2012
Inga Talvik
Tartu, Estonia

2011
Kyaw Linn
Maynmar

2010
Parayil S. Bindu
Bangalor, India

2009
Uduak Mayen Offiong
Abuja, Nigeria

2008
Ikeolu Lagunju
Ibadan, Nigeria

2007
David E. Kombo
Dars Es Salaam, Tanzania

2006
Gia Melikoshvili
Tbilisi, Georgia

2005
Lusine Kirakosyan
Yerevan, Armenia

2004
Natalia A. Yermolenko
Voronezh, Russia

2003
David Chkhartishvili
Tbilisi, Georgia

2002
Vedrana Milic Rasic
Belgrade, Serbia

2001
Dimitrios Zafeiriou
Thessalonikki, Greece

2000
Brahim Tabarki-Melaiki
Brussels, Belgium

1999
Magda L. Nunes
Porto Alegre, Brazil

1998
Ana Keleme
Novi Sad, Yugoslavia

1997
Aleksandra Djukic
Belgrade, Yugoslavia

1996
Shan Wei Song
Beijing, China

1995
Nina Barisic
Zagreb, Croatia

1994
Lai Choo Ong
Kuala Lampur, Malaysia

1993
Anu Soot
Tartu, Estonia

1992
Qin Jiong
Beijing, China

1991
Sergi A. Antoniuk
Curitiba, Brazil

1990
Najoua Miladi
Tunis, Tunisia

1989
Meral Ozmen
Istanbul, Turkey

Tauen Chang Junior Member Award Recipients

2022
Mekka Garcia
NYU Langone Health

Laura Gilbert
Washington University in St. Louis

Riley Kessler
Children's Hospital of Philadelphia

Ezgi Saylam
Nationwide Children's Hospital

2021
Rhandi Christensen
University of Toronto

Darius Ebrahimi-Fakhari
Boston Children's Hospital

Laura Gilbert
Washington University in St. Louis

Hannah Wellman
University of Colorado

2020
Natalie K. Katz
Children's Mercy Hospital

Travis Larsh
Children's Hospital Cleveland Clinic

Kshama Ojha
University of Louisville

Sonal Sharma
Children's Mercy Hospital & Clinics

2019
Lauren Chamberlain
Duke University Medical Center

Darius Ebrahimi-Fakhari
Boston Children's Hospital

Aram Kim
Children's Hospital of Pittsburgh

Youssef A. Kousa
Children's Hospital National Medical Center

2018
Adrienne Bruce
Cincinnati Children's Hospital Medical Center

Sara Fridinger
Children's Hospital of Philadelphia

Melissa Hutchinson
Children's Hospital of Philadelphia

Jeffrey A. Strelzik
Children's National Health System

Elizabeth Troy
University of Colorado

2017
Ka Ye Clara Chan
Loma Linda University Children's Hospital

Hsaio-Tuan Chao
Baylor College of Medicine

Rachel Goldstein Hirschberg
Boston Children's Hospital

Carla Watson
Children's Hospital of Michigan

2016
Sonika Agarwal
Baylor College of Medicine

Darius Ebrahimi-Fakhari
Boston Children's Hospital

Juliane Gust
Seattle Children's Hospital

Manisha Malik
Emory University

2015
Robert Blake
Cincinnati Children's Hospital Medical Center

Dana Marafie
Texas Children's Hospital

Davut Pehlivan
Texas Children's Hospital

Siddharth Srivastava
Kennedy Krieger Institute

2014
Jonathan Kurz
Children's National Medical Center

Neggy Rismanchi
University of California San Diego

Siddharth Srivastava
Kennedy Krieger Institute

Kavita Thakkar
Pittsburgh Children's Hospital

Tauen Chang Junior Member Award Recipients | continued

2013
Anuja Jindal
Pittsburgh Children's Hospital

Archana Patel
Boston Children's Hospital

Pilar Pichon
Loma Linda University

Mark Schomer
Boston Children's Hospital

Mitchell Williams
Children's Hospital of Michigan

2012
Partha Ghosh
Clevland Clinic Foundation

J.J. Gold
University of California San Diego

Gayatri Mainali
Cleveland Clinic Foundation

Christopher B. Oakley
Johns Hopkins Medical Institute

2011
Partha Ghosh
Cleveland Clinic Foundation

Andrea Pardo
Cincinnati Children's Hospital Medical Center

Thitiwan Simasathien
University of Alabama-Birmingham

Syndi Seinfeld
Virginia Commonwealth University

2010
Dawn Gano
University of British Columbia

Radhika Dhamija
Mayo Clinic

Patricia Musolino
Massachusetts General Hospital

Thitiwan Simasathien
University of Alabama-Birmingham

2009
Bennett Gertz
Children's National Medical Center

Ryan Lee
Kennedy Krieger Institute

John Mytinger
University of Virginia

Brandon Zielinski
University of California San Francisco

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

2007
Keith Abe
Stanford University Medical Center

Tarannum Lateef
Children's National Medical Center

Joseph Scafidi
Children's National Medical Center

Marie-Pierre Thibeault-Eybalin
McGill University

2006
Nicholas Abend
Children's Hospital of Philadelphia

Lori Billinghurst
University of Alberta

Holly Dudley-Harrell
Children's Hospital of Cincinnati

Jena Khera
The Cleveland Clinic

2005
William Benko
Children's National Medical Center

Alexander Bassuk
Children's Memorial Hospital Chicago

Josh Bonkowsky
University of Utah Medical Center

Robert Safier
Children's Hospital of Pittsburgh

Renée Shellhaas
Children's Hospital of Philadelphia

2004
Ignacio Valencia
St. Christopher's Hospital

Brannon Morris
Mayo Clinic

Haim Bassan
Boston Children's Hospital

William Benko
Children's National Medical Center

2003
Taeun Chang
Children's National Medical Center

Yoshimi Sogawa
Schneider Children's Hospital

Ignacio Valencia
St. Christopher's Hospital

Adeline Vanderver
Children's National Medical Center

2002
Taeun Chang
Children's National Medical Center

Mirjana Maletic-Savatic
SUNY Stony Brook

Lauren Plawner
Stanford University Medical Center

Michael Seyffert
University of Washington Medical Center

Tauen Chang Junior Member Award Recipients | continued

2001
Maria Acosta
Children's National Medical Center

Randa Jarrar
Mayo Clinic

Steven Miller
UC San Francisco

Jayne Ness
Children's Hospital of Alabama

2000
Sucheta Joshi
Stanford University Medical Center

Lauren Plawner
Stanford University Medical Center

Monique Ryan
Boston Children's Hospital

Mustafa Sahin
Boston Children's Hospital

1999
June Caruso
Rhode Island Children's Hospital

Debra Holder
Texas Children's Hospital

Carolyn Menache
Boston Children's Hospital

1998
June Caruso
Rhode Island Children's Hospital

Andrea Gropman
Children's National Medical Center

Alyssa Reddy
Children's Hospital of Alabama

Janet Soul
Boston Children's Hospital

1997
Gyula Acsadi
Children's Hospital of Detroit

Ann Bergin
Johns Hopkins University

Edwin Demeritte
Children's Hospital of Detroit

Sanford Shu
Loma Linda University

1996
Gyula Acsadi
Children's Hospital of Detroit

Joseph Gleeson
Boston Children's Hospital

Andrea Gropman
Children's National Medical Center

Mary Sutton
Boston Children's Hospital

CHILD NEUROLOGY SOCIETY

Outstanding Junior Member Post Graduate Award Recipients

2022
Travis Larsh
Cincinnati Children's Hospital Medical Center

Avantika Singh
Boston Children's Hospital

2021
Eric M. Chin, MD
Kennedy Krieger Institute,

Thiviya Selvanathan
The Hospital for Sick Children

2019
Giulia Beneditti
Seattle Children's Hospital

2018
Bhooma Aravamuthan
Boston Children's Hospital

Elana Pinchefsky
The Hospital for Sick Children

M. Richard Koenigsberger Scholarship Recipients

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

2022
Stephen Chrzanowski
Boston Children's Hospital

2021
Jennifer Keene, MD, MS, MBA
Washington University in St Louis

2020
Katelyn Bricker
North Carolina Memorial Hospital

2019
David Ritter
Cincinnati Children's Hospital Medical Center

2018
Tayyba Anwar
Children's National Medical Center

2017
Davut Pehlivan
Baylor College of Medicine

2016
Ann McCarthy
Children's Hospital Philadelphia

2015
Vincent Carson
Pittsburg Children's Hospital

2014
Joshua Bear
University of California San Francisco

2013
Louis Dang
Children's Hospital of Michigan

AAP Section on Neurology Trainee Travel Award Repients

2022
Alexis Karlin
Children's Hospital of Philadelphia

2019
E. Justine Record
Children's Hospital National Medical Center

2018
Kerri Neville
Michigan Medicine

2017
Audie Espinoza
University of Utah

2016
Sharoon Qaiser
University of Kentucky

2015
Jennifer Jaskiewicz
Walter Reed National Military Medical Center

CNS/PECN Training Director Award Recipient

2022
TBD

2021
Miya Asato
Pittsburgh, PA

2019
Karen Ballaban-Gil
Bronx, NY

2018
Bruce K. Shapiro
Baltimore, MD

2017
Sidney M. Gospe Jr.
Seattle, WA

2016
David K. Urion
Boston, MA

2015
Robert Rust
Charlottesville, VA

2014
Steve Leber
Ann Arbor, MI

2013
Harvey Singer
Baltimore, MD

Bhuwan Garg High School Student Neuroscience Prize Recipients

2022
Aliya Fisher
New York, NY

2021
Meagan Ryan
Ossining, NY

2020
Pratik Vangal
Portland, OR

2019
Shan Lateef
Manassas, VA

2018
Amy Shteyman
Great Neck, NY

2017
Lauren Singer
Scarsdale, NY

2016
Ryan Infante
Armonk, NY

2015
Amrita Mohanty
Woodbury, MN

2014
Laura Mariah Herman
Ft. Lauderdale, FL

2013
Anna Thomas
San Jose, CA

2012
Vincent Shieh
Bronx, NY

2011
Spencer Chan
Forest Hills, NY

2010
Pragya Kakani
Jericho, NY

2009
Inar Zhang
Mercer Island, WA

2008
Lauren Lisann
Dix Hills, NY

2007
David Shiovitz
Briarcliff Manor, NY

2006
Shoshana Tell
Coral Springs, FL

2005
Max Christie
Briarcliff Manor, NY

2004
Debashish Zircar
Bronx, NY

2003
Henry Marr
Alhambra, CA

2002
Corinna Zygourakis
Houston, TX

2001
Melanie Napier
Laurelton, NY

2000
Rishikesh Dalal
Lenexa, KS

1999
Nihar Gupta
New York, NY

1998
Karla Malloy
Richmond, VA

Claire Chee Award for Excellence

2022
TBD

2021
Toni Kavanagh
Pelham, New York

2020
Jennifer McCrave
Boston, MA

2019
Courtney Wellman
Kansas City, MO

2018
Cheryl Cahill
Boston, MA

2017
Jennifer Boyd
Toronto, ON

2016
Kathryn O'Hara
Richmond, VA

2015
Nancy Elling
Washington, DC

2014
Jo Ellen Lee
Columbus, OH

2013
Cheryl Fischer
New York, NY

2012
Jane Lane
Birmingham, AL

2011
Yolanda Harris
Birmingham, AL

2010
Julie Sprague-McRae
Fremont, CA

2009
Christine O'Dell
Bronx, NY

2008
Irene M. Elliott
Toronto, ON

2007
Elizabeth Tate
Springfield, IL

2006
Amy Vierhile
Rochester, NY

2004
Jane Meyer
Cottage Grove, WI

2003
Elizabeth F. Hobdell
Chester Brook, PA

2002
Rhonda Roell Werner
New Berlin, WI

2001
Claire Chee
Philadelphia, PA

2000
Jan Mims
Minneapolis, MN

Nurse Practitioner Excellence Award

2022
TBD

2021
Patricia McGoldrick
Pelham, New York

2020
Dianne Kulasa-Luke
Akron, OH

2019
Erin Fecske
Kansas City, MO

2018
Scott B. Turner
Birmingham, AL

2017
Rebecca Schultz
Houston, TX

2016
Sue Yudovin
Los Angeles, CA

2015
Regina Laine
Boston, MA

51st Annual Meeting of the Child Neurology Society Scientific Program

Cincinnati, OH

October 12 – October 15, 2022

Bruce H. Cohen, MD, FAAN, President, CNS
Yasmin Khakoo, MD; Chair & Bhooma Aravamuthan, MD, DPhil; Co-Chair,
CNS Scientific Selection and Program Planning Committee

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

The Minnesota Medical Association designates this live and enduring activity for a maximum of 30.75 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

NOTE: Program book went to press in July. Session times may have been revised. For most recent and reliable schedule information, consult Fall/Annual Meeting edition of CNS Connections, CNS website, and CNS Annual Meeting Website

PROGRAM

Wednesday, October 12

8:00 AM-11:00 AM

SYMPOSIUM I: CHILD NEUROLOGY FOUNDATION SYMPOSIUM: Clinical Trials in Pediatric Neurology: Our Role in Improving Participation and Outcomes
Supported by the Child Neurology Foundation

Organizer: Child Neurology Foundation

Welcome
Anup D. Patel, MD, FAAN, FAES; Nationwide Children's Hospital, The Ohio State University, Columbus, OH
Erika Fullwood Augustine, MD, MS; Kennedy Krieger Institute, Baltimore, MD

The Importance of Clinical Trials to Patients:

How Clinical Trials can Impact to Patient Outcomes
Tracy Dixon-Salazar, PhD; Lennox-Gastaut Syndrome (LGS) Foundation, San Diego, CA

Common Barriers to Patient Involvement in Clinical Trials
Kimbra Edwards, PhD; CISCRP, Boston, MA

The Critical Roles of the Provider:

The Importance of Clinician Involvement and Possible Roles
Bruce H. Cohen, MD, FAAN; Akron Children's Hospital; Akron, OH

Typical Barriers and Practical Considerations to Clinicians in Fulfilling these Roles
E. Martina Bebin, MD, MPA; University of Alabama at Birmingham, Birmingham, AL

Supporting Patients: Best Practices for Discussing Clinical Trials with Patients
Shafali Spurling Jeste, MD; Children's Hospital Los Angeles, Los Angeles, CA

Avoiding Common Mistakes in Discussions
Ariel M. Lyons-Warren, MD, PhD; Baylor College of Medicine, Houston, TX

11:30 AM-1:30 PM **KENNETH F. SWAIMAN CNS LEGACY LUNCHEON**

Welcome and Introduction:
Bruce H. Cohen, MD, FAAN; President, Child Neurology Society

Presentation of 2022 Arnold P. Gold Foundation Humanism in Medicine Award

- Jorge Vidaurre, MD; Nationwide Children's Hospital, The Ohio State University, Columbus, OH

Presentation of 2022 D'Souza Award Recipients

- Robert K. Sebunya, MD, M.phil; Uganda Martyrs University Nkozi, Mother Kevin Post Graduate School, Kampala, Uganda
- Paulina C. Tejada, MD; Pontificia Universidad Católica de Chile, Santiago, Chile

Presentation of 2022 CNS/PECN Training Director Award

- Tim Lotze, MD; Baylor College of Medicine, Texas Children's Hospital, Houston, TX

Presentation of 2022 Roger & Mary Brumback Lifetime Achievement Awards

- Jeffrey Buchhalter, MD, PhD; University of Calgary, Cumming School of Medicine, Calgary, Canada
- Roger Larson, CAE, CNS Executive Director, St. Paul, MN
- Michael Noetzel (*presented posthumously*)

Presentation of 2022 Bhuwan Garg High School Student Neuroscience Award

- Aliya Fisher, New York, NY

Presentation of 2022 Taeun Chang Junior Member Awards

- Mekka Garcia, MD; NYU Langone Health, New York, NY
- Laura Gilbert, DO, MBA; Washington University in St. Louis, St. Louis, MO
- Riley Kessler, MD; Children's Hospital of Philadelphia, Philadelphia, PA
- Ezgi Saylam, MD; Nationwide Children's Hospital, Columbus, OH

Presentation of 2022 Outstanding Junior Member Award-Post Graduate

- Travis Larsh, MD; Cincinnati Children's Hospital Medical Center, Cincinnati, OH
- Avantika Singh, MD; Boston Children's Hospital, Boston, MA

Presentation of 2022 M. Richard Koenigsberger Scholarship Award

- Stephen Chrzanowski, MD, PhD; Boston Children's Hospital, Boston, MA

Presentation of 2022 AAP Award

- Alexis Karlin, MA, MD; Children's Hospital of Philadelphia, Philadelphia, PA

2:00 PM-5:30 PM **Professors and Educators of Child Neurology (PECN)**

PECN Business Meeting (2:00 PM - 3:30 PM)

Organizer: Nancy Bass, MD; University Hospitals of Cleveland/ Rainbow Babies and Children's Hospital, Case Western Reserve University School of Medicine, Cleveland, OH

Introduction and Agenda
Nancy Bass, MD; University Hospitals of Cleveland/ Rainbow Babies and Children's Hospital, Case Western Reserve University School of Medicine, Cleveland, OH

Preference Signaling and the Match
Margie Ream, MD, PhD; Nationwide Children's Hospital, Columbus, OH

Forgivable Family Leave for Trainees with Q&A
Margie Ream, MD, PhD; Nationwide Children's Hospital, Columbus, OH

RRC Change: Program Director Minimum FTE Support with Q&A
Danny Rogers, MD, PhD; University of New Mexico, Albuquerque, NM

Match Report
Leon Dure, MD; Heersink School of Medicine, University of Alabama at Birmingham, Birmingham, AL

CNCDP-K12 Report
Bradley L. Schlaggar MD PhD; Kennedy Krieger Institute, Baltimore, MD

Minority Research Scholars Program
Erika Fullwood Augustine, MD, MS; Kennedy Krieger Institute, Baltimore, MD

Updates AAP Section of Pediatric Neurology
Tim Lotze, MD; Baylor College of Medicine, Texas Children's Hospital, Houston, TX

Updates AAN Section of Child Neurology with Q&A
David E. Mandelbaum, MD, PhD; Alpert Medical School of Brown University, Providence, RI

PECN (CME Portion): Educational Tools (3:30 PM -5:30 PM)

PECN Digital Committee and Social Media Tools
Jaclyn Martindale, DO; Wake Forest University School of Medicine, Winston-Salem, NC
Kathryn Idol Xixis, MD; University of Virginia, Charlottesville, VA
Jessica Goldstein, MD; University of Minnesota, M Health Fairview Masonic Children's Hospital, Minneapolis, MN

Development of a Child Neurology Ethics Curriculum
William D. Graf, MD; Connecticut Children's, University of Connecticut, Farmington, CT

LGBTQ: Tools for Residency Education
Jonathan Strober, MD; UCSF Benioff Children's Hospital, San Francisco, CA

2:00 PM-7:30 PM **EXHIBIT HALL**

6:00 PM-7:30 PM **WELCOME RECEPTION**

8:00 PM-10:00 PM **MOVEMENT DISORDERS VIDEO ROUNDS** *(Formerly Movement Disorders SIG)*

Thursday, October 13

7:00 AM-9:00 AM **PLATFORM I, II & III**

PLATFORM I

7:00 AM-7:15 AM PL1-1: Juhasz et al
Deep cerebral venous remodeling in Sturge-Weber syndrome: Hemispheric differences and clinical correlates

7:15 AM-7:30 AM PL1-2: Felling et al
Thrombolysis in Pediatric Stroke Extended Results Study – Long term Outcomes after Mechanical Thrombectomy

7:30 AM-7:45 AM PL1-3: Ihnen et al
Developmental Profiles in Early-Life Tuberous Sclerosis Complex (TSC)

7:45 AM-8:00 AM PL1-4: Garcia et al
Quality Improvement Project: Number of Neurofibromatosis Type I Patients with Unidentified Bright Objects (UBOs) on MRI that Developed Subsequent Non-Optic Gliomas

8:00 AM-8:15 AM PL1-5: Karlin et al
Childhood Cerebral Sinovenous Thrombosis and Risk for Epilepsy

8:15 AM-8:30 AM PL1-6: Bruckert et al
White matter properties of the optics pathway in children with neurofibromatosis type 1 with and without optic pathway gliomas

8:30 AM-8:45 AM PL1-7: Song et al
Targeting USP7 as a Novel Treatment in Malignant Glioma

8:45 AM-9:00 AM PL1-8: Christensen et al
Cerebral Venous Sinus Thrombosis in Preterm Infants

PLATFORM II

7:00 AM – 7:15 AM PL2-1: Sederman et al
Estimating US Prevalence and Diagnosis Rates for Rare Developmental and Epileptic Encephalopathies (DEEs)

7:15 AM – 7:30 AM PL2-2: Yuskaitis et al
Loss of DEPDC5 after cortex formation is sufficient to cause focal seizures in a mouse model

7:30 AM – 7:45 AM PL2-3: Turk et al
Machine Learning approaches to classifying and predicting disease progression in Adrenomyeloneuropathy

7:45 AM – 8:00 AM PL2-4: Gropman et al
From bedside to bench and clinical practice: A comprehensive study of two rare mitochondrial neurodegenerative diseases MELAS and LHON-Plus and functional Investigations of Mitochondrial Energy Metabolism

8:00 AM – 8:15 AM PL2-5: Calame et al
Genetic variation in the DExH-box helicase DHX9 perturbs neurodevelopment & peripheral nerve axon function

8:15 AM – 8:30 AM PL2-6: Saffari et al
The Clinical, Molecular and Neuroimaging Spectrum of ZFYVE26-Related Hereditary Spastic Paraplegia (SPG15) – A Cross-Sectional Analysis of 36 Patients

8:30 AM – 8:45 AM PL2-7: Chrzanowski et al
Preliminary creatine kinase muscle isoenzyme values from a supplemental newborn screening program for Duchenne muscular dystrophy

8:45 AM – 9:00 AM PL2-8: Kessler et al
Low Diagnostic Yield from Biochemical CSF Neurotransmitter Testing in Infants

PLATFORM III

7:00 AM – 7:15 AM PL3-1: Eisner et al
The Relationship between Sleep, Cognition and Behavior in Children with Newly-Diagnosed Epilepsy over 36 months

7:15 AM – 7:30 AM PL3-2: Singh et al
Epilepsy Outcomes for Surgical Candidates with Infantile Spasms

7:30 AM – 7:45 AM PL3-3: Wu et al
Randomized Controlled Trial of Erythropoietin for Neonatal Hypoxic-Ischemic Encephalopathy (HIE)

7:45 AM – 8:00 AM PL3-4: Eisman et al
Early Biomarkers in the Prediction of Later Functional Impairment in Term Children with Cerebral Palsy

8:00 AM – 8:15 AM PL3-5: Larsh et al
Comparison of Impairment in Functional Tic Disorders versus Tourette Syndrome

8:15 AM – 8:30 AM PL3-6: Saylam et al
Assessing sleep quality in children with migraines: Implementation of electronic health record cue and using actigraphy

8:30 AM – 8:45 AM PL3-7: Gilbert et al
Identifying upper extremity features of dystonia in people with cerebral palsy

8:45 AM – 9:00 AM PL3-8: Saxena et al
Respiratory rate variability at NICU discharge may predict cerebral palsy risk

WELCOME & GENERAL SESSION

9:30 AM – 12:15 PM **SYMPOSIUM II: PRESIDENTIAL SYMPOSIUM: *Quality and Capitated Care***
Organizer: Bruce H. Cohen, MD, FAAN; Akron Children's Hospital, Akron, OH

Co-Organizer: Jeffrey Buchhalter, MD, PhD; University of Calgary, Cumming School of Medicine, Calgary, Canada

Introduction and Discussion of the Importance of QI/QM to CNS Members
Bruce H. Cohen, MD, FAAN; Akron Children's Hospital, Akron, OH

Creating a Quality Improvement Ecosystem at AAN
Lyell K. Jones, Jr. MD; Mayo Clinic, Rochester, MN

Development of Child Neurology QMs at AAN
Bhooma Aravamuthan MD, DPhil; Washington University School of Medicine, St. Louis, MO

Description of Rationale and Requirements for a Learning Health System (LHS)
Jeffrey Buchhalter, MD, PhD; University of Calgary, Cumming School of Medicine, Calgary, Canada

Descriptions of LHS in Pediatrics
Anup D. Patel, MD, FAAN, FAES; Nationwide Children's Hospital, The Ohio State University, Columbus, OH

LHS for Peds/Adult Epilepsy: Early Wins
Zachary M. Grinspan, MD, MS; Weill Cornell Medicine, New York, NY

Leveraging LHS to Study Health Care Disparities
Fiona Baumer, MD, MS; Stanford University School of Medicine, Palo Alto, CA

Q&A
Bruce H. Cohen, MD, FAAN; Akron Children's Hospital, Akron, OH

11:30 AM – 7:00 PM **EXHIBIT HALL**

12:30 PM – 2:00 PM **EXHIBITS, POSTER REVIEW & GUIDED POSTER TOUR #1**

2:30 PM – 3:00 PM **Martha Bridge Denckla Award Lecture:** *Looking Back but More Importantly Looking Forward in Cerebral Palsy*
Michael Shevell, MDCM, FRCP, FCAHS; Montreal Children's Hospital, McGill University Montreal, Quebec, Canada

3:00 PM – 5:15 PM **SYMPOSIUM III: GLOBAL NEUROLOGY: *The Global Situation of Child Neurology Practice During the COVID 19 Pandemic and Other Natural Disasters. Clinical Care and Education***
Organizer: Jorge Vidaurre, MD; Nationwide Children's Hospital, The Ohio State University, Columbus, OH

Chikungunya, Zika and COVID: Neurological Consequences and Impact in Child Neurology Care Across Latin America
Paulina C. Tejada, MD; Pontificia Universidad Católica de Chile, Santiago, Chile

Building Child Neurology Capacity in Africa During Disruptive Disasters: Ideas for Low Resourced Communities
Robert K. Sebunya, M.D, M.phil; Uganda Martyrs University Nkozi, Mother Kevin Post Graduate School, Kampala, Uganda

Practicing Child Neurology on Conflict Zones. Lessons Learned
Volodymyr Kharytonov, MD PhD; Clinical Hospital "Psychiatry", Kyiv, Ukraine

The Potential for Device Technology use in Healthcare: Applicability During Times of Reduced Access
Dave Clarke, MBBS; Dell Medical School, University of Texas at Austin, Austin, TX

5:30 PM – 7:00 PM **EXHIBITS, POSTER REVIEW (WINE & CHEESE) & GUIDED POSTER TOUR #2**

Friday, October 14

8:00 AM – 8:15 AM **AWARD PRESENTATIONS & GENERAL SESSION**

Child Neurology Foundation/PERF Scientific Grant & Award Announcements

ACNN Award Announcements

8:15 AM – 8:45 AM **Philip R. Dodge Young Investigator Award Lecture:** *The diagnosis and pathophysiology of dystonia in cerebral palsy*
Bhooma Aravamuthan MD, DPhil; Washington University School of Medicine, St. Louis, MO

8:45 AM – 9:30 AM **Bernard Sachs Award Lecture:** *Brain Health in the Neonate: From Connectome to Home*
Steven Paul Miller, MDCM, MAS, FRCPC; University of British Columbia (BC), BC Children's Hospital, Vancouver, British Columbia, Canada

9:45 AM – 12:00 PM **SYMPOSIUM IV: ETHICS: *Neuropalliative Care Across the Age Spectrum***
Organizer: William D. Graf, MD; Connecticut Children's, University of Connecticut, Farmington, CT

Neuropalliative Care in Adults
Lynne P. Taylor, MD; Alvord Brain Tumor Center, University of Washington, Seattle, WA

Antenatal Neuropalliative Care
William D. Graf, MD; Connecticut Children's, University of Connecticut, Farmington, CT

Neuropalliative Care in Neonates
Monica Lemmon, MD, Duke University School of Medicine, Durham, NC

Neuropalliative Care in Children with Severe Neurological Disorders and Neurodevelopmental Disabilities
Audrey Foster-Barber, MD, PhD; University of California, San Francisco, San Francisco, CA

12:30 PM – 1:45 PM **SEMINAR 1: CEREBRAL PALSY: *What is CP? A Consensus-Based Approach***
Organizer: Bhooma Aravamuthan MD, DPhil; Washington University School of Medicine, St. Louis, MO

The Meaning of "Non-progressive"
Michael Shevell, MDCM, FRCP, FCAHS; Montreal Children's Hospital, McGill University Montreal, Quebec, Canada

The Meaning of "Developing Fetal or Infant Brain"
Ann Tilton, MD; LSU Health Sciences Center New Orleans, New Orleans, LA

Contributions of Different Etiologies to CP
Michael Kruer, MD; Phoenix Children's Hospital, Phoenix, AZ

The Meaning of a CP Diagnosis for Community Members and Other Stakeholders
Paul Gross, BA, President, CEO & Co-Founder; Cerebral Palsy Research Network, Greenville, SC

12:30 PM – 1:45 PM **SEMINAR 2: NEURODEVELOPMENTAL DISORDERS: *Neurological and Neurodevelopmental Challenges in Sickle Cell Disease: Stroke and Beyond***
Organizer: Eboni Lance, MD, PhD, Kennedy Krieger Institute, Baltimore, MD

Update on Neurological Complications of Sickle Cell Disease: Stroke Risk and Prevention, Headaches, and Seizures
Lori Jordan, MD, PhD; Vanderbilt University Medical Center, Nashville, TN

Advanced Neuroimaging and New Therapeutics in Sickle Cell Disease
Melanie Fields, MD, MSCI, Washington University, St. Louis, MO

Neurodevelopmental Disorders and Developmental Screening in Sickle Cell Disease
Eboni Lance, MD, PhD, Kennedy Krieger Institute, Baltimore, MD

12:30 PM – 1:45 PM **SEMINAR 3: NEURO-ONCOLOGY: A Case-Based Approach to Acute Neuro-toxicities in Childhood Cancer Patients**
Organizer: Cynthia J. Campen, MD, MScE; Stanford University, Stanford, CA

Moderator: Sonia Partap, MD, MS; Stanford University & Lucile Packard Children's Hospital, Palo Alto, CA

Traditional Chemotherapy Agents
Nicole Ullrich, MD, PhD, FAAN; Boston Children's Hospital, Boston, MA

Targeted Agents
Cynthia J. Campen, MD, MScE; Stanford University, Stanford, CA

Immunotherapy
Juliane Gust, MD, PhD, Seattle Children's, University of Washington, Seattle, WA

2:15 PM – 4:30 PM **SYMPOSIUM V: NEUROIMMUNOLOGY: *Advancements in Pediatric Neuroimmunological Diseases***
Organizer: Grace Gombolay, MD; Emory University, Children's Healthcare of Atlanta, Atlanta, GA

Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorders
Tanuja Chitnis, MD; Mass General Brigham, Harvard Medical School, Boston, MA

Myelin Oligodendrocyte Glycoprotein Associated Disorders
Giulia Fadda, MD, McGill University, Montreal, Quebec, Canada

Acute Flaccid Myelitis and Mimickers
Teri Schreiner, MD MPH; Children's Hospital Colorado, University of Colorado, Aurora, CO

Anti-NMDA Receptor Encephalitis and Other Autoimmune Encephalitis
Grace Gombolay, MD; Emory University, Children's Healthcare of Atlanta, Atlanta, GA

4:30 PM – 5:00 PM **CNS BUSINESS MEETING**

5:00 PM – 6:30 PM **JUNIOR MEMBER SEMINARS**

6:15 PM – 7:00 PM **SCIENTIFIC PROGRAM & PLANNING COMMITTEE MEETING**

7:00 PM – 9:00 PM **CLOSING GALA**

Saturday, October 15

7:00 AM – 8:15 AM **SEMINAR 4: EDUCATION: *Studying What Matters: Incorporating Patients and Families into Pediatric Neurology Research***

Organizer: Monica Lemmon, MD, Duke University School of Medicine, Durham, NC

The Power of Parents and Advocacy Groups
Betsy Pilon, Executive Director; Hope for HIE, West Bloomfield, MI

Incorporating Stakeholders into Study Design and Analysis: Lessons from the Neonatal Seizure Registry
Renée Shellhaas, MD, MS; Michigan Medicine, University of Michigan, Ann Arbor, MI

Aligning Proposals with Funding Priorities in Patient-centered Design
Adam L. Hartman, MD; NINDS, NIH, Rockville, MD

7:00 AM – 8:15 AM **SEMINAR 5: FETAL NEUROLOGY: *Advances in Fetal Neurology: Emerging Ideas and Future Landscape***

Organizer: Sonika Agarwal, MBBS, MD; Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Fetal Neurology Consortium and Registry Workgroup – Fetal Neurology Program Survey Results
Sonika Agarwal, MBBS, MD; Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Advances in Fetal Neurogenetics: Emerging Ideas and Future Landscape
Lisa Emrick, MD; Baylor College of Medicine, Houston, TX

Advances in Fetal Neuroimaging: Emerging Ideas and Future Landscape
Tomo Tarui, MD; Tufts Medical Center, Boston, MA

Advances in Fetal Neurotherapeutics and Interventions
David Neal Franz, MD; Cincinnati Children's Hospital/University of Cincinnati College of Medicine, Cincinnati, OH

7:00 AM – 8:15 AM **SEMINAR 6: DIVERSITY: *Disability in Child Neurology: Society, Medicine and the Person***

Organizer: Danielle Guez Barber, MD PhD, Children's Hospital of Philadelphia, Philadelphia, PA

An Introduction to Disability and Ableism
Young-Min Kim, MD; Loma Linda University Children's Hospital, Loma Linda, CA

History of Ableism in Child Neurology
Alison Christy, MD, PhD; Providence Health and Services, Portland, OR

Ableism and the Individual
Diana M. Cejas, MD, MPH; University of North Carolina at Chapel Hill, Carolina Institute for Developmental Disabilities, Chapel Hill, NC

Panel Discussion, Q&A and Case Studies
Moderator: Danielle Guez Barber, MD PhD, Children's Hospital of Philadelphia, Philadelphia, PA

- Diana M. Cejas
- Alison Christy, MD, PhD
- Young-Min Kim, MD

8:45 AM – 9:30 AM **Hower Award Lecture:** *Lessons that Viruses have Taught us about Fairness and Justice in Medicine*

Leon G. Epstein, MD; Ann & Robert Lurie H. Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL

9:45 AM – 12:00 PM **SYMPOSIUM VI: BEHAVIORAL NEUROLOGY: *Spanning the Divide: Anxiety and Mood Disorders Co-occurring with Neurologic Disorders***

Organizer: Jennifer Vermilion, MD; University of Rochester, Rochester, NY

Overlapping Neural Circuits in Movement Disorders and Mood Disorders: Implications for Diagnosis and Treatment
Jonathan W. Mink, MD, PhD; University of Rochester, Rochester, NY

Tourette syndrome: Bridging the Border between Neurology and Psychiatry
Jennifer Vermilion, MD; University of Rochester, Rochester, NY

Tuberous Sclerosis Complex Associated Neuropsychiatric Disorders: Insights and Opportunities
Tanjala T. Gipson, MD; University of Tennessee Health Sciences Center, Memphis, TN

Understanding and addressing psychiatric comorbidities in Child Neurology
Devin C. McNulty, PhD; Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine, Chicago, IL

12:15 PM – 4:15 PM

CNS Clinical Research Annual Workshop 2022 – Pediatric Neurology Clinical Trials – Trial Design
Organizer: Ariel Maia Lyons-Warren, MD, PhD; Baylor College of Medicine, Houston, TX

Co-Organizer: Josh Bonkowsky, MD, PhD; University of Utah School of Medicine, Primary Children's Hospital, Salt Lake City, UT
Co-Organizer: Janet Soul, MDCM, FRCPC; Boston Children's Hospital, Harvard Medical School, Boston Mass, Boston, MA
Co-Organizer: Angela Hewitt, MD, PhD; University of Rochester Medical Center, Rochester, NY
Co-Organizer: Daniel Calame, MD, PhD; Baylor College of Medicine, Houston, TX

Welcome
Ariel Maia Lyons-Warren, MD, PhD; Baylor College of Medicine, Houston, TX

Introduction to Clinical Research Study Design
Jennifer Vermilion, MD; University of Rochester, Rochester, NY

Breakout Sessions

Finding the Right Grant for your Clinical Research Study
Adam L. Hartman, MD; NINDS, NIH, Rockville, MD

Statistics by Study Design: Selecting the Right Type of Analysis for your Clinical Research Study
Paul S. Horn, PhD; Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Coffee Break & Networking

How to Get Involved in Multi-Site Clinical Research Trials
Darcy Krueger, MD, PhD; Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Q&A

12:15 PM – 4:15 PM

Biomedical Writing Workshop
Organizer and Presenter: E. Steve Roach, MD; University of Texas Dell Medical School, Austin, TX

Introduction: Why Manuscripts are Rejected
E. Steve Roach, MD

Outwitting Writer's Block
E. Steve Roach, MD

Break

Revising Manuscripts & Responding to Reviews
E. Steve Roach, MD

Rules of the Road: Permissions, Consents, and Other Potholes
Phillip L. Pearl, MD, Boston Children's Hospital, Boston, MA

Meet the Editors

- Yasmin Khakoo, MD, FAAN; Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY
- E. Steve Roach, MD
- Phillip L. Pearl, MD

2022 ACNN Conference

Cincinnati, OH

October 13 – October 14, 2022

PROGRAM

Thursday, October 13

8:00 AM – 8:15 AM **Welcome**

8:15 AM – 9:30 AM **Janet Brucker Keynote Address:** ***Everyday Clinical Ethics in Pediatric Neurology Nursing***
Elaine Meyer, PhD, RN, MBE; Boston Children's Hospital, Center for Bioethics, Harvard Medical School, Boston, MA

9:30 AM – 10:00 AM ***Strength for the Journey: Palliative Care for the Neurology Population***
Tristen Dinkel, Nurse Coordinator- Rett Clinic and Neurogenetic & Neurodegenerative Disease Clinic; Children's Hospital Colorado, Colorado Springs, CO

10:00 AM – 10:15 AM ***Break***

10:15 AM – 10:45 AM ***Panel Discussion: Palliative Care***

10:45 AM – 11:15 AM ***Post Intensive Care Syndrome in Pediatrics***
Rebecca Schultz, PhD, APRN, CPNP-PC; Texas Woman's University,Texas Children's Hospital, Baylor College of Medicine, Houston, TX

11:15 AM – 12:00 PM ***Early Recognition of the Neurologic Phenotype and Diagnostic Investigations in Pediatric Patients with MEN2B***
Julie Hogan, CPNP-AC/PC; Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD

12:00 PM – 12:15 PM ***Business Meeting and Awards Presentation***

12:15 PM – 1:00 PM ***Lunch***

1:00 PM – 1:30 PM ***Innovative Clinical Practice Award Presentation: TBD***

1:30 PM – 2:00 PM ***QEEG: Past, Present, and Future***
Michele Mills, RN, MSN; Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL

Erica Prendergast, RN, DNP; Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL

2:00 PM – 2:15 PM ***Break***

2:15 PM – 3:00 PM ***Acute Self-Management with Rescue Therapies in Epilepsy Care***
Nancy Santilli, Consultant; Santilli Global, LLC, Sunnyvale, CA

Patty Osborne Shafer, RN, MN, FAES; Shafer Consulting, Wilmington, MA

Patricia Dean, APRN, MSN, CNRN; Comprehensive Epilepsy Program, Nicklaus Children's Hospital, Miami, FL

3:00 PM – 3:45 PM ***Neurocardiogenic Syncope: Defining the Falls and Fits***
Martha Willis, RN, MS, CNS, APRN-PC/AC; Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Friday, October 14

8:15 AM – 8:30 AM **Welcome**

8:30 AM – 9:15 AM ***Pediatric Tic Disorders, an Integrative Approach and the Explosion of Functional Tic-Like Movements***
Chelsey Stillman, MPAS, PA-C; Children's Hospital Colorado, Aurora, CO

9:15 AM – 10:00 AM ***Functional Neurological Disorders: What Do We Know?***
Elizabeth Rende, PNP; CentraCare Health, Saint Cloud, MN

10:00 AM – 10:30 AM ***Break***

10:30 AM – 11:00 AM ***Dopamine Responsive Dystonia in a General Pediatric Neurology Practice***
Linda Bucher, FNP; Children's Hospital Colorado, Colorado Springs, CO

11:00 AM – 11:30 AM ***Pediatric Abusive Head Trauma: Outpatient Care and Outcomes***
Medina Oikeh, APRN; Baylor College of Medicine/Texas Children's Hospital, Houston, TX

11:30 AM – 12:15 PM ***Bilateral Ptosis, Zosteriform Rash and Flaccid Bladder in a 10-Year-Old Boy***
Sara Adducchio, PNP; Dayton Children's Hospital, Dayton, OH

Irma Reyes, Pediatric Neurologist; Dayton Children's Hospital, Dayton, OH

12:15 PM – 1:00 PM ***Lunch***

1:00 PM – 1:30 PM ***Long-COVID Headaches and Neurological Symptoms in Pediatrics: What Do We Know?***
Deanna Duggan, Assistant Professor/ Pediatric Nurse Practitioner; Baylor College of Medicine, Texas Children's Hospital, The Woodlands, TX

1:30 PM – 2:15 PM ***Post-Acute Sequelae of COVID 19: A Pediatric Neurology Perspective***
Rasha Srouji, NP; Boston Children's Hospital, Boston, MA

Margaret Wilson-Murphy; Boston Children's Hospital, Boston, MA

2:15 PM – 2:30 PM ***Break***

2:30 PM – 3:30 PM ***From Triage to Treatment: When Acute Treatment at Home Doesn't Stop a Child's Migraine Pain***
Susan LeCates, APRN-CNP; Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Marielle Kabbouche, MD, FAHS; Director of Infusion and Inpatient Headache Programs, Professor in Neurology, Child Neurology and Headache Medicine; Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Paula Manning, RN, BSN; Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Wendi Lopez, Psy.D.; Cincinnati Children's Hospital Medical Center, Cincinnati, OH

3:30 PM – 4:00 PM **Posters**

PLATFORM PRESENTATIONS

Platform Session 1: Thursday, October 13 (7:00 AM – 9:00 AM)

PL1-1. Deep cerebral venous remodeling in Sturge-Weber syndrome: Hemispheric differences and clinical correlates

Juhasz C (Detroit, MI), Luat A, Behen M, Gjolaj N, Jeong J-W, Chalasani S, Chugani H, Kumar A

Objective: Enlarged deep medullary veins (EDMVs) in patients with Sturge-Weber syndrome (SWS) often occur and expand during the early disease course and may provide compensatory venous drainage in brain regions affected by the leptomeningeal venous malformation (LVM). We evaluated potential hemispheric differences and clinical correlates of EDMVs in children with unilateral SWS.

Methods: Fifty children (median age: 4.6 years) with unilateral SWS underwent brain MRI including susceptibility-weighted imaging (SWI); children ≥2.5 years of age (n=40) also had a formal neurocognitive evaluation. EDMVs in the affected hemisphere were assessed on SWI in five deep venous regions, a composite EDMV score (ranging 0-15) was calculated, compared between patients with right and left SWS, and correlated with clinical variables.

Results: EDMVs were present in 89% (24/27) of right and 78% (18/23) of left SWS brains. Extensive EDMVs (score >6, indicating EDMVs in >2 deep venous regions) were more common in right (37%) than in left SWS (9%; p=0.02). All patients with EDMV scores >4 (n=19) had rare (less than monthly) seizures, while 35% (11/31) of patients with EDMV scores ≤4 had monthly or more frequent seizures (p=0.003). In patients with right-hemispheric SWS and at least two LVM-affected lobes, more extensive EDMVs were associated with higher IQ (Spearman's rho=0.55, p=0.02).

Conclusions: Enlarged deep medullary veins are common in unilateral SWS, but extensive deep veins appear to develop more commonly in children with right SWS. The data support the concept that extensive deep venous remodeling during the early disease course may contribute to better clinical outcomes in unilateral SWS.

Keywords: Neurocutaneous Disorders, Neuroimaging

PL1-2. Thrombolysis in Pediatric Stroke Extended Results Study – Long term Outcomes after Mechanical Thrombectomy

Felling R (Baltimore, MD), Abraham M, Hallam D, Barry D, Ichord R, Jordan L, Kansagra A, Lee S, Dowling M, Amlie-Lefond C

Objective: The Thrombolysis in Pediatric Stroke (TIPS) Extended Results Study is an international, multicenter, retrospective study arising from primary stroke centers developed through the TIPS Trial. We aimed to describe clinical outcomes of children with stroke due to large vessel occlusion who were treated with mechanical thrombectomy (MT).

Methods: Retrospective data were collected on all patients aged 18 and younger treated with MT at the enrolling site or an outside hospital prior to referral to study sites between 2010-2019. Outcomes were defined by the pediatric stroke outcome measure severity classification scale (PSOM-SCS) at 3 and 12 months after stroke.

Results: We enrolled 42 children with a median age 13.7 years. Anterior circulation (internal carotid, M1, or M2) was involved in 32 patients and posterior circulation (basilar artery) in 10 patients. The median time from stroke to MT was 6.5 hours for anterior circulation and 15.1 hours for posterior circulation (p=0.05). High rates of recanalization (>mTICI 2b) were achieved (71.8% anterior vs 100% posterior). At 12 months, 69% of children with anterior circulation strokes and 60% with posterior circulation strokes had no to mild disability (n.s.).

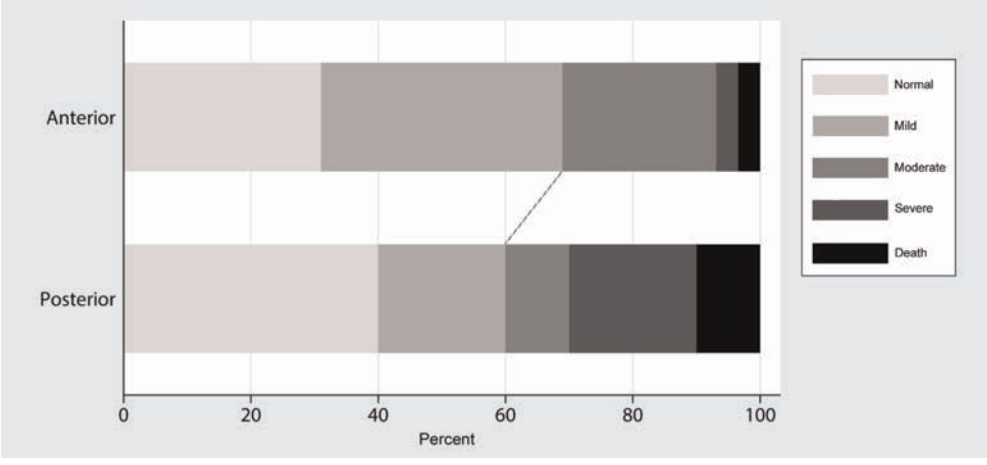


FIGURE 1. Neurological outcomes after MT based on PSOM-SCS. The dashed line indicates our cutpoint between favorable and unfavorable outcomes. The propotion of favorable versus unfavorable outcomes was not statistically different between anterior and posterior circulation strokes. Abstract PL 1-2

There was one symptomatic ICH following MT. Subclinical hemorrhagic transformation and vasospasm were more common than adult reports (33% and 19%, respectively).
Conclusions: MT is feasible in children with similar recanalization rates to adults. Favorable outcome was achieved in most patients, with no difference between anterior and posterior circulation strokes. Further work needs to define predictors of poor outcome to guide patient and device selection.
Keywords: Stroke (including other Vascular Disorders), Critical Care

PL1-3. Developmental Profiles in Early-Life Tuberous Sclerosis Complex (TSC)

Ihnen S.-K (Cincinnati, OH), Alperin S, Capal J, Horn P, Griffith M, Cohen A, Peters J, Warfield S, Kroeck M, Sahin M, Wu J, Bebin M, Northrup, Krueger D

Objective: As a precursor to developing individualized treatment strategies for patients with Tuberous Sclerosis Complex (TSC), we sought to identify early predictors of developmental outcomes at 36 months of age.

Methods: TSC patients ages 0-12 months were enrolled and followed until 36 months in the TSC Autism Centers of Excellence Research Network (TACERN). Mullen Scales of Early Learning (MSEL) and Vineland Adaptive Behavior Scales II (VABS) were administered serially. Hierarchical clustering analysis was performed to identify sub-groups based on MSEL and VABS sub-scores at 36 months. Subgroups were interrogated for differences in tuber volume and seizure burden, candidate biomarkers of development. These biomarkers were then combined with MSEL and VABS subscores at 12 months to predict outcomes at 36 months of age using logistic regression.
Results: Developmental quotients (DQs) from VABS and MSEL sub-scores were calculated for n=129 patients. Hierarchical clustering yielded two sub-groups (Figs. 1 and 2), with the higher-scoring group (n=74) associated with lower tuber volumes ($p<0.001$) and notably lower prevalence of epilepsy ($p<0.05$) compared to the lower-scoring group (n=55). Backwards elimination on a logistic regression model yielded a three-variable solution for predicting eventual outcome at

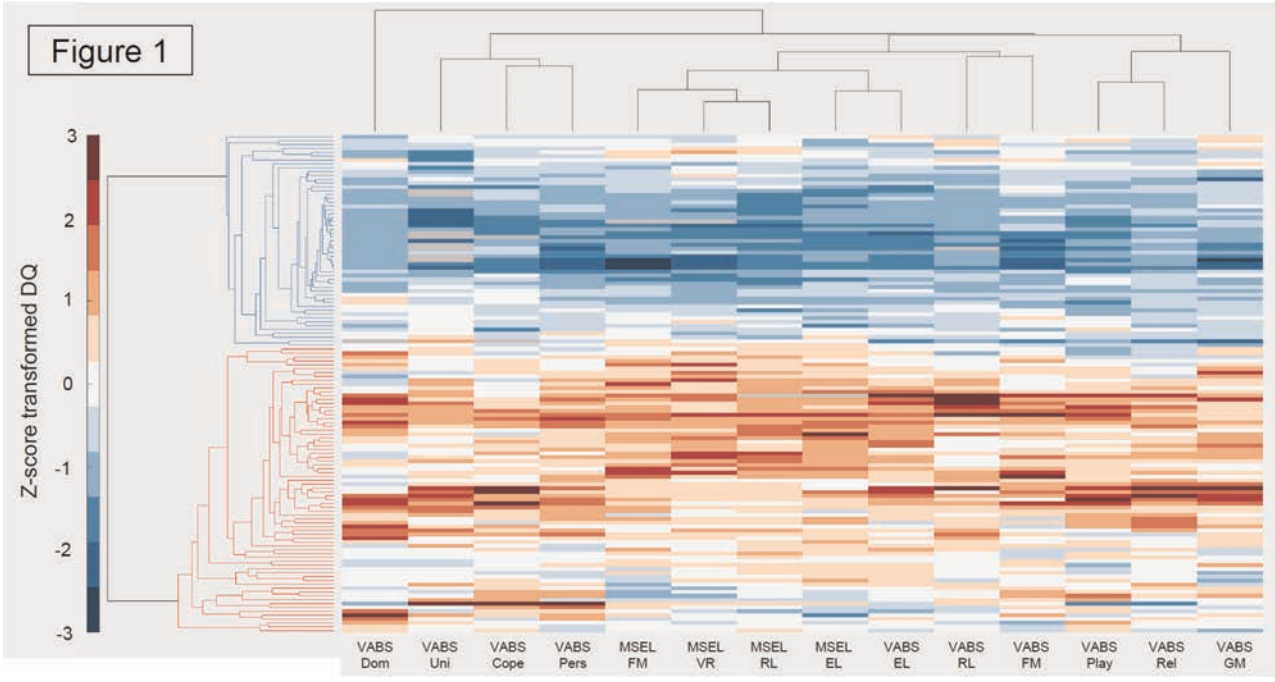


FIGURE 1: Clustergram derived from hierarchical clustering of n=129 patients using n=14 developmental quotients (DQs) obtained at 36 months of age, n=10 from the Vineland Adaptive Behavior Scales II (VABS) and n=4 from the Mullen Scales of Early Learning (MSEL). Each patient is represented as one tick on the colored dendrogram on the left, which splits into two large sub-groups. The blue group at the top of the figure (n=55) is generally lower-scoring and the red group at the bottom of the figure (n=74) is generally higher-scoring. Each individual patient is furthermore assigned one row across the page, with that patient's score for each sub-scale depicted as a shaded cell in one of 14 columns, labeled across the x-axis (see abbreviation key below). Scores are Z-score transformed DQs, as shown in the color scale, with warm colors positive and cool colors negative. Patients who cluster together on the dendrogram have similar developmental patterns, with the length of the line connecting two ticks proportional to the overall dissimilarity between two individuals. Similarly, the relative similarity or dissimilarity between the 14 sub-scales can be inferred by examining the dendrogram at the top of the figure and noting the length of the line connecting any pair of columns. For example, the shortest distance connects the MSEL VR and MSEL RL sub-scales, suggesting that amongst the 14 sub-scales, scores on the MSEL visual reception and receptive language sub-scales are the most congruent within individuals in this sample. Abbreviation key: VABS DOM = domestic; VABS UNI = community; VABS COPE = coping skills; VABS PERS = personal; MSEL FM = fine motor; MSEL VR = visual receptive; MSEL RL = receptive language; MSEL EL = expressive language; VABS EL = expressive language; VABS RL = receptive language; VABS FM = fine motor; VABS PLAY = play and leisure time; VABS REL = interpersonal relationships; VABS GM = gross motor; VABS RL = receptive language. Abstract PL 1-3

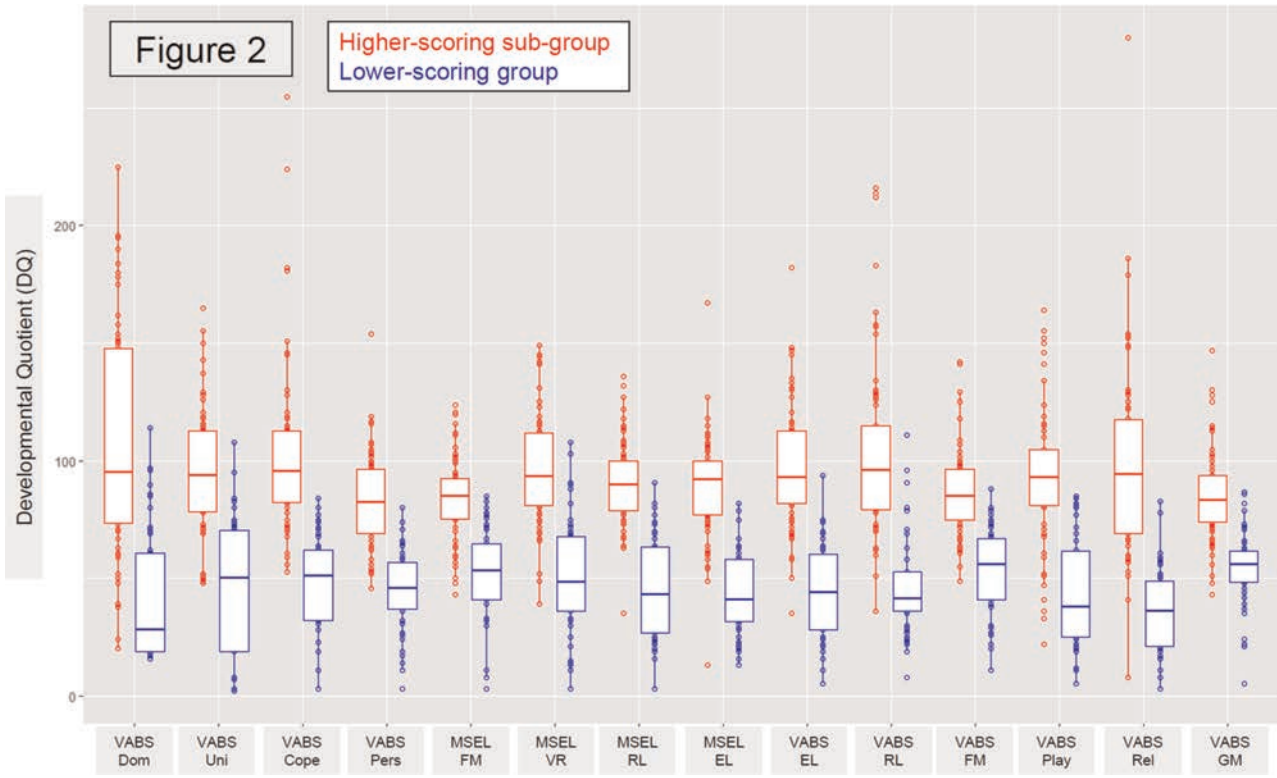


FIGURE 2: Boxplots for individual sub-scales of the Mullen Scales of Early Learning (MSEL) and Vineland Adaptive Behavior Scales II (VABS) split and color-coded by cluster assignment at 36 months. Scores are plotted as developmental quotients. As shown, the red group (n=74) is generally higher-scoring and the blue group (n=55) is generally lower-scoring. Abstract PL 1-3

36 months of age, with 91% specificity and 73% accuracy: 1) parietal lobe tuber proportion, 2) VABS expressive language DQ at age 12 months and 3) VABS gross motor DQ at 12 months.

Conclusions: At age 36 months, two sub-groups diverge based on multi-domain developmental subscales. Epilepsy burden, tuber volume and developmental test results ascertainable at earlier timepoints predict later sub-group assignment.

Keywords: Neurocutaneous Disorders, Cognitive/Behavioral Disorders (including Autism), Epilepsy/Sleep

PL1-4. Quality Improvement Project: Number of Neurofibromatosis Type I Patients with Unidentified Bright Objects (UBOs) on MRI that Developed Subsequent Non-Optic Gliomas

Garcia M (New York, NY), Jandhyala N, Kim M, Segal D, Yohay K

Objective: To assess whether our current surveillance of Neurofibromatosis type I (NF1) patients with unidentified bright objects and/or non-optic gliomas on imaging are appropriate.

Methods: We reviewed a series of 1373 patients (ages 8 months to 86 years) with NFI followed at our institution from 2012-2021. All MR imaging (MRI) were screened for UBOs and non-optic gliomas which were then correlated with clinical records.

Results: We found 538 (39.2%) patients with UBOs on MRI and 161 (11.7%) patients with non-optic glioma. The mean number of MRIs for those with UBOs or gliomas was 5.09 (range 1-50) over 6.24 years, with an average frequency of 1.4 MRIs per year. UBOs were most frequently observed in the thalamus, basal ganglia, and cerebellum. Gliomas were commonly located in the cerebellum and brainstem. Seventy-six (47.2%) gliomas were found in the location of prior UBOs. Those with UBOs were significantly more likely to have gliomas than those without, with a frequency of 25.7% vs 4.7%, respectively ($p<0.001$). Of those with gliomas, 35.4% received treatment: 70% had surgery and 60% had other treatments, 50% of which was chemotherapy.

Conclusions: Our data suggests that many NF1 patients develop both UBOs and gliomas. Many gliomas develop in regions previously noted to have UBOs. Most importantly, those with UBOs are more likely to develop gliomas, with many developing in the location of a prior UBO. This finding could indicate a need for changes in management and monitoring of UBOs found on imaging.

Keywords: Brain Tumors/Oncology, Neurcutaneous Disorders, Neuroimaging

PL1-5. Childhood Cerebral Sinovenous Thrombosis and Risk for Epilepsy

Karlin A (Philadelphia, PA), Kumar N, Vossough A, Ichord R, Abend N, Beslow L

Objective: To determine the cumulative incidence and clinical predictors of acute symptomatic seizures (AS) and epilepsy after pediatric cerebral sinovenous thrombosis (CSVT).

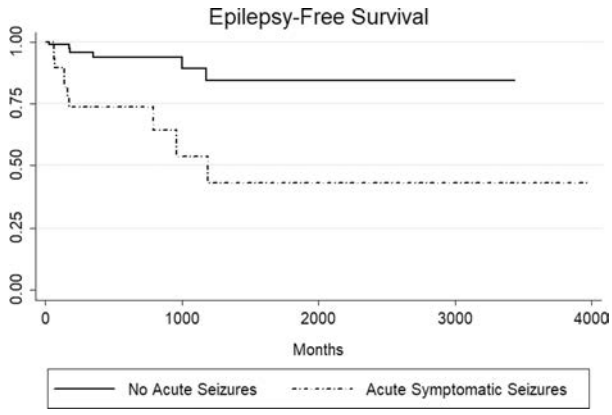


Figure Legend. Kaplan Meier curves demonstrating epilepsy-free survival among those with and without acute symptomatic seizures Abstract PL 1-5

Methods: We performed a retrospective analysis of 143 participants with neonatal or childhood CSVT confirmed on CT/CTV or MRI/MRV enrolled January 1, 2008 to December 31, 2020 from a single-center prospective consecutive stroke cohort. Medical records were reviewed for neuroimaging, electroencephalogram, and clinical data. AS were defined as seizures that occurred within 7 days of CSVT symptom onset. Epilepsy was defined as two or more unprovoked seizures at least 24 hours apart and >7 days from CSVT symptom onset. Survival analysis was used to evaluate the cumulative incidence of epilepsy. Cox proportional hazards models were used to evaluate risk factors for epilepsy.

Results: Of 143 subjects, 35 were neonates (24.5%), and among non-neonates, the median age was 6.1 years (IQR 1.6-11.8 years). AS occurred in 34 (24%) and epilepsy in 16 (11%). One-year and three-year epilepsy-free survival were 89% (95%CI 80-94%) and 79% (95%CI 65-88%). In multivariable analysis, AS (HR 3.73, 95%CI 1.24-11.24) and deep thrombus location (HR 3.45, 95%CI 1.01-11.77) predicted epilepsy. Pediatric Stroke Outcome Measure scores at last follow-up were worse in those with epilepsy (median score 1, IQR 1-5) compared to those without epilepsy (median score 0, IQR 0-1), p<0.001, rank-sum.

Conclusions: AS occurred in approximately one quarter of our cohort. At 3 years, nearly 80% were expected to be epilepsy-free. Those with epilepsy had worse outcomes than those without. Risk factors for epilepsy included AS and deep thrombosis.

Keywords: Stroke (including other Vascular Disorders)

PL1-6. White matter properties of the optics pathway in children with neurofibromatosis type 1 with and without optic pathway gliomas

Bruckert L (Stanford, CA), Lerma-Usabiaga G, Beres S, McKenna E, Yeom K, , Travis K, Campen C

Objective: Optic pathway glioma (OPG) is a childhood tumor of the visual pathway, which is often associated with the genetic disorder neurofibromatosis type 1 (NF1). As many as 15-20% of children with NF1 will develop an OPG, which can occur anywhere along the visual pathway including the optic nerves, chiasm, tracts, and radiations. Clinicians are unable to predict which gliomas will progress, needing treatment and which gliomas will stabilize or spontaneously regress. Describing the white matter characteristics of NF1- associated OPG is the first step in understanding tumor genesis in NF1. This study aims to characterize white matter properties of the entire optic pathway in children with NF1 with and without optic pathway gliomas.

Methods: Retrospective cohort study of 25 children with NF1 with OPGs (agemean= 9.5 y, 13 male), 21 children with NF1 without OPGs (agemean= 9.7 y, 12 male), and 31 age- and sex- matched controls (agemean= 9.5 y, 16 male), who underwent diffusion MRI at 3T (25 directions, b=1000 s/mm2, 1x b=0 volumes). We developed an automated pipeline to identify in each child the bilateral optic nerves, tracts, and radiations using probabilistic tractography. We extracted fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD) of these pathways and compared them across groups using mixed analyses of variance

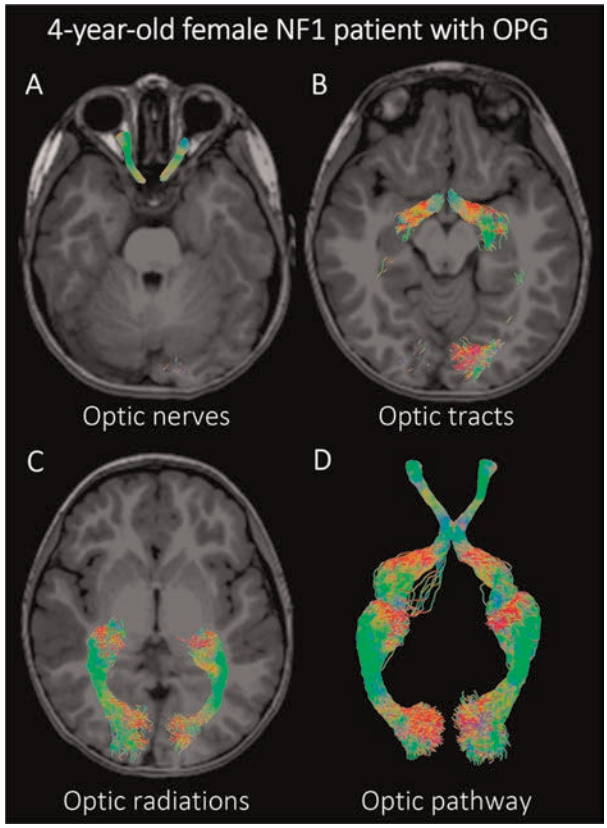


FIGURE 1. Tractography of the visual pathway. The streamlines from our automated tractography of the left and right optic nerves (A), optic tracts (B), and optic radiations (C) are overlaid on a T1-weighted image of a representative child with NF1 with optic pathway glioma (OPG). (D) 3D tract rendering of all three parts of the visual pathway of the same representative child. Red, green, and blue colors correspond to the diffusion RGB-color map and represent the direction of maximum diffusivity: red = left-right, green = anterior-posterior, blue = superior-inferior. Abstract PL 1-6

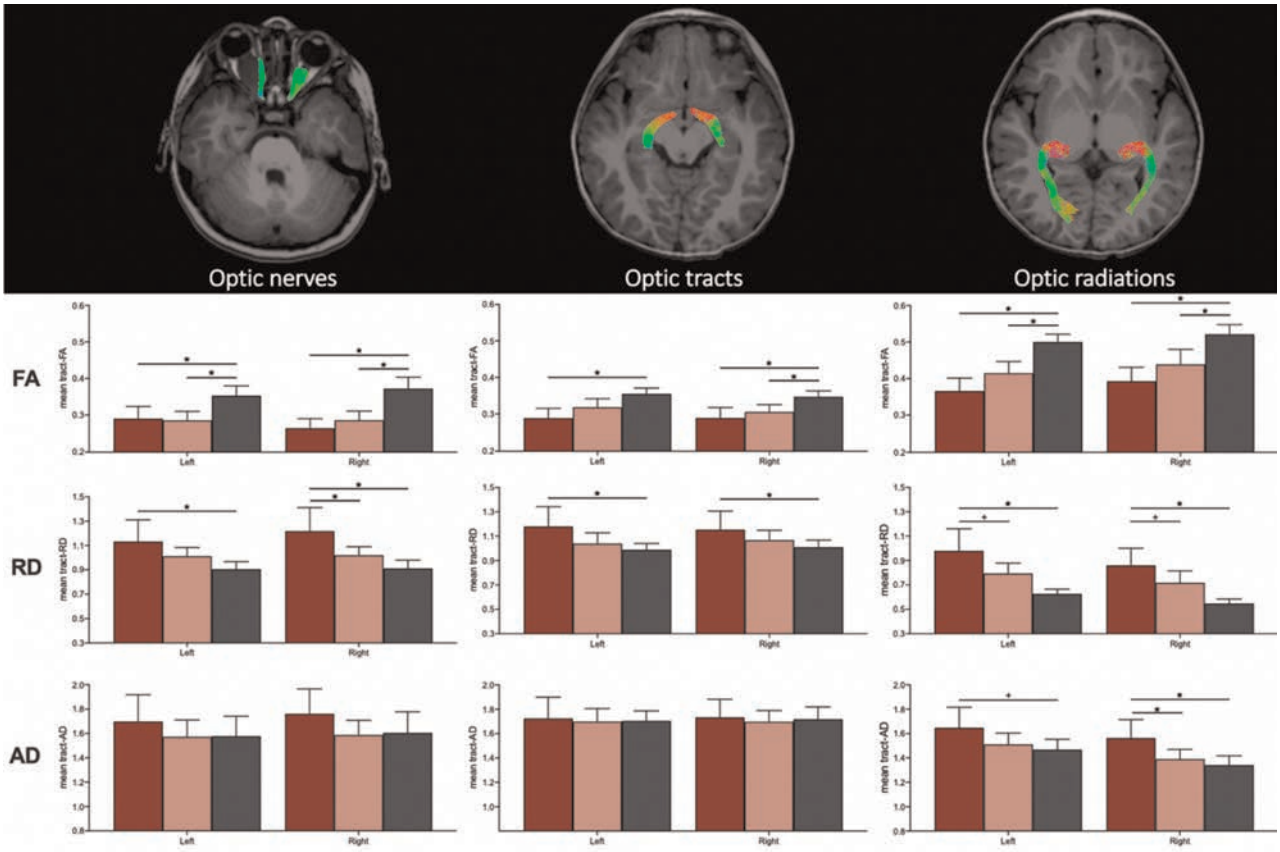


FIGURE 2. Mean tract-diffusion metrics of the visual pathway. Top row shows renderings of the optic nerves (left), tracts (middle), and radiations overlaid on T1-weighted images of another representative child with NF1 with optic pathway glioma (1-year-old male). Bar graphs below show mean tract-fractional anisotropy (FA, top), radial diffusivity (RD, middle), and axial diffusivity (AD, bottom) of the visual pathway plotted for each group (dark red = NF1 children with OPGs, light red = NF1 children without OPGs, grey = control children). Error bars indicate the 95% confidence interval. Mixed analysis of variance revealed a significant main effect of group for the entire visual pathway indicating that children with NF1 had lower FA but higher RD values in the optic nerves (FA: $p < 0.001$; RD: $p = 0.002$), tracts (FA: $p < 0.001$; RD: $p = 0.037$), and radiations (FA: $p < 0.001$; RD: $p < 0.001$). Significant differences in mean tract-diffusion metrics among the three groups as assessed by post hoc comparisons are indicated by an asterisk ($p < 0.05$, corrected for multiple comparison using Tukey's test). Abstract PL 1-6

(ANOVA) with hemisphere (left vs. right) as the within-subject and group (NF1 with OPG vs. NF1 without OPG vs. controls) as the between-subject and factor. We corrected for post-hoc multiple comparisons using Tukey's test.

Results: Using our automated tractography pipeline, we were able to reconstruct the optic nerves, tracts and radiations in most children (Figure 1). Compared to controls, children with NF1 had significantly decreased FA in all three parts of the visual pathway (Figure 2). FA did not significantly differ between children with NF1 with and without OPGs. Decreases in FA were predominantly driven by increase in RD in children with NF1 (Figure 2).

Conclusions: Microstructural differences were observed along the entire visual pathway in children with NF1 with and without OPGs compared to controls. Novel findings were that these differences could be examined and observed in the most anterior part of the visual pathway.

Keywords: Brain Tumors/Oncology, Neurocutaneous Disorders

PL1-7. Targeting USP7 as a Novel Treatment in Malignant Glioma

Song H (New York, NY), Cho H, Hoxha E

Objective: CNS tumors are the most common solid tumor in children. Glioblastoma (GBM) represents the most common primary malignant CNS tumor and carries dismal prognosis. Apoptosis evasion and treatment resistance in GBM stem-like cell (GSC) contributes to treatment failure in GBM. USP7 (also called HAUSP) deubiquitinase was recently implicated in selective cancers; however, role of USP7 in glioma remain poorly understood. Here, we report a novel role for USP7 in GBM.

Methods: We compared USP7 expression and protein level in glioma and patient- derived GSC to non-tumor counterparts. We examined mechanisms and effects of USP7 using gain- and loss-of-function manipulations on a series of functional assays using patient-derived GSC.

Results: USP7 expression and level are elevated in GBM compared to non-tumor brains, and high USP7 expression is associated with poor survival. USP7 is preferentially expressed

in GSC and is co-expressed with neural stem cell markers. Functional analyses show that knockdown of USP7 by shRNA (1) inhibits GSC growth, proliferation and tumor sphere formation and (2) induces apoptosis. Consistent with these findings, pharmacological inhibition of USP7 promotes GSC growth arrest and induces cell death, in part through decreasing HDM2 and upregulating p53 and p21, identifying USP7 as a potential druggable target in GBM treatment.
Conclusions: Collectively, these data define a novel role for USP7 in GBM malignant behavior and propose USP7 as a promising target in currently incurable malignant gliomas.
Keywords: Brain Tumors/Oncology, Translational/Experimental Therapeutics, Neuroscience

PL1-8. Cerebral Venous Sinus Thrombosis in Preterm Infants

Christensen R (Toronto, ON, Canada), Krishnan P, deVeber G, Dlamini N, MacGregor D, Pulcine E, Moharir M

Objective: Neonatal cerebral venous sinus thrombosis (CVST) can lead to severe brain injury and long-term neurodevelopmental impairments. Previous studies of neonatal CVST have mainly included term infants. In this study, we examined the clinical and radiological features, treatment and outcome of CVST in preterm infants.
Methods: This was a retrospective cohort study of preterm infants (gestational age <37 weeks) with radiologically confirmed CVST. All MRI/MRV and CT/CTV scans were re-reviewed by the study authors. Clinical and radiological data were analysed using descriptive statistics, ANOVA and chi-square tests.
Results: A total of 26 preterm infants with CVST (males 73%, mean gestational age: 33 ± 3.3 weeks) were included. Of these, 65% were late preterm, 27% very preterm and 8% extreme preterm. Neonatal comorbidities included infection (35%), surgery (23%), hypoxic ischemic encephalopathy (19%) and thrombophilia (19%). Most were symptomatic at presentation (seizures 50%, abnormal exam 50%). Radiological features included transverse sinus thrombosis (85%), periventricular (46%) and intraventricular (42%) hemorrhage and white matter lesions (19%). Most (69%) were treated with anticoagulants. Anticoagulation was not associated with new or worsening intracranial hemorrhage. There were no differences between treatment groups (anticoagulation vs. no treatment) in recanalization, clinical outcome or death. Clinical outcome at follow-up ranged from no impairment (50%), mild impairment (25%) and severe impairment (25%).
Conclusions: Preterm infants with CVST are often symptomatic, however up to one quarter may be asymptomatic. Preterm CVST was associated with a distinct pattern of brain injury including transverse sinus thrombosis, white matter injury and intraventricular hemorrhage. Anticoagulation treatment of preterm CVST appeared to be safe with no hemorrhagic complications.
Keywords: Neonatal & Fetal Neurology, Stroke (including other Vascular Disorders), Neuroimaging

PLATFORM SESSION 2: Thursday, October 13 (7:00 AM – 9:00 AM)

PL2-1. Estimating US Prevalence and Diagnosis Rates for Rare Developmental and Epileptic Encephalopathies (DEEs)

Sederman R (Morristown, NJ), Oldham M, Mahalingam R, Sullivan J

Objective: Prevalence estimates for DEEs rely on small patient samples or relative comparisons to pediatric epilepsy.[1] Over

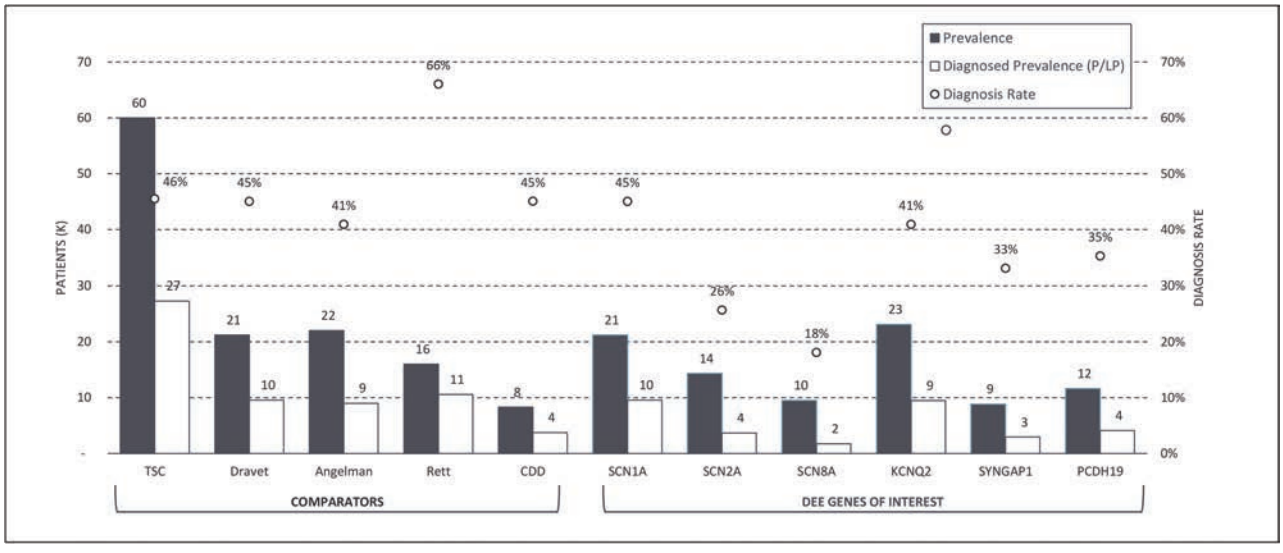


FIGURE 1. Prevalence, Diagnosed Prevalence, and Diagnosis Rates for Comparator Pediatric Seizure Conditions and Select DEE Genes Abstract PL 2-1

50% of patients with DEEs remain undiagnosed (lack of genetic testing, genetic heterogeneity, and phenotypic variability of DEEs[2,3]). Our objective was to develop data-driven, supportable estimates for US prevalence and diagnosis rates for select DEEs.
Methods: Using claims and genetic testing data (Nov 2019–Oct 2021), the model was initially developed for 5 pediatric seizure conditions with ICD-10 codes: TSC, Dravet, CDKL5, Angelman, Rett. Based on this analysis, we developed analogs and applied them to select genes associated with DEEs without an ICD-10: SCN2A, SCN8A, KCNQ2, PCDH19, SYNGAP1, as well as SCN1A (associated with Dravet).
Results: 22.4K patients had claims for analogs with ICD-10s. 3,299 patients had a claim for genetic testing. 545 patients had a pathogenic/likely pathogenic finding in a gene of interest. Prevalence estimates ranged from 8,830 (SYNGAP1) to 23,124 (KCNQ2). Calculated diagnosis rate ranged from 18% (SCN8A) to 41% (KCNQ2). (See Figure 1.) Higher projected DEE diagnosis rates were correlated with a higher proportion of pathogenic/likely pathogenic results in the genetic testing data[4-11].
Conclusions: The methodology provides a defensible approach to quantify prevalence and diagnosis rate for conditions that lack robust published epidemiology. This approach is calibrated for DEEs specifically but may be considered for other genetic diseases that have overlapping symptoms and are included on the same multi-gene panel. Improved quantification of prevalence and diagnosis rates can help with patient identification and support the opportunity for new drug development.
Keywords: Rare Diseases, Genetics

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PL2-2. Loss of DEPDC5 after cortex formation is sufficient to cause focal seizures in a mouse model

Yuskaitis C (Boston, MA), Groff K, Morici C, Modasia J, Osipovich M, Liang Y, Sahin M

Objective: *DEPDC5*-related epilepsy is the most common cause of familial focal epilepsy and an increase risk of Sudden-Unexplained Death in Epilepsy (SUDEP). It remains unknown whether seizures due to DEPDC5 loss-of-function are a result of *in utero* cortical developmental defects or later neuronal dysfunction of mTORC1 signaling mechanisms.
Methods: We developed a postnatal, adeno-associated virus (AAV) mediated focal cortical *Depdc5* knockout mouse model. Viral vectors containing either 2/8AAV-GFP-Cre or control 2/8AAV-GFP were injected into the unilateral motor cortex of postnatal day zero (P0) *Depdc5* floxed (*Depdc5$^{f/f}$* or *Depdc5$^{f/-}$*) mouse pups. We analyzed cortical layer markers at P10 and mTOR activity by phosphorylation of S6 (pS6) and pentylenetetrazol(PTZ)-induced seizures at 6-10 weeks of age.
Results: The AAV-Cre injected hemisphere of injected *Depdc5$^{f/f}$* mice resulted in a significant reduction of DEPDC5 expression and increase in neuronal pS6 compared to the contralateral hemisphere by western blot and immunohistochemistry. No changes were identified in control AAV-GFP injected mice. Cortical lamination was not disrupted by AAV-Cre or AAV-GFP injection. Injection of PTZ (65mg/kg) lead to seizures in 95% (21/22) of AAV-Cre injected *Depdc5* mice compared to 64% (9/14) of AAV-GFP injected *Depdc5* mice ($p=0.01$, Chi-square). Of those with seizures, 38% (8/21) of AAV-Cre injected mice had seizure-induced death compared to none of the AAV-GFP injected mice ($p=0.03$, Chi-square).
Conclusions: Postnatal DEPDC5 loss without disruption of early cortical defects is sufficient to cause epilepsy and SUDEP. Restoration of DEPDC5 function represents a viable treatment approach.
Keywords: Epilepsy/Sleep, Genetics, Neuroscience

PL2-3. Machine Learning approaches to classifying and predicting disease progression in Adrenomyeloneuropathy

Turk B (Baltimore, MD), Fine A, Fan Y, Wei J, Keller J, Raymond G, Unberath M, Fatemi A

Objective: Adrenomyeloneuropathy (AMN) is the slow progressive phenotype of adrenoleukodystrophy (ALD). The challenge in AMN is assessing the disease trajectory: Disease course has both variable progression rates and differences in sensory vs motor dysfunction. There is currently no prognostic tool for AMN disease progression. The objectives of this study were 1) to explore and cluster disease trajectories, and 2) develop tools to predict individual disease progression.

Methods: Walking-test, sensorimotor data from the laboratory measured gait, sway, and strength as well as neurological function were used to generate mean individual patient trajectories from 148 patients. Feature selection and clustering methods were used to generate initial labels. This pseudo-ground-truth was then used to train and optimize a Bayesian neural network (BNN), using the cross-entropy between the network's class prediction and the unsupervised cluster assignment.

Results: 2-year cluster analyses show 'slow progressors' dysfunction increases in sensory domains i.e. sway amplitude, whereas 'fast progressors' show both sway, as well as hip

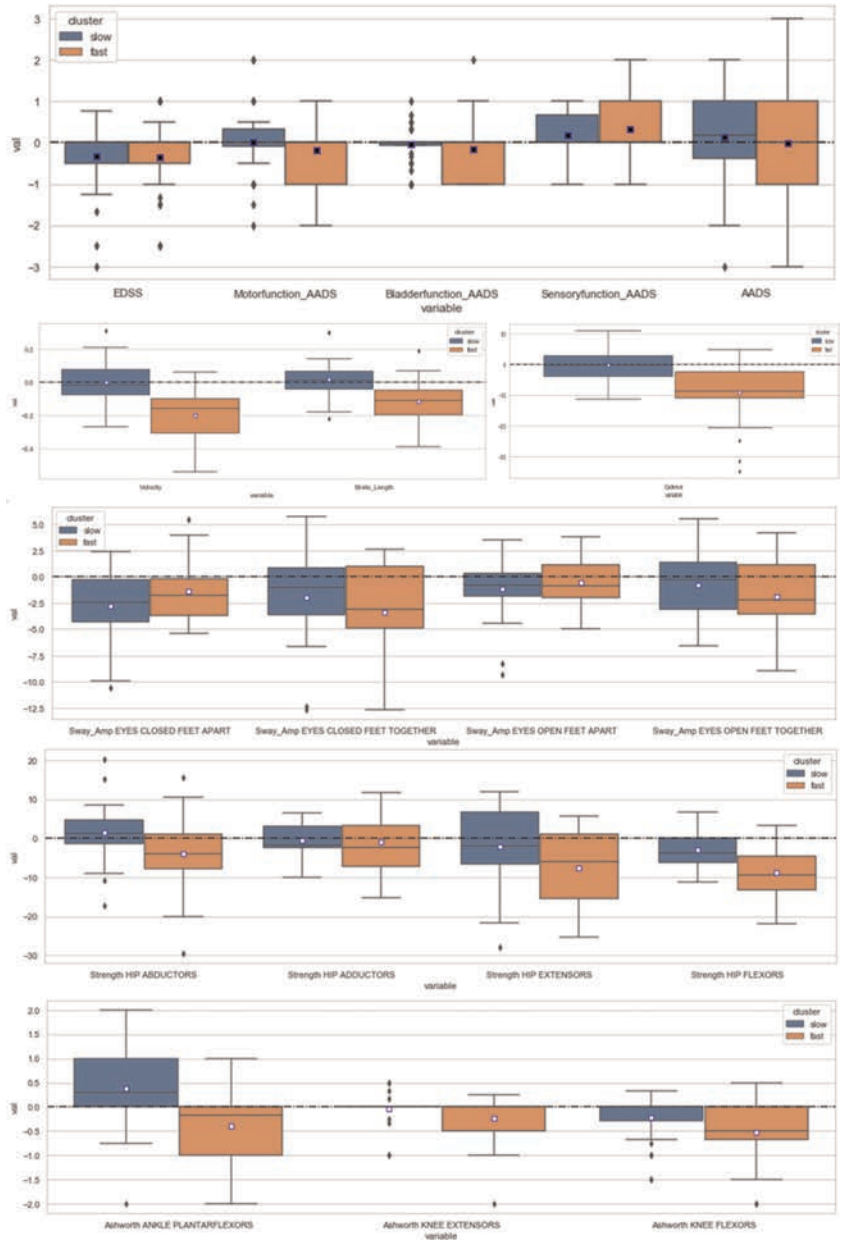


FIGURE 1 2-year mean delta of Adrenomyeloneuropathy (AMN) disease trajectories majority vote final clusters. EDSS and AADS not used during clustering. Absolute values of each variable with, transformed direction, whereby higher values = improvement, lower = worse/dysfunction. n=148 Abstract PL 2-3

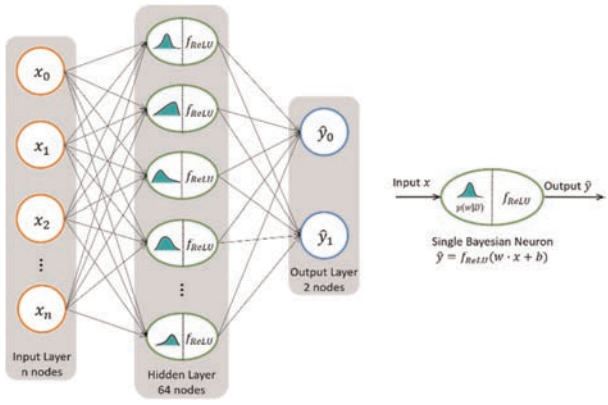


FIGURE 2 – Bayesian Neural Network (BNN) architecture used to predict disease progression by reporting measure of uncertainty, i.e. % chance of individual patient being fast or slow progressor. Abstract PL 2-3

strength and 25ft walking tests. These groups did not correlate with 2-year change in EDSS (Expanded Disability Status Scale). A BNN using 1 year of patient data demonstrated AUCs of predicting 1 year disease progression of 0.904, 2-year disease progression of 0.821.

Conclusions: This study demonstrates the feasibility of both using machine learning methods in creating trajectory labels, providing clinical insight into AMN progression, as well as using deep learning to predict an individual's rate and phenotypic progression subtype. Using an AI-based tool to predict these may assist therapeutic management and facilitate patient selection for clinical trial.

Keywords: Rare Diseases

PL2-4. From bedside to bench and clinical practice: A comprehensive study of two rare mitochondrial neurodegenerative diseases MELAS and LHON-Plus and functional Investigations of Mitochondrial Energy Metabolism

Gropman A (Washington, DC), Uittenbogaard M, Chiaramello A

Objective: MELAS (mitochondrial encephalopathy, lactic acidosis, stroke-like episodes) and LHON-Plus (Leber's hereditary optic neuropathy-Plus) are progressive neurodegenerative diseases with overlapping and divergent clinical neurological symptoms. Patients harbor maternally inherited pathogenic variants affecting the oxidative phosphorylation (OXPHOS) system and share a common molecular etiology of Complex I deficiency. The objectives were to elucidate the pathogenic molecular mechanisms of MELAS and LHON-Plus and unmask the molecular etiology shared by these two divergent patient populations, and discover shared biochemical endpoints based on the patient's signature of mitochondrial energy metabolism in the context of their clinical phenotypes and heteroplasmy.

Methods: 20 MELAS patients and 20 LHON-Plus were recruited. Heteroplasmy was measured by long-range PCR followed by Next-Generation Sequencing. Live-cell energy metabolic assays were performed on patient-derived fibroblasts using the Seahorse technology.

Results: Our live-cell bioenergetic assays revealed a deficit in the spare energy capacity hindering the ability to avert bioenergetic exhaustion in MELAS and LHON-Plus fibroblasts. All the LHON-Plus fibroblasts had a reduced basal OXPHOS. Regardless of their heteroplasmic load and mitochondrial genotype, MELAS and LHON-Plus fibroblasts showed a decreased spare respiratory capacity, a key bioenergetic parameters to avert chronic energy exhaustion upon high energy expenditure. The amplitude of this deficit is not dictated by the level of heteroplasmy.

Conclusions: Clinically, this deficit in spare energy capacity has profound clinical implications in two systems known to be targeted in these patient populations: muscle and brain. We conclude that spare energy capacity is a relevant biochemical endpoint to test therapeutic candidate molecules in these patients.

Keywords: Translational/Experimental Therapeutics, Rare Diseases, Neurometabolic Disorders

PL2-5. Genetic variation in the DExH-box helicase DHX9 perturbs neurodevelopment & peripheral nerve axon function

Calame D (Houston, TX), Garrett L, Jolly A, Dawood M, Kurolap A, Henig N, Fatih J, Herman I, Du H, Mitani T, Becker L, Rathkolb B, Seisenberger C, Marschall S, Hunter J, Gerard A, Heidlebaugh A, Challman T, Spillmann R, Jhangiani S, Coban-Akdemir Z, Lalani S, Revah-Politi A, Iglesias A, Guzman E, Baugh E, Boddaert N, Rondeau S, Clothide O, Barcia G, Tan Q, Thiffault I, Sheikh K, Biliciler S, Mei D, Melani F, Shashi V, Yaron Y, Undiagnosed Diseases Network, Marafi D, Pehlivan D, Posey J, Gibbs R, Gailus-Durner V, Guerrini R, Fuchs H, Hrabě de Angelis M, Hölter S, Lupski J

Objective: The DExD/H-box superfamily consists of 58 RNA helicases. Several paralogues underlie neurodevelopmental disorders (NDD), yet most lack disease associations and have unknown functions in neuronal homeostasis. *DHX9*, the DExH-box helicase 9 gene, is highly expressed in the developing and adult nervous system and regulates fundamental processes including transcription, R-loop resolution, and homologous recombination (HR); yet its function in the nervous system remains enigmatic.

Methods: To explore DHX9's role in the human nervous system, we performed a primary analysis of >30,000 exomes and genomes and searched GeneMatcher for heterozygous, ultra-rare, predicted damaging *DHX9* variants due to *DHX9*'s severe constraint against missense and loss-of-function (LoF) variation in gnomAD. *Dhx9*$^{-/-}$ mice were generated using International Mouse Phenotyping Consortium 'knockout first' targeting strategy and underwent detailed phenotypic characterization.

Results: Genomic analyses identified 16 individuals with qualifying *DHX9* variants and NDDs or axonal Charcot-Marie-Tooth disease (CMT2). Parental genotyping

demonstrated *DHX9* variants occurred *de novo* (11 trios available). Heterozygous *DHX9* missense variants clustered in functional protein domains required for helicase activity, nucleic acid binding, or nuclear localization. LoF variants caused mild NDD, whereas missense variants caused CMT2 and mild or severe NDD. *Dhx9*$^{-/-}$ mice demonstrate neurologic abnormalities including hypoactivity in novel environments, tremor, reduced grip strength and body mass, and sensorineural hearing loss.

Conclusions: These data provide compelling evidence for *DHX9* variation as a cause of autosomal dominant (AD) NDD or CMT2, implicate biologically plausible disease mechanisms, and dissect the role of DHX9, R-loops, HR, and single- and double-strand DNA break repair in neurodevelopment, neurodegeneration, & genomic stability.

Keywords: Genetics, Rare Diseases, Neuromuscular Disorders

PL2-6. The Clinical, Molecular and Neuroimaging Spectrum of ZFYVE26-Related Hereditary Spastic Paraplegia (SPG15) – A Cross-Sectional Analysis of 36 Patients

Saffari A (Boston, MA), Neuser S, Strelko O, Mo A, Rosengarten H, Jordan C, Davis M, Sahin M, Blackstone C, Yang E, Ebrahimi-Fakhari D

Objective: To describe the clinical and molecular features of *ZFYVE26*-related hereditary spastic paraplegia (HSP) in order to promote clinical trial readiness.

Methods: 36 patients with bi-allelic variants in *ZFYVE26* were recruited from our Registry for Early-onset Hereditary Spastic Paraplegia (NCT04712812). A cross-sectional analysis was conducted using standardized questionnaires. Disease severity was quantified using the Spastic Paraplegia Rating Scale (SPRS). Results were compared to 66 previously published cases.

Results: While symptom onset was in early childhood, a molecular diagnosis was reached at a median age of 14.5 years (IQR=5), indicating a significant diagnostic delay. 39 distinct variants in *ZFYVE26* were identified. Most patients presented with developmental delay or a learning disability. This preceded the onset of motor symptoms by several years. Spasticity in the lower extremities involved the ankles first, with subsequent progression to proximal areas. Spasticity in the upper extremities was seen in a subset (33%, mean age: 35.7±3.1 (SD) years). Extrapyramidal movement disorders and neurogenic bladder dysfunction were common. Swallowing dysfunction was reported in 4 individuals with advanced disease. Brain MR imaging showed a thin corpus callosum and signal changes of the anterior forceps as well as non-specific cortical and cerebellar atrophy in a subset of patients. The mean SPRS score was 23.2±12.5 (SD), with a median spasticity subscore of 6 (IQR=5). Both scores showed moderate correlation with disease duration (R_{adj}^2=0.4 and R_{adj}^2=0.41).

Conclusions: We delineate the clinical, neuroimaging and molecular spectrum of *ZFYVE26*-related HSP, demonstrate the progressive evolution of the disease and validate clinical rating scales as quantitative disease monitoring tools.

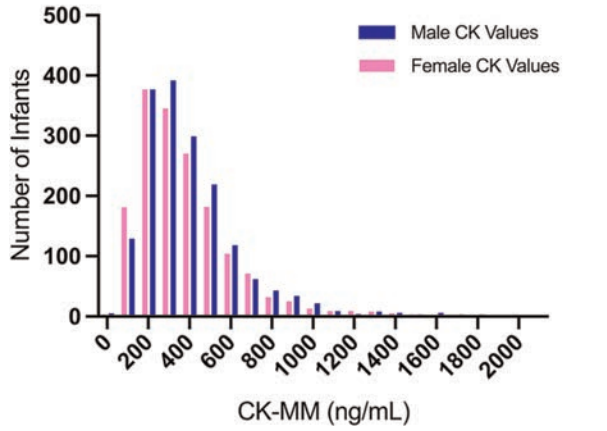
Keywords: Movement Disorders (including Cerebral Palsy), Rare Diseases, Genetics

PL2-7. Preliminary creatine kinase muscle isoenzyme values from a supplemental newborn screening program for Duchenne muscular dystrophy

Chrzanowski S (Boston, MA), Iragavarapu M, Sheldon Y, Ghosh P, Darras B, Parad R

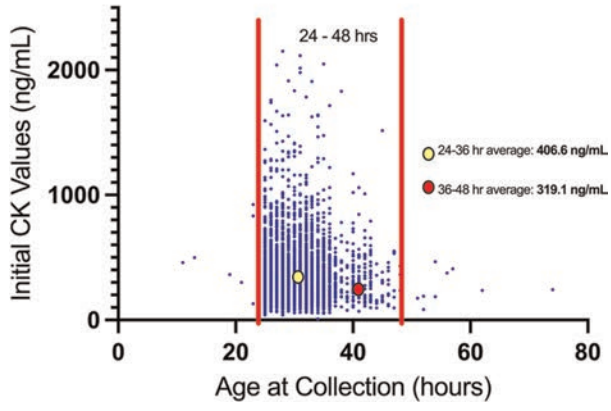
Objective: Duchenne muscular dystrophy (DMD) is not currently included in the federal Recommended Universal Screening Panel for treatable newborn screening (NBS) disorders. With new modifying therapies and improved screening methods, NBS for DMD may now be justified. We demonstrate the feasibility of using a DMD NBS algorithm based on single dried bloodspot (DBS) creatine kinase muscle isoenzyme (CK-MM) and *DMD* next-generation sequencing.

Figure 1. Distribution of Initial CK-MM Values



Abstract PL 2-7

Figure 2. CK-MM vs. Age at Collection



Abstract PL 2-7

Methods: An extra DBS was obtained when the routine state mandated NBS sample was collected. After an FDA approved CK-MM immunoassay was performed, *DMD* NGS was performed for when [CK-MM] was greater than 97.5%. We describe [CK-MM] as a function of age, APGAR score, biologic sex, and mode of delivery.

Results: Approximately 80% of families (n=3,395) opted for DMD NBS between 6/7/21 and 2/3/21 at Brigham and Women's Hospital. [CK-MM] 25% and 75% interquartile ranges were 223 ng/mL and 489 ng/mL, with a mean of 396 ± 278 ng/mL. Mean CK-MM decreased significantly from 406 to 319 ng/mL between 24 and 48 hours of life. NGS was performed on 82 infants with [CK-MM] above the cutoffs, though, no NGS results have diagnosed DMD to date. Lower APGAR scores were associated with higher [CK-MM].

Conclusions: Optional NBS for DMD is feasible in conjunction with current NBS infrastructure. CK-MM values in newborns unaffected by DMD decline between 24 and 48 hours of life, during the state mandated times of collection. Based on our cutoffs, we have not yet detected a Duchenne affected newborn, though optimization of the screening algorithm and process continues.

Keywords: Neuromuscular Disorders, Neonatal & Fetal Neurology, Rare Diseases

PL2-8. Low Diagnostic Yield from Biochemical CSF Neurotransmitter Testing in Infants

Kessler R (Philadelphia, PA), Patel A, Fung F, Kessler S

Objective: Neurotransmitter (NT) disorders arise from defects in neurotransmitter synthesis, metabolism, or transport. Diagnosis by biochemical analysis of cerebral spinal fluid (CSF) is labor intensive, costly, and requires lumbar puncture. Widespread use of massively parallel genetic sequencing may obviate the need for CSF analysis. We describe the diagnostic yield of CSF NT testing in an unselected population of infants undergoing testing for any presentation.

Methods: Children's Hospital of Philadelphia electronic medical records were queried to identify all CSF NT tests sent for analysis between 1/1/2008 and 12/31/2017. Patients were included if they were less than one year of age at the time of testing and excluded if they had inadequate clinical information or missing test results. The primary endpoint was the proportion of patients with a diagnostic test result.

Results: Of the 192 patients analyzed, median age was 3 months (range 0-11). Seizures were the primary presenting sign in 143 patients (75%) (Table 1). Seven patients (3.6%) had a potentially diagnostic abnormal CSF NT (Table 2). Of the total cohort, 86 (45%) received an etiologic diagnosis, and of these, 50 (58%) diagnoses came from genetic testing (2% SNP array, 32% gene panel, 42% whole exome sequencing, 24% targeted genetic testing).

Conclusions: The diagnostic yield of biochemical CSF NT testing was low. Of patients without known etiologic diagnoses at the time of testing, CSF NT led to an etiologic diagnosis in one patient (0.5%), and possibly one other. This study provides evidence that may be useful in crafting contemporary infantile encephalopathy diagnostic guidelines.

Keywords: Neurometabolic Disorders, Genetics

TABLE 1. Characteristics of the cohort (N=192). Abstract PL 2-8

Characteristic	Patients N (%)
Demographics	
Female	95 (49)
Race	
White	117 (61)
Black	35 (18)
Asian	9 (4.7)
Native American/ Alaska Native	1 (0.5)
Other	27 (14)
Hispanic or Latino	19 (10)
Clinical Presentation	
Gestational Age > 37 Weeks	156 (85)
Microcephalic	12 (22)
Dysmorphic	12 (22)
Seizures at Time of Presentation	143 (75)
Focal	73 (51)
Generalized	69 (48)
Infantile Spasms	66 (96)
Unknown	1 (0.7)
Movement Disorder	34 (18)
Hypotonia	81 (44)
Hypertonia	38 (21)
Abnormal Eye Movements[1]	23 (13)
Developmental Delay	72 (39)
Dysautonomia	4 (2.2)
Apnea	24 (13)
Family History	
Consanguinity	7 (4)
Epilepsy, Movement Disorder, or Developmental Delay	14 (8)

[1]Not related to seizures

TABLE 2. Patients with potentially diagnostic CSF NT results. Abstract PL 2-8

Patient	CSF NT abnormality	Suggested Disorder	Presumptive treatment	Genetic Testing performed	Final diagnosis
1	Low homovanillic acid	Tyrosine hydroxylase deficiency	Carbidopa/levodopa	Targeted gene sequencing	*SMARD1* pathogenic variant
2	Elevated neopterin, tetrahydrobiopterin at upper limit of normal	Aicardi-Goutières Syndrome	None	Microarray, targeted gene sequencing	Aicardi-Goutieres Syndrome
3	Elevated 3-O-methyldopa, elevated Pyridoxal 5'-phosphate	Pyridoxal 5'-phosphate (P5P) oxidase deficiency	P5P supplementation	Epilepsy panel, microarray, targeted gene sequencing	*SCN2a* pathogenic variant
4	Low homovanillic acid (P5P not tested)	Dopamine metabolism defect	None	Epilepsy panel, microarray, mitochondrial panel, targeted gene sequencing	*PNPO* pathogenic variant
5	Low homovanillic acid, 5-methyltetrahydrofolate at lower limit of normal	Cerebral folate transport deficiency	Folinic acid	Epilepsy panel, microarray, targeted genetic sequencing	None
6	Elevated neopterin	Aicardes-Goutieres syndrome	None	Microarray, targeted gene sequencing	Aicardi-Goutieres Syndrome
7	Low homovanilic acid, low 5-hydroxyindoleacetic acid	Defect in tetrahydrobiopterin metabolism	L-dopa/tryptophan and synthetic tetrahydrobiopterin	Microarray, whole exome sequencing, mitochondrial panel, other gene panels	None

PLATFORM SESSION 3: Thursday, October 13 (7:00 AM – 9:00 AM)

PL3-1. The Relationship between Sleep, Cognition and Behavior in Children with Newly-Diagnosed Epilepsy over 36 months

Eisner J (Sacramento, CA), Oyegbile-Chidi T, Harvey D, Stone C, Dunn D, Jones J, Byars A, Hermann B, Austin J

Objective: Children with epilepsy experience more sleep, behavioral and cognitive challenges than healthy children. However, the literature is limited in describing the relationship between sleep, epilepsy, cognition and behavior and their interactions over time. This study aims to understand the relationship between sleep, cognition, mood and behavior in children with new-onset epilepsy as assessed by multiple informants at multiple time periods using multiple dependent measures.

Methods: 332 participants ages 6-16 years old were recruited within 6 weeks of their first seizure. The comparison group consisted of 266 healthy siblings. Participants underwent sleep evaluation by a parent, cognitive evaluation, and behavioral and mood evaluation. These evaluations were completed at baseline, 18 months later, and 36 months later.

Results: Compared to controls, children with new-onset epilepsy had more sleep disturbance, higher rates of behavioral problems and depression, and lower cognitive scores over the 36-month study. Sleep was significantly correlated with behavior, cognitive scores and depression. Children with epilepsy were more likely to have abnormal sleep and those children had higher rates of behavioral problems, depression and cognitive impairment compared to children in the normal sleep group.

Conclusions: This is the first demonstration of the nature, strength and persistence of the relationship between sleep, cognition and behavior over time in a large cohort of children with new-onset epilepsy, as assessed by multiple informants. The results indicate that children with epilepsy are at a high risk of sleep, cognitive, behavioral and mood problems. Therefore, early screening may be essential for optimizing quality of life.

Keywords: Epilepsy/Sleep, Cognitive/Behavioral Disorders (including Autism)

PL3-2. Epilepsy Outcomes for Surgical Candidates with Infantile Spasms

Singh A (Boston, MA), Briscoe Abath C, Hadjinicolaou A, Salussolia C, Yuskaitis C, Harini C

Objective: Epilepsy surgery is an option for pharmacoresistant infantile spasms (IS) with epileptogenic lesions. We compared seizure outcomes among lesional IS patients (eligible for resective epilepsy surgery) who had medical-therapy alone *versus* those who underwent additional surgical therapy (lobar, multilobar or hemispherectomy).

Methods: We conducted a retrospective case-control study of all IS patients evaluated at our center born between 2013-2020. Among 408 screened patients, 76 (19%) were found to be candidates for resective epilepsy surgery. Data collection included demographic, clinical, imaging, electroencephalographic, developmental and seizure outcome (Engel 1-2 deemed favorable).

Results: Among the 76 lesional IS patients (51% male), 19 were excluded due to insufficient data or inadequate length of follow-up (<12 months). For the remaining 57 patients, median age at spasm-onset was 5 months and median duration of follow-up since spasm-onset was 43 months.53% (n=30) patients were managed medically-only, 18 (60%) were seizure/spasm-free, 12 (40%) had ongoing seizures (including 5 with ongoing spasms).Epilepsy surgery (n=27) performed at median age of 18 months resulted in favorable outcome in 22 (81%). Incomplete resection had poorer seizure outcome ($p<0.05$). Hemispherectomy was the most common surgery (60%), followed by lobectomy/lesionectomy (30%), and multilobar resection/disconnection (10%). Seizure outcomes did not vary between early (within 6 months of spasm onset) vs later surgery.

Conclusions: Among IS patients eligible for epilepsy surgery, nearly half were medically managed with successful elimination of seizures in 60%. After epilepsy surgery, favorable seizure outcome occurred in 81% with significantly better results following complete resection.

Keywords: Epilepsy/Sleep, Neuroimaging

PL3-3. Randomized Controlled Trial of Erythropoietin for Neonatal Hypoxic-Ischemic Encephalopathy (HIE)

Wu Y (San Francisco, CA), Maitre N, Chang T, Glass H, Kuban K, Gonzalez F, Mayock D, O'Shea M, Lowe J, Wisnowski J, Comstock B, Heagerty P, Juul S

Objective: To determine the safety and efficacy of erythropoietin as a novel treatment in newborns undergoing therapeutic hypothermia (TH) for HIE.

Methods: In a phase III multicenter, randomized, double-blind trial (HEAL, NCT02811263), 501 infants ≥36 weeks' gestation undergoing TH for moderate/severe HIE received erythropoietin 1000 U/kg or saline placebo IV within 26 hours of birth, and at 2, 3, 4, and 7 days of age. Primary outcome was death or neurodevelopmental impairment (NDI) of any severity at 22-36 months of age. NDI was defined as cerebral palsy, GMFCS ≥1, or cognitive score < 90 on Bayley III.

Results: Baseline features did not differ significantly between erythropoietin (N=257) and placebo (N=243) groups (Table 1). There was no significant difference in the rate of death or NDI between erythropoietin and placebo groups (53% vs. 50%; RR 1.03, 95% CI 0.86-1.24, Figure 1). There was no modification of treatment effect according to sex or HIE severity. The percentage of infants that experienced each pre-specified type of serious adverse event (SAE) did not differ significantly by treatment group. However, the average number of SAEs per subject was higher in the erythropoietin group (0.86 vs. 0.67; RR 1.26, 95% CI 1.01-1.57). The proportion of infants with 1 or more SAE was higher in the erythropoietin group (53% vs. 44%; RR, 1.21, 95% CI 1.00 to 1.45).

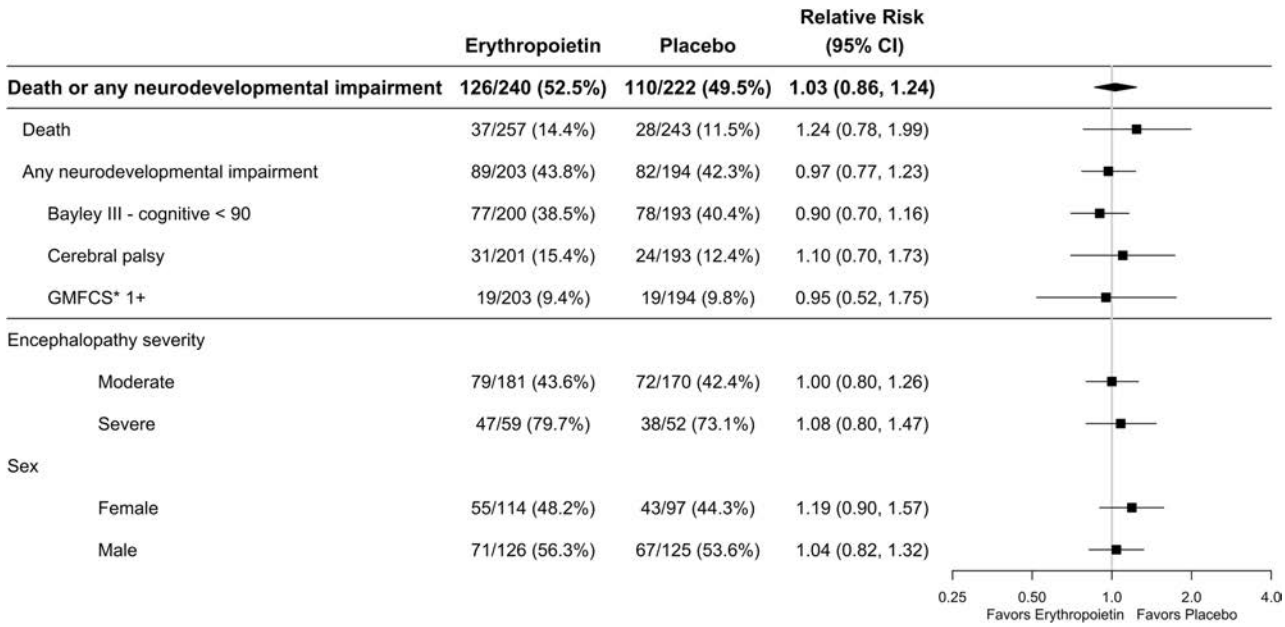


FIGURE 1. Forest plot of effect of erythropoietin on primary outcome of death or any neurodevelopmental impairment, stratified by sex and severity of encephalopathy. Abstract PL 3-3

TABLE 1. Baseline characteristics of HEAL study participants, by treatment group. Abstract PL 3-3

	Erythropoietin	Placebo	Overall
Maternal characteristics, n (%)	N=257	N=243	N=500
Race			
White	183 (71%)	173 (71%)	356 (71%)
Black	28 (11%)	38 (16%)	66 (13%)
Asian	18 (7.0%)	16 (6.2%)	33 (6.6%)
Other	28 (11%)	17 (6.0%)	45 (9.0%)
Hispanic ethnicity	63 (25%)	59 (24%)	122 (24%)
Age (years), mean (SD)	29.6 (6.3)	30.0 (6.6)	29.6 (6.3)
Education, high school or less	102 (40%)	83 (34%)	185 (37%)
Parity = 1 (including subject)	145 (56%)	141 (58%)	286 (57%)
Pregnancy and Delivery Complications			
Maternal chorioamnionitis or fever	38 (15%)	27 (11%)	65 (13%)
Maternal pre-eclampsia or eclampsia	22 (8.6%)	23 (9.5%)	45 (9.0%)
Gestational diabetes	33 (13%)	25 (10%)	58 (12%)
Maternal obesity (body mass index >30)	47 (18%)	42 (17%)	89 (18%)
Sentinel event	71 (28%)	72 (30%)	143 (29%)
Shoulder dystocia	14 (5.4%)	18 (7.4%)	32 (6.4%)
Placental abruption	40 (16%)	31 (13%)	71 (14%)
Prolapsed cord	10 (3.9%)	13 (5.3%)	23 (4.6%)
Uterine rupture	13 (5.1%)	11 (4.5%)	24 (4.8%)
Cesarean section delivery	170 (66%)	159 (65%)	329 (66%)
Outborn delivery	214 (83%)	201 (83%)	415 (83%)
Infant Characteristics			
Female	122 (48%)	103 (42%)	225 (45%)
Birth weight (grams), mean (SD)	3332 (572)	3414 (614)	3372 (594)
Gestational age (weeks), mean (SD)	39.1 (1.4)	39.2 (1.5)	39.1 (1.5)
5 minute Apgar, median (IQR)	3 (2, 5)	3 (2, 5)	3 (2, 5)
10 minute Apgar, median (IQR)	5 (3, 7)	5 (3.8, 6)	5 (3, 7)
Resuscitation > 10 minutes[†]	243 (95%)	217 (89%)	460 (92%)
Lowest pH[‡], mean (SD)	6.95 (0.17)	6.91 (0.17)	6.93 (0.17)
Worst base deficit[§], mean (SD)	18.0 (6.0)	18.5 (6.8)	18.3 (6.4)
Severe encephalopathy[§]	59 (23%)	54 (22%)	113 (23%)

[†]Required ongoing resuscitation with chest compressions and/or mechanical ventilation at 10 minutes of age.
[‡]Worst pH and base deficit among cord arterial, cord venous, and arterial blood gas samples taken before 60 minutes of age.
[§]Severe encephalopathy as defined by Sarnat.

Conclusions: Erythropoietin administered to newborns undergoing TH did not reduce the risk of death or NDI. The practice of adding erythropoietin to TH when treating HIE is unwarranted.
Keywords: Neonatal & Fetal Neurology, Translational/ Experimental Therapeutics

PL3-4. Early Biomarkers in the Prediction of Later Functional Impairment in Term Children with Cerebral Palsy

Eisman S (Montreal, QC, Canada), Husein N, Oskoui M, Kirton A, Shevell M

Objective: To identify possible early biomarkers that could predict later functional capabilities in children at-risk for cerebral palsy (CP).
Methods: Data from 869 term children with CP were extracted from the Canadian Cerebral Palsy Registry (CCPR). Univariate analyses were conducted to measure the association between readily available objective early biomarkers (neonatal encephalopathy [NE], cord or first hour of life pH, magnetic resonance imaging [MRI]) and functional outcomes such as mobility and feeding status. This was followed by multivariable regressions modeled to study whether adding predictors would affect the strength of the observed association.
Results: Patients with NE have higher odds of having an assigned GMFCS level of IV-V (odds ratio [OR] 2.87, 95% confidence interval [CI] 2.07-3.97), and are more likely to require dependent tube feeding (OR 2.09, 95% CI 1.12-3.88). This was similarly seen in patients with MRI findings of deep gray matter injury, watershed injury, near total brain injury and/or cortical malformation [mobility status (OR 5.13, 95% CI 3.73-7.11) and feeding status (OR 4.87, 95% CI 2.57-9.75)]. Patients with cord or first hour of life pH ≤ 7 were also more likely to predict dependent mobility status (OR 2.86, 95% CI 1.76-4.69), however, not significantly more likely to predict eventual dependent feeding status (OR 1.47, 95% CI 0.58-3.32).
Conclusions: This study demonstrates that NE, MRI findings and cord or first hour of life pH can reliably predict later cerebral palsy related functioning. These associations can be used to inform and clarify early prognosis discussions between caregivers and health professionals.
Keywords: Movement Disorders (including Cerebral Palsy), Neonatal & Fetal Neurology

PL3-5. Comparison of Impairment in Functional Tic Disorders versus Tourette Syndrome

Larsh T (Cincinnati, OH), Wu S, Gilbert D

Objective: The Mini-Child Tourette Syndrome Impairment Scale (mini-CTIM) is a validated clinical tool for assessing, in children and adolescents with tic disorders, tic and non-tic related impairment in home, school, and social settings. Recently, in the context of the COVID-19 pandemic, there has been a dramatic increase in youth presenting with new

		Functional Tics (n=89)	Tourette Syndrome (n=89)	Effect (TS)	SE	DF	t/z value	p-value
Age, mean (SD)		15.6 (2.0)	15.1 (2.1)					0.13
Sex, n (%)		83 F (93.2%)	42 F (47.2%)					< 0.001
Mini-CTIM-C, mean (SD)	Tic	9.9 (8.9)	8.6 (8.7)	-2.4	1.6	153	-1.47	0.15
	Non-Tic	11.1 (9.4)	11.2 (9.1)	-1.3	1.9	128	-0.96	0.49
Mini-CTIM-P, mean (SD)	Tic	10.0 (8.2)	8.6 (7.7)	-2.1	1.4	166	-1.48	0.14
	Non-Tic	10.3 (8.7)	9.2 (7.9)	-1.4	1.6	142	-0.88	0.37
Brought to ED because of movements, n (%)	Yes	27 (31.0%)	10 (11.3%)	-0.89	0.45	171	-1.97	0.048
Homeschool because of movements, n (%)	Yes	12 (14.1%)	2 (2.2%)	-2.0	0.9	170	-2.2	0.027
Movements cause pain, n (%)	Yes	63 (72%)	48 (53.9%)	-0.4	0.4	172	-1.14	0.25
Movements injure my child's body, n (%)	Yes	42 (48.8%)	10 (16.7%)	-1.4	0.4	170	-3.34	< 0.001
Currently being treated by a psychiatrist, n (%)	Yes	36 (41.9%)	15 (17.0%)	-1.3	0.4	170	-3.04	0.002
Currently being treated by a psychologist or therapist, n (%)	Yes	54 (62.1%)	29 (32.9%)	-0.9	0.4	171	-2.59	0.009
Concerns about ADHD, attention span, hyperactive/impulsive/disruptive behavior, n (%)	Yes	43 (50.0%)	51 (58.6%)	-0.1	0.36	169	-0.19	0.85
Concerns about obsessive behavior or anxiety, n (%)	Yes	64 (74.4%)	60 (68.2%)	-0.3	0.4	170	-0.7	0.52
Concerns about compulsive behaviors or routines, n (%)	Yes	25 (29.8%)	23 (26.7%)	-0.3	0.4	166	-0.67	0.51

TABLE 1. Clinical Characteristics and Results. Abstract PL 3-5

onset functional tics (FT). However, the degree of associated impairment is unknown. Thus, we sought to compare impairment in FT versus Tourette Syndrome (TS).
Methods: This is a retrospective, cross-sectional study of new visit patients presenting during 2021. Eighty-nine new diagnoses of FT were identified and compared to a randomly selected, age-matched cohort of 89 youth with TS. All families completed an intake questionnaire, which includes 4 questions about the impact of movements (visit to the Emergency Department-ED, home schooling, pain, injury), the mini-CTIM-P for parents, and mini-CTIM-C for children. The mini-CTIM has two parts (max score:42): motor/vocal tic impairment (mini-CTIM Tic) and impairment related to ADHD/OCD/anxiety/rages/other (mini-CTIM Non-Tic).
Results: Diagnosis didn't have a significant effect on mini-CTIM scores. However, specifically due to tic-like movements, significantly more FT respondents reported taking their child to the ED, home schooling their child, or injury to their child's body.
Conclusions: Despite dramatic symptoms, FT patients' impairment ratings at home, school and social environment do not appear to be elevated compared with TS. However, a higher percentage of FT report ED visits, school environment removal, or injury due to movements. Adolescents with FT and TS both experience significant and highly variable level of impairment.
Keywords: Movement Disorders (including Cerebral Palsy), COVID-19, Cognitive/Behavioral Disorders (including Autism)

PL3-6. Assessing sleep quality in children with migraines: Implementation of electronic health record cue and using actigraphy

Saylam E (Columbus, OH), Ramani P, James B, Savage M, Jambhekar S, Veerapandiyan A

Objective: To implement an electronic health record (EHR) alert to screen pediatric patients with migraines seen in the neurology clinics for sleep quality using Child and Adolescent Sleep Checklist (CASC), and to evaluate the effectiveness of the alert in screening children with migraines for sleep quality; to use actigraphy as a tool to study sleep quality in patients who were identified to have poor sleep habits using CASC
Methods: The first step of the study was a 3 month retrospective review of patients less than 21 years of old with migraines to determine the percentage of patients in whom sleep quality was assessed. We implemented the CASC questionnaire in the EHR and providers were encouraged to use the questionnaire to assess the sleep habits. Those who scored higher than 18 were referred to see sleep medicine specialist to address the sleep habits. The percentage of patients in whom sleep quality was assessed and poor sleep quality was identified prior to and after implementation of EHR alert was determined.
Results: Prior to EHR alert implementation, 5/90 (5.5%) patients with migraines were assessed for sleep quality. Post implementation, 122/135 (90.4%) patients were assessed for sleep quality using CASC implemented in EHR. 70/122 patients scored higher than 18 on the questionnaire and were referred to sleep medicine specialist / polysomnography. Actigraphy was completed in 14 subjects.
Conclusions: Assessing sleep habits using CASC cued in the EHR demonstrated markedly improved identification of children with migraine with poor sleep habits. Detailed results will be discussed at the conference.
Keywords: Headache/Migraine

PL3-7. Identifying upper extremity features of dystonia in people with cerebral palsy

Gilbert L (St. Louis, MO), Gandham S, Pearson T, Ueda K, Aravamuthan B

Objective: To identify expert-cited features of upper extremity dystonia in people with cerebral palsy (CP).
Methods: Dystonia in CP is debilitating yet under-diagnosed, particularly when co-existent with spasticity. Subjective expert consensus remains the diagnostic gold standard, but the specific features leading experts to make a dystonia diagnosis remain unclear. To determine expert-cited features of dystonia, we performed a conventional content analysis of consensus-building discussions between three pediatric movement disorder specialists as they evaluated upper extremity dystonia severity in 26 neurologic exam videos of seated subjects with CP and spasticity.
Results: 45.8% of discussion codes related to body region, movement, or examination features (with the remainder on severity score deliberation and dystonia diagnostic difficulty). Experts cited "overflow" movements in the "shoulder," "arm," and "wrist" significantly more frequently when discussing dystonia presence (14.3% of codes) vs. absence (4.4%, $p < 0.0001$, comparison of proportions). In contrast, experts cited "brisk," "fluid" movements with "no impact on function" and "mirror movements" significantly more frequently regarding dystonia absence (11.3%) vs. presence (2.6%, $p<0.0001$). In videos where diagnostic consensus was reached only after consensus-building discussion (4/26 videos), the repetitive hand "open/close" exam maneuver was cited significantly more frequently (3.9%) than for videos where consensus was reached prior to any discussion (0.5%, $p<0.0001$).
Conclusions: Experts use distinct movement features to diagnose upper extremity dystonia in people with CP and spasticity. Efforts like this can be used to codify the defining features of dystonia in people with CP and thus help refine and standardize dystonia diagnosis.
Keywords: Movement Disorders (including Cerebral Palsy)

PL3-8. Respiratory rate variability at NICU discharge may predict cerebral palsy risk

Saxena A (St. Louis, MO), Stamer H, Smith E, Aravamuthan B

Objective: Absence of normal "fidgety" movements between 2-5 months corrected age as per the Prechtl General Movements Assessment (GMA) has high sensitivity and specificity for CP diagnosis. However, GMA scoring requires subjective assessment by trained experts, limiting broad standardized use. We sought to identify objective kinematic and physiologic metrics corresponding to GMA scoring as potential auxiliary facilitators of early CP diagnosis.
Methods: Infants 8-25 weeks corrected age in a tertiary-care NICU follow-up clinic were assessed for ranges and variances of: 1) Pulse and respiratory rate (RR) over the 24 hours before NICU discharge; and 2) Hand and foot movement in GMA videos (quantified leveraging open-source pose estimation

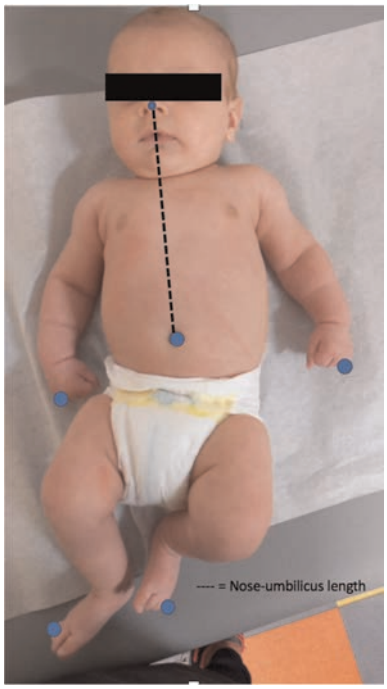


FIGURE 1 Key points labeled in pose estimation software (nose, umbilicus, hands, feet). Hand movement and foot movement were calculated across both limbs relative to umbilicus movement, normalized to nose-umbilicus length. Abstract PL 3-8

software). Abnormal GMA score predictors were determined using binary logistic regression.

Results: Compared to infants with normal GMA scores (N=18/31), those with abnormal scores (N=13/31) had: 1) Increased RR range (average of 44.5 breaths/min vs. 33.1, $p<0.01$, t-test) and variance (180.7 breaths^2/min^2 vs. 115.7, $p<0.01$); and 2) Decreased range of hand movement (0.96 vs. 1.3, $p=0.04$) and foot movement (0.9 vs. 1.3, $p= 0.04$) normalized to nose-to-umbilicus distance (Fig 1). RR range and variance were the only significant predictors of abnormal GMA scores ($p<0.01$, binary logistic regression).

Conclusions: Objective GMA analogue development has focused on quantifying "fidgety" movements. Vital sign assessment to predict CP risk has focused on hemodynamic variability. In contrast, we found RR variability at NICU discharge predicts abnormal GMA scores. Therefore, RR variability, likely due to neonatal brain injury, might be an auxiliary predictor of CP.

Keywords: Movement Disorders (including Cerebral Palsy)

BRAIN TUMORS/ONCOLOGY

1. Tumor resident B-cell receptor characteristics are associated with better overall survival for patients with neuroblastoma

Kacsoh D (Orlando, FL), Patel D, Hsiang M, Gozlan E, Chobrutskiy A, Blanck G

Objective: Neuroblastoma (NBL) is a common pediatric cancer affecting the sympathetic nervous system. Genetic and demographic factors determine risk stratification. Patients in the high-risk group have a 40% survival despite aggressive treatment. Immune receptor complementarity-determining region-3 (CDR3) domains in the tumor microenvironment represent a highly variable region of amino acid (AA) sequences often directly involved with antigen binding. Thus, we hypothesize that specific CDR3 chemical properties of B-cell receptors (BCRs) associate with better or worse overall survival probabilities.

Methods: We mined the TARGET project, tumor RNAseq files for BCR recombination reads. AA sequences of CDR3s were characterized based on single-value chemical parameters, chemical sequence motifs, and homology, defined by chemically similar AA sequences.

Results: (i) Variations of the CDR3s of IGK and IGL associated with significant differences in overall survival based on the omega parameter (a measure of the mixture of proline and charged AAs). (ii) Survival-related differences in the instability index (the measure of protein instability) were noted for IGK. (iii) Variations in the polyproline index for IGH associated with survival distinctions. (iv) Differences in immune checkpoint gene expression were noted among the IGL homology groups.

Conclusions: Chemical properties of tumor resident CDR3s reflect survival distinctions, which may reflect differences in a patient's immune response to NBL. Results indicate that CDR3 AA sequence features may be useful as novel risk stratification parameters, and aid in decisions regarding therapies, e.g., CDR3 features correlating with immune checkpoint gene expression may contribute to a decision to employ immune checkpoint blockade treatments.

Keywords: Brain Tumors/Oncology, Infections/Neuroimmunology, Genetics

2. The Use of Trametinib in Infants with Symptomatic NF1-associated Congenital Plexiform Neurofibromas

Rosser T (Los Angeles, CA), Powers K, Rangan K, Robison N

Objective: Plexiform neurofibromas are benign peripheral nerve sheath tumors that present in approximately 50% of individuals with neurofibromatosis type 1 (NF1). Their invasive nature has the potential to cause severe morbidity. In April 2020, the U.S. FDA approved the use of selumetinib, a MEK inhibitor, for the treatment of NF1-associated, inoperable, symptomatic plexiforms in children 2-18 years of age but the use of these medications in younger children has not been well studied.

Methods: We present two cases of infants with NF1 and congenital plexiform neurofibromas who have been successfully treated with the MEK inhibitor trametinib, administered as a tablet dissolved in water.

Results: Patient 1 presented at 2 months of age with poor feeding, apparent pain and decreased right arm movement. His work up led to the diagnosis of NF1 with a large cervical/thoracic spinal and brachial plexus mass consistent with a plexiform neurofibroma. Patient 2 presented at 2 weeks of life with an apparent life-threatening event and was diagnosed with right neck plexiform causing stridor and respiratory distress in the setting of familial NF1. In both cases, treatment

with trametinib led to improved pulmonary and neurologic function as well as decreased pain within several months. Neuroimaging has shown shrinkage and stability of the plexiforms.
Conclusions: Formal development of pediatric formulations and evaluation of the use of MEK inhibitors in children under 2 years of age with NF1 and plexiform neurofibromas are critical to safely expanding these effective medical treatment options to this vulnerable patient population.
Keywords: Brain Tumors/Oncology

COGNITIVE/BEHAVIORAL DISORDERS (INCLUDING AUTISM)

3. Tuber involvement of the right fusiform face area predicts autism spectrum disorder in children with tuberous sclerosis complex

Kroeck M (Boston, MA), Cohen A, Wall J, McManus P, Ovchinnikova A, Sahin M, Krueger D, Bebin M, Northrup H, Wu J, Warfield S, Peters J, Fox M

Objective: Tuberous Sclerosis Complex (TSC) is associated with focal non-malignant brain "tubers" and a high incidence of autism spectrum disorder (ASD). While ASD is traditionally considered a non-lesional/distributed disorder, analysis of the tuber burden and locations associated with autism may provide insight into non-syndromic ASD. Here, we investigate the relationship between tuber location and ASD diagnosis using detailed tuber tracing and spatial statistical models in a large, well-characterized cohort.
Methods: We delineated tuber locations for 115 TSC participants with and without ASD (n = 31 vs 84) from the Tuberous Sclerosis Complex Autism Center of Excellence Research Network (TACERN) and assessed overall tuber burden, lobar and *a priori* ASD region involvement, and voxel-wise lesion symptom mapping (VLSM) associated with ASD. We then calculated the risk of ASD associated with any findings.
Results: There was no significant ASD-related differences in tuber burden at the whole-brain, lobar level, or within *a priori*regions of interest. However, VLSM analysis identified that having tubers involving the right fusiform face area (FFA), an area of particular interest in non-syndromic autism, was associated with a 6-fold increased risk of developing ASD.
Conclusions: While TSC is a rare cause of ASD, there is a strong association between tuber involvement of the right FFA and ASD diagnosis. This highlights a potentially causative mechanism for developing autism in TSC that may also be relevant in non-syndromic ASD. Further work will assess whether individual symptoms of ASD map onto different brain circuits in TSC.
Keywords: Cognitive/Behavioral Disorders (including Autism), Neuroimaging, Rare Disesases

4. Coordinate Network Mapping of Disparate Atrophy Patterns in Attention Deficit Hyperactivity Disorder Shows Convergence on the Intersection Between the Reward and Salience/Attention Brain Networks

Wall J (Brookline, MA), Taylor J, Kroeck M, McManus P, Fox M, Warfield S, Cohen A

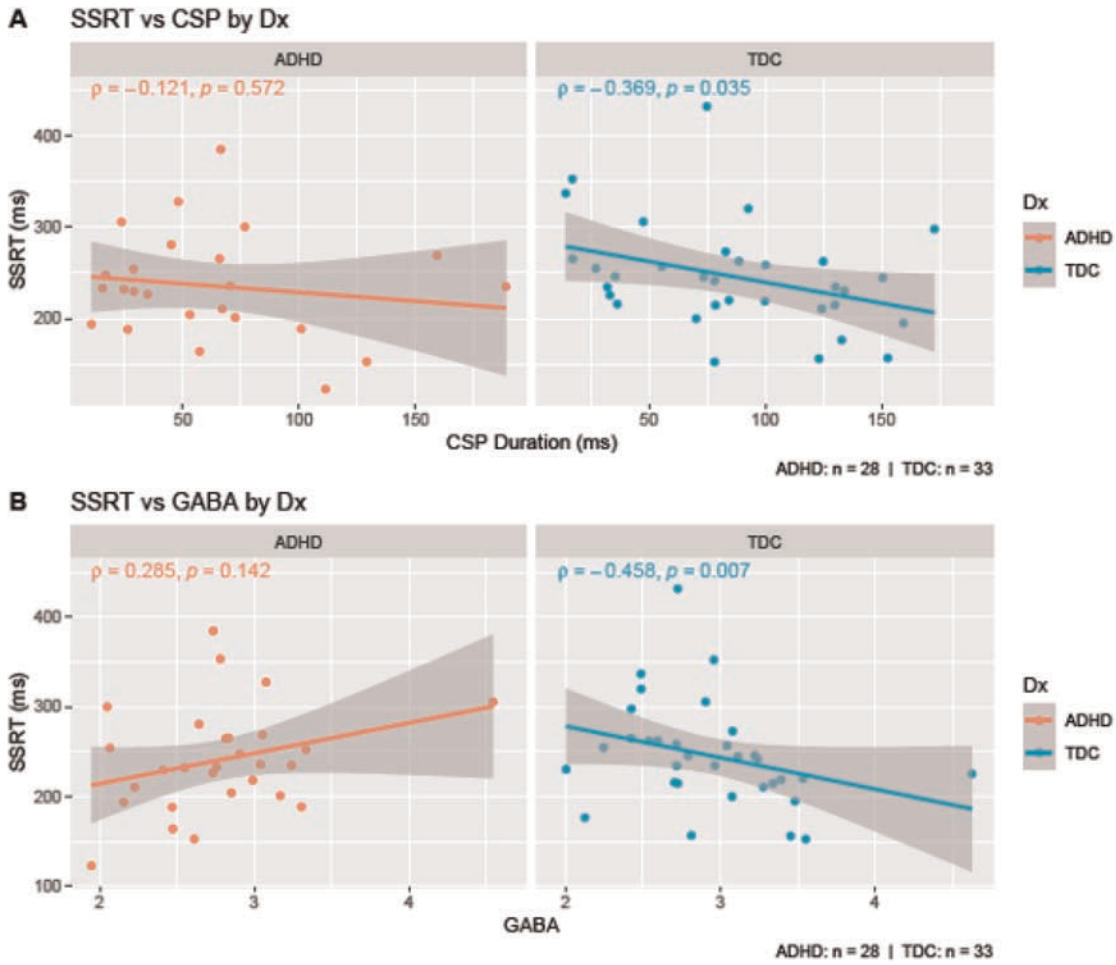
Objective: While individual neuroimaging studies have identified numerous brain differences associated with attention deficit hyperactivity disorder (ADHD), meta-analyses have typically failed to yield consistent regional involvement. This has often been attributed to heterogenicity in the ADHD population, however another explanation may be that ADHD is caused by network alterations rather than individual regions. Here, we examine network-level convergence of atrophy patterns in ADHD using a recently developed "coordinate network mapping (CNM)" technique.
Methods: Using coordinates from 29 studies (N=1548 participants) of localized volume atrophy in individuals with ADHD compared to healthy controls, we conducted anatomical likelihood estimate (ALE) analyses, a traditional method of determining above-chance convergence between experiments. Then, in a separate CNM analysis, we generated connectivity maps for each study using a pediatric normative connectome to identify regions of strong connections and statistically compared these maps to identify consistent areas of connectivity.
Results: Reported atrophy patterns varied widely across the brain and ALE analyses yielded no significant clusters. However, CNM revealed that atrophy locations in ADHD were consistently located within a network connected to the brainstem, cerebellum, thalamus, basal ganglia, anterior cingulate cortex, orbital/middle/inferior frontal gyri, hippocampus, and insula/frontal operculum.
Conclusions: Our connectivity analyses indicate consistent network involvement in ADHD atrophy patterns, specifically in the reward and cingulo-opercular networks, potentially associated with reward processing and attention deficits in this population. Further work will clarify whether this atrophy is a cause or down-stream effect of ADHD-related symptoms, and whether these findings are specific to ADHD.
Keywords: Cognitive/Behavioral Disorders (including Autism), Neuroimaging, Neuroscience

5. Inhibitory Biomarkers of Action Stopping in Children with ADHD

Gilbert D (Cincinnati, OH), Ewen J, Huddleston D, Wu S, Cecil K, Edden R, Horn P, Crocetti D, Mostofsky S

Objective: In children with Attention Deficit/Hyperactivity Disorder (ADHD), a core domain of impaired cognitive control is inefficient response inhibition. This multimodal study investigated the relationship of response inhibition to two dominant motor cortex (M1) inhibitory biomarkers in children.
Methods: In 61 right-handed, 8-to-12-year-old children (ADHD n=28, 68% male, 57% white); typically developing (TD) controls n=33, 64% male, 67% white), we evaluated 1) response inhibition, using an anticipated-response stop signal reaction time (SSRT) task; 2) left M1 inhibitory physiology, using Transcranial Magnetic Stimulation (TMS) to measure cortical silent period (CSP) duration; and 3) left M1

Figure 1



ADHD attention deficit/hyperactivity disorder. TDC Typically developing controls. SSRT = Stop Signal Reaction Time in milliseconds (ms) (lower number is better); CSP cortical silent period in right motor cortex evoked by transcranial magnetic stimulation. GABA gamma amino butyric acid level in international units in left S1M1 voxel, by magnetic resonance spectroscopy.

Abstract 5

inhibitory neurochemistry, using Magnetic Resonance Spectroscopy (MRS) to measure gamma-amino butyric acid (GABA+) levels in a sensorimotor (S1M1) voxel. Diagnostic groups were compared and relationships between SSRT and biomarkers were modeled with regression and bivariate correlations.

Results: There were no diagnostic group differences in any of these measures. However, regression modeling demonstrated a moderating effect of ADHD diagnosis ($p < 0.01$) on the relationships of both dominant motor cortex inhibitory physiology (CSP duration; $p = 0.02$) and neurotransmitters (GABA+ concentration; $p < 0.01$) to response inhibition (SSRT). Post hoc correlation showed for TD children, but not those with ADHD, associations between better response inhibition (faster SSRT) and both longer CSP duration ($r = -0.38$; $p = 0.03$) and higher GABA+ concentration ($r = -0.46$; $p < 0.01$).

Conclusions: This multi-modal study suggests response inhibition may be reflected by measures of inhibitory physiology and neurochemistry in dominant motor cortex and, further, that these relationships may be disrupted in children with ADHD.

Keywords: Cognitive/Behavioral Disorders (including Autism), Neuroscience, Neuromaging

6. Cognitive and Adaptive Trajectories Across Age in Fragile X Syndrome

Berry-Kravis E (Chicago, IL), Potter S, Raspa M, Wheeler A, Gable J, Erickson C, Tartaglia N

Objective: To define the trajectories of adaptive behavior and cognition across age in fragile X syndrome (FXS)

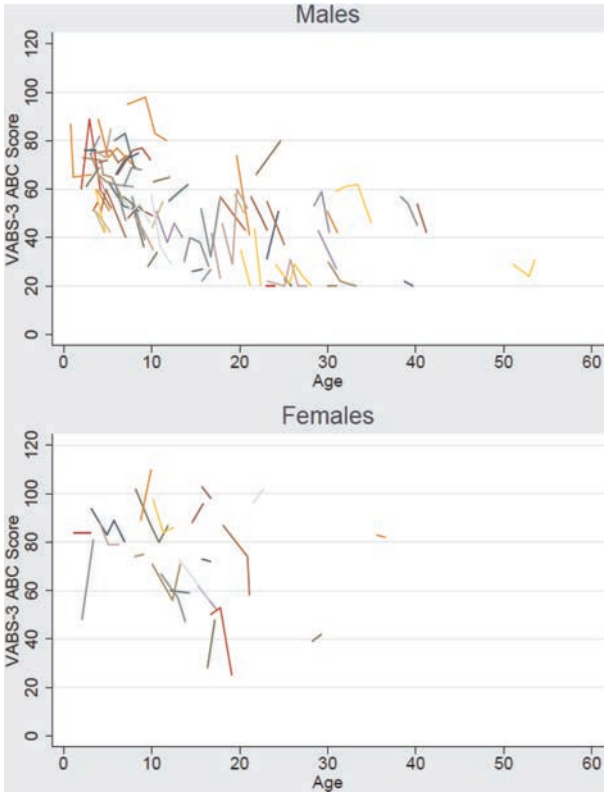
Methods: Participants (N=196; 147M, 49F) enrolled at three sites in the FORWARD natural history study of FXS

underwent yearly assessments of cognitive ability using the Stanford-Binet 5th Edition (SB-5) and adaptive functioning using the Vineland Adaptive Behavior Scales 3rd Edition (Vineland-3/VABS-3) for 1-4 years of follow up. Spaghetti plots reflecting individual trajectories were generated, and overall change per year calculated for composite scores for males and females.

Results: The cohort was age 14±11 years, was 87% white (9% Hispanic) and 7% African American, and had co-morbid autism in 32% (males) and 18% (females). Baseline adaptive behavior composite (ABC) was 54±17 (males) with communication 48±21, daily living skills 56±19 and socialization 58±20; and 71±22 (females) with communication 66±25, daily living skills 75±25 and socialization 72±22. Multilevel models indicated the ABC declined by 1.3 points per year of age for males and females (Figure 1). Baseline SB5 full scale IQ was 45±8 (males) and 63±18 (females). FSIQ declined by 0.3 points per year for males and females, although this is an underestimate due to floor effects.

Conclusions: Adaptive and cognitive standard scores decline with age in FXS due to inability to keep pace with typical development. The natural rate of change is important to define for future disease-targeted interventions. Increased accuracy can be obtained using z-deviation-based scoring to minimize floor effects and growth score values are needed to measure developmental progress in FXS and distinguish slower-than-normal growth from regression.

Keywords: Cognitive/Behavioral Disorders (including Autism), Rare Diseases, Genetics



Abstract 6

7. Developmental and EEG Characteristics of SLC6A1-Related Disorder

Goodspeed K (Dallas, TX), Cartwright J, Dooley K, Sirsi D, Lee M

Objective: SLC6A1 is becoming one of the leading causes of epilepsy and autism spectrum disorder, but little is known of the full spectrum of disease severity. Single allelic variants of SLC6A1 lead to impaired function of the GABA-Transporter Type 1, and many precision therapeutics are in development. Here we present findings from our specialty clinic for SLC6A1-Related Disorder and prospective natural history study.

Methods: Patients with confirmed SLC6A1-Related Disorder by clinical genetic testing had a standardized medical history and neurological exam. A subset enrolled in the prospective natural history study and completed a 4-hour video EEG.

Results: We evaluated 24 SLC6A1-Related Disorder patients. Of these, 17 completed a 4-hr EEG and 5 completed a psychological evaluation. All patients presented between birth and 24-months with developmental delay, hypotonia, or seizures. All but one had delayed milestones, and 7/24 had regression. Seizure semiologies include absence, atonic, and myoclonic seizures. Intermittent rhythmic delta activity (IRDA) and generalized spikes are the most prevalent finding on EEG. Levetiracetam, Valproic Acid, and Clobazam are the most frequently used anti-seizure medications, and a high prevalence of patients have behavioral side effects with levetiracetam (9/12). On standardized testing 3/5 met criteria for autism spectrum disorder and all demonstrated adaptive abilities in the very low to low average range.

Conclusions: This is the first prospective observational study of SLC6A1-Related Disorder. We demonstrated that absence epilepsy with IRDA on EEG and deficits in adaptive abilities are common. We will continue to explore these findings in our prospective natural history study.

Keywords: Cognitive/Behavioral Disorders (including Autism), Genetics, Epilepsy/Sleep

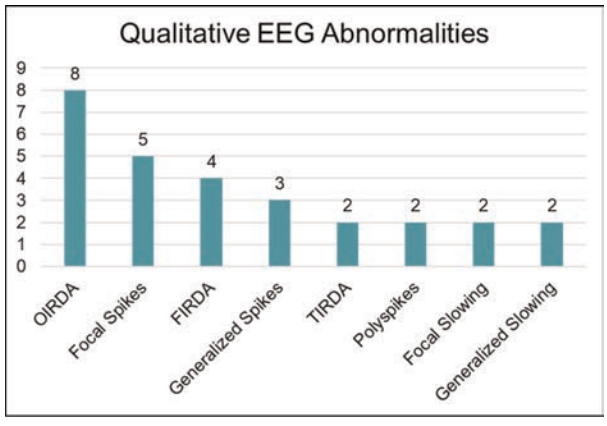


FIGURE 1 - Qualitative EEG findings from prospective SRD natural history study (n=17). Abstract 7

Table 1: SLC6A1-Related Disorder Specialty Clinic Demographics & Clinical Overview. Abstract 7

Demographics	
Age Range	17m to 24yr 4m (mean 6yr)
Male : Female	11: 13
Age at First Concern	Birth to 6m: Hypotonia and Motor Delay 24m: Seizures
Clinical Presentation	
Developmental Milestones Mean Onset (range) *First Word 20/24, Phrase 13/23 *Developmental Regression 7/24	• Sitting – 9m (5-13m) • Walking – 19m (11-33m) • Babbling – 14m (6-36m) • First Word – 25m (10-52m) • Phrase Speech – 34m (23-54m)
Seizure Onset & Semiology (n=14)	Mean Onset 24m • Staring spells: 4-60m • Drop spells: 12-36m • Myoclonic Jerks: 24-30m
Psychological Assessments	
Adaptive Behavior Assessment Scale (n=4) Mean (Range)	• General Adaptive Composite – 76.5 (75-79) • Conceptual – 69 (60-75) • Social – 82 (74-89) • Practical – 81 (75-87)
Childhood Autism Rating Scale (n=5) Mean (Range)	• Total Score – 29 (23-37.5)
Differential Abilities Scale – II (n=3) Mean (Range)	• General Conceptual Ability – 72 (58-82)
Developmental Profile (n=3) Mean (Range)	• General Development – 78 (69-84)

Table 1: Demographics of interviewees. Abstract 8

Demographic Variable	**Category**	**Frequency**
Interview participants	Caregiver only*	12
	Patient/Caregiver Dyad **	9
	Patient Only	1
Caregiver sex	Female	20
	Male	2
Caregiver relationship to patient	Parent	17
	Sibling	1
	Child	1
	Other caregiver[#]	2
Patient Information (Includes all 22 patients, even if they did not participate in the interviews.)		
Patient Age	Mean: 29.6 years, Median: 25.5 years, Range 19-62 years	
Patient Sex	Female	8
	Male	14
Patient Race/Ethnicity	White	17
	Asian	1
	Black	1
	Hispanic/Latino	2
	Other	1

*One interview included two caregivers (mother and father). All other caregiver-only interviews consisted of only one caregiver.
**6 mother-and-patient dyads, 1 father-and-patient dyad, 1 sister-and- patient dyad, and 1-daughter-and-patient dyad. Patient participation was variable: one communicated through caregiver, one participated in only first 30 minutes to limited extent, others participated equally to caregivers.
[#]Other caregivers: 1 host-home provider, 1 legal guardian through a state agency.

8. The New Frontier of Adult Neurodevelopmental Care: What do Patients and Caregivers Value?

Sanders J (Denver, CO), Dafoe A, Glaros C, Holliman B

Objective: We aimed to explore patient and caregiver values around adult neurodevelopmental care.

Methods: In this qualitative study, a trained research assistant conducted 22 semi-structured virtual interviews from September 2021 to February 2022 with randomly selected adults with Neurodevelopmental Disabilities (NDD) and/or their caregivers. Each patient had at least one appointment in the Adult NDD Clinic, which started in October 2020. Interviews were recorded and professionally transcribed. An inductive codebook was developed and reconciled through an iterative process; transcripts were coded in Atlas.ti with 20% double-coding. Major themes were developed through team discussion.

Results: Most interviewees were caregivers of patients with NDD (12); 9 interviews were with patient/caregiver dyads; 1 interview was with a patient alone. Characteristics of the participants are detailed in Table 1. Four main themes emerged from the interviews (Table 2). Overall, families value knowledgeable providers who 1) take the whole patient

Table 2: Themes with representative quotations. Abstract 8

Theme	Description of Theme	Quotations
Whole Patient Care	Patients and caregivers value providers who see the "whole picture," and who take the developmental disability into account, but also do not overlook other medical needs.	"We find people that will work with autism, or we find people that will work with brain injury. For him, nothing is—if you use only interventions that would work for autism, it's incomplete. If you use only the brain injury component, it's incomplete. They have to mesh. Sometimes one comes out more than the other." "I think when you're talking development, I don't know that the regular doctors that we see for individual conditions or concerns ever really approached it from a developmental kind of point of view. That was just totally different approach, which of course, we appreciated that 'cause most doctors… don't look at the big picture of why did this happen in the first place? I just felt like she connected on that level so much better and quicker."
Engagement and Communication	They valued engaging directly with the patient, being prepared for possible challenging behaviors, and setting expectations. Caregivers and patients valued providers who got to know the patient.	"Dr. Sanders talked to her. She touched her. A lotta doctors don't even physically touch her, and so, those are things that I guess really hit home with us." "Well, I think it's extremely important to have support staff that understand the behaviors—potential behaviors of people with intellectual disabilities so that they aren't frightened or shocked when something happens that's a little bit out of the ordinary. It's really important for staff people to convey empathy, and understanding, and a knowledge that the way DD people can behave isn't because they're bad people or that they're not controlling their behavior, but just things can happen, and just a calm reassuring presence."
Coordinated Care	They valued providers and systems that worked together, shared knowledge, and had open lines of communication among different specialties, and also in the transition from pediatric to adult care.	"It would be nice if all the pieces—all the people, or all the specialties that we need to do to have a better life—were all in one place instead of, oh, you need to see a cognitive behavior therapist, but you need to go to a whole 'nother clinic or hospital or—if everybody was in one place and they worked together, and maybe could discuss each client case in one place. More connection, I guess, so that everybody had a little bit of knowledge of what the other person was working on and saw."
Connections to Resources	Caregivers and patients expressed the importance of supporting them through helping them connect with and navigate access to community resources.	"If there was a social worker that sat down and went through a bunch of different things like, "This is where you can get help with this, and this is where you can get help with that." If there were more connections like that in various clinics or certain situations or, "Here's a person that you can refer to and—if you have questions." Sometimes I think that would be really helpful as far as—'cause there's a difference between a doctor telling you something and then going out and living it." "I think in the perfect world, instead of Dr. Sanders sending us out with a catalog, she would have someone in her office contact me. She may send me out with a catalog, but she'll have someone contact me and say, "I have contacted <Service>. They are going to be in contact with you." I was sent out with the resources. The hope is that I initiate a phone call, and that starts things rolling in the proper way. There's that trust."

picture into account, 2) engage with patients and their needs, 3) provide coordinated care. They also value 4) connecting with and navigating community resources. Participants valued providers who directly engage with patients and are prepared for challenging behaviors. They also expressed the importance of providers who know about available resources and can facilitate connections to other services.

Conclusions: The need for adult neurodevelopmental care is growing; more individuals with complex, childhood-onset conditions are living into adulthood. Better understanding of patient and caregiver values can help shape this emerging field to meet the needs of this unique, often overlooked and underserved, population during the challenging transition to adulthood and beyond.

Keywords: Cognitive/Behavioral Disorders (including Autism), Equity, Diversity, Inclusion

9. Sex-Dependent Structure of Socioemotional Salience, Executive Control, and Default Mode Networks in Preschool-Aged Children with Autism

Zielinski B (Salt Lake City, UT), Andrews D, Lee J, Solomon M, Rogers S, Heath B, Nordahl C, Amaral D

Objective: To determine sex differences in large scale brain network structure in preschool-aged children with autism (ASD, n=122) and typically-developing controls (TDC, n=122) within the Socioemotional Salience (SN), Executive Control (ECN), and Default Mode (DMN) Networks.

Methods: We used structural covariance MRI (scMRI) to determine network-level differences in gray matter structure within the SN, ECN, and DMN, intrinsic connectivity

Table 1: Participant Demographics. Abstract 9

	ASD Male (n=61)	ASD Female (n=61)	TD Male (n=61)	TD Female (n=61)
Age (Months)	36.49 (6.17)	38.67 (6.32)	36.75 (6.34)	38.42 (6.90)
IQ	65.76 (23.24)	66.09 (23.93)	102.72 (11.65)	108.58 (11.69)
ADOS CSS	7.68 (1.91)	7.42 (1.81)	-	-
ADOS SA-CSS	7.01 (1.71)	6.93 (1.65)	-	-
ADOS RRB-CSS	8.50 (1.53)	8.18 (1.55)	-	-

Note: Values are given as mean (standard deviation). ASD = Autism spectrum disorder, TD = non-autistic typically developing controls, ADOS = Autism Diagnostic Observation Schedule, CSS= calibrated severity score, SA-CSS= social affective calibrated severity score, RRB-CSS= restricted and repetitive behavior calibrated severity score

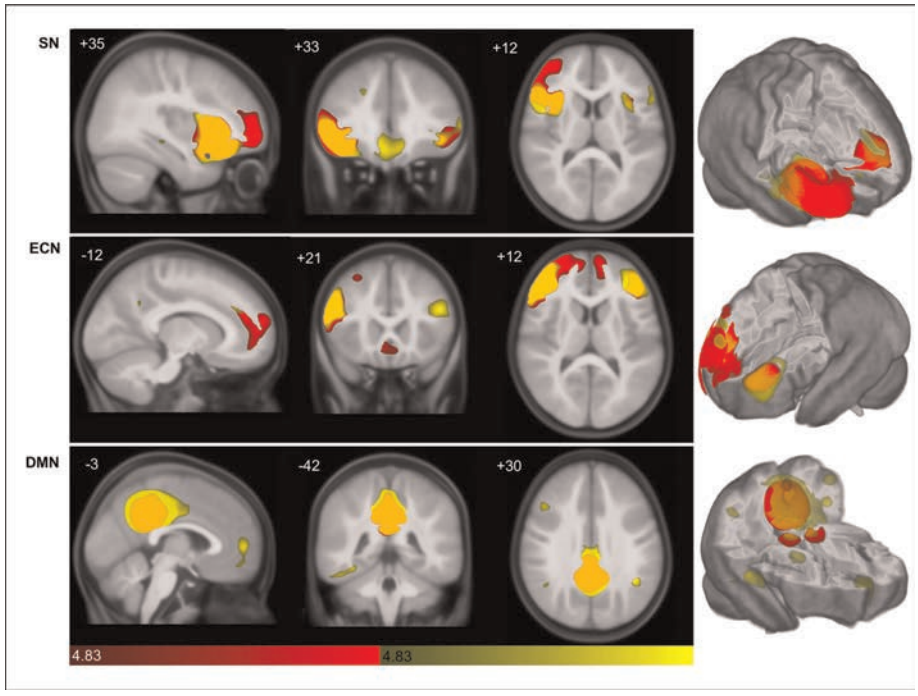


FIGURE 1. Structural covariance map of the salience, executive-control, and default mode networks in males and females. Statistical parametric maps depict brain regions in which gray matter intensity covaried with that of the seed ROI in each network in males (red) and females (yellow; common regions depicted in orange). (Top) Salience Network covariance patterns appear more spatially distributed in females, with greater locally extensive frontal covariance seen in males. (Middle) Executive-Control Network scMRI map in females again reflects greater spatial distribution, whereas males show frontal midline extension. (Bottom) scMRI maps of Default Mode Network again demonstrate greater anterior-posterior distribution in females, versus little covariance in males. scMRI data are T-statistic maps ($p<0.01$, FWE-corrected) displayed on the average anatomical template of all subjects. The left side of the image corresponds to the right side of the brain. n=122 per group. FWE, family-wise error; ROI, region of interest; scMRI, structural covariance MRI. Abstract 9

networks implicated in autism. Right hemisphere seed regions-of-interest were placed within core anatomical hubs of each network (hub): SN (anterior frontoinsula), ECN (dorsolateral prefrontal cortex), DMN (posterior cingulate). Using SPM, General Linear Model condition (diagnosis or sex)-by-covariate analyses were performed for each network, resulting in T-statistic (p<0.01, FWE corrected) covariance maps for each condition as well as group-by-sex interactions.

Results: Overall, structural covariance network (SCN) topology was consistent with prior literature. In general, SN and ECN were more extensive in TDC, whereas DMN was more extensive in ASD, as well as 'posteriorized' and right-shifted. Males had similar volume but different topology in SN and ECN compared to females, but females had greater covariance in DMN. Interaction effects demonstrated that ASD males had greater covariance than TDC males, whereas ASD females had decreased covariance compared to TDC females in distinct network nodes.

Conclusions: Consistent with prior reports, we found that the SN, ECN, and DMN are underdeveloped in early childhood, although principal hubs and nodes are represented to varying degrees. Our findings suggest that autism is associated with atypical network structure in young children, and at least some of these atypicalities are influenced by biological sex.**Keywords:** Cognitive/Behavioral Disorders (including Autism), Neuroimaging, Neuroscience

10. Withdrawn

11. Brain networks identified by Lesion Network Mapping are altered in Autism Spectrum Disorder proportionate to symptom prevalence

McManus P (Goffstown, NH), Edwards A, Drew W, Wall J, Fox M, Cohen A

Objective: Autism Spectrum Disorder (ASD) is associated with significant behavioral and social deficits. However, it is poorly understood how ASD's variety of etiologies lead to its heterogeneous symptom presentation and severity. Abnormalities in different brain regions have been identified, but how these relate to specific symptoms remains unclear. Here, we use the Autism Brain Imaging Data Exchange (ABIDE) dataset to evaluate if abnormalities in networks implicated by causal Lesion Network Mapping (LNM) data correlate with the prevalence of similar symptoms in non-lesional ASD.

Methods: ABIDE fMRI data was manually preprocessed for functional connectivity and demographic metadata extracted. Brain regions identified from LNM for approximately 30 neuropsychiatric conditions were used as seed regions to generate individual functional connectivity maps for each participant from ABIDE. ASD-related differences (n=825) versus typically developing controls (n=997) were identified, controlling for age, sex, site, and scanner. The degree of differences for each symptom was then compared to the prevalence of similar symptoms in ASD.

Results: ASD-related functional connectivity differences were concentrated in LNM-identified networks for symptoms common in ASD, e.g., language difficulty, depression and prosopagnosia, and rare in networks associated with lesion-induced symptoms uncommon in ASD. This correlation persisted after controlling for multiple important variables.

Conclusions: The brain networks identified by LNM for specific symptoms also appear to be relevant for non-lesional conditions like ASD. This suggests that networks underlying various neurological processes are at least partially dissociable and consistent across individuals. Further validation in other datasets/conditions will substantiate if symptom networks are truly universal.

Keywords: Cognitive/Behavioral Disorders (including Autism), Neuroimaging

12. Neurofunctional and neuroanatomical markers of EBF3-related neurodevelopmental disorders

Lerma V (Houston, TX), Serrallach B, Denghausen E, Franzen R, Deisseroth C, Amaya S, Corriveau M, Devara E, Goin-Kochel R, Meoded A, Chao H-T

Objective: Early B-cell factor 3 (EBF3) is a Collier/Olfactory/EBF (COE) transcription factor that regulates nervous system development. Heterozygous *EBF3* whole-gene deletion cause 10q26-deletion syndrome, and heterozygous single-gene variants cause Hypotonia, Ataxia, Delayed Development Syndrome (HADDS). HADDS is a neurodevelopmental disorder (NDD) associated with neurological and psychiatric features, including autism. In this study, we quantified neurocognitive performance, neurobehavioral function, and neuroanatomical findings in affected individuals to investigate functional deficits, vulnerable brain regions, and genotype-phenotype associations.

Methods: Executive function, social function, adaptive function, and autism comorbidity was assessed in 11 EBF3-related NDD and 4 neurotypical siblings (NT) (5-15 years, M=9.53, SD=3.66). Retrospective neuroimaging scans were collected in a separate group of 15 affected individuals (0-15 years, M=4.06, SD=4.44). Cerebellar volume and 2D-parameters of the cerebellar vermis and brainstem were compared to normative values.

Results: Affected individuals showed significant alterations in global executive function (regulation of behavior, emotion, and cognition), global social function (social awareness, social cognition, and social communication), and global adaptive function (adaptive daily living and socialization skills). Interestingly, social motivation and adaptive communication was intact. Moreover, individuals with *EBF3* coding variants in the zinc finger (ZNF) motif have smaller craniocaudal diameter of the cerebellar vermis compared to normative values. This neuroanatomical finding was absent in individuals with other *EBF3* variant types, suggesting that *EBF3* ZNF variants are more deleterious.

Conclusions: These results delineate neurogenetic substrates responsible for cognition, behavior, and brain regions impacted by EBF3 dysfunction. The findings may help improve cognitive remediation strategies specific to *EBF3*-related NDD, facilitate prognostication, and aid personalized therapeutics.

Keywords: Cognitive/Behavioral Disorders (including Autism), Genetics, Neuroimaging

13. Need for Change! - State of services for children and young people with neurodisability in Abuja, Nigeria: A prototype special centre study

Ohiaeri C (Abuja, Nigeria), Takon I

Objective: To ascertain the state of services for children and young people with neurodisability in Abuja and the perspective of providers and users, using a prototypecentre as template.

Methods: Following literature review, questionnaires were designed and administered to the service providers and services users (patients and their parents). A 4-hour visit to the prototype centre was uundertaken with direct assessment and observation and interview of staff. Information gathered was analysed and documented

Results: Childhood Neuro-disability is prevalent in Abuja based on anecdotal reports and case histories. Legislation and policy for special education exist with limitations. There is lack of evidence of Government input in supporting services for children with disability despite the Government ministries and Statutory agencies having mandates for this service. Most of the Specialist Child development centres are privately owned or run by NGO's. The quality of the service from the private centres are dependent on their staff skill sets, resources and equipment.Referrals for assessments are mainly through self-referral, schools or hospitals. There is limited multidisciplinary assessment and limited access to funding for existing services. Staff training and development is also very limited and unregulated.

Conclusions: Services for children with neurodisability remains suboptimal in Nigeria. Barriers to accessing services include high and unaffordable cost and limited access to skilled and trained professionals. Government's support in the establishment of public-funded centres in Nigeria and training of professionals will help address this huge gap.

Keywords: Cognitive/Behavioral Disorders (including Autism), Neurorehabilitation

14. Barriers to Adult Neurodevelopmental Care: Insights from Qualitative Interviews with Patients and their Caregivers

Sanders J (Denver, CO), Dafoe A, Glaros C, Dorsey Holliman B

Objective: We aimed to identify and explore barriers that patients and/or their caregivers face when seeking adult healthcare.

Methods: We conducted 22 semi-structured interviews from September 2021 to February 2022. All interviews were recorded and professionally transcribed. Participants were randomly selected adults with NDD and/or their caregivers (Table 1) who had appointments in the new Adult NDD Clinic in the past year. An inductive codebook was developed and reconciled through an iterative process and transcripts were coded in Atlas.ti, with 20% double-coding. Coded data was analyzed within and across interviews to identify major themes, with the team meeting frequently to discuss emerging patterns.

Results: Characteristics of the patients and caregivers are detailed in Table 1. Major barriers to care for adults with NDD and their caregivers included 1) difficulty transitioning from pediatric to adult care, 2) finding doctors and programs who accepted patients with NDD, 3) difficulty getting into clinics, including long wait times and travel distance, and 4) limitations with the ability of the physical space to promote successful visits for patients with NDD. Major themes and representative quotes are in Table 2.

Conclusions: While many barriers are rooted deeply in systemic issues of the U.S. healthcare and social support systems, some of the discussed obstacles to adult care can be overcome with reasonable changes to clinic structures and

Table 1: Demographics of interviewees. Abstract 14

Demographic Variable	Category	Frequency
Interview participants	Caregiver only*	12
	Patient/Caregiver Dyad **	9
	Patient Only	1
Caregiver sex	Female	20
	Male	2
Caregiver relationship to patient	Parent	17
	Sibling	1
	Child	1
	Other caregiver[#]	2
Patient Age	Mean: 29.6 years, Median: 25.5 years, Range 19-62 years	
Patient Sex	Female	8
	Male	14
Patient Race/Ethnicity	White	17
	Asian	1
	Black	1
	Hispanic/Latino	2
	Other	1

*One interview included two caregivers (mother and father). All other caregiver-only interviews consisted of only one caregiver.

**6 mother-and-patient dyads, 1 father-and-patient dyad, 1 sister-and- patient dyad, and 1-daughter-and-patient dyad. Patient participation was variable: one communicated through caregiver, one participated in only first 30 minutes to limited extent, others participated equally to caregivers.

[#]Other caregivers: 1 host-home provider, 1 legal guardian through a state agency.

Table 2: Themes about Barriers to Neurodevelopmental Care with Representative Quotations. Abstract 14

Theme	Description of Theme	Quotations
Transitioning from Pediatric to Adult Care	Caregivers and patients struggled with the loss of services that occurs in educational, social, and medical settings when their loved ones become adults. They also grieved the loss of long-term trusting relationships with pediatric providers and practices.	"As he got to adult stage, a lot of services had fallen off. 'Cause either you couldn't find anybody or just that whole transition." "I think the biggest barrier was not having a trained neurologist help us navigate everything that was going on with him as an adult. We had a trained neurologist and a pediatrician when he was a child. Finding somebody—a trained neurologist was very—for him—was very, very difficult within the [Adult] Health system." "They kind of dump you after school is out. It's kind of like, there you go…. It was kind of like I belong to this autism parent group, and we all talk about how somebody didn't get the memo that autism ends at 18, when they leave school, or 21."
Finding a doctor	They had difficulty accessing doctors for many reasons, including insurance status (providers' limitations on Medicaid) as well as limited provider knowledge and comfort with adults with neurodevelopmental disabilities.	"Medicaid is a huge barrier for finding—it's a huge barrier for finding a doctor. However, finding a doctor that knows how, even sort of, to deal with somebody like <Patient> is huge as well." "I wish I could change the system in some way. I wish. There are so many families out there that are suffering because they're dealing with these same just scary, dangerous neuropsychiatric symptoms, and they can't find a psychiatrist who's willing to treat their kid, and there's no inpatient care when things get really dangerous, and there is very little understanding in the medical community of how horrendous this situation is."
Accessing clinics	Families were split on their opinions about tele-medicine. They noted barriers of navigating busy medical centers and mobility limitations with parking and transportation. Also, long wait times, both for getting an appointment and once they were in the waiting room, were barriers to care.	"These virtual appointments are nice for not having to drive like that." "Also, we've had some experiences where apparently emergencies have come up when we've come in to her office for a scheduled appointment, and we've had to wait a couple of hours to see her in the—I guess you'd call it an examining room, but it's more of an office. That is extremely hard when you have a person with neurodevelopmental issues to try to keep them entertained, and distracted, and calm. I really think it was about a two-hour wait before we saw the doctor the last time we were in."
Physical space limitations	They wanted clinical spaces that could accommodate their loved ones with neurodevelopmental disabilities and support success getting through visits.	"The meeting rooms are very small, and the lobby where patients waiting to see the doctor is very small, so when I walk in there, I honestly am somewhat afraid of what could happen if <Name> all of a sudden gets anxious and is too close to another patient that he could push, or shove, or slap someone, or whatever. I would think it would be really helpful for developmentally disabled patients to have more space so that they're spread out and it lessens the chance that there could be aggression going on." "There were no fidget toys. There were no sensory swings. There was nothing that <Patient> could take off of a bookcase and use to get through his appointment. It doesn't cost a lot of money and, boy, would that be wonderful."

care coordination practices. Future clinic development and training should incorporate perspectives of patient and family experiences to address the barriers to high quality adult care, particularly, improving care coordination and access to adult specialists.

Keywords: Cognitive/Behavioral Disorders (including Autism), Equity, Diversity, Inclusion

15. Fine Motor Abilities in Infants at Heightened Risk for Autism Spectrum Disorder

Dove K (Pittsburgh, PA), Iverson J

Objective: Research has shown that fine motor (FM) delays are apparent in 6-month-old infants who are younger siblings of children with Autism Spectrum Disorder (ASD) and are therefore at heightened risk of ASD diagnosis. These FM deficits have been illustrated in the Mullen Scales of Early Learning (MSEL), however the MSELprovides only presence or absence information regarding motor behaviors. This study aims to evaluate what FM behaviors were exhibited when infants failed FM items on the MSEL, and whether patterns of failed FM tasks may predict future ASD or Language Delay (LD) diagnosis or ASD symptom severity as measured by the Autism Diagnostic Observation Schedule (ADOS).

Methods: Fifty-seven infants at heightened-risk for ASD with 36-month ADOS assessments and diagnostic outcome measures were included in the study. MSEL FM items five through nine were selected as past heightened-risk infant studies have shown poorer performance on these items. Reviewers were blinded to risk-level, ADOS results, and final diagnoses. Failed items were classified based on supplemental behaviors including oral exploration, grasp quality, and play behavior.

Results: Due to small sample size, ASD and LD outcomes were pooled to create a communication disorders group. Categorical analysis with Fisher's exact test yielded a statistically significant difference between the ASD+LD and non-diagnosis failure rates on ulnar palmar peg grasp (p=0.043), yielding higher rates of immature palmar grasp behaviors in infants later diagnosed with ASD or LD.

Conclusions: Performance in fine motor skills in 6-month-old infants at heightened-risk for ASD correlate with later communication disorder diagnoses.

Keywords: Cognitive/Behavioral Disorders (including Autism)

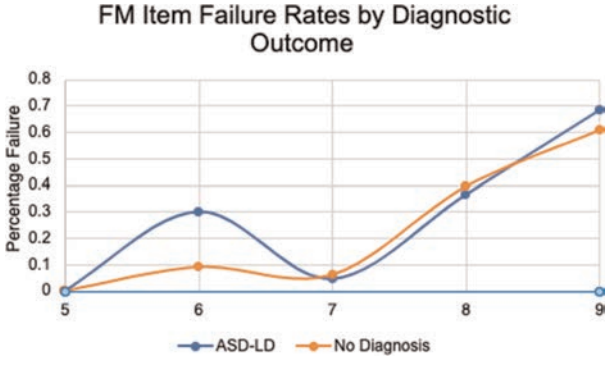


FIGURE 1: MSEL Fine Motor Item Failure Rates by Diagnostic Outcome. ASD-LD: Autism Spectrum Disorder and Language Delay Infants. No Diagnosis: No developmental diagnosis. Item 5: hands held generally open. Item 6: Ulnar palmar peg grasp. Item 7: Radial palmar block grasp. Item 8: Observations of block play. Item 9: Radial palmar block grasp with complete thumb opposition. Abstract 15

16. Adult Life in Fragile X Syndrome

Berry-Kravis E (Chicago, IL), Gable J, Raspa M, Hunter J, Edwards A, Wheeler A, Weber J

Objective: To characterize transition services, employment and program participation, living arrangements, and engagement in social activities in adults with fragile X syndrome (FXS)

Methods: A descriptive analysis was performed for the participants in the FORWARD natural history study of FXS who were age ≥18 at any time during follow up (N=541; 414M, 127F). The most recent evaluation was used for analyses for those with >1 evaluation at age ≥18.

Results: The cohort ranged in age from 18 to 65 years (N=157 age 18-20, N=237 age 21-30, N=102 age 31-40, N=45 age >40) and was 88% white (7% Hispanic) and 6% African American. In 50% of families there was more than one child with special needs in the home. Behavior challenges were mainly anxiety in 87%, and irritability/aggression in 44%. Transition planning meetings were held for 83% and these were variably helpful. In this cohort, 23% were in school/transition programs, 25% day program/workshop, 16% supported employment, 7% employment without supports, 9% college/trade school, and 10% volunteering; 63% were in their program for over 20 hours a week. Residence was with the parents for 80%, and in a group home for 8%, with a small percentage in each of multiple other settings. Social activities included Special Olympics (27%), informal socialization with friends (27%), religious activities (26%), clubs (10%), park district programs (13%), and peer buddies programs (7%).

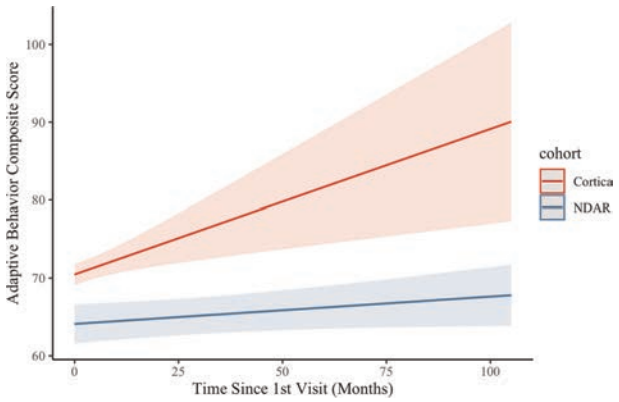
Conclusions: This data helps understand adult life for individuals with FXS, as well as identify gaps in support services and programs for adults with FXS and other intellectual disabilities.

Keywords: Cognitive/Behavioral Disorders (including Autism), Rare Diseases, Genetics

17. A Comprehensive, Personalized, Medically Based Care Model Improves Adaptive Behavior Outcomes in Autism vs Standard of Care

Brandes-Aitken A (New York, NY), DiMarino E, Marco E, Hattangadi N, Shapiro K

Objective: This study examined the effects of treatment at Cortica on adaptive behaviors in children with Autism Spectrum Disorder (ASD). Currently, the standard of care for adaptive behavior deficits in ASD is Applied Behavior Analysis (ABA). The Cortica model involves a comprehensive program including ABA in addition to multidisciplinary



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developmental therapies, overseen by a neurodevelopmental physician. We analyzed longitudinal change in the Vineland Adaptive Behavior Scales over the course of Cortica care compared to standard ASD care received by children included in the National Database of Autism Research (NDAR).

Methods: Children with an ASD diagnosis (Cortica N=343, NDAR N=103) were assessed up to 7 times between the ages of 2-12 years. We constructed multilevel models to characterize growth curves within each adaptive behavior domain (composite score, communication, socialization, and daily living skills). We included a time X cohort interaction term to compare relative rates of growth in the Cortica sample versus the NDAR sample.

Results: Multilevel models showed a main effect of time, such that adaptive behaviors demonstrated improvement over course of treatment for both cohorts in all domains (B≥.19, p≤.003). Further, we found a significant cohort X time interaction for the adaptive behavior composite score (B=-0.15, p=.01), communication (B=-0.19, p=.04), socialization (B=-0.18, p=.01) but not daily living skills. All interactions indicated that children in the Cortica cohort showed increased growth in adaptive behaviors relative to children in the NDAR cohort.

Conclusions: Children with ASD receiving care at Cortica resulted in improved adaptive behavior development compared to a cohort of children receiving typical care.

Keywords: Cognitive/Behavioral Disorders (including Autism)

18. Subtle Neurologic Signs in Chromosome 16p11.2 Deletion and Duplication

Sprigg B (Seattle, WA), Steinman K

Objective: Copy number variants (CNVs) of chromosome 16p11.2 are among the most common known genetic etiologies for neurodevelopmental disorders such as autism spectrum. Difficulties with motor skills seen in this population have not been explained by identification of typical neurologic signs. The aim of the current study is to examine the frequency of subtle neurologic signs that may underlie difficulties with motor skills.

Methods: Subjects are a subset of the Simons Variation in Individuals Project participants with 16p11.2 deletion (n=9; 6-12 years old) or duplication (n=6, ages 6-14). Participants were assessed with the Physical and Neurological Exam for Subtle Signs (PANESS). Median z-scores on timed portions of the PANESS were compared to norms (by age, gender, and handedness) from the battery using Wilcoxon signed-rank tests (threshold for significance $p<0.05$).

Results: Regardless of CNV, subjects exhibited multiple subtle neurologic signs on all summary scores of the PANESS. Scores for dysrhythmia, overflow movements, gaits and stations, and total PANESS were high in both groups, but without statistically significant differences between groups (Table 1). Subjects with duplication performed more poorly ($p<0.05$) on timed patterned movements compared to norms, while subjects with deletions exhibited primarily timed repetitive movement slowness (Table 2).

Conclusions: Among a cohort of subjects with 16p11.2 deletions and duplications, subtle neurologic findings were common. The nature of speed-based motor challenges experienced by those two groups seems to differ by CNV. These findings may point to specific neural pathways that underlie motor skills challenges in these 16p11.2 CNVs, which warrant further investigation.

Keywords: Cognitive/Behavioral Disorders (including Autism)

Table 1. PANESS summary scores by CNV. Abstract 18

	Deletion Median (range)	Duplication Median (range)	P-value
Total Dysrhythmia (scored 0-13)	7 (1, 11)	8 (3, 9)	0.50
Total Overflow Movements, Irrespective of Age (scored 0-31)	11 (2, 26)	15.5 (9, 20)	0.20
Total Gaits and Stations (scored 0-49)	21 (15, 23)	18 (11, 22)	0.08
Total PANESS (scored 0-119)	44.5 (30, 68)	49 (33, 60)	0.35

Table 2. Z-scores for timed repetitive and patterned movements compared to age, gender, and handedness norms. Abstract 18

		Deletion		Duplication	
	Side	**Median (range)**	**P-value**	**Median (range)**	**P-value**
Timed Repetitive Movements					
Foot tap	Right	-2.6 (-11.0, -1.3)	0.01	-4.0 (-23.8, 1.3)	0.17
	Left	-0.6 (-10.4, 0.0)	0.03	-2.1 (-3.7, 1.0)	0.12
Hand pat	Right	-1.6 (-4.6, -0.2)	0.01	-1.4 (-14.5, 0.6)	0.12
	Left	-2.16 (-4.9, -0.5)	0.01	-1.8 (-16.6, 0.6)	0.12
Finger tap	Right	0.285 (-2.2, 2.5)	0.40	-0.8 (-4.1, 0.9)	0.17
	Left	0.5 (-1.9, 1.9)	0.78	-1.2 (-8.0, 1.8)	0.17
Timed Patterned Movements					
Heel/toe tap	Right	0.2 (-7.9, 1.9)	0.89	-1.8 (-6.3, 2.4)	0.17
	Left	-0.1 (-2.4, 1.5)	0.87	-1.9 (-3.9, 1.4)	0.07
Hand pronate/supinate	Right	-1.9 (-7.3, 1.0)	0.04	-2.9 (-5.2, -0.9)	0.03
	Left	-1.5 (-10.4, 1.7)	0.07	-2.6 (-5.2, -0.5)	0.03
Finger apposition	Right	-0.6 (-4.2, 1.4)	0.33	-3.7 (-19.8, -0.3)	0.03
	Left	-0.3 (-3.9, 1.2)	0.33	-3.4 (-26.0, -0.7)	0.03

19. The association of quantitative EEG & heavy metal levels in children with Autism spectrum disorder: A cross sectional study

Gulati S (New Delhi, India), Sharma S, Sharma R, Ahmed A, Y, Pandey R, Purkayastha K, Quadri J, Sherrif A

Objective: To correlate the underlying pathogenesis of autism spectrum disorder(ASD) with mean blood levels of mercury(Hg), Chromium(Cr), Manganese(Mn), Selenium(Se) &lead(Pb)& further correlation with quantitative EEG

***Table 1. Comparison of blood levels of heavy metals between ASD and Control groups.* Absract 19**

Heavy Metals (ppb or µg/L)	**Normal values of heavy metals in Blood**	**ASD (N=180) Median (Range)**	**Controls (N=180) Median (Range)**	**P value**
Mercury (Hg)	< 10	27.82 (.001-60.93)	0.001 (.001-51.8)	< 0.001
Chromium (Cr)	20 to 30	65.5 (.001-128.0)	0.001 (.001-128.1)	< 0.001
Manganese (Mn)	4.2 to 16.5	44.9 (.001-89.6)	11.35 (4 - 88.9)	< 0.001
Nickel (Ni)	0.14 to 0.65	0.001 (.001-80.3)	0.001 (.001-.5)	0.051
Copper (Cu)	12 to 1400	1201.2 (.001-2063.3)	1014.8 (73.4-1913.5)	0.65
Zinc (Zn)	35 to 5500	5891.5 (135.3-9567.6)	6211.35 (437.4-9456.9)	0.91
Arsenic (As)	<62	0.001 (.001-24)	0.001 (.001-21.9)	0.111
Lead (Pb)	<100	102.8 (.001-414.1)	47.4 (10.1-181.7)	< 0.001
Selenium	70 to 150	182.5 (0.91-353)	130(10.6-342.04)	< 0.001
Iron (Fe)	-	22672.79 (284.8-963821.6)	423219.6 (2609.2-1348394)	~50(non-significant)

TABLE 2: Summary of spectral power and Coherence results: ASD vs Control. Abstract 19

Conditions	Gamma	Beta	UA	LA2	LA1	Theta	Delta
Eyes closed	↑	↑	NS	NS	↑	↑	NS
Eyes Open	NS	NS	NS	NS	NS	↑	NS
Picture memory (encoding)	NS	NS	NS	NS	NS	NS	NS
DSFT	NS	NS	↑	↑	↑	↑	↓
Word memory	Number is too small for analysis					↓-Decrease	
Verbal fluency						↑- Increase	
coherence results							
Conditions	**Gamma**	**Beta**	**UA**	**LA2**	**LA1**	**Theta**	**Delta**
Eyes closed	↓	NS	NS	NS	↓	NS	NS
Eyes Open	NS	NS	NS	NS	↓	↓	↓
Picture memory (encoding)	NS	NS	NS	NS	NS	NS	NS
DSFT	↑	NS	NS	↓	↓↑	NS	NS
Word memory	Number is too small for analysis					↓-Decrease	
Verbal fluency						↑- Increase	

DSFT: digit span forward test, UA: Upper alpha, LA2: Lower alpha2, LA1: Lower alpha1, NS: not significant

Methods: In this study, 180 ASD children (aged 3-12years) diagnosed as per the DSM-5 and 180 age matched controls having developmental profile (DP3) with standard score more than 84 were recruited. Blood samples were collected in EDTA metal-free tubes, were processed for Inductively-Coupled-Plasma-Mass-Spectroscopy. EEG was recorded from 128 electrodes using an Electrical Geodesics (EGI) high-density EEGsystem (Netstation) & digitized @ 1000Hz. Impedance was kept below 50kΩ. EEG was recorded at 0.1-Hz high-pass/100Hz low-pass filtering & 50Hz notch

Results: ASD subjects (153 males/27 females, 6.5±1.6 years, Childhood *Autism Rating Scale (*CARS): 36.59±2.38, Developmental Quotient(DQ): 59.94±5.86) had significantly high levels of Hg, Cr, Mn ($p=0.01$ for all three);Se & Pb ($p=0.001$) (Table 1). The spectral power of gamma(γ), beta (β), lower alpha1(lα1), theta(θ) & coherence of γ, lα1, during eyes-closed condition was significantly ($p < 0.0005$) low & the spectral power of θ & coherence of lα1, θ, δ, was significantly low ($p < 0.0005$) during eyes-open condition in ASD compared to controls (Table 2). γ band had positive correlation with Cr, Zinc (Zn), Pb & negative correlation with Nickel(Ni). β band had positive correlation with Fe, Se, Ni, Pb & negative correlation with Copper, Mn, Arsenic.

Conclusions: The study is suggestive of impaired coherence pattern in children with ASD during attention task. ASD children have different qEEG correlates, as well as, significantly high blood Hg, Cr, Mn, Se& Pb levels as compared age matched controls

Keywords: Cognitive/Behavioral Disorders (including Autism), Neuroscience, Education

20. Comorbidities in children with cerebral palsy: A cross-sectional study

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Objective: To determine the prevalence of comorbidities among children with cerebral palsy (CP), and characteristics predictive of different comorbidities.

Methods: Children of age 2-18 years with a confirmed diagnosis of CP were enrolled in this cross-sectional study undertaken between April 2018 and October 2021 at a tertiary care centre in India. Comorbidities were assessed in the following domains: motor function, cognition, vision, hearing, communication, epilepsy, sleep, pain, gastrointestinal dysfunction, and behaviour.

Results: Among 436 children who were screened, 384 were study-eligible (Figure 1) and included hemiparetic CP (52, 13.5%), dyskinetic CP (58, 15.1%), spastic diplegia (70, 18.2%), spastic quadriparesis (92, 24%), and mixed CP (110, 28.6%) (Table 1). The most common comorbidities included visual impairment (357, 93%), epilepsy (245, 64%), cognitive impairment (241, 62.7%), poor

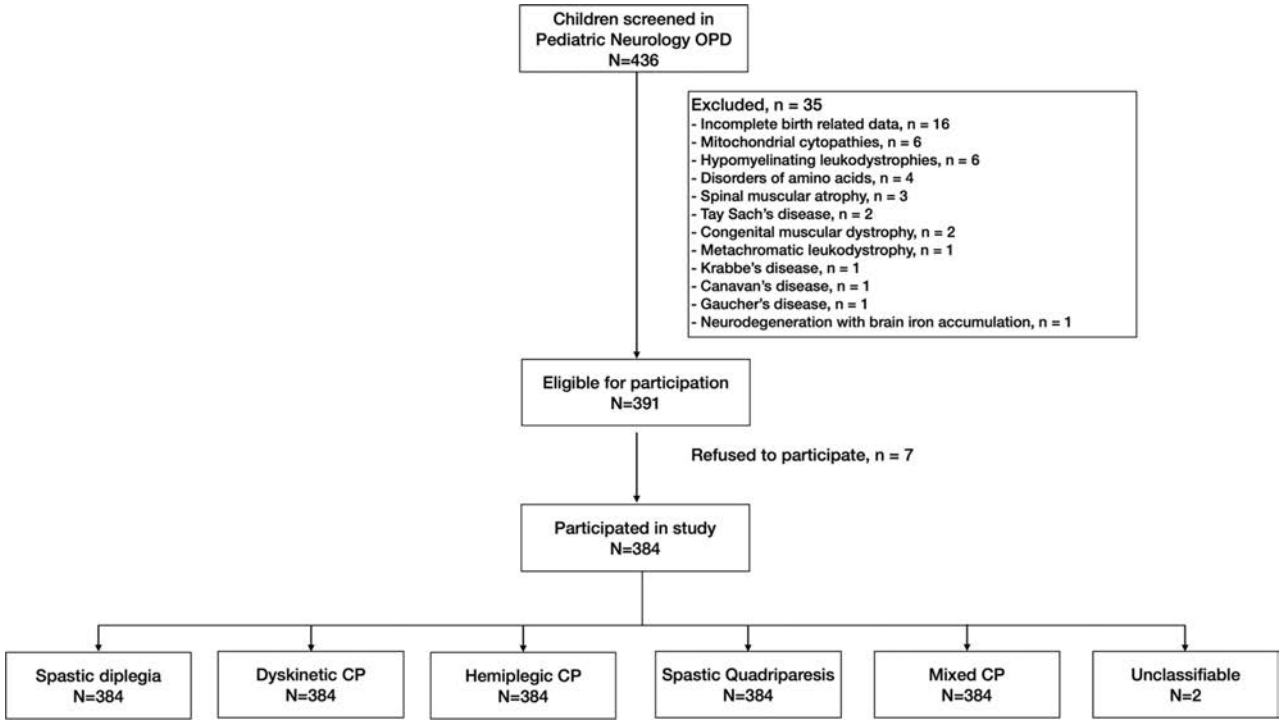

FIGURE 1. Flow of patients. Abstract 20

TABLE 1. Baseline data. Abstract 20

Characteristic	Overall, N = 384[1,2]	Dyskinetic CP, N = 58[1]	Hemiparetic CP, N = 52[1]	Mixed CP, N = 110[1]	Spastic Diplegia, N = 70[1]	Spastic Quadriplegia, N = 92[1]
Age, months	78 (38)	93 (42)	72 (41)	82 (37)	66 (27)	77 (41)
Male	251 (65%)	50 (86%)	36 (69%)	77 (70%)	30 (43%)	56 (61%)
Gestational age						
Mean (SD)	37(4)	38(3)	37(4)	38(2)	33(3)	38(3)
Term	231(60%)	43(74%)	32(62%)	81(74%)	7(10%)	66(72%)
Moderate to late preterm	97 (25%)	13 (22%)	11 (21%)	25 (23%)	29 (41%)	19 (21%)
Very preterm	48 (13%)	1 (1.7%)	7 (13%)	4 (3.6%)	31 (44%)	5 (5.4%)
Extremely preterm	8 (2.1%)	1 (1.7%)	2 (3.8%)	0 (0%)	3 (4.3%)	2 (2.2%)
Mode of delivery						
Vaginal	241 (63%)	36 (62%)	39 (75%)	58 (53%)	49 (70%)	58 (63%)
LSCS	130 (34%)	21 (36%)	13 (25%)	46 (42%)	21 (30%)	28 (30%)
Instrumental	13 (3.4%)	1 (1.7%)	0 (0%)	6 (5.5%)	0 (0%)	6 (6.5%)
Birth Weight, grams	2,343 (796)	2,715 (709)	2,300 (880)	2,563 (582)	1,451 (439)	2,548 (752)
Etiology/ Risk Factors						
Antenatal factors	32	0	10	9	4	7

TABLE 1 (Continued)

Characteristic	Overall, N = 384[1,2]	Dyskinetic CP, N = 58[1]	Hemiparetic CP, N = 52[1]	Mixed CP, N = 110[1]	Spastic Diplegia, N = 70[1]	Spastic Quadriplegia, N = 92[1]
Genetic	23 (6.0%)	0 (0%)	10 (19%)	3 (2.7%)	1 (1.4%)	7 (7.6%)
Intrauterine infections	9 (2.3%)	0 (0%)	0 (0%)	6 (5.5%)	3 (4.3%)	0 (0%)
Birth related factors	320	58	40	82	66	74
Hypoglycemia	102 (26.6%)	0 (0%)	0 (0%)	61 (55%)	0 (0%)	41 (45%)
Perinatal asphyxia	90 (23.4%)	35 (60%)	7 (13%)	14 (13%)	7 (10%)	27 (29%)
Prematurity	81 (21.1%)	2 (3.4%)	11 (21%)	3 (2.7%)	59 (84%)	6 (6.5%)
Neonatal sepsis	74 (19.3%)	7	0	35	10	22
Neonatal jaundice	24 (6.3%)	21 (36%)	0 (0%)	3 (2.7%)	0 (0%)	0 (0%)
Perinatal stroke	23 (6.0%)	0 (0%)	22 (42%)	1 (0.9%)	0 (0%)	0 (0%)
Birth trauma	17 (4.4%)	4 (6.9%)	1 (1.9%)	2 (1.8%)	1 (1.4%)	9 (9.8%)
Etiological factors after neonatal period	26	0	0	17	0	9
Febrile encephalopathy	13 (3.9%)	0 (0%)	0 (0%)	10 (9.1%)	0 (0%)	3 (5.4%)
Surgery related hypoxia	11 (2.9%)	0 (0%)	0 (0%)	7 (6.4%)	0 (0%)	4 (4.3%)
Traumatic brain injury/ drowning	2	0	0	0	0	2
Unknown	6 (1.6%)	0 (0%)	2 (3.8%)	2 (1.8%)	0 (0%)	2 (2.2%)

[1]Mean (SD); n (%)
[2]Two patients from the cohort could not be classified into any of sub-categories.
*One patient with intrauterine infection also had neonatal sepsis and later developed mixed CP
Abbreviations: CP: cerebral palsy; LSCS: lower segment caesarean section;

TABLE 2. Prevalence of comorbidities among children with cerebral palsy. Abstract 20

Characteristic	Overall, N = 384[1,2]	Dyskinetic CP, N = 58[1]	Hemiparetic CP, N = 52[1]	Mixed CP, N = 110[1]	Spastic Diplegia, N = 70[1]	Spastic Quadriplegia, N = 92[1]
Functional status						
GMFCS						
1	30 (7.8%)	0 (0%)	27 (52%)	0 (0%)	3 (4.3%)	0 (0%)
2	59 (15%)	2 (3.4%)	18 (35%)	2 (1.8%)	35 (50%)	2 (2.2%)
3	56 (15%)	11 (19%)	2 (3.8%)	9 (8.2%)	29 (41%)	5 (5.4%)
4	65 (17%)	19 (33%)	5 (9.6%)	24 (22%)	3 (4.3%)	13 (14%)
5	174 (45%)	26 (45%)	0 (0%)	75 (68%)	0 (0%)	72 (78%)

TABLE 2 (Continued)

Characteristic	Overall, N = 384[1,2]	Dyskinetic CP, N = 58[1]	Hemiparetic CP, N = 52[1]	Mixed CP, N = 110[1]	Spastic Diplegia, N = 70[1]	Spastic Quadriplegia, N = 92[1]
No understanding of any communication	137 (36%)	28 (48%)	1 (1.9%)	53 (48%)	9 (13%)	
Phrases understood	145 (38%)	28 (48%)	4 (7.7%)	45 (41%)	28 (40%)	
Vocabulary understood	102 (27%)	2 (3.4%)	47 (90%)	12 (11%)	33 (47%)	
Speech communication						
No gestural communication	178 (46%)	38 (66%)	0 (0%)	73 (66%)	4 (5.7%)	62 (67%)
Normal verbal communication	8 (2.1%)	0 (0%)	4 (7.7%)	0 (0%)	4 (5.7%)	0 (0%)
Only gestural communication	109 (28%)	17 (29%)	8 (15%)	34 (31%)	25 (36%)	24 (26%)
Vocabulary produced with partial verbal communication	89 (23%)	3 (5.2%)	40 (77%)	3 (2.7%)	37 (53%)	6 (6.5%)
Visual impairment (data for 383)						
Visual Impairment	357 (93%)	50 (86%)	49 (94%)	99 (90%)	68 (99%)	89 (97%)
Impaired Visual acuity	246 (64%)	29 (50%)	27 (52%)	71 (65%)	52 (74%)	66 (72%)
Refractive error	94 (25%)	6 (10%)	13 (25%)	37 (34%)	14 (20%)	24 (26%)
Squint	150 (39%)	14 (24%)	19 (37%)	45 (41%)	25 (36%)	47 (51%)
Fundus abnormalities	293 (76%)	47 (81%)	35 (67%)	79 (72%)	54 (77%)	77 (84%)
Abnormal VEP	248 (72%)	22 (42%)	18 (44%)	79 (77%)	53 (88%)	74 (86%)
Abnormal BERA	113 (30%)	36 (62%)	2 (3.8%)	35 (32%)	14 (20%)	25 (27%)
Social Quotient, Mean (SD)	32 (29)	20 (21)	71 (22)	15 (14)	59 (24)	15 (15)
Normal	43 (11%)	3 (5.2%)	23 (44%)	1 (0.9%)	15 (22%)	1 (1.1%)
Borderline	10 (2.6%)	0 (0%)	5 (9.6%)	0 (0%)	5 (7.2%)	0 (0%)
Mild	41 (11%)	1 (1.7%)	11 (21%)	2 (1.8%)	24 (35%)	3 (3.3%)
Moderate	49 (13%)	10 (17%)	10 (19%)	8 (7.3%)	17 (25%)	4 (4.3%)
Severe	43 (11%)	6 (10%)	3 (5.8%)	20 (18%)	3 (4.3%)	11 (12%)
Profound	198 (51%)	38 (66%)	0 (0%)	79 (72%)	5 (7.2%)	73 (79%)
Dental caries	182 (48%)	25 (43%)	31 (60%)	53 (48%)	45 (64%)	28 (30%)
Difficulty in biting	204 (53%)	32 (55%)	6 (12%)	75 (68%)	23 (33%)	66 (72%)
Insufficient chewing	202 (52%)	36 (62%)	3 (5.8%)	76 (69%)	20 (29%)	65 (71%)
Persistent drooling	217 (57%)	38 (66%)	14 (27%)	70 (64%)	29 (41%)	65 (71%)
Lack of appetite	105 (27%)	18 (31%)	0 (0%)	36 (33%)	12 (17%)	38 (41%)
Swallowing difficulties	205 (53%)	33 (57%)	11 (21%)	62 (56%)	25 (36%)	72 (78%)
Nasal regurgitation	42 (11%)	9 (16%)	3 (6.2%)	20 (18%)	0 (0%)	10 (11%)
Coughing while feeding	140 (36%)	35 (60%)	3 (5.8%)	43 (39%)	10 (14%)	47 (51%)
Vomiting	50 (13%)	8 (14%)	0 (0%)	6 (5.5%)	11 (16%)	24 (26%)

TABLE 2 (Continued)

Characteristic	Overall, N = 384[1,2]	Dyskinetic CP, N = 58[1]	Hemiparetic CP, N = 52[1]	Mixed CP, N = 110[1]	Spastic Diplegia, N = 70[1]	Spastic Quadriplegia, N = 92[1]
Abdominal pain/ colic	56 (15%)	8 (14%)	0 (0%)	13 (12%)	12 (17%)	23 (25%)
≥2 episodes of wheezing requiring hospitalization	83 (22%)	11 (19%)	5 (9.6%)	23 (21%)	14 (20%)	29 (32%)
Bowel frequency						
>3 times a week	25 (6.5%)	7 (12%)	2 (3.8%)	2 (1.8%)	1 (1.4%)	11 (12%)
2-3 times a week	109 (28%)	20 (34%)	4 (7.7%)	49 (45%)	12 (17%)	24 (26%)
≤1 times a week	250 (65%)	31 (53%)	46 (88%)	59 (54%)	57 (81%)	57 (62%)
Meal duration (minutes per meal)	38 (18)	39 (20)	25 (10)	39 (20)	35 (12)	44 (17)
Overall GI dysfunction						
Normal	88(23%)	7 (12%)	38 (73%)	6 (5.5%)	34 (49%)	3 (3.3%)
Mild dysfunction	72(19%)	19 (33%)	12(23%)	9 (8.2%)	23 (33%)	9 (9.8%)
Moderate dysfunction	134 (35%)	12 (21%)	1 (1.9%)	58 (53%)	13 (19%)	49 (53%)
Severe dysfunction	90 (23%)	20 (34%)	1 (1.9%)	37 (34%)	0 (0%)	31 (34%)
Pain						
Significant pain	230 (60%)	37 (64%)	9 (17%)	88 (80%)	22 (31%)	72 (78%)
Epilepsy						
Epilepsy	245 (64%)	27 (47%)	24 (46%)	88 (80%)	24 (34%)	81 (88%)
Age of onset of seizures	8 (15)	4 (14)	17 (21)	7 (16)	16 (23)	5 (8)
Types of seizures						
Generalized seizures	119 (31%)	13 (22%)	13 (25%)	48 (44%)	7 (10%)	38 (41%)
Focal seizures	120 (31%)	23 (40%)	22 (42%)	33 (30%)	13 (19%)	28 (30%)
Multifocal seizures	225 (59%)	26 (45%)	15 (29%)	85 (77%)	18 (26%)	80 (87%)
Myoclonic seizures	157 (41%)	18 (31%)	2 (3.8%)	61 (55%)	7 (10%)	68 (74%)
Drug resistant epilepsy	163 (42%)	17 (29%)	7 (13%)	67 (61%)	6 (8.6%)	65 (71%)
West syndrome	145 (38%)	18 (31%)	2 (3.8%)	61 (55%)	7 (10%)	56 (61%)
Lennox Gastaut syndrome	128 (33%)	14 (24%)	0 (0%)	61 (55%)	5 (7.1%)	47 (51%)
Seizure free for 2 years	22 (5.7%)	2 (3.4%)	3 (5.8%)	6 (5.5%)	7 (10%)	4 (4.3%)
Sleep related comorbidities						
Sleep impairment	176 (60.7%)	38 (66%)	8 (15%)	70 (64%)	6 (8.6%)	54 (59%)
Bedtime resistance	28 (9.7%)	12 (21%)	8 (15%)	5 (4.5%)	3 (4.3%)	0 (0%)
Sleep onset delay	126 (43.4%)	37 (64%)	13 (25%)	53 (48%)	7 (10%)	16 (17%)
Impaired sleep duration	102 (35.2%)	34 (59%)	11 (21%)	36 (33%)	10 (14%)	11 (12%)

TABLE 2 (Continued)

Characteristic	Overall, N = 384[1,2]	Dyskinetic CP, N = 58[1]	Hemiparetic CP, N = 52[1]	Mixed CP, N = 110[1]	Spastic Diplegia, N = 70[1]	Spastic Quadriplegia, N = 92[1]
Sleep anxiety	40 (13.8%)	23 (40%)	7 (13%)	6 (5.5%)	2 (2.9%)	2 (2.2%)
Night waking	106 (36.6%)	36 (62%)	11 (21%)	39 (35%)	6 (8.6%)	14 (15%)
Parasomnia	8 (2.8%)	2 (3.4%)	5 (9.6%)	0 (0%)	1 (1.4%)	0 (0%)
Sleep disordered breathing	80 (27.6%)	21 (36%)	5 (9.6%)	29 (26%)	5 (7.1%)	20 (22%)
Day time sleepiness	106 (36.6%)	25 (43%)	5 (9.6%)	44 (40%)	3 (4.3%)	29 (32%)
Internalizing score ≥84th centile	132 (34%)	23 (40%)	6 (12%)	53 (48%)	14 (20%)	34 (37%)
Externalizing score ≥84th centile	70 (18%)	12 (21%)	15 (29%)	17 (15%)	13 (19%)	13 (14%)
Total score ≥ 84th centile	165 (43%)	29 (50%)	17 (33%)	57 (52%)	21 (30%)	39 (42%)

TABLE 3. Univariable analysis of risk of comorbidities based on diagnosis and GMFCS. Abstract 20

Variable	Odds Ratio (95% Confidence Interval)					p
Regression analysis, based on underlying type of CP, with reference to hemiparetic CP						
Type of Cerebral palsy	**Hemiparetic CP**	**Spastic Diplegia**	**Dyskinetic CP**	**Mixed CP**	**Spastic quadriplegia**	
GMFCS	Reference	24.1 (7.68, 107)	>2.5 x 10^9 (0, Inf)	>2.5 x 10^9 (0, Inf)	>2.5 x 10^9 (0, Inf)	<0.001
Social quotient		-11 (-18, -4.4)	-51 (-58, -44)	-55 (-61, -49)	-55 (-62, -49)	<0.001
Visual impairment		4.16 (0.52, 85.5)	0.38 (0.08, 1.41)	0.55 (0.12, 1.86)	1.82 (0.33, 10.1)	0.018
Hearing impairment		6.25 (1.64, 41.1)	40.9 (11.2, 266)	11.7 (3.35, 73.9)	9.47 (2.65, 60.6)	<0.001
Speech comprehension and communication		10.5 (4.04, 33.2)	263 (59.9, 1964)	76.8 (27.7, 258)	98.7 (33.3, 357)	<0.001
Epilepsy		0.61 (0.29, 1.27)	1.02 (0.48, 2.16)	4.67 (2.30, 9.70)	8.59 (3.83, 20.5)	<0.001
Drug resistant epilepsy		0.81 (0.22, 2.92)	4.13 (1.31, 14.1)	7.75 (2.93, 22.5)	9.87 (3.64, 29.5)	<0.001
GI Dysfunction		0.61 (0.26, 1.37)	0.62 (0.26, 1.42)	3.37 (1.32, 8.85)	2.77 (1.08, 7.30)	<0.001
Pain		1.99 (0.84, 5.00)	7.63 (3.21, 19.7)	17.3 (7.61, 43.2)	15.6 (6.74, 39.5)	<0.001
Sleep impairment		0.46 (0.14, 1.46)	10.7 (4.01, 31.4)	13.9 (5.60, 38.0)	14.0 (5.41, 40.1)	<0.001
Internalizing score		1.92 (0.71, 5.78)	5.04 (1.95, 14.9)	7.13 (3.00, 19.8)	4.49 (1.85, 12.7)	<0.001
Externalizing behavior		0.56 (0.24, 1.32)	0.64 (0.26, 1.54)	0.45 (0.20, 1.00)	0.41 (0.17, 0.94)	0.2

TABLE 3 (Continued)

Variable	Odds Ratio (95% Confidence Interval)				p
Total score on CBCL	0.88 (0.41, 1.92)	2.06 (0.96, 4.53)	2.21 (1.12, 4.49)	1.51 (0.75, 3.13)	
Regression analysis, based on underlying type of GMFCS level, with reference to hemiparetic CP					
GMFCS	**1**	**2**	**3**	**4**	**5**	
Social quotient	Reference	-14 -21, -7.7)	-38 (-44, -31)	-65 (-71, -59)	-70 (-76, -65)	<0.001
Visual impairment		0	0	0	0	-
Hearing impairment		2.52 (0.60, 17.3)	7.19 (1.88, 47.5)	8.97 (2.40, 58.6)	6.94 (1.99, 43.9)	<0.001
Speech comprehension and communication		4.36 (1.11, 29.1)	84 (20.3, 591)	114 (27, 813)	159 (42.1, 1052)	<0.001
Epilepsy		1.44 (0.54, 4.18)	3.06 (1.17, 8.77)	7.78 (2.98, 22.5)	18.6 (7.57, 51)	<0.001
Drug resistant epilepsy						
GI dysfunction		2.05 (0.77, 5.41)	1.45 (0.56, 3.71)	2.51 (0.94, 6.70)	4.43 (1.81, 10.6)	0.004
Pain		0.60 (0.17, 2.23)	4.73 (1.67, 15.7)	11.2 (3.94, 37.8)	19.4 (7.33, 61.5)	<0.001
Sleep impairment		1.70 (0.36, 12.2)	4.25 (1.01, 29.4)	24.3 (5.99, 166)	46.1 (12.1, 305)	<0.001
Internalizing score		7.40 (1.35, 138)	10.6 (1.98, 197)	25.6 4.99, 470)	20.7 (4.27, 373)	<0.001
Externalizing score		0.73 (0.27, 1.99)	0.71 (0.26, 1.95)	0.38 (0.13, 1.10)	0..39 (0.7, .99)	0..14
Total score		1.29 (0.51, 3.43)	1.51 (0.60, 4.02)	2.48 (1.01, 6.49)	1.92 (0.85, 4.63)	0.2

functional status (239, 62.2%), sleep impairment (176, 60.7%), pain (230, 60%), gastrointestinal dysfunction (224, 58.3%), language impairments (178, 46%) and behavioural abnormalities (165, 43%) (Table 2). As compared to hemiparetic CP, the odds (95% CI) of visual impairment, hearing impairment, communication abnormality, epilepsy, gastrointestinal dysfunction, pain, sleep impairment, and internalizing behaviour in a child with spastic quadriparesis were 1.82 (0.33-10.1), 9.47 (2.65-60.6), 98.7 (33.3-357), 8.59 (3.83-20.5), 2.77 (1.08-7.30), 15.6 (6.74-39.5), 14.0 (5.41-40.1), and 4.49 (1.85-12.7). Overall, the prevalence and severity of comorbidities were worst for spastic quadriparesis and mixed CP, and worsened with increasing GMFCS scales (Table 3).

Conclusions: These findings demonstrate a high prevalence of comorbidities beyond the functional domains. Identification of same is needed for holistic care of children with CP.

Keywords: Cognitive/Behavioral Disorders (including Autism), Neurorehabilitation

21. The analysis of Spectrum of Co-morbidities in children with ASD (Autism Spectrum Disorder): a retrospective study

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Objective: To study the diverse spectrum of co-morbidities in pediatric with ASD and their association with the severity of symptoms in ASD children as measured on Childhood Autism Rating Scale (CARS).

Methods: A retrospective analysis of ASD (DSM-5 criteria) children (aged 2-18 years) between January-2017 to March-2021 was done. Total of 1872 children [1582 males (84.5%) and 290 females (15.5%), median age of 5.6 + 3.3years with interquartile-range 5.1-8.5years] were enrolled. Regularly follow-up was done at an interval of 1-3months. Symptom severity and behavioural co-morbidities were done by CARS and Autism Behaviour Checklist (ABC). Behavioural therapy

and medications were prescribed in accordance with co-morbidities and severity.

Results: In this study 80% of the ASD children (1499/1872) had co-morbidity, of which 35% had more than one comorbidity. Attention deficit hyperactivity disorder was the most common behavioural comorbidity (57.55%), followed by disruptive behaviour (4.51%) and obsessive-compulsive disorder (1.42%). Amongst all children, 62% had a psychiatric comorbidity (Table-1). Systemic abnormalities, neurological co-morbidities were common (52.6%) and included global developmental delay/intellectual disability, sleep abnormalities, epilepsy, isolated speech/ language delay and sensory processing disorder. The assessment at 3months showed significant (p<0.0001) (Table-2) improvement in core features as measured by mean CARS score. Significantly high ABC scores were observed in patients with speech/language delay, specific learning disability, sensory processing disorder, wandering and genetic disorder.

Table 1. Comorbidities observed in patients with ASD in our study population. Abstract 21

Comorbidity	Number of individuals (%)
Psychiatric and behavioural comorbidities:	989 (53%)
• Attention deficit hyperactivity disorder	151 (8.1%)
• Specific learning disability	148 (7.9%)
• Disruptive behaviour and aggression	82 (4.4%)
• Mood disorder	77 (4%)
• Food selectivity	66 (3.5%)
• Obsessive compulsive disorder	44 (2.4%)
• Adolescent issues	32 (1.7%)
• Wandering behaviour	15 (0.8%)
• Anxiety disorder	
Neurological comorbidities:	984 (52.6%)
• Intellectual disability/ global developmental delay	788 (42.1%)
• Sleep abnormalities	215 (11.5%)
• Epilepsy	151 (8.1%)
• Isolated speech/ language delay	126 (6.7%)
• Sensory processing disorder	56 (3%)
• Locomotor impairment	
Other clinical comorbidities:	90 (4.8%)
• Dysmorphism	77 (4.1%)
• Gastrointestinal problems	76 (4.1%)
• Vision/ hearing impairment	7 (0.4%)
• Obesity	
Other genetic/metabolic disorders:	23 (1.1%)
• Genetic/ metabolicFragile X	17
syndromeRett syndromeTuberous	3
sclerosisPropionic acidemiaOrnithine	1
Transcarbamylase (OTC) deficiency	1
• DMD	1
• Unknown	3
	1847

Table 2. Outcome of behavioural therapy in children with ASD. Abstract 21

	Severity of ASD			
Total patients (n=1872)	Mild to moderate (CARS ≤37)	Severe (CARS >37)	Mean CARS score (±CI)	Mean ABC score (±CI)
Pre-therapy	1074	798	36.92 ± 5	83.34 ± 16.06
Post-therapy	1486	386	34.27 ± 4.07	73.74 ± 13.61
p-value	< 0.001		<0.0001	<0.0001

Conclusions: The comorbidities observed in 80% of the ASD patients did not affect the severity of ASD. Post-therapy significant improvement in their functional outcome was observed. A holistic scrupulous approach is necessary for best outcome.

Keywords: Cognitive/Behavioral Disorders (including Autism)

COVID-19

22. Side effect profiles of the COVID-19 Vaccine Amongst Patients with Mitochondrial Disease

Gordon-Lipkin E (Bethesda, MD), Kruk S, Thompson E, Marcum C, McGuire P

Objective: Patients with mitochondrial disease (MtD) have expressed hesitancy regarding the COVID-19 vaccine due to concerns around safety and efficacy. This study documents the clinical experience of patients with MtD who have received the COVID-19 vaccine.

Methods: An online questionnaire was distributed through MtD advocacy groups from July 2021-March 2022.

Results: 66 patients or their caregivers responded. Fourteen were children. 65% had a known pathogenic variant. 20% had a diagnosis of immunodeficiency/immunocompromised. 12% reported a previous adverse reaction to a vaccine. 85% received mRNA vaccines and 15% received other types. Within one week of dose #1, the most common symptoms were injection site reaction (62%),fatigue(47%),aches(26%), headache(24%),weakness(18%) and fever(10%); 15% had no symptoms. 1/65 had severe allergic reaction and none had metabolic decompensation. After 7 days 10% reported prolonged headache, fatigue or muscle pain. One patient had a metabolic crisis 30 days after.

For those who received a second dose, symptoms <7 days included injection site reaction (66%), fatigue (48%), aches

(36%), headache (34%), weakness (26%) and fever (18%); 13% had no symptoms. 3 reported metabolic decompensation. 12% reported prolonged symptoms more than 7 days after the second dose. For side effects related to the COVID-19 vaccine, only one patient required hospitalization and 7 required a visit to a doctor's office/ED.
Conclusions: In this sample, most patients with MtD mild vaccine side effects and severe adverse events were rare. Only one patient required hospitalization for a metabolic crisis one month after vaccination with an unclear causative link.
Keywords: COVID-19, Neurometabolic Disorders

23. Pediatric Small Fiber Neuropathy Following COVID-19 Infection: The First Reported Case

Squire M (Durham, NC), Trau S

Objective: To present the first reported pediatric case of small fiber neuropathy (SFN) as a sequela of COVID-19 infection.
Methods: A case of a pediatric patient with "long-COVID" manifesting as SFN is presented.
Results: A previously healthy 7-year-old female presented to our outpatient child neurology clinic with rapid-onset, progressive pain beginning two weeks after acute COVID-19 infection. The pain began in the lower extremities rapidly progressed over the next three weeks to involve the entire body surface. An extensive work-up was completed including serum and CSF studies for autoimmune, infectious, and inflammatory processes. MRI of the brain and spine as well as EMG were also performed. All of these returned within normal limits. Gabapentin provided minimal relief. She was admitted to the hospital for IVIG and methylprednisolone and reported modest, but temporary, improvement of her pain. Skin biopsy was performed and was consistent with small fiber neuropathy. She developed sedation to gabapentin and was transitioned to duloxetine. Infusions of IVIG and methylprednisolone were continued outpatient; however, they were discontinued after two months due to anaphylaxis. Due to continuing symptoms, duloxetine was increased; on follow up one month later, her pain had essentially resolved.
Conclusions: Small fiber neuropathy has been rarely reported in adults as a manifestation of "long-COVID". This is the first reported pediatric case. Similar to previously reported adult cases, our patient responded exceptionally well to management with duloxetine.
Keywords: COVID-19, Neuromuscular Disorders

CRITICAL CARE

24. Trends in Quantitative EEG use in Pediatric Critical Care Across North America

Benedetti G (Seattle, WA), Morgan L, Sansevere A, Harrar D, Guerrioro R, LaRovere K, Kielian A, Lalgudi Gansesan S, Wainwright M, Press C

Objective: Describe current use of quantitative electroencephalography (qEEG) in North American pediatric intensive care units (ICUs).
Methods: An electronic survey was distributed to members of the Pediatric Neurocritical Care Research Group, Pediatric

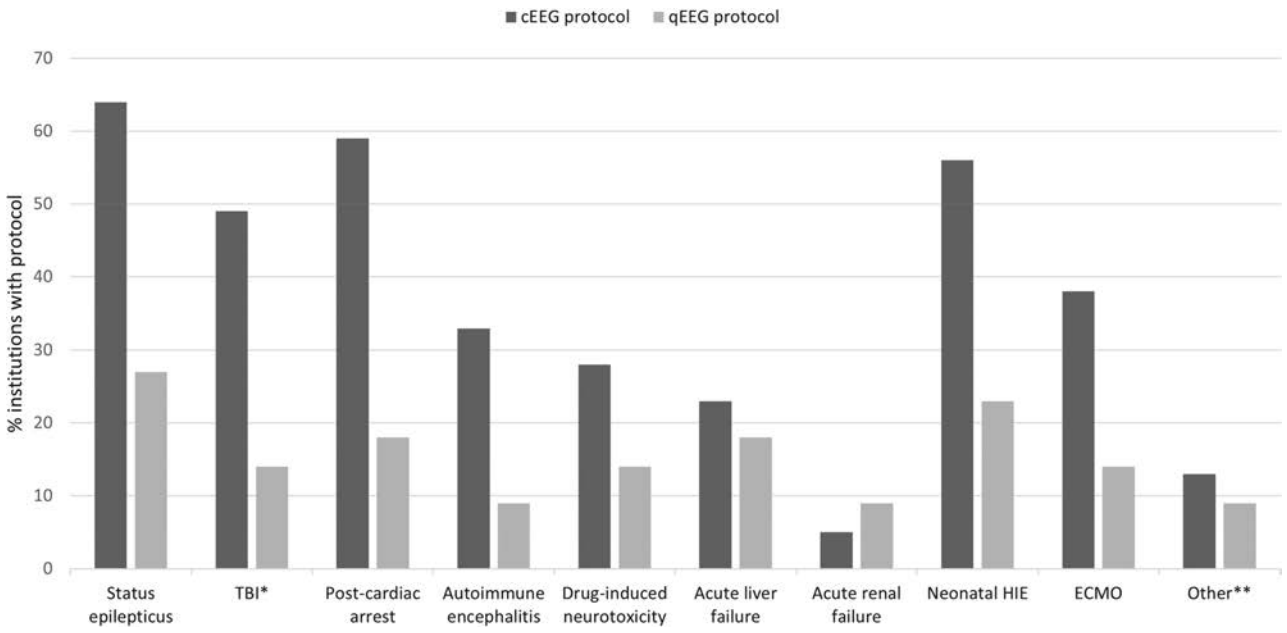


FIGURE 1: Institutional ICU continuous and quantitative EEG monitoring protocols ECMO = extracorporeal membrane oxygenation; EEG = electroencephalogram; ICU = intensive care unit; TBI = traumatic brain injury *Moderate to severe TBI **Other cEEG protocols included post-operative neonates after high-risk congenital heart disease surgery, patients on neuromuscular blockade at high risk for seizures, intracranial hemorrhage, post-operative cardiac surgery patients on ECMO. Other qEEG protocols included perioperative monitoring of patients with moyamoya diseaseFigure 2: Clinical scenarios for which qEEG is applied and favored qEEG trends for clinical use in pediatric ICUs. Abstract 24

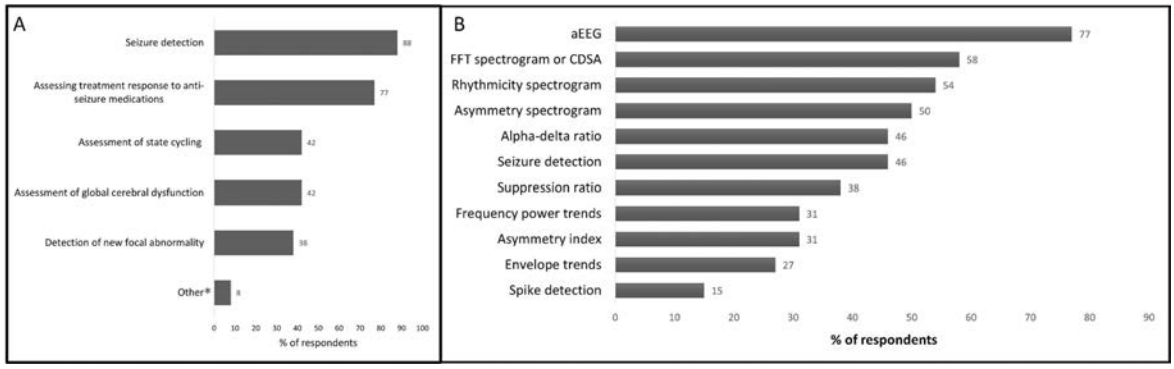


FIGURE 2: Clinical scenarios for which qEEG is applied and favored qEEG trends for clinical use in pediatric ICUs aEEG = amplitude-integrated electroencephalogram; CDSA = color density spectral array; FFT = fast Fourier transform **Macroperiodic oscillations and burst suppression. Abstract 24

Status Epilepticus Research Group, and neurointensivists in 16 Canadian pediatric ICUs. Questions addressed demographics, qEEG acquisition and analysis for research, qEEG in clinical practice, training, and education.

Results: Fifty respondents from 39 institutions completed the survey (response rate 32% [39/121]). Most practiced at academic institutions, 76% (37/50) in the United States, 24% (12/50) in Canada. Over half of institutions utilize qEEG in their ICUs (56% [22/39]). qEEG utilization was associated with institutions with an established neurocritical care (NCC) program, ≥200 NCC consults/year, ≥1500 ICU admissions/year, and ≥4 ICU EEGs/days ($p<0.05$ for all). Neuromonitoring protocols for specific conditions included qEEG at 41% (9/22) of centers (Figure 1). The most useful trends included amplitude-integrated EEG, fast Fourier transform spectrogram, and rhythmicity spectrogram (Figure 2). Nearly all (92% [24/26]) respondents using qEEG endorsed it enhanced care of critically ill children, while 85% (22/26) identified lack of training as a major barrier to qEEG use. Standardized review varied and reporting was rare (1/22). Specific training was required by 14% (3/22) of institutions, while 32% (7/22) had established education curricula.

Conclusions: Quantitative EEG was utilized in ICU care at more than half of the institutions surveyed, but reviewing, reporting, and application of this tool remains highly variable. The high rate of perceived clinical value supports continued investment into defining optimal pediatric trends, standardizing reporting, and expanding education.

Keywords: Critical Care, Education

DEMYELINATING DISORDERS

25. MOG and AQP4 antibodies among children with multiple sclerosis and controls

Gaudioso C (St. Louis, MO), Mar S, Casper T, Codden R, Nguyen A, Aaen G, Benson L, Chitnis T, Francisco C, Gorman M, Goyal M, Graves J, Greenberg B, Hart J, Krupp L

Objective: To determine the frequency of myelin oligodendrocyte glycoprotein (MOG)-IgG and aquaporin-4 (AQP4)-IgG among pediatric-onset multiple sclerosis (POMS) patients and healthy controls; determine whether seropositive cases fulfilled their respective diagnostic criteria; compare characteristics and outcomes in seronegative *vs* seropositive children; and identify features associated with final diagnosis.

Methods: POMS patients and healthy controls were enrolled at 14 US sites through a prospective case-control study from November 2011 to March 2018. Serum AQP4-IgG and MOG-IgG were assessed using live cell-based assays.

Results: AQP4-IgG was negative among all 1196 participants, 493 POMS and 703 controls. MOG-IgG was positive in 30/493 cases (6%) and zero controls. Twenty-five of 30 MOG-IgG positives (83%) had MOG-IgG-associated disease (MOGAD) while 5/30 (17%) maintained an MS diagnosis on re-review of records. MOGAD cases were more commonly female (21/25 [84%] *vs* 301/468 [64%]; $p=0.044$), younger (mean 8.2 ± 4.2 *vs* 14.7 ± 2.6 years; $p<0.001$), had initial optic nerve symptoms (16/25 [64%] *vs* 129/391 [33%]; $p=0.002$) or acute disseminated encephalomyelitis (ADEM) (8/25 [32%] *vs*9/468 [2%]; $p<0.001$); they less commonly had initial spinal cord symptoms (3/20 [15%] *vs* 194/381 [51%]; $p=0.002$), Epstein-Barr virus (EBV) positivity (11/25 [44%] *vs* 445/468 [95%]; $p<0.001$), or cerebrospinal fluid oligoclonal bands (5/25 [20%] *vs* 243/352 [69%]; $p<0.001$).

Conclusions: MOG-IgG and AQP4-IgG were not identified among controls confirming their high specificity for pediatric demyelinating disease. Five percent (25/493) of those with prior POMS diagnoses ultimately had MOGAD; none had AQP4-IgG positivity. Features associated with a final MOGAD diagnosis included initial ADEM phenotype, younger age at disease onset, and lack of EBV exposure.

Keywords: Demyelinating Disorders

26. Cerebral Visual Impairment in Children with Adrenoleukodystrophy

Corre C (Rochester, NY), Bambery M, Nagy A, Bennett C, Andonian H, Kelly D, Merabet L, Eichler F

Objective: X-linked adrenoleukodystrophy is a single gene disorder whose cerebral demyelinating phenotype in children, CCALD, causes rapid neurologic decline, ultimately progressing to total neurologic disability. With advances in

newborn screening and hematopoietic stem cell transplantation (HSCT), it is now possible to halt the progression of CCALD at increasingly earlier timepoints in the disease course. Higher order visual processing deficits are a particularly relevant focus of study as they may serve as an early marker of neurologic decline and potentially identify an earlier window for treatment. The objective of this study was to characterize the prevalence, presentation, and neuroimaging correlates of cerebral visual impairment (CVI) associated with CCALD.

Methods: Medical records were retrospectively reviewed for all male CCALD patients seen at Massachusetts General Hospital from June 2005-July 2020. Neurological assessments and neuropsychological tests were reviewed to assess for signs and symptoms of CVI. Brain MRIs were reviewed to evaluate lesion burden.

Results: Fifty-seven percent of CCALD patients had findings suggestive of CVI, most commonly a deficit or decline in visual-motor integration (34%) or in visual perceptual reasoning (34%), as assessed by formal neuropsychological testing. CVI was present in 32% of patients with very early lesions (Loes score ≤3) and in 31% of patients with no evidence of structural damage to visual pathways on brain MRI.

Conclusions: CVI is prevalent not just among untreated, advanced symptomatic CCALD patients, but also in those with very early lesions who have undergone successful HSCT. Even patients considered ideal transplant candidates may not experience functionally optimal outcomes.

Keywords: Demyelinating Disorders, Neuroimaging, Neuroopthalmology

27. The phenotypic spectrum of pediatric onset TUBB4A-related leukoencephalopathies: A new classification system among the pediatric population

Charsar B (Philadelphia, PA), Gavazzi F, Hamilton E, Patel V, Shults J, D'Aiello III R, Stellingwerff M. Sherbini O, Simons C, Schmidt J, Pizzino A, Muirhead K, Adang L, van der Knaap M, Vanderver A

Objective: To conduct a natural history study of individuals with mutations in the b-tubulin gene, *TUBB4A,* and pediatric onset, to identify the most common disease features, distinct disease cohorts, and existing genotype-phenotype correlations.

Methods: A multi-centered retrospective chart review of individuals with childhood onset of *TUBB4A*-related leukodystrophy (n=180) under an IRB-approved protocol. Latent class and survival analysis was performed on a subset of our cohort (n=68), and Kaplan Meier curves were created to determine the time-to-event for specific outcomes, including gastrostomy tube (G-tube) placement.

Results: Using latent class analysis, two features emerged for cohort classification: acquisition of head control and p.-Asp249Asn (D249N) genotype. Disease severity was closely associated with onset before 12 months (early infantile, n=104), which was further divided based on acquisition of head control. Individuals presenting after 12 months (n=76) presented within a range of 1 to 21 years of age (median 1.5, IQR 0.94), with a predominance of late infantile presentations. The canonical Hypomyelination with Atrophy of the Basal Ganglia (H-ABC) syndrome with the D249N mutation was associated with late infantile presentation and represented 16% of total cases. D249N late infantile patients were able to achieve more developmental milestones but lost them sooner and more quickly than non-D249N late infantile patients. G-tube placement occurred in 42% (44/104), 36% (10/28), and 6% (3/48) of early infantile, D249N, and non-D249N late infantile affected individuals, respectively.

Conclusions: The delineation of these three distinct cohorts will help predict the evolutionary trajectory of individuals with *TUBB4A*-related leukodystrophy and inform future clinical trial design and efficacy.

Keywords: Demyelinating Disorders, Rare Diseases, Genetics

28. Virtual Reality Testing in Boys with Adrenoleukodystrophy: Monitoring Cerebral Visual Impairment

Bambery M (Boston, MA), Corre C, Kelly D, Nagy A, Becker C, Manley C, Bennett C, Mallack E, Merabet L, Eichler F

Objective: X-linked adrenoleukodystrophy (X-ALD) is an inherited single gene disorder that causes progressive inflammatory demyelination in 30-40% of boys. The demyelination predominantly affects the visual pathways in brain but symptoms of visual processing remain poorly characterized. To define the extent of cerebral visual impairment (CVI) and visual processing deficits, we performed prospective testing using virtual reality (VR) based visual search tasks in boys with childhood cerebral ALD (CCALD). The objective of this study was to characterize the extent of CVI in CCALD through VR testing.

Methods: VR environments combined with a Tobii Eye Tracking System were used to assess search performance among boys with CCALD in the Massachusetts General Brigham Leukodystrophy Clinic from April 2019-March 2022. All patients had confirmed X-ALD by genetic or biochemical testing and were confirmed by brain MRI to have CCALD. Two VR based tasks (one static and another dynamic) required searching for targets on a screen among varying levels of visual complexity.

Results: Virtual reality testing was completed in 20 patients with CCALD and 38 controls. We found a reduced task performance determined by success rate, reaction time, and load sensitivity in CCALD patients compared to controls. The overall reaction time for patients with CCALD was 24% longer compared to controls for the static task and 76% longer for the dynamic task. Visual acuity did not correlate with performance.

Conclusions: Higher order visual processing is impaired in children with CCALD. VR tasks have the potential to detect and measure deficits at the bedside, even when visual acuity is intact.

Keywords: Demyelinating Disorders, Neurometabolic Disorders, Genetics

29. Incidence of pediatric acute disseminated encephalomyelitis during the COVID-19 pandemic: a nationwide population-based retrospective cohort study

Hwang J (Seoul, Republic of Korea), Ko YJ, Choi SA, Chae SA

Objective: Acute disseminated encephalomyelitis (ADEM) is an immune-mediated demyelinating disorder, usually followed by infections. It has been also reported as a neurologic manifestation related to coronavirus disease (COVID-

19). We aimed to determine the temporal trends in incidence of ADEM before and during the pandemic and correlation between the incidence of ADEM and infectious pathogens.
Methods: Pediatric (age < 19 years) ADEM hospitalizations with discharge diagnosis were identified from the Health Insurance Review and Assessment Service database from 2016 to 2020. We compared the incidence of ADEM before and during the COVID-19 pandemic by using general linear model. A nationwide data of infectious pathogens was extracted from the National Infectious Disease Surveillance System. Pearson correlation analysis was used to determine the correlation between the incidence of ADEM and infectious pathogens.
Results: A total of 187 new-onset ADEM cases were identified. The incidence of ADEM was 0.34-0.48/100,000 persons per year before the pandemic, which has been dropped to 0.22/100,000 persons per year during the COVID-19 pandemic. A moderate correlation was found between the incidence of ADEM and acute respiratory virus infections ($r = 0.28$, $p = 0.03$), especially with rhinovirus ($r = 0.27$, $p = 0.03$), parainfluenza virus ($r = 0.24$, $p = 0.06$), adenovirus infection ($r = 0.22$, $p = 0.09$).

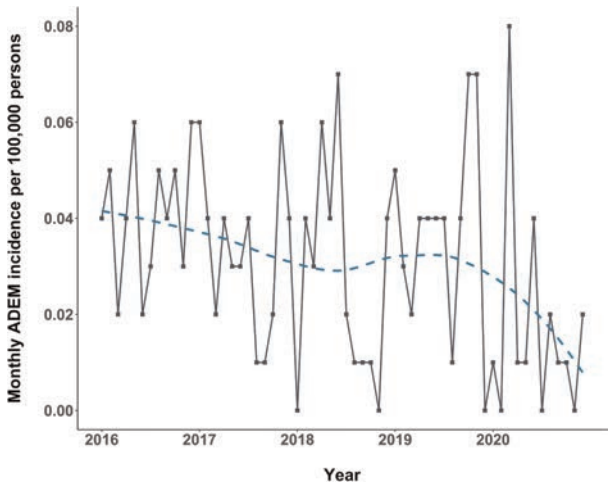


FIGURE 1. Monthly incidence of ADEM per 100,000 persons in each year (2016-2020). Abstract 29

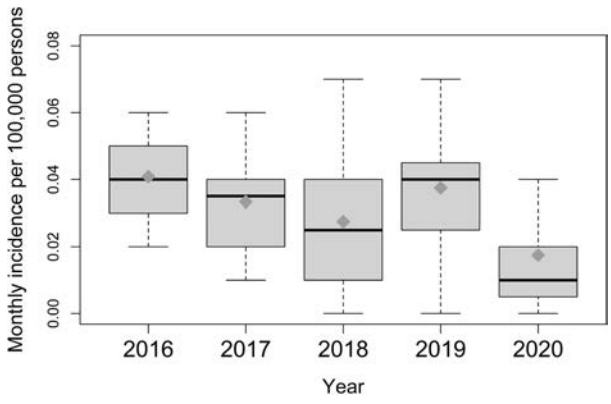


FIGURE 2. Box plots presenting the monthly incidence of ADEM in each year. Abstract 29

Conclusions: In this large nationwide pediatric cohort of ADEM hospitalization, the incidence of ADEM has been decreased during the COVID-19 pandemic. This might be related to a decline of acute respiratory virus infections, which are potential triggering factors for ADEM.
Keywords: Demyelinating Disorders, COVID-19

30. iPSC-derived human neuronal and oligodendrocyte models to unravel H-ABC pathophysiology and emerging anti-sense therapy

Garcia L (Philadelphia, PA), Almad A, Sase S, Takanohashi A, Woidill S, Vanderver A

Objective: Hypomyelination with Atrophy of Basal Ganglia and Cerebellum (H-ABC) is a progressive leukodystrophy with heterozygous p.Asp249Asn mutation in tubulin beta class IVA (TUBB4A) gene which demonstrates deficits in oligodendrocytes (OLs), cerebellar, and striatal neurons. We aimed to differentiate OLs and neurons from human induced pluripotent stem cells (hiPSCs) from H-ABC individuals; assess pathophysiology after *TUBB4A* deletion in hiPSC-derived neurons; and demonstrate antisense oligonucleotides (ASOs) as a therapeutic intervention.
Methods: hiPSCs from affected ($TUBB4A^{D249N}$), as well as non-affected ($TUBB4A^{WT}$) individuals, and isogenic controls using complete deletion of *TUBB4A* ($TUBB4A^{KO}$) were differentiated towards medium spiny neurons (MSNs). Immunostaining and QRT-PCR were used to determine neuronal and OLs differentiation and fate. To identify the best ASO candidate, MSNs were treated for one week with ASOs and *TUBB4A* downregulation, dose response, and cytotoxicity were assessed.
Results: MSNs (CTIP2) and OLs (O4) from $TUBB4A^{D249N}$ and $TUBB4A^{WT}$ expressed typical markers. However, $TUBB4A^{D249N}$MSNs exhibited decreased CTIP2 counts, and increased apoptosis compared to healthy control neurons (n=3, p<0.0001) at days 37-45. The deletion of *TUBB4A* partially ameliorated cellular phenotype (n=16, p=0.0022). ASO treatment of$TUBB4A^{WT}$ and $TUBB4A^{D249N}$ MSNs displayed significant and maximum *TUBB4A* downregulation (n=3, p<0.0001) with no induction of apoptosis (n=3, p>0.05).
Conclusions: These studies establish $TUBB4A^{D249N}$ iPSC-MSNs and OLs as cellular models of H-ABC. Efficacy of ASO candidates tested on mutant neurons and OLs provides a unique translational therapeutic platform. This study will provide proof-of-principle of *TUBB4A* silencing as a treatment strategy for H-ABC.
Keywords: Demyelinating Disorders, Translational/ Experimental Therapeutics, Rare Diseases

31. HLA DRB1 and DQBI allelic expression in an Indian cohort of pediatric onset central acquired demyelination syndrome: initial trends from an ambispective observational study

Chakrabarty B (New Delhi, India), Deepak R, Gulati S, Mitra D, Kumar A, Chaudhary P, Meena A, Pandey R, Upadhyay A

Objective: To describe HLA DRB1 and DQB1 allelic expressions in a cohort of children and adolescents aged 6 months to 18 years with acquired demyelination syndrome (ADS) of central nervous system (CNS)

Methods: *Design and setting*: Ambispective longitudinal observational study, tertiary care teaching centre in north India*Population*: Suspected pediatric onset (6months-18 years) CNS-ADS cases.*Investigations*: MRI of brain, spine and orbits with contrast, serum HLA DRB1 and DQB1 typing, cerebrospinal fluid oligoclonal bands and serum anti-aquaporin-4 (AQP-4) and myelin oligodendrocyte glycoprotein (MOG) antibodies*Treatment*: Acute episodes (pulse methylprednisolone followed by oral steroids, non-responders: rituximab/plasma exchange/intravenous immunoglobulin) and relapse (azathioprine with/without rituximab).
Results: *Population*: 45 cases, median age at disease onset 120 months (IQR:78-144), 26/45 males*Final diagnoses*: MOG-ADS (17), clinically isolated syndrome (11), multiple sclerosis (MS, 8), AQP4-ADS (5) and acute disseminate encephalomyelitis (4)*HLA typing prevalence*:- HLADRB104 in MOG-ADS (8/17 compared to 5/28 in others, p=0.04)- HLADRB104 predictive of recurrence in MOG-ADS (4/5 in recurrent compared to 4/12 in monophasic, p=0.08)- HLADRB103 in MS (4/8 in MS and 3/37 in others, p=0.004).- HLADRB103 and DQB102 combination in MS (3/8 in MS and 3/37 in others, p=0.03).
Conclusions: The HLA DRB1 and DQB1 expression from an Indian cohort of pediatric CNS-ADS shows discriminatory ability for monophasic versus recurrent subtypes, however the numbers are small. This fact should be explored further to identify recurrent variants at the earliest and initiate long-term immunomodulation for optimal outcome.
Keywords: Demyelinating Disorders

32. Imaging Features and Clinical Characteristics of Relapsing and Non-relapsing in Pediatric MOG Antibody Disease

Marcus L (Birmingham, AL), Ness J, Singh S

Objective: MOGAD is increasingly recognized in children with a variety of imaging features. Some children have isolated events while others relapse. The study evaluates clinical, demographic and imaging features of 30 children with MOGAD and evaluates differences between relapsing and non-relapsing groups.
Methods: MOGAD is increasingly recognized in children. Some children have isolated disease while others relapse. The study evaluates clinical, demographic and imaging features of 30 children and seeks to evaluate differences between the single attack and relapse groups. Another purpose is to identify the frequency of MOGAD associated imaging and clinical features in our patients.
Results: There were 16/30 (53%) relapsing and 14/30 (47%) single attack patients with average follow-up of 58.4 months. Although not significant statistically, CIS was more common in non-relapsing group (64%), while relapsing patients more often presented with ADEM (62%). The relapsing group had a higher percentage of lesions in the optic nerve, peripheral cortex, periventricular white matter and conus medullaris, while more patients in the non-relapsing group demonstrated restricted diffusion in brain parenchymal lesions. The imaging features between the groups were not significantly different.
Conclusions: The most common phenotypes of MOGAD patients are CIS and ADEM. The most common imaging features are long segment ON and perineural inflammation, brain cortical and peripheral white matter lesions, thalamic hyperintensities, and long segment central cord lesions. There were no significant imaging, clinical or demographic differences between relapsing and non-relapsing patients. Without predictive characteristics for future relapse, patients should have regular clinical and imaging follow-up.
Keywords: Demyelinating Disorders, Neuroimaging

33. Diagnostic Dilemma in Pediatric CMT

Veerapandiyan A (Little Rock, AR), Elumalai V

Objective: To study the delay in diagnosis of Charcot Marie Tooth (CMT) disease in patients with and without known family history.
Methods: Retrospective chart review of patients with CMT disease followed in neuropathy clinic at Arkansas Children's hospital. We analyzed medical records of 54 patients, documented the time course and steps taken to reach a definitive diagnosis.
Results: Our study population consists of 48% females. CMT type 1A type was the most common type (55%). In patients with family history, symptoms were first noted at a mean age of 3.7 years, and concerns were expressed to primary care providers at a mean age of 5 years. Mean ages at the time of clinical diagnosis and genetic diagnosis were 7.2 years and 8 years respectively. In patients without a family history, symptoms were first noted at a mean age of 5.6 years, and concerns were expressed to primary care providers at a mean age of 6.7 years. Mean ages at the time of clinical diagnosis and genetic diagnosis were 9.3 years and 10.3 years respectively. The most common initial symptoms are abnormal gait (46%), frequent falling (44.4%) and feet pain (33.3%). Patients first consulted orthopaedics (40%), genetics (24%) and physiotherapy (20%). Final diagnosis was confirmed by neurology (71%).
Conclusions: A delay of about 4 years between symptom onset and diagnosis in children with family history and for children without family history it is about 5 years. In children with family history symptoms were recognized at earlier age. More data will be presented in the meeting.
Keywords: Demyelinating Disorders

EDUCATION

34. Steps Towards Transition – Assessing knowledge and providing education for adolescents with epilepsy

MacDonald S (Dayton, OH), Heffelfinger K, Krysiak T, Kumar G

Objective: Our aim was to develop a process to provide education to adolescents with epilepsy based on the results of the Seizure Safety Questionnaire, which was implemented to assess self-care and transition readiness.

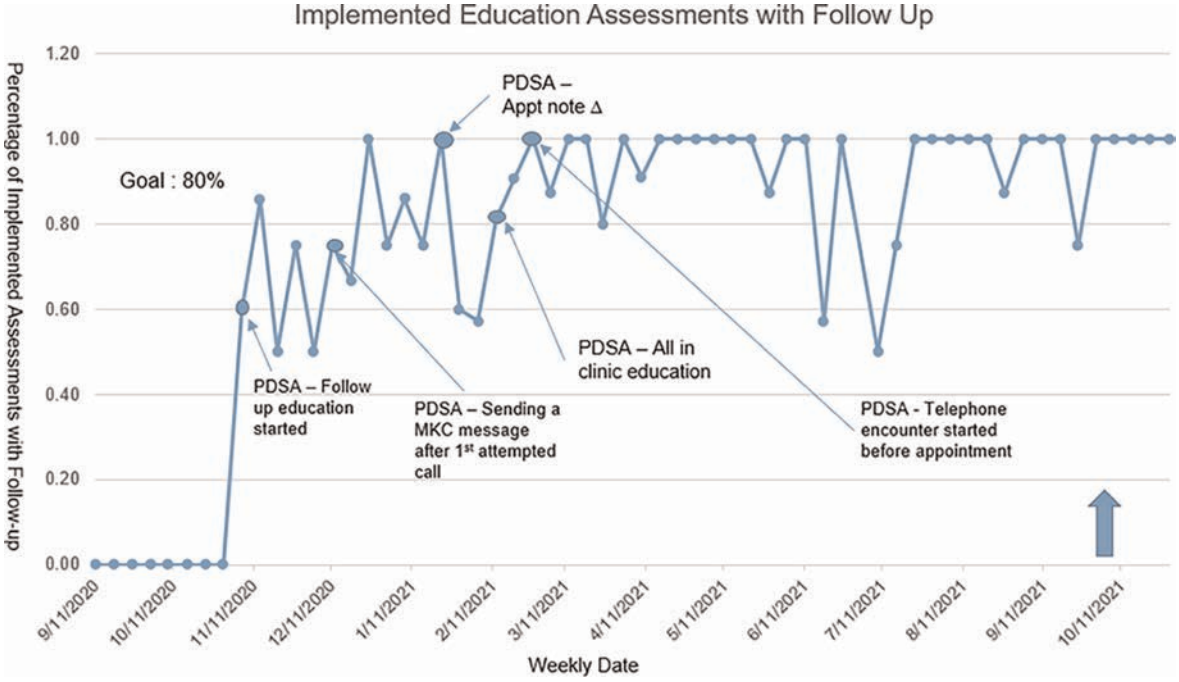


FIGURE 1. Abstract 34

PDSA Summary

Intervention	Key Driver	Cycle 1	Cycle 2	Cycle 3
Calling families/patients after questionnaire completed to provide education	Follow up seizure education by staff	**Plan-Summary**: Have patients complete questionnaire during visit, call the next week to provide education as needed **Plan-Prediction**: Hope to contact at least 80% of families for education **Study-Results:** Nurses did well with calling, had a hard time getting families to return calls **Act:** Adapt	**Plan-Summary**: Send a MyKids Chart message to those families who do not answer after the first attempted phone call **Plan-Prediction**: Hope to reach families by MKC who don't answer the phone **Study-Results:** Many families did not have MKC set up. **Act:** Abandon	**Plan-Summary**: **Plan-Prediction**: **Study-Results:** **Act:**
Providing seizure education to patients who had previously completed a questionnaire after their in person clinic appointment.	Follow up seizure education by staff	**Plan-Summary**: Have a nurse in clinic to provide seizure education as needed to patients who had previously completed a questionnaire **Plan-Prediction**: Hope to provide education to 100% of patients **Study-Results:** Worked well, many parents were excited that we were working with the patients, occasional patient missed d/t schedules and short staffing **Act: Adapt**	**Plan-Summary**: Change appointment visit note to indicate that education was planned for after visit **Plan-Prediction**: Hope to set in place reminders for staff that education is needed **Study-Results:** Worked well. Helped alert providers as well as staff rooming patients that education was expect. Also helped if a patient called to cancel or reschedule **Act: Adapt**	**Plan-Summary**: **Plan-Prediction**: **Study-Results:** **Act:**
Provide seizure education in person to every patient	Follow up seizure education by staff Implementation of educational assessment in EPIC	**Plan-Summary**: Every patient who was identified as needing to complete a seizure questionnaire, or having completed one in the past, received education after their appointment **Plan-Prediction**: Hope to continue providing education to >80% of patients identified. **Study-Results:** Providing in person education continued to work well. **Act: Adapt**	**Plan-Summary**: Hard to track if education was completed. Nurses to start using education assessment created in EPIC to help guide education in clinic and to see if this helps tracking education. **Plan-Prediction**: Hope to establish main place to look for prior education and questionnaire results. **Study-Results:** Well, hard to track in a chart review. Having a central place to chart a note would be better for chart review. **Act: Adapt**	**Plan-Summary**: Create an encounter before visit identifying diagnosis, history, medications. Goal to have central place to chart education and notes **Plan-Prediction**: Hope to establish reminder for staff that education is needed and central place for charting education. **Study-Results:** Well. Encounters help to remind nurses that education needs to be done. Also helps in later chart review to see that education has been completed, and how patient responded to the education. **Act: Adopt**

FIGURE 2. Abstract 34

Methods: Quality Improvement Project (QIP) methodology was used to administer the Seizure SAFETY questionnaire and to provide education to the patients. Teams nurses and clinic staff were educated on the questionnaire and education to provide based on questionnaire results. Adolescent epilepsy patients 13-18 years were recruited. PDSA cycles included how to contact patients for education, how to chart the education and questionnaire results in EPIC and how to help patients and staff understand the value of education.The outcome measure, percent of patients who completed a questionnaire and received education, was calculated based on the number of adolescent patients with epilepsy who attended an in person visit and completed a questionnaire.
Results: The number of completed questionnaires with education provided went from 0% in November 2020 to 100% over the course of one year. Barriers identified included families not returning phone calls or MyKid's Chart messages. We established a plan to follow up with patients and families during their clinic visit leading to a higher success rate. Barriers include time restraints for clinic staff and families.
Conclusions: Self-care evaluation and transition readiness was identified in adolescents with epilepsy. Education based on this evaluation led to an improvement in their knowledge of their diagnosis and overall scores on the questionnaire. This process facilitates preparing patients to transition to an adult provider.
Keywords: Education

35. New ACGME program support requirements - A threat to Child Neurology training in the U.S.

Rogers D (Albuquerque, NM), Thompson Stone R, Goldstein J

Objective: The ACGME recently approved changes to the minimum required FTE for child and adult neurology residency program directors, reducing required protected time from 0.35 to 0.2 for programs with 6 or fewer residents while simultaneously increasing required support for programs with 7 or more residents to 0.4 or above. 90% of child neurology divisions do not provide support for education beyond minimum ACGME requirements. We set out to investigate implications of these changes.
Methods: Existing databases(CNS, FRIEDA) and crowdsourcing were used to verify the size of all U.S. child and adult neurology programs. We calculated the cumulative FTE support before and after the ACGME change and made comparisons within sub-groups.
Results: The new ACGME requirements reduce the minimum protected time for 67% of child neurology residency program directors. Cumulative required protected time for all U.S. child neurology programs decreased by 23% (28.15 → 21.2 FTE). Conversely, adult neurology programs saw an increase in protected time by 22% (59.1 → 72.1 FTE). FTE support also shifted from smaller to larger programs with a 43% decrease in support for small programs.
Conclusions: The impact of ACGME required protected time favors adult over child neurology programs, and large over small programs. For residencies with 6 or fewer total residents, there is regression to FTE levels lower than the past decade, despite increase in administrative burden on program directors in recent years. Within institutions hosting small programs, this could direct GME money away from pediatric neurology and discourage faculty involvement in child neurology education.
Keywords: Education

36. Procedural and neurophysiology education in child neurology residency programs

Chow Haws C (Phoenix, AZ), Jarrar R

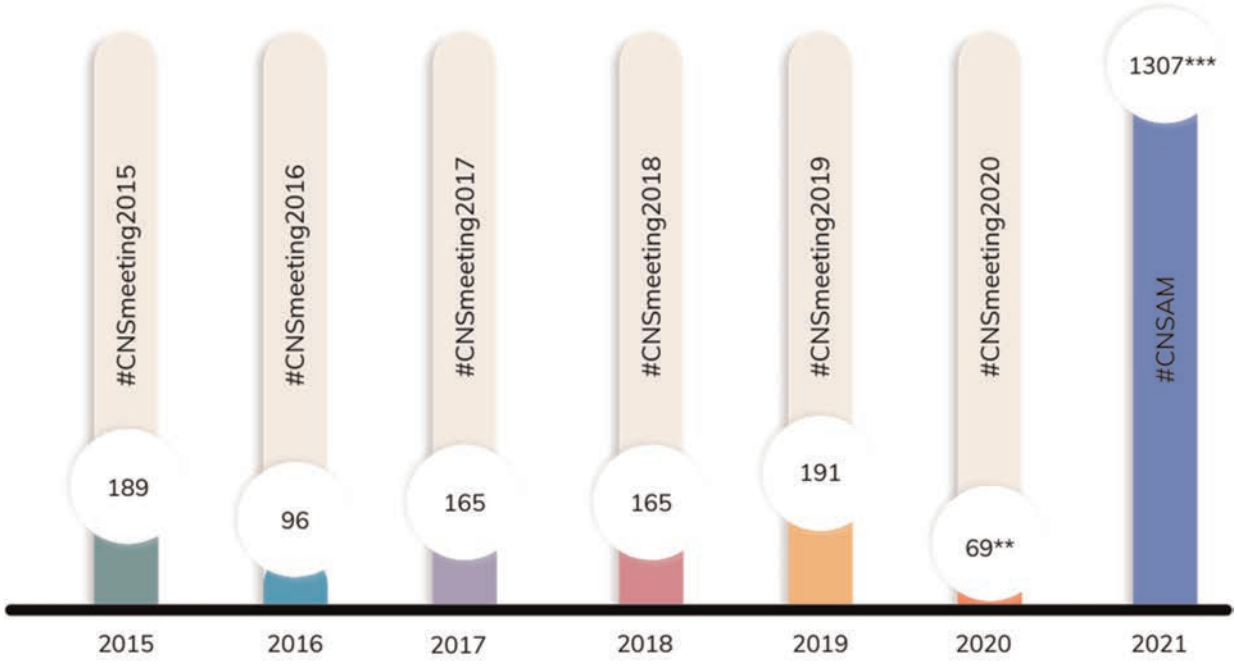
Objective: There is no published literature regarding procedural and neurophysiology training in child neurology residencies, including lumbar puncture, nerve injections, botulinum toxin injections, reading and interpreting electroencephalograms (EEG), and performing and interpreting electrodiagnostic studies (EMG). We sought to understand the current state of this training, assess educational barriers, and discuss ways to improve future training.
Methods: An anonymous REDCap survey was developed by the authors. Questions included multiple choice, satisfaction scales, importance and confidence scales, and free text comments. Links to the survey were emailed to 84 child neurology program coordinators in November 2021, and they were asked to forward the survey to their child neurology residents.
Results: There were 43 total participants, of which 28 were PGY-4 and PGY-5 residents. Overall, 88% of child neurology residents think the quality of teaching at their institution is excellent or good. When compared with EEG, there is less didactic and teaching specifically for EMG (88% vs 59%), and how neurophysiology is taught varied greatly. The number of procedures performed by PGY-4 and PGY-5 residents appear to reflect their importance levels, as well as their confidence in performing the procedure independently. Based on qualitative responses, educational barriers include not having enough exposure, not being taught how to technically perform, allowing residents to try these procedures, and limited number of patients.
Conclusions: This survey demonstrated variability in training among child neurology residency programs. Overall comments suggest that training in the future may include more emphasis on these procedures and less emphasis on inpatient or adult neurology training.
Keywords: Education

37. #CNSAM: The Past, the Present, and the Future

Martindale J (Winston Salem, NC), Lakhotia A, Hsieh D

Objective: In order to optimize outreach, visibility and educational initiatives we aim to 1) analyze Twitter activity associated with the Child Neurology Society (CNS) account, and 2) to analyze annual meeting hashtag use.
Methods: We analyzed Twitter data from the official CNS Twitter account (@ChildNeuroSoc) between 2015-2021 as well as the annual meeting hashtag #CNSAM. Using Twitter Analytics[1], Symplur Healthcare Hashtags[2], and manual review, we gathered data on numbers of tweets, impressions, profile visits, new followers, mentions, and hashtag use. Surrounding the annual meeting, we gathered hashtag use before, during and after meeting with categorization of participating accounts as societal, medical centers, pharmaceutical, individual, partner organizations, journals and other.

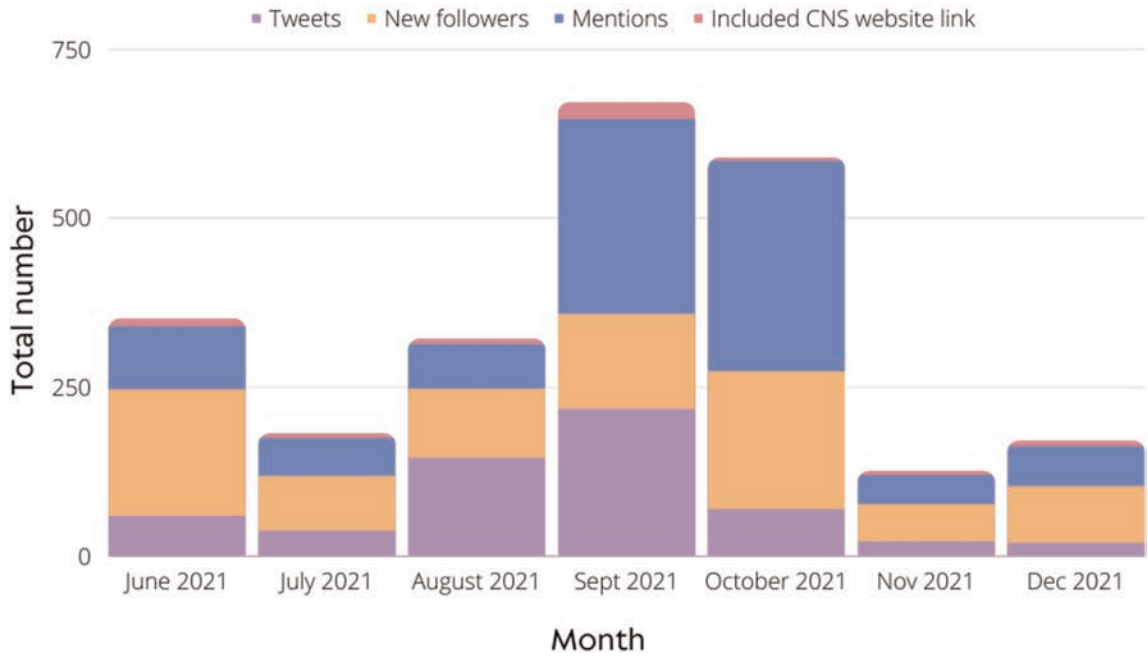
FIGURE 1: TOTAL ANNUAL MEETING HASHAG USE*



* as of 12/31/2021
** virtual due to COVID-19
*** hybrid due to COVID-19

Abstract 37

FIGURE 2: TWITTER ANALYTICS



Abstract 37

Results: Between 2015-2021, there were 22 tweets and 264 followers. In June 2021, the Twitter account re-launched with a new strategy and handle @ChildNeuroSoc to increase visibility. Within 6 months there was 432% follower growth, 574 original tweets, 32.5k profile visits, 914 mentions, and 449.1k impressions. 71 (12%) tweets included Child Neurology Society website links. The annual meeting hashtag #CNSAM had 1,307 uses total with 25% surrounding annual meeting (Figure 1). Majority of uses were from individual members. The meeting month (October 2021) had the most impressions, mentions and new followers with 128k impressions, 204 mentions and 310 new followers (Figure 2).
Conclusions: There was significant engagement with the CNS Twitter account during the first 6 months of re-launching, particularly surrounding the annual meeting. Use of hashtags and live conference posts can share content and drive engagement to and beyond our members[3-6].
Keywords: Education, History of Child Neurology, Neuroscience

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EPILEPSY/SLEEP

38. Distinct human motor cortex single-cell transcriptome of mitochondrial genes in inhibitory neurons compared to excitatory neurons

Jakkamsetti V (Dallas, TX), Ma Q, Pascual J

Objective: Our previous study implicated inhibitory neuron dysfunction contributing to seizures in mitochondrial disorder pyruvate dehydrogenase deficiency. To explore if inhibitory neurons could be more susceptible to deficits of other mitochondrial genes too, we examined their neuron-specific transcriptomes.
Methods: 338 mitochondrial genes were examined for common clinical manifestations in the Human Phenotype Ontology database. Of these, 280 mitochondrial and 26 tubulin genes were assayed for neuron-specific differences. Human motor cortex M1 single-cell RNA-seq data was obtained from the 10x genomics single-cell RNA database at Allen's Brain Map. Gene sets were analyzed for Gene Ontology using EnrichR.
Results: Clinical manifestations for mitochondrial gene deficits were predominantly neurological with seizures prominent. Principal component analysis revealed distinct clusters of excitatory and inhibitory neuron mitochondrial gene expression (MANOVA-Wilks test p-value<0.0001). Higher mitochondrial gene expression was seen in parvalbumin-expressing interneurons but not in excitatory neurons when compared to tubulin genes (reads per sample in millions: mitochondria 1.64±0.2, tubulin 1±34, p<0.01). Using mitochondrial gene expression, a support vector machine-learning algorithm could predict cell type with high accuracy. Parvalbumin interneurons had an expression pattern distinct from other inhibitory neurons (MANOVA-Wilks test p-value<0.0001) with highest expression in layer 4. For mitochondrial genes with highest expression in parvalbumin-positive interneurons, Gene Ontology analysis (p-value <0.0001) revealed them to be primarily involved in aerobic electron transport chain and ATP synthesis.
Conclusions: Inhibitory neurons, especially fast-spiking parvalbumin-expressing interneurons had higher expression of mitochondrial genes. Our findings may offer insights into the pathophysiology and future investigation of refractory seizures in patients with mitochondrial deficits.
Keywords: Epilepsy/Sleep, Neurometabolic Disorders, Genetics

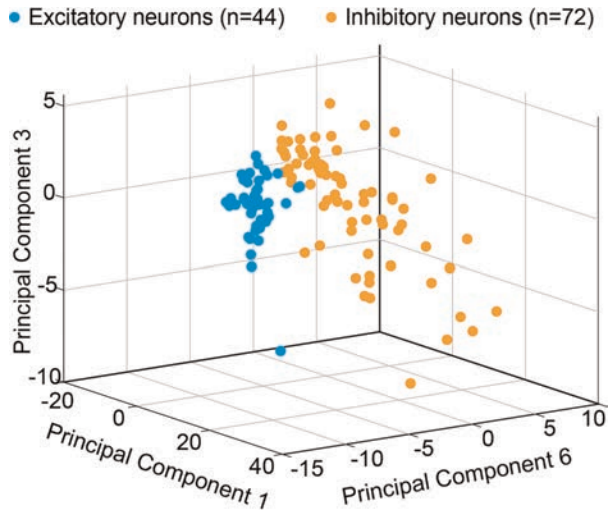


FIGURE 1. PCA analysis of single-cell RNA-seq expression of 280 mitochondrial genes (normalized to average of 26 tubulin gene's expression in each cell) reveals distinct expression in inhibitory neurons. Abstract 38

39. Targeting upstream open reading frames of SCN1A to boost translation of Nav1.1 in Dravet Syndrome

Safran J (Ann Arbor, MI), Loughman A, Lin G, Vaid S, Dang L

Objective: Dravet Syndrome (DS) is typically caused by haploinsufficiency of *SCN1A*, which encodes the protein Nav1.1. One therapeutic strategy is to boost expression of the non-mutated allele. We hypothesize that targeting upstream open reading frames (uORFs) with antisense oligonucleotides (ASOs) in *SCN1A* will result in augmented translation of Nav1.1.

Methods: We constructed luciferase reporter plasmids that contained the uORFs and the initial coding sequence of *SCN1A* to quantify translation of the primary open reading frame (pORF). We disrupted the uORFs by mutating the upstream AUG start codons (uAUGs) of this reporter plasmid. The mutant and wild-type plasmids were used for luciferase enzyme assays after transfecting them into HEK293 cells or subjecting them to *in vitro* transcription and translation reactions. We designed ASOs to bind uORFs and tested their effect on luciferase activity.

Results: When the four uAUGs most proximal to the primary AUG start site (pAUG) were mutated, there was a 6.9-fold increase in luciferase expression in transfected HEK293 cells ($p<0.0001$). Individually mutating either of the two uAUGs most proximal to the pAUG increased luciferase activity by 1.5-fold ($p<0.001$). Treatment with individual and combinations of ASOs targeting the 4 uAUGs did not significantly increase luciferase activity *in vitro*.

Conclusions: The presence of uORFs interferes with translation from the pORF in *SCN1A*, and mutating the uAUGs increased pORF translation efficiency. This suggests that targeting uORFs in *SCN1A* is a viable therapeutic strategy in DS. Treatment with ASOs targeted to the uAUGs did not increase luciferase activity, leaving room for design optimization.

Keywords: Epilepsy/Sleep, Genetics, Translational/Experimental Therapeutics

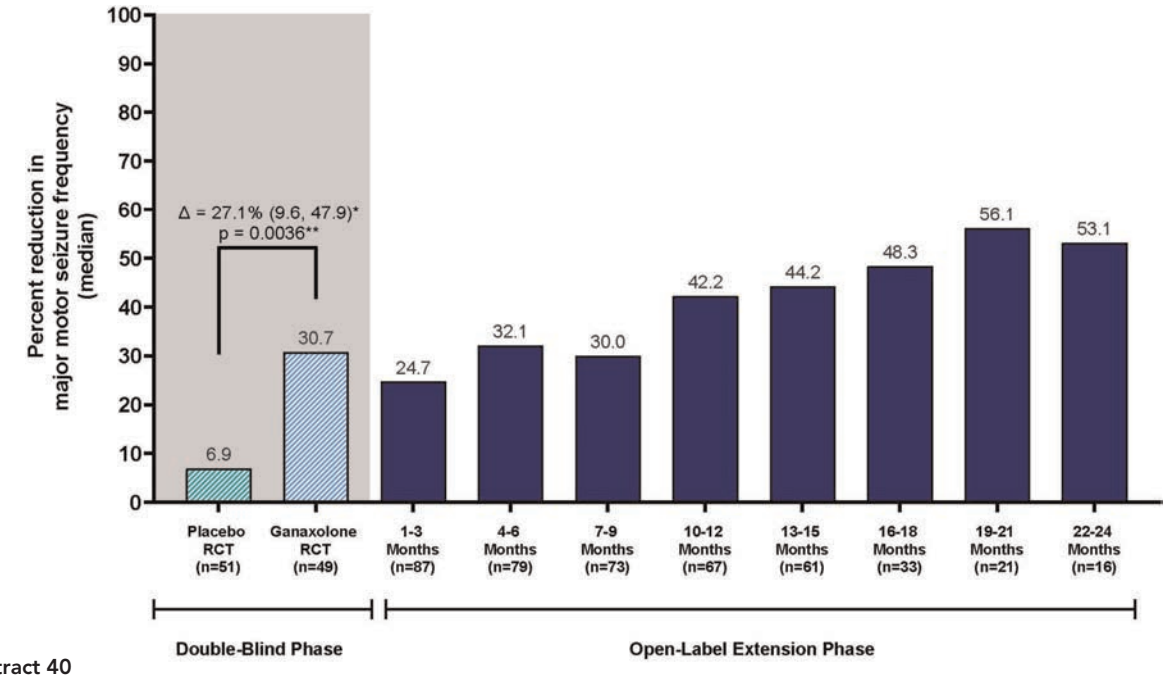
40. Extended duration ganaxolone treatment for seizures associated with CDKL5 Deficiency Disorder: 1-year minimum open-label extension follow-up

Pestana-Knight E (Cleveland, OH), Demarest S, Devinsky O, Amin S, Aimetti A, Rybak E, Miller I, Hulihan J, Olson H

Objective: Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a developmental and epileptic encephalopathy characterized by global developmental impairment and early-onset, refractory seizures. In a recent placebo-controlled study, ganaxolone significantly reduced major motor seizure frequency (MMSF) in patients with CDD. Here we report on safety and seizure-related data at a minimum of 1year in the open-label extension (OLE).

Methods: Patients with CDD (2-19 years) who completed the double-blind phase were eligible to receive ganaxolone in the OLE. Reductions in MMSF from pre-randomization baseline to 3-month intervals in the OLE, safety, and tolerability were assessed (data cut 22June2021).

Results: Of the 101 patients randomized, 88 (87.1%) continued into the OLE. Median age was 5 years and 79.5% were female. Median baseline 28-day MMSF was 50.6. Thirty-four subjects had discontinued due to lack of efficacy (n=12), adverse event (n=10), or withdrawal (n=10) as the most common reasons. During Months 1-3, 4-6, 7-9, and 10-12 in the OLE, patients experienced a median reduction in MMSF of 24.7% (n=87), 32.1% (n=79), 30.0% (n=73), and 42.2% (n=67), respectively. During months 13-24, MMSF reductions ranged from 44.2% to 56.1%.



Abstract 40

Seizure (22.7%), somnolence (20.5%), vomiting (18.2%), and pyrexia (17.0%) were the most commonly reported adverse events. One death occurred due to sepsis, but deemed unrelated to study treatment.
Conclusions: Ganaxolone was generally well-tolerated in the OLE with safety findings consistent with the double-blind phase. Reductions in MMSF at 1year and beyond provide supportive evidence for the maintenance of effect of ganaxolone in seizures associated with CDD.
Keywords: Epilepsy/Sleep, Rare Diseases, Genetics

41. Assessing determinants of ECG changes in pediatric epilepsy

Bartlett B (Houston, TX), Miyake C, Anderson A, Lai Y-C

Objective: Cardiovascular complications including sudden cardiac death is increasingly recognized as an important epilepsy-associated comorbidity. However, little is known about the progression of cardiac changes. We hypothesize that cardiac alterations occur as function of epilepsy duration.
Methods: We prospectively enrolled children 1 month to 18 years of age presenting to an epilepsy center. An ECG was obtained at the time of enrollment and reviewed by a pediatric cardiologist. Clinical information including demographics and details of the epilepsy course was collected. An ECG alteration was defined as changes in axis, QRS morphology, ST segment, or T wave. We analyzed categorical variables using Chi square and continuous variables using Mann-Whitney test. Values are expressed as n (%) or median [interquartile range].
Results: 213 patients were enrolled. 100 patients (47%) exhibited ECG changes, most commonly in the ST segment (17.4%) and T wave (11.3%). Compared to the normal ECGs, the altered ECGs had a longer epilepsy duration (46.1 [17.5 - 90.7] months vs. 72.8 [32.5 - 128.2] months, $p = 0.004$). Specifically, longer epilepsy duration was associated with T wave changes (58 [20.3 - 103.0] months vs. 93.9 [37.6 - 163.6] months, $p = 0.03$) and right axis deviation (59.2 [21.5-104.1] months vs. 127.3 [83.7-161.1] months, p=0.01).
Conclusions: ECG changes become more prevalent with longer epilepsy duration in children. These changes can reflect an altered cardiac electrophysiology which may provide early risk biomarkers for a future cardiovascular complication.
Keywords: Epilepsy/Sleep

42. Examination of the Inter–Seizure-Cluster Interval Over Time in Pediatric Patients in a Phase 3, Long-Term Open-Label, Repeat-Dose Safety Study of Diazepam Nasal Spray for the Treatment of Seizure Clusters

Misra S (San Diego, CA), Sperling M, Rao V, Peters J, Wheless J, Carrazana E, Rabinowicz A

Objective: Inter-seizure–cluster intervals (ISCI; the period between seizure clusters) have been studied for prophylactic antiseizure medications but not intermittent rescue treatments. Diazepam nasal spray (Valtoco®) is approved for acute treatment of seizure clusters in patients with epilepsy age ≥6 years. This novel post-hoc analysis explores ISCI in pediatric and adult patients with epilepsy and seizure clusters from a long-term safety study of diazepam nasal spray to assess whether ISCI changes with treatment over time.
Methods: Patients (6-65 years) were administered diazepam nasal spray in this 12-month safety study. ISCI was evaluated across four consecutive 90-day periods; a pediatric subgroup (6-17 years) was also examined. Paired *t* test assessed statistical significance.
Results: Of 175 patients enrolled, 163 received ≥1 dose of diazepam nasal spray (mean age, 23.1 years). Of 151 patients with ISCI data, 120 had data in Period 1 and ≥1 other period; 76 had ≥1 ISCI across all Periods 1-4. Mean ISCI increased significantly in both cohorts for all periods (P<0.01); no effect of concomitant medication change was observed. Among patients 6-17 years with data across all Periods 1-4 (n=32), mean ISCI increased from 13.0 (Period 1) to 25.9 days (Period 4; P=0.024; Figure).
Conclusions: Patients in the overall 12-month study and the pediatric subgroup using diazepam nasal spray for clusters demonstrated a statistically significant increase in ISCI. The increasing time may reflect a beneficial effect of cluster treatment, raising the possibility that intermittent treatment alters the underlying biology of clusters. This warrants further study.
Keywords: Epilepsy/Sleep

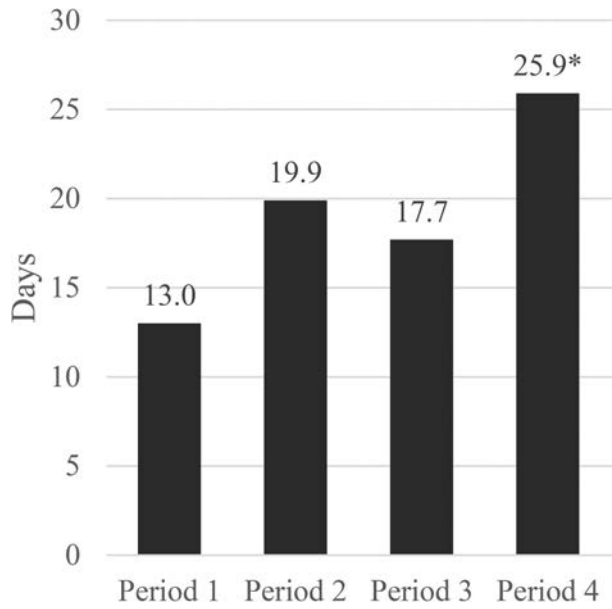


FIGURE Mean Inter–Seizure-Cluster Interval Over Time for Patients with Data Across Periods 1-4 (Sensitivity Analysis), Age 6–17 Years (n=32) *P=0.024, compared with Period 1 Period 1 = Day 1–90; Period 2 = Day 91–180; Period 3 = Day 181–270; Period 4 = Day 271–360. Abstrct 42

43. Do Patients With Lennox-Gastaut Syndrome Respond Differently to Diazepam Nasal Spray (Valtoco®) Than Other Patients with Pediatric Encephalopathies? Final Safety and Effectiveness Results From a Phase 3, Long-Term Open-Label, Repeat-Dose Safety Study

Tarquinio D (Atlanta, GA), Wheless J, Segal E, Misra S, Rabinowicz A, Carrazana E

Objective: To explore possible differences in long-term safety of diazepam nasal spray (Valtoco®) to treat seizure clusters

TABLE 1. Demographics and Treatment Exposure. Abstract 43

Characteristics	Pediatric Epileptic Encephalopathies (n=64)	Lennox-Gastaut Syndrome (n=9[a])
Sex, n (%)		
Male	29 (45.3)	5 (55.6)
Female	35 (54.7)	4 (44.4)
Age, years		
Mean (SD)	10.1 (3.2)	13.4 (10.4)
Range	6–17	6–38
Weight, kg		
Mean (SD)	32.6 (15.7)[b]	38.1 (35.1)[c]
Duration of exposure, n (%)		
<6 months	3 (4.7)	1 (11.1)
6 to <12 months	9 (14.1)	2 (22.2)
≥12 months	52 (81.3)	6 (66.7)
Seizure clusters, n (%)		
Treated	1402	171
Treated with second dose	149 (10.6)	7 (4.1)

[a]2 patients >18 years of age.
[b]n=63.
[c]n=8.

TABLE 2. Treatment-Emergent Adverse Events (TEAEs) Abstract 43

Patients With TEAEs, n (%)	Pediatric Epileptic Encephalopathies (n=64)	Pediatric Lennox-Gastaut Syndrome (n=7)
≥1 TEAE	57 (89.1)	6 (85.7)
Serious TEAE	25 (39.1)	4 (57.1)
Treatment-related	0	0
TEAE leading to discontinuation	0	0
Death	0	0
Most common TEAEs	(≥5 patients)	(≥2 patients)
Seizure	17 (26.6)	4 (57.1)
Nasopharyngitis	14 (21.9)	0
Pyrexia	13 (20.3)	2 (28.6)
Upper respiratory tract infection	10 (15.6)	1 (14.3)
Influenza	9 (14.1)	1 (14.3)
Pneumonia	8 (12.5)	1 (14.3)
Constipation	7 (10.9)	1 (14.3)
Vomiting	7 (10.9)	0
Diarrhea	6 (9.4)	1 (14.3)
Pharyngitis streptococcal	6 (9.4)	1 (14.3)
Somnolence	6 (9.4)	0
Urinary tract infection	6 (9.4)	2 (28.6)
Ear infection	5 (7.8)	0
Cough	5 (7.8)	1 (14.3)
Status epilepticus	5 (7.8)	1 (14.3)
Nausea	3 (4.7)	2 (28.6)
Treatment-related TEAEs (≥2 patients in either group)	10 (15.6)	1 (14.3)
Epistaxis	2 (3.1)	1 (14.3)

between patients with Lennox-Gastaut syndrome (LGS) and a broader pediatric epileptic encephalopathies group.

Methods: Patients aged 6–65 years with treated, drug-resistant epilepsy and frequent seizure clusters received age- and weight-based diazepam nasal spray, with second doses given 4–12 hours later, if needed.

Results: Of 163 treated patients, 78 were pediatric (age 6–17 years). Nine patients (7 pediatric, 9.0% of pediatric patients; 2 adults) were diagnosed with LGS; 64 (82.1%) were in the pediatric encephalopathies group (Table 1). There were 171 treated clusters in the LGS group and 1402 in the encephalopathies group. Second doses (proxy of effectiveness) were administered in 7 (4.1%) and 149 (10.6%) of treated clusters, respectively. Retention rates (to study closure) were 78.1% and 77.8%, respectively.Treatment-emergent adverse events (TEAEs) were reported in 6 of 7 (85.7%) pediatric patients with LGS and 57 (89.1%) patients with

encephalopathies (Table 2). The only treatment-related TEAE in ≥2 patients in either group was epistaxis (n=2). There were no treatment-related serious TEAEs and no discontinuations due to TEAEs or deaths in either group.

Conclusions: Safety and effectiveness of diazepam nasal spray were similar in patients with LGS compared with pediatric epileptic encephalopathies overall in this long-term safety study. The low percentage of seizure clusters administered a second dose suggests initial-dose effectiveness in these treatment-resistant patients. Results show no new safety signals and high retention in both groups.

Keywords: Epilepsy/Sleep

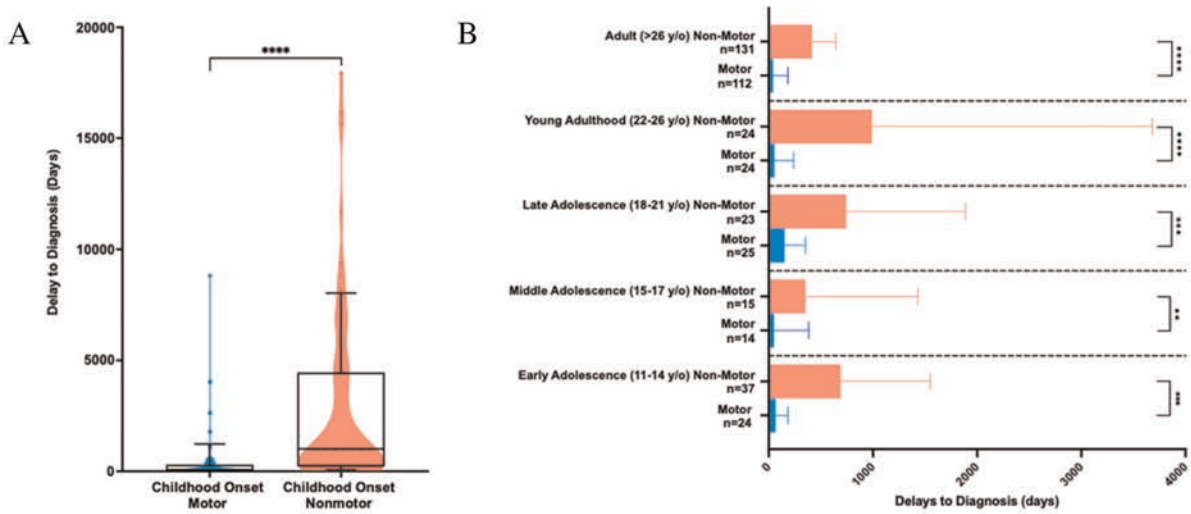
44. Significant delays to diagnosis and morbidity observed in non-motor childhood-onset focal epilepsy

Ferrer M (New York, NY), Jandhyala N, Pellinen J, Dlugos D, Park K, Thio L, French J

Objective: To investigate delays to diagnosis in childhood focal epilepsy, the characteristics predictive of delays, and the morbidity associated with these.

Methods: This was a retrospective analysis utilizing enrollment data from the Human Epilepsy Project, an international multi-institutional study that collected data from 34 sites. At enrollment subjects completed a seizure diary identifying onset, frequency, and characteristics of seizures prior to diagnosis.

Results: A total of 444 participants were analyzed, 121 participants reported onset of focal seizures at age 18 or below. Of these, 74 participants reported onset of focal non-motor seizures and 47 participants reported onset of focal motor seizures. Focal non-motor seizures had 16 times longer delay to diagnosis compared to motor focal seizures (1,014 vs 63 days; p<0.001; *Figure 1*). The non-motor group experienced more seizures prior to diagnosis than the motor group (p<0.0001). Notably, 69% of participants with focal non-motor epilepsy



C

Examples of Non-Motor Seizure Semiology
Déjà vu, dizziness
Disorientation, feeling "as if in a dream"
Episodes of hearing loud sounds in head
Spells of feeling dizzy and anxious
Gastric discomfort, nausea, visual distortions
Inability to read/understand words
Burning smell, then headache
Feeling of remembering a dream, nausea, feeling "not present" "out of it"
Ringing in ears lasting minutes
Abdominal rising sensation, amnesia
Metallic taste, severe déjà vu and spinning sensation lasting seconds
Frontal head pain and sensation of time slowing down

Figure 1.

Delay in diagnosis was greater in initial non-motor seizures (A) Delays to diagnosis of focal seizures with onset ≤ 18 years of age stratified by initial seizure semiology. Non-motor seizures were associated with significant longer delays to diagnosis, this delay was 16 times longer in the non-motor childhood onset group vs. the motor childhood onset group (1,014 vs 63 days; p<0.001). Violin plots illustrate the data density with overlying box and whisker plots (whiskers max is 90% and min 10%). The shaded area is proportional to the number of participants in each group. **(B)** When stratified by developmentally distinct age groups delays to diagnosis of non-motor seizures were observed across all groups. **(C)** Examples of descriptions given by participants with non-motor seizures. **** $p < 0.0001$; ***$p = 0.0001$; ** $p = 0.001$; Mann-Whitney test.

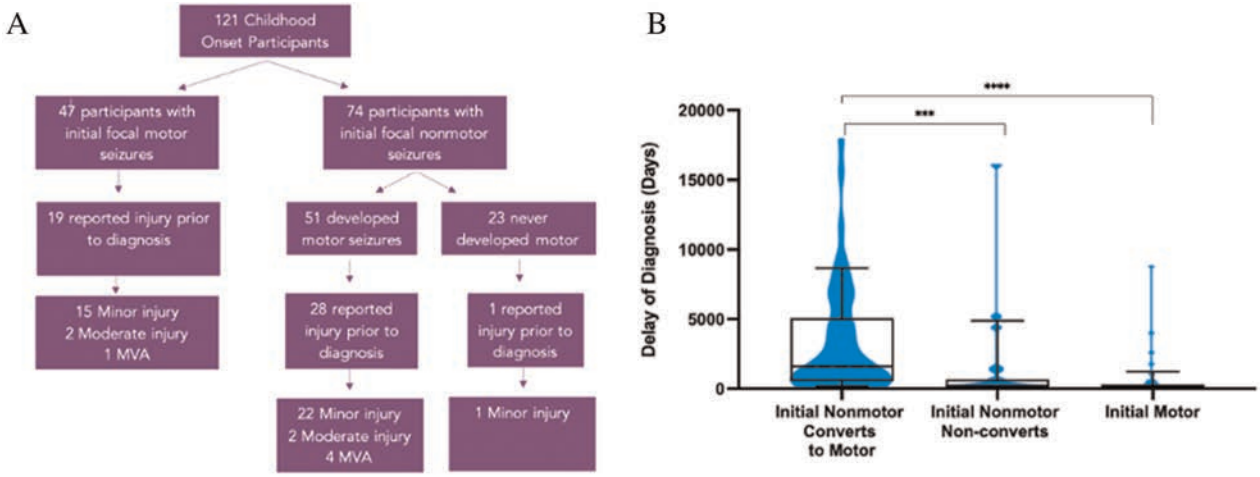


Figure 2.

Longer delays to diagnosis and more injuries were observed in non-motor childhood onset participants who later developed motor symptoms (A) Over half of children with non-motor type epilepsy went on to develop motor-type seizures and these reported more injuries (54.9%) vs those who did not go on to develop motor seizures (4.3%; p <0.001). **(B)** Non-motor childhood-onset participants who converted to motor type seizures experienced the greatest delays in diagnosis when compared to both non-motor and motor only groups (median 1615 days vs 221 days vs 61 days) **** p < 0.0001; ***p = 0.0001; Mann-Whitney test.

Abstact 44

went undiagnosed until conversion to motor seizures. This group reported more injuries vs those who did not go on to develop motor seizures (54.9% vs 4.3%; p<0.001, *Figure 2*) and experienced longer delays in diagnosis when compared to both non-motor and motor only groups (median 1615 vs 221 vs 61 days; p<0.0001; p=0.0001). Lack of recognition by patients and doctors accounted for the delay in more than 2/3 of participants.

Conclusions: This study highlights the disproportionate delay to diagnosis experienced by individuals with focal non-motor seizures and shows this disparity extends to childhood-onset individuals. These delays are associated with more seizures, but also potentially preventable injuries.

Keywords: Epilepsy/Sleep

45. Predictive Value of Video alone in Diagnosis of Epileptic vs Paroxysmal Non-Epileptic Events in Children

Burr T (Louisville, KY), Modiano Y, Raichur P, Barton C, Sah J, Farber D, Brock D, Karia S, Karakas C

Objective: To determine the diagnostic predictive value of videos of habitual events with or without additional clinical data in differentiating the paroxysmal non-epileptic events (PNE) from epileptic seizures (ES) in children.

Methods: Admissions to our epilepsy monitoring unit between June 2020 to December 2020 were analyzed for concerning events. The diagnosis was made based on corroboration with simultaneous EEG activity. Four child neurologists blinded to the diagnosis of the patients formulated a diagnostic impression

TABLE 1. Diagnostic accuracy for the entire sample collapsed across raters for videos only and videos plus clinical data. Abstract 45

	Video only	Video and Clinical Data
Accuracy (95% CI)	74.54% (68.18 to 80.20%)	77.31% (71.14 to 82.72%)
Sensitivity (95% CI)	80.83% (72.64 to 87.44%)	78.33% (69.89 to 85.33%)
Specificity (95% CI)	66.67% (56.31 to 75.96%)	76.04% (66.25 to 84.17%)
PPV (95% CI)	75.19% (69.27 to 80.30%)	80.34% (73.87 to 85.53%)
NPV (95% CI)	73.56% (65.24 to 80.49%)	73.74% (66.24 to 80.07%)
LR+ (95% CI)	2.42 (1.80 to 3.26)	3.27 (2.26 to 4.73)

TABLE 1 (Continued)

	Video only	Video and Clinical Data
LR- (95% CI)	0.29 (0.19 to 0.43)	0.28 (0.20 to 0.41)
Odds ratio (95% CI)	8.44 (4.53 to 15.71)	11.48 (6.06 to 21.74)

Notes: Accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios (LR+/LR-), and odds ratios for video ratings for video ratings for across the entire sample and home video ratings plus clinical information for the entire sample. All ratings are compared against v-EEG diagnoses of epileptic seizures as compared with nonepileptic events.

TABLE 2. Common semiologic features identified in videos separated by the diagnostic group with significant testing for group differences. Abstract 45

Semiology	Non-Epileptic (n = 120)	Epileptic (n = 96)	Group differences
Occurrence from sleep	46 (38.8%)	47 (49.0%)	$X^2 = 2.46$
Staring	32 (26.7%)	20 (20.8%)	$X^2 = 0.99$
Change in facial expression	7 (5.8%)	17 (17.7%)	$X^2 = 7.62$**
Behavioral arrest	16 (13.3%)	17 (17.7%)	$X^2 = 0.79$
Generalized stiffening	7 (5.8%)	16 (16.7%)	$X^2 = 6.58$*
Bilateral myoclonic jerking	30 (25.0%)	13 (13.5%)	$X^2 = 4.39$*
Unresponsiveness	9 (7.5%)	12 (12.5%)	$X^2 = 1.52$
Repetitive eye blinks	5 (4.2%)	12 (12.5%)	$X^2 = 5.11$*
Eye deviation	3 (2.5%)	11 (11.5%)	$X^2 = 7.06$*
Head version	7 (5.8%)	11 (11.5%)	$X^2 = 2.21$

Notes: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. This table only includes semiologic features that were present in 10% or more of videos for at least one diagnostic group.

based upon the review of the video alone and video plus clinical information. Features of the video which helped to make a diagnosis were identified by the raters as a part of a survey.
Results: A total of 54 patients were included (ES n=24, PNE n=30). Diagnostic accuracy was calculated for each reviewer and combined across all the ratings. Diagnostic accuracy by video alone was 74.5% with a sensitivity of 80.8% and specificity of 66.7% (Table-1). Providing raters with basic clinical information in addition to the videos did not significantly improve diagnostic accuracy above the videos alone (p>0.05). Inter-rater reliability between four raters using Fleiss' free-marginal kappa showed moderate agreement. The epileptic group was significantly more likely to demonstrate changes in facial expression, generalized stiffening, repetitive eye blinks, and eye deviation when compared with the nonepileptic group which was more likely to display bilateral myoclonic jerking (Table-2).
Conclusions: Video review of habitual events by Child Neurologists may be helpful in reliably distinguishing ES from PNE in children, even without included clinical information.
Keywords: Epilepsy/Sleep

46. Machine learning to predict response to the ketogenic diet in pediatric epilepsy: a retrospective cohort study

Lu S (Atlanta, GA), Holt P, Johnson M, Gedela S, Bhalla S, Zhang G, Gombolay M, Gombolay G

Objective: To identify specific clinical patient characteristics that predict if the ketogenic diet (KD) will improve seizure frequency in pediatric patients with drug-resistant epilepsy (DRE).
Methods: A retrospective study was performed in children from January 1, 2008 to June 30, 2021 in a single pediatric quaternary referral center.Children on the KD for one year were included. Patient and diet characteristics, including seizure frequency were obtained from medical records. Exclusion criteria included patients with Glucose Transporter 1 (GLUT-1) deficiency or pyruvate dehydrogenase (PDH) deficiency. Primary exposures were body mass index (BMI), age at starting the diet, length of time between first seizure and starting the diet, and number of antiseizure medications prior to starting the diet.
Results: At 12 months after diet initiation, 97 patients were on the KD and had seizure numbers recorded. Seventy-one (73%) had at least 50% improvement, with 84/97 (87%) had any improvement at 12 months. Multivariate logistic regression modeling with backward stepwise selection and machine learning (ML) identified that BMI and the number of seizures per week prior to diet initiation were significant predictors for response at one year. ML also identified that seizure types (absence, clonic, and electrical status epilepticus during slow-wave sleep (ESES)) as features of secondary importance.
Conclusions: Number of seizures prior to the KD and BMI were the most significant predictors for response to KD. Machine learning methods also identified potential seizure types that may predict successful response to KD. Further studies are needed to examine these findings.
Keywords: Epilepsy/Sleep

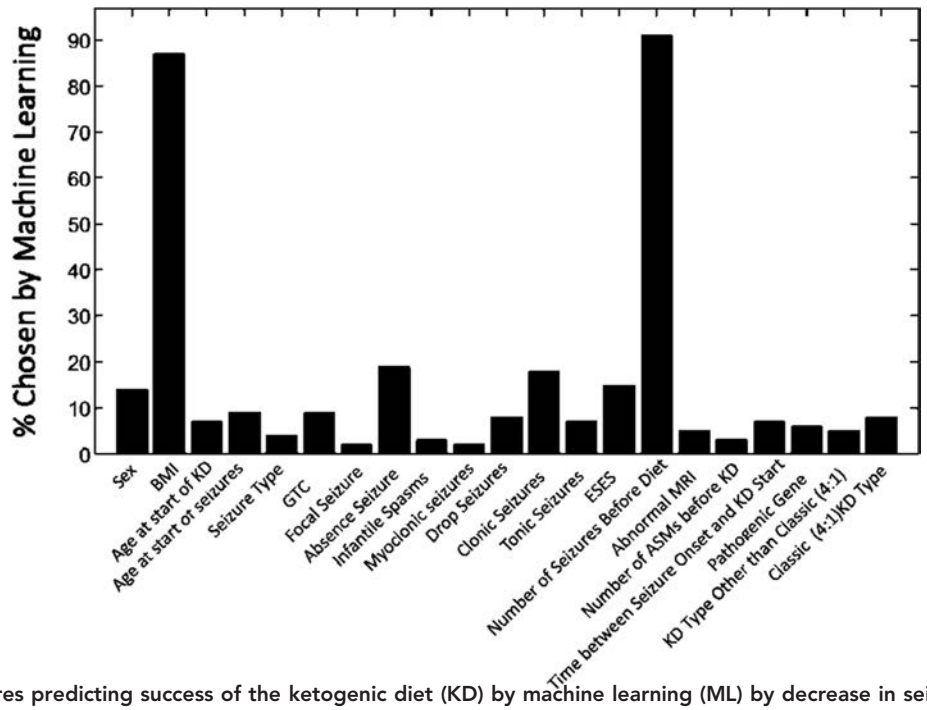


FIGURE 1: Features predicting success of the ketogenic diet (KD) by machine learning (ML) by decrease in seizures at one-year (N=97). The higher frequency at which a characteristic is selected by the ML algorithm, the more likely that feature is to be a significant predictor for KD response. BMI: body mass index, KD: ketogenic diet, GTC: generalized tonic clonic seizures, ESES: Electrical status epilepticus in sleep, MRI: magnetic resonance imaging, ASM: anti-seizure medications; 4:1: ratio of 4 fat grams to 1 protein and carbohydrate gram. Abstract 46

47. Questionnaire based prevalence of sleep problems in normal and diseased population of children and adolescents aged 2-18 years and their association with academic impairment, an observational study

Chakrabarty B (New Delhi, India), Zulfiqar L, Gulati S, Jauhari P, Chaudhary P, Meena A, Pandey R, Upadhyay A, Rajan A, Tripathi M, Kabra S, Jain V, Sikka K

Objective: To describe in children and adolescents aged 2-18 years- Prevalence of sleep disorders in normal and diseased population, and- Association of academic performance with sleep disorders.

Methods: The study was conducted in a tertiary-care teaching hospital in north India. Normal population comprised of children and adolescents attending a public school or the

TABLE 1: Age-wise and academic performance-wise percentage distribution of sleep related symptoms according to CASEQ (developed based on ICSD-3). Abstract 47

Age (years)	Insomnia	SRBD	Hypersomnia	CRSWD	Parasomnia	SRMD	Overall
2-5	16.1	8	1.5	14.6	5.1	19.7	30.7
5-10	21.6	18	1.8	10.8	8.6	27	51.8
10-18	28.5	22	8	21	5	16	46.5
p value	0.02	0.003	0.002	0.01	0.3	0.02	0
Academic performance							
Poor	46.7	22.2	3.3	27.8	4.4	33.3	60
Average	21.8	20.2	4.8	15.3	6.5	24.2	52.8
Good	14	11.3	3.9	10.41	3.2	13.1	29.4
p value	0	0.01	0.7	0.001	0.001	0	0

(SRBD: Sleep Related Breathing Disorder, CRSWD: Circadian Rhythm Sleep Wake Disorder, SRMD: Sleep Related Movement Disorder)

Table 2: Percentage distribution of sleep related symptoms according to CASEQ (developed based on ICSD-3) which are significantly different in normal and diseased population. Abstract 47

	Normal	DMD	SMA	Asthma	CP	p value
Insomnia	22.7	38.5	23.1	38.1	24	0.02
SRBD	16.9	21.2	15.4	42.9	22	0
CRSWD	15.4	13.5	15.4	30.2	8	0.03
Overall	44.7	61.5	46.2	65.1	44	0.008

(SRBD: Sleep Related Breathing Disorder, CRSWD: Circadian Rhythm Sleep Wake Disorder, SRMD: Sleep Related Movement Disorder)

study-hospital with minor ailments whereas diseased population comprised of those with Duchenne muscular dystrophy (DMD), spinal muscular atrophy (SMA), asthma and cerebral palsy (CP) attending the study hospital. They all underwent questionnaire-based evaluation as part of the CASEQ (Childhood and Adolescent Sleep Evaluation Questionnaire) development and validation study.[1]

Results: Overall, 750 subjects were enrolled (median age: 9 years {IQR:6-12} with 65.2% males, 559 normal and 191 diseased {Asthma:63, DMD:52, CP:50 and SMA:26)}. On questionnaire-based evaluation, in the normal population, sleep disorders were prevalent in 44.7% (commonest being insomnia and sleep related movement disorder {SRMD}) compared to 56% (commonest being insomnia in DMD, CP and SMA and sleep related breathing disorder {SRBD} in asthma) in the diseased population(p=0.007). In the normal population, those with academic impairment had significantly more overall sleep problems as well as individual sleep disorders compared to those who were academically good(p=0.001). Sleep problems were significantly less prevalent in 2-5 years (30.7%) compared to 5-10(51.8%) and 10-18(46.5%) years group (p=0.002).

Conclusions: Sleep related problems are common in children and adolescents, more so in diseased than normal population. Normal children with academic impairment have significantly more sleep problems compared to those without.

Keywords: Epilepsy/Sleep

Reference

1. Zulfiqar L, Chakrabarty B, Gulati S, Jauhari P, Pandey RM, Tripathi M, et al. The Childhood and Adolescent Sleep Evaluation Questionnaire (CASEQ): Development and validation of an ICSD-3-based screening instrument, a community and hospital-based study. J Sleep Res. 2022;31:e13479.

48. In Tuberous Sclerosis Complex, Infantile Spasms Typically Require More Than One Tuber Impacting the Brain Network Connected to the Globus Pallidus

Ovchinnikova A (Boston, MA), Kroeck M, Wall J, McManus P, Bebin E.M., Wu J, Northrup H, Krueger D, Sahin M, Warfield S, Peters J, Cohen A

Objective: Tuberous Sclerosis Complex (TSC) is the most common cause of Infantile Spasms (IS), a sudden-onset epilepsy syndrome associated with poor neurodevelopment. Recently, we found that overall connectivity between tuber locations and the globi pallidi (GPi) is strongly associated with IS. Here, we test whether connectivity from a single "hot tuber" is a superior predictor of IS.

Methods: Binary maps of tuber distributions from 123 children with (n=74) and without (n=49) infantile spasms were algorithmically separated into individual tuber labels. We then calculated the connectivity between each tuber and the GPi using a pediatric normative connectome. We isolated the single tuber with the highest functional connectivity to the GPi, and used these pair-wise connections to perform: 1) multiple variable logistic regression to predict IS, and 2) k-fold cross validation prediction to determine the accuracy for predicting IS.

Results: Using the single tuber in each patient with the highest connectivity to the GPi still predicts IS in TSC but is generally less predictive than using the overall tuber distribution. However, for individual cases where the connectivity between a single tuber and the GPi is extremely high, individual tuber connectivity was more predictive than the overall tuber distribution.

Conclusions: While connectivity between tubers and the GPi is strongly associated with IS, this study suggests that only in extreme cases, which are identifiable, is this due to a single cortical tuber. If replicated, this information has significant importance for epilepsy planning in TSC patients and informs models seeking to predict IS in TSC.

Keywords: Epilepsy/Sleep, Neuroimaging, Neuroscience

49. Non-coding exon 1 deletions in the CDKL5 gene lead to CDKL5 deficiency

Haviland I (Boston, MA), Swanson L, Soucy A, Denny A-M, Percy A, Schreiber J, Yu T, Olson H

Objective: Deletions in exon 1 of the 5'-UTR of the cyclin-dependent kinase-like 5 (*CDKL5*) gene have variably been reported by clinical laboratories and in the literature as (likely) pathogenic or of uncertain significance. Our aim was to establish which deletions in this region are associated with CDKL5 deficiency disorder (CDD), a severe X-linked developmental and epileptic encephalopathy.

Methods: We describe genetic and phenotypic characteristics for four individuals with *CDKL5* partial gene deletions restricted to the 5'-UTR enrolled in the CDKL5 Clinic Study at Boston Children's Hospital, based on review of clinical genetic test results and medical history. We performed research-based RNA sequencing on fibroblast samples from two individuals.
Results: Four individuals with chromosome X deletions including a portion of the 5'-UTR of the *CDKL5* gene (range: 2,354-54,900 bp) presented characteristic features of CDD, including medically refractory infantile-onset epilepsy, global developmental delay, cortical visual impairment, and swallowing dysfunction. No alternate genetic diagnoses were identified, and RNA sequencing from one individual with a deletion encompassing the main exon 1 showed normalized expression of *CDKL5* mRNA below 50% compared to mother's sample. One individual with a small *de novo* deletion in an alternate 5'-UTR (between exons 1-2 of the primary brain-expressed transcript) has been seizure-free from 3-17 years of age; RNA sequencing results are pending.
Conclusions: Deletions including the main exon 1 of the *CDKL5* gene are associated with CDD. Smaller 5'-UTR deletions may require further expert clinical and genetic assessments including RNA sequencing for precision diagnosis and related disease-specific treatment approaches.
Keywords: Epilepsy/Sleep, Genetics, Rare Diseases

50. Characterizing Connectivity of Seizure Onset Zones using CCEPs

Wu H (Cincinnati,OH), Ervin B, America O, Buroker J, Greiner H, Holland K, Arya R

Objective: Accurate delineation of the seizure onset zone (SOZ) is critical for patients with drug resistant epilepsy undergoing epilepsy surgery evaluation. Cortico-cortical evoked potentials (CCEPs) can be a useful technique to help characterize the networks associated with SOZs, which we hypothesize can act as network hubs with a tendency to generate and/or amplify ictal activity.
Methods: Data for 10 pediatric patients with drug resistant epilepsy who underwent CCEPs were analyzed. CCEPs were elicited by a train of 10 stimulations from pairs of stereoelectroencephalopagrahy (SEEG) electrodes using biphasic square-wave pulses (duration 0.3ms, amplitude 4 mA). Cortical activity was recorded at all other recording sites. Absolute areas under the curve of the averaged CCEPs N1 response represented magnitude of response. SOZ was ascertained by visual analysis of SEEG per usual clinical process. Number of electrode pairs that produced a N1 response following stimulation of the SOZ (outbound connections) was compared the number of electrode pair stimulations that produced a N1 response within SOZ (inbound connections).
Results: SOZs tend to have greater number of outbound connections compared to inbound connections. Stimulation of the seizure onset zones generated 175 N1 responses elsewhere in the brain compared to 145 total N1 responses generated within the SOZs from stimulation elsewhere.
Conclusions: SOZs may act as network amplifiers that propagate signal to other parts of the brain. CCEPs can assess the number of inbound vs outbound connections through a network hub. In the future, this can be a valuable biomarker of SOZs in patients undergoing epilepsy surgery evaluation.
Keywords: Epilepsy/Sleep

51. Electrical Stimulation Mapping in Patients with Tuberous Sclerosis Complex

Vedala K (Cincinnati, OH), Aungaroon G, Arya R

Objective: This study aims to compare the thresholds and incidences of functional and adverse responses in patients undergoing ESM between those with TSC and those with MRI-negative epilepsy. We test the hypothesis that cortical excitability is different in TSC patients compared to those with MRI-negative epilepsy.

TABLE 1: Scaled threshold current as a function of whether the patient TSC/CDIIB, age, and electrode type. Electrode type was excluded from the lower extremity motor and sensory response data due to low number of responses in SDE. Abstract 51

Threshold current (scaled) ~ factor(TSC or CDIIB) + age + electrode_type

	Variable	Slope	95% CI	p-value	
Language	TSC/CDIIB (vs Unknown)	-1.265	[(-2.027) - (-0.377)]	0.005	**
	Age	-0.073	[(-0.119) - (-0.022)]	0.078	
	SEEG (vs SDE)	0.559	[(-0.211) - (1.328)]	0.209	
Face	TSC/CDIIB (vs Unknown)	-1.180	[(-2.042) - (-0.318)]	0.003	**
	Age	-0.046	[(-0.087) - (-0.005)]	0.049	*
	SEEG (vs SDE)	-0.239	[(-0.951) - (0.472)]	0.526	
UE	TSC/CDIIB (vs Unknown)	0.612	[(-0.291) - (1.514)]	0.220	
	Age	-0.069	[(-0.152) - (0.015)]	0.148	

TABLE 1 (Continued)

Threshold current (scaled) ~ factor(TSC or CDIIB) + age + electrode_type

	Variable	Slope	95% CI	p-value	
	SEEG (vs SDE)	0.447	[(-0.498) - (1.391)]	0.381	
LE	TSC/CDIIB (vs Unknown)	0.895	[(-0.091) - (1.881)]	0.058	
	Age	-0.050	[(-0.184) - (0.085)]	0.531	
Sensory	TSC/CDIIB (vs Unknown)	0.501	[(-1.412) - (2.414)]	0.626	
	Age	-0.012	[(-0.134) - (0.111)]	0.859	
AD	TSC/CDIIB (vs Unknown)	-0.160	[(-0.224) - (-0.097)]	0.008	**
	Age	-0.279	[(-0.320) - (-0.238)]	0.019	*
	SEEG (vs SDE)	0.473	[(-0.119) - (1.065)]	0.130	
Seizure	TSC/CDIIB (vs Unknown)	-0.592	[(-0.697) - (-0.486)]	0.029	*
	Age	-0.074	[(-0.163) - (0.016)]	0.133	
	SEEG (vs SDE)	0.408	[(-0.693) - (1.510)]	0.481	

TABLE 2: (a) Scaled threshold current only for TSC/CDIIB patients as a function of age and electrode type. Electrode type was excluded from the lower extremity motor and sensory response data due to low number of responses in SDE. (b) Scaled threshold current only for unknown etiology patients as a function of age and electrode type. Electrode type was excluded from motor and sensory responses due to low number of responses in SDE. Abstract 51

Threshold current (scaled) for TSC/CDIIB ~ age + electrode_type

	Variable	Slope	95% CI	p-value	
Language	Age	-0.084	[(-0.158) - (-0.010)]	0.006	**
	SEEG (vs SDE)	0.192	[(-1.021) - (1.406)]	0.782	
Face	Age	-0.063	[(-0.102) - (-0.023)]	0.016	*
	SEEG (vs SDE)	-0.249	[(-0.895) - (0.397)]	0.469	
UE	Age	-0.069	[(-0.146) - (0.008)]	0.125	
	SEEG (vs SDE)	0.439	[(-0.330) - (1.209)]	0.299	
LE	Age	-0.048	[(-0.199) - (0.103)]	0.603	
Sensory	Age	-0.012	[(-0.128) - (0.104)]	0.857	
AD	Age	-0.316	[(-0.359) - (-0.274)]	0.007	**
	SEEG (vs SDE)	0.536	[(-0.069) - (1.142)]	0.102	
Seizure	Age	-0.097	[(-0.211) - (0.016)]	0.077	
	SEEG (vs SDE)	0.544	[(-0.924) - (2.012)]	0.496	

TABLE 2 (Continued)

Threshold current (scaled) for Unknown etiology ~ age + electrode_type					
	Variable	**Slope**	**95% CI**	**p-value**	
Language	Age	-0.019	[(-0.175) - (0.313)]	0.731	
	SEEG (vs SDE)	0.723	[(-1.648) - (3.094)]	0.452	
Face	Age	-0.038	[(-0.251) - (0.175)]	0.521	
UE	Age	-0.054	[(-0.364) - (0.246)]	0.736	
Sensory	Age	-0.005	[(-0.239) - (0.227)]	0.965	
AD	Age	-0.094	[(-0.184) - (-0.004)]	0.058	
	SEEG (vs SDE)	-0.184	[(-1.770) - (1.401)]	0.826	
Seizure	Age	-0.018	[(-0.281) - (-0.083)]	0.018	*
	SEEG (vs SDE)	-0.015	[(-1.158) - (1.127)]	0.980	

Table 3: Incidence of responses as a function of etiology type, electrode type, age, and scaled current. Electrode type was excluded from lower extremity motor and sensory responses due to low number of responses in SDE.

Incidence of Responses ~ factor(TSC+CDIIB vs unknown) + electrode type (SEEG vs SDE) + age + current (scaled)					
	Variable	**OR**	**95% CI**	**p-value**	
Language	TSC/CDIIB (vs Unknown)	0.224	(0.052 - 0.965)	0.031	*
	SEEG (vs SDE)	1.022	(0.062 - 16.885)	0.293	
	Age	1.254	(1.036 - 1.517)	0.020	*
	Current (scaled)	1.158	(0.880 - 1.523)	0.295	
Face	TSC/CDIIB (vs Unknown)	0.929	(0.180 - 4.788)	0.398	
	SEEG (vs SDE)	1.338	(0.298 - 6.005)	0.703	
	Age	1.069	(0.975 - 1.172)	0.056	
	Current (scaled)	1.077	(0.790 - 1.469)	0.111	
UE	TSC/CDIIB (vs Unknown)	0.820	(0.173 - 3.888)	0.802	
	SEEG (vs SDE)	4.794	(0.957 - 24.009)	0.057	
	Age	0.920	(0.821 - 1.030)	0.148	
	Current (scaled)	1.358	(1.068 - 1.727)	0.013	*
LE	TSC/CDIIB (vs Unknown)	0.786	(0.050 - 12.412)	0.864	
	Age	0.817	(0.613 - 1.089)	0.168	
	Current (scaled)	1.520	(0.957 - 2.415)	0.076	
Sensory	TSC/CDIIB (vs Unknown)	0.033	(0.003 - 0.322)	0.003	**
	Age	1.014	(0.876 - 1.175)	0.106	
	Current (scaled)	1.426	(1.058 - 1.922)	0.020	*
AD	TSC/CDIIB (vs Unknown)	1.884	(1.581 - 2.244)	0.043	*

TABLE 3 (Continued)

Incidence of Responses ~ factor(TSC+CDIIB vs unknown) + electrode type (SEEG vs SDE) + age + current (scaled)					
	Variable	**OR**	**95% CI**	**p-value**	
	SEEG (vs SDE)	0.563	(0.124 - 2.552)	0.456	
	Age	1.015	(0.916 - 1.124)	0.078	
	Current (scaled)	1.208	(1.055 - 1.384)	0.006	**
Seizure	TSC/CDIIB (vs Unknown)	1.498	(0.562 - 3.990)	0.050	
	SEEG (vs SDE)	0.452	(0.156 - 1.305)	0.142	
	Age	1.028	(0.950 - 1.112)	0.495	
	Current (scaled)	1.351	(0.875 - 2.085)	0.174	

Methods: ESM recordings at the Cincinnati Children's Comprehensive Epilepsy Center were reviewed in 25 patients with known TSC and/or focal cortical dysplasia type IIB (CDIIB) and 10 patients with unknown epilepsy etiology. Data were collected on age, type of electrodes, and the incidence and thresholds of functional response, after-discharges, and seizures. Data were compared using linear mixed model regression analysis.
Results: Patients with TSC/FCDIIB had lower thresholds for language (-1.265; p=0.005) and face motor (-1.180; p=0.003) responses. They also had a lower threshold to incur ADs (-0.160; p=0.008) and seizures (-0.592; p=0.029). Furthermore, they had lower incidence of all functional responses, with statistical significance in language (OR 0.224; 95% CI 0.052-0.965; p=0.031) and sensory (OR 0.033; 95% CI 0.003-0.322; p=0.003) responses. In addition, patients with TSC/FCDIIB had higher incidence of ADs (OR 1.884; 95% CI 1.581-2.244; p=0.043) and ESM-induced seizures (OR 1.498; 95% CI 0.562 - 3.990; p=0.050).
Conclusions: Compared to patients with unknown epilepsy etiology, those with TSC/FCDIIB require lower stimulation thresholds to produce language responses, face motor responses, ADs, and seizures, suggesting higher cortical excitability in TSC patients. However, these relative lower thresholds are not seen with sensory or upper and lower extremity motor responses, suggesting possible regional differences in cortical excitability.
Keywords: Epilepsy/Sleep, Neurocutaneous Disorders

52. A pathogenic variant of the DNM1L mitochondrial gene associated with super-refractory status epilepticus (SE) in a 15-year-old female

Prabhu N (Little Rock, AR), Arya K, Drake P, Arulprakash N, Cobb S, Manbeck C, Willis E, Burrow T, Fry D, Samanta D, Perkins F

Objective: To report a challenging case of a rapid exome sequencing diagnosed DNM1L mitochondrial gene pathogenic variant presenting as new onset super-refractory SE in a 15 year old
Methods: Case report
Results: A 15-year-old female, without prior seizures, presented with new-onset convulsive SE. Pharmacological coma was induced as benzodiazepine and nonbenzodiazepine antiseizure medicines (ASM) were unsuccessful to abort SE. Multiple attempts of variable duration of infusion cycles (midazolam, propofol, pentobarbital, ketamine) were unable to prevent recurrent SE despite adjunctive immunomodulation (steroids, immunoglobulin, anakinra, and plasmapheresis) and other ASMs. Rapid whole-exome sequencing was performed, which revealed a heterozygous, autosomal dominant, c.1207 C>T p. (R403C) de-novo dynamin-1-like (DNM1L) variant associated with dysfunctional mitochondrial and peroxisomal fusion. DNM1L pathogenic variants may cause childhood-onset super-refractory SE with an extremely poor prognosis and extensive global cortical atrophy, as seen in our patient. In this context, as SE persisted for >3 weeks, the family withdrew care. Our patient is the oldest such reported case and uniquely, had pre-existing high functioning autism and non-verbal learning disorder.
Conclusions: Rapid exome sequencing for epilepsy is primarily used in early infancy when treatable metabolic disorders are prevalent. Although early-onset epilepsy is common in mitochondrial disease, de novo SE can manifest in a later age group. This case reveals the expanding phenotypic spectrum associated with DNM1L variants and highlights the diagnostic importance of rapid whole-exome sequencing in cases with refractory SE of uncertain etiology in a later age group, which may facilitate etiology-specific treatment (avoidance of valproate) and early prognostication.
Keywords: Epilepsy/Sleep

53. Spectrum of disease caused by C191R, R157G, and A39V TBC1D24 mutations: A study of eleven patients

Sondhi V (Pune, India), Dubey R, Saini L, Badal S, Sannalli K, Irshad M, Kurup A, Jha R, Patel H, Goswami J

Objective: To describe the phenotypic spectrum of early-onset epilepsy associated with mutations in *TBC1D24*
Methods: A retrospective review of all genetic testing performed at five centers since Jan 2018 was performed. All children with *TBC1D24* variants were considered eligible.

Patients were excluded if the mutations were non-pathogenic. Patient data, including details of clinical, laboratory, neurophysiological, and neuroimaging features, genetic mutations, and therapeutic interventions, were chronicled using a case record form.

Results: Eleven patients (six female) belonging to eight families were included. The patients were homozygous to 571 T/C (n=3), 469 C/G (n=3), or 116 C/T (n=4) variants, giving the amino acid changes of C191R, R157G, and A39V, respectively, or compound heterozygotes for either of these three mutations (n=1). Irrespective of the genotype, the patients exhibited early-onset epileptic encephalopathy characterized by focal seizures (11/11), epilepsia partialis continua (n=11/11), and infantile spasms (n=7/11). The median age of onset of seizures was one month (IQR= 1 to 2 months). Brain MRI demonstrated cortical atrophy in 6/11 patients; no structural abnormality was identified for other patients. Electrographic features included slow background activity (n=8/11), multifocal paroxysmal inter-ictal epileptiform discharges (n=9/11), hypsarrhythmia (n=1), and focal migrating discharges (n=2). All patients had drug-resistant epilepsy, and 10/11 patients died at a median age of 14 months (IQR= 11 to 17 months).

Conclusions: This study demonstrates that early-onset epileptic encephalopathy with predominantly focal seizures should raise the suspicion of *TBC1D24* mutation. Patients with this disorder have drug-resistant epilepsy and are at high risk of early death from status epilepticus.

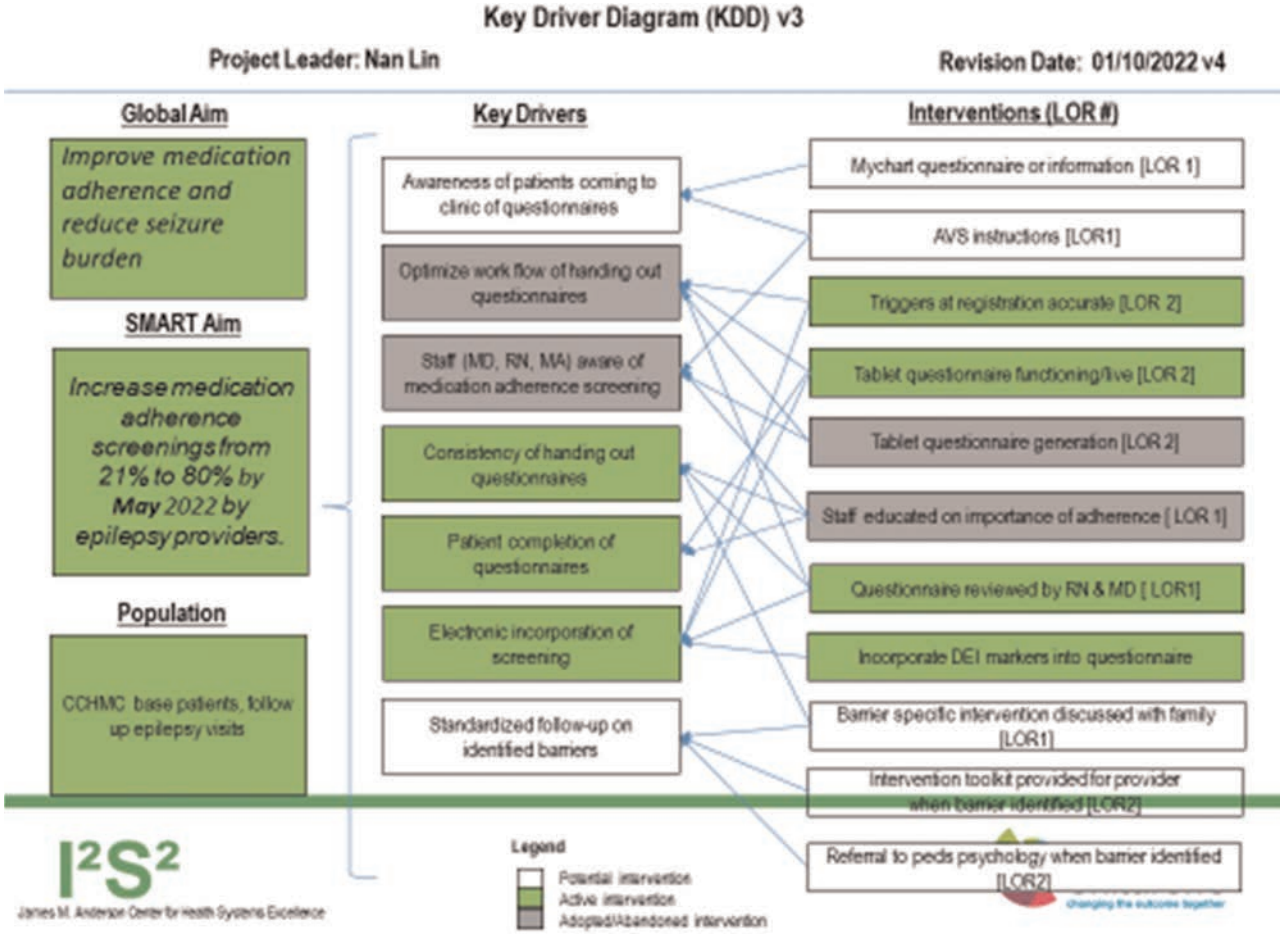
Keywords: Epilepsy/Sleep, Genetics

54. Improving Medication Adherence as Part of a Learning Heathcare System

Lin N (Cincinnati, OH), Tencer J, Buchhalter J, Grimm J, Cronin S, Whitesell K, Clifford L, Hagans C, Holland K

Objective: Medication non-adherence is associated with increased risk of seizures, healthcare costs and morbidity/mortality in children with epilepsy. We know, however, that non-adherence rates in this population range from 30-60% in literature. The identification of medication nonadherence is also crucial for appropriate provider treatment recommendations. Therefore, in partnership with Epilepsy Learning Healthcare System (ELHS), pediatric psychology and the pediatric epilepsy division at Cincinnati Children's Hospital Medical Center, we aim to improve our medication non-adherence screening rates

Methods: This is a quality improvement project where we implemented the 18-item Barrier to Medication Adherence Screening Tool adopted by the Epilepsy Learning Healthcare System (ELHS) to increase our screening for follow up



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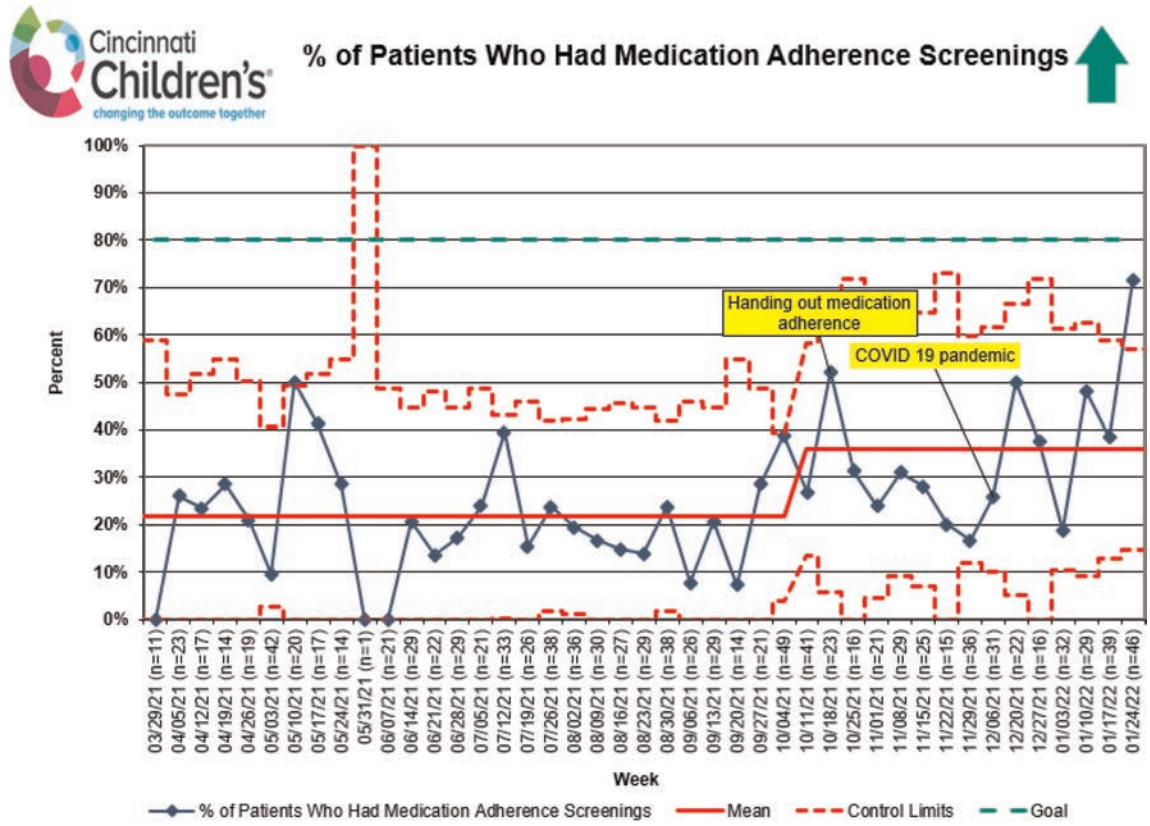

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patients in our epilepsy clinic. All epilepsy providers have been included. Our Plan-Do-Study-Act (PDSA) cycles were focused on interventions such as adjustment of the screening tool wording and refining how to administer the screening forms into the current clinic work flow in collaboration with our nurses and medical assistants.

Results: We have increased our screening rates from baseline 21% to 36%.

Conclusions: Implementation of the formal ELHS Adherence Screening Tool allowed us to screen for barriers to non-adherence at a rate higher than our previous screening methods. There is a lot of room for improvement. Future PDSA cycles include expanding to all providers in neurology clinic, implementation of an automated electronic health record survey on patient check-in and collection of longitudinal data including demographics and diversity data.

Keywords: Epilepsy/Sleep

55. Pharmacoepidemiology Foundations for Comparative Effectiveness Research in Pediatric Epilepsy -- First and Second line therapy for children 0 to 5 years.

Grinspan Z (New York, NY), Wu A, Axeen E, Coryell J, Demarest J, Demarest S, Gaillard W, Goodkin H, Morgan L, Sands T, Wu J, Yozawitz E, Zafar M, Patel A

Objective: Understanding which anti-seizure medications (ASMs) are selected first and second for children with epilepsy can prioritize questions for comparative effectiveness research.

Methods: We used electronic health record data from 15 centers in the Pediatric Epilepsy Learning Healthcare System (2017-2020) to examine the first ASMs prescribed for children with epilepsy from age 0 to 5 years. In the subgroup who first received levetiracetam, we examined which ASM was prescribed second. To estimate equipoise, we highlighted questions where two or more ASMs were used at least 15%.

Results: 13,153 children had a first ASM prescribed (median age 2.49 years [1.03, 3.79]; 44% F). For children 0-3 months, phenobarbital was most common (45%; 479 of 1058). For other ages, levetiracetam was most common (56%; 6796 of 12095). The second most prescribed was oxcarbazepine (13%; 1616 of 12095). 1875 children were initially prescribed levetiracetam then a second ASM (median age 2.54 [interquartile range 1.22 to 3.75] years; median of 80 [20 to 223] days after the first prescription of levetiracetam). Under 6 months, phenobarbital was most common (36%; 71 of 196). Above 6 months, the four most common ASMs were oxcarbazepine (31%; 514 of 1679), clobazam (17%; 293 of 1679), zonisamide (14%; 236 of 1679), and valproic acid (10%; 166 of 1679).

Conclusions: There are opportunities to compare the effectiveness of ASMs for first line (levetiracetam, oxcarbazepine) and second line (oxcarbazepine, clobazam, zonisamide, valproic acid). For second line, two ASMs were used at least 15% (oxcarbazepine, clobazam) suggesting equipoise on their relative effectiveness.

Keywords: Epilepsy/Sleep

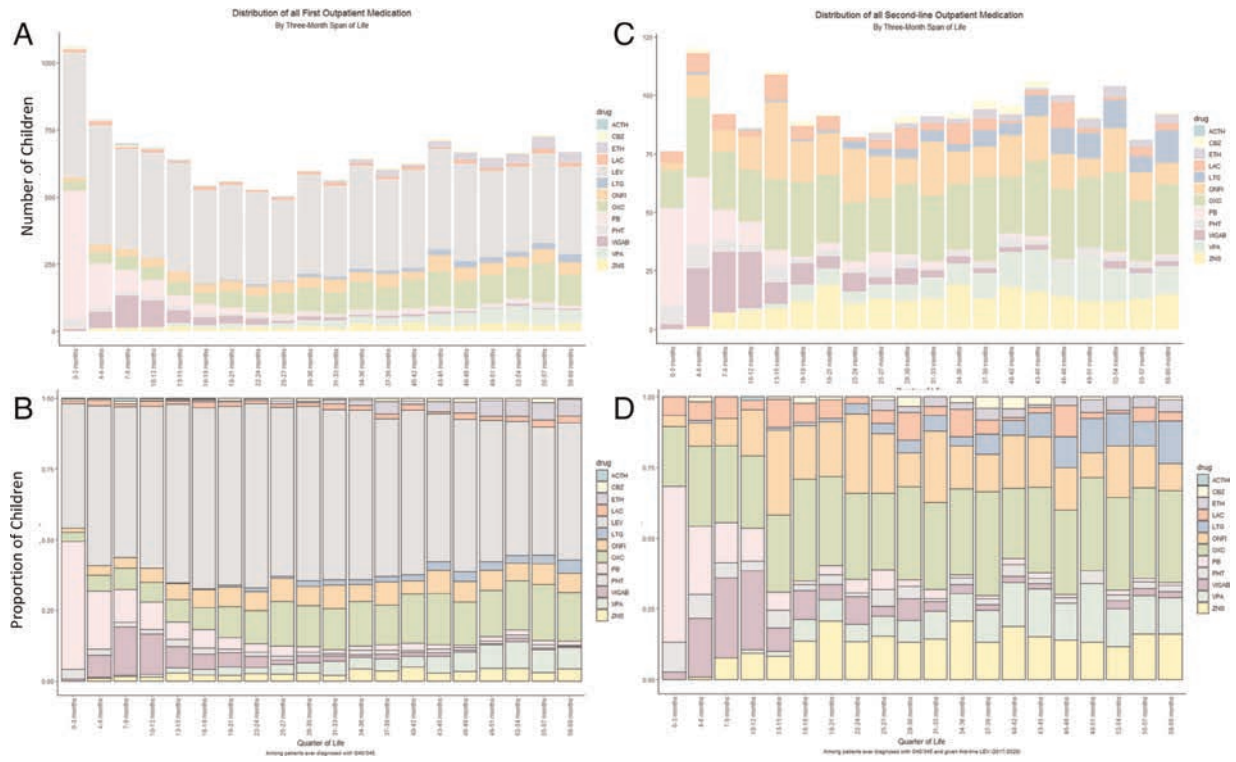

FIGURE. Distribution of first (panel A, B) and second (C, D) anti-seizure medication prescribed for children with epilepsy (any diagnosis of ICD9 345 or ICD 10 G40), by absolute number of children (A, C) and as percentage of the whole (B, D), in three-month age ranges, 0 to 60 months. ACTH = Adrenocorticotropic Hormone, CBZ = Carbamazepine, ETH = Ethosuximide, LAC = Lacosamide, LEV = Levetiracetam, LTG = Lamotrigine, ONFI = clobazam, OXC = oxcarbazepine, PB = phenobarbital, PHT = phenytoin, VIGAB – vigabatrin, VPA = valproic acid, ZNS = zonisamide. Abstract 55

56. Development of Conceptual Models for Dravet Syndrome and Lennox–Gastaut Syndrome

Andrews S (Cambridge, MA), Nacson A, Sams L, Symonds T, Benitez A, Asgharnejad M, Hoffman D

Objective: Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS) are rare developmental and epileptic encephalopathies (DEEs) characterized by medically refractory seizures, severe cognitive and neurological delays or declines, and a range of social, behavioral, and communication problems. Clinical trial outcomes are needed that assess stakeholder priorities for such rare and heterogeneous conditions. Here, we describe the development of patient-centered

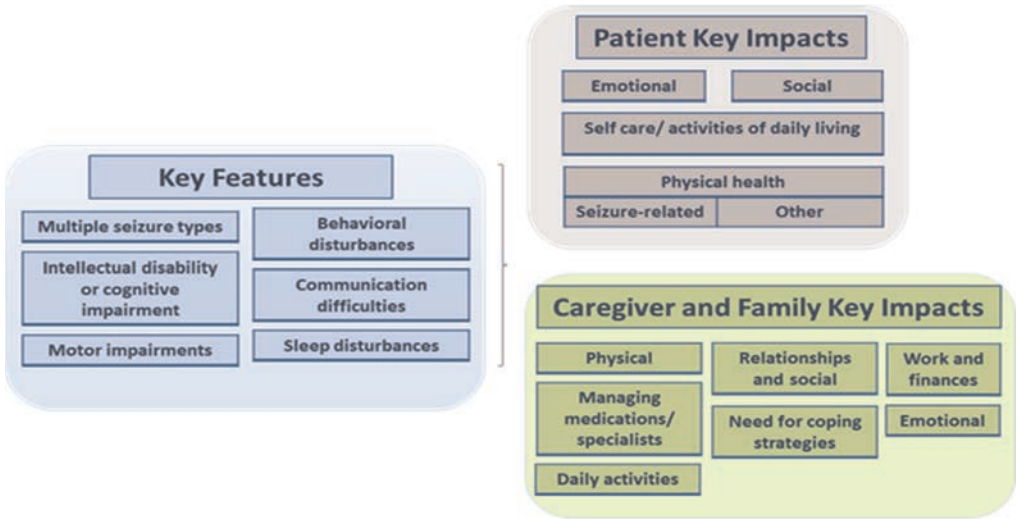

FIGURE 1. Conceptual model of key features and impacts for developmental and epileptic encephalopathies (e.g., DS and LGS). Abstract 56

conceptual models defining the key features and impacts of these syndromes on patients, caregivers, and families.
Methods: Literature searches were conducted in Embase, Medline, and PsycINFO to identify qualitative studies that describe clinical features or patient and caregiver experience with DS and LGS. Owing to limited data availability, all study designs were considered from studies published between 2006–2020 in English. A draft conceptual model was developed for each condition using extracted data on symptoms and impacts. These models were refined using feedback from semi-structured qualitative interviews with clinicians and patient advocates (PAs).
Results: Eight relevant articles were identified from the literature search (five on DS; three on LGS). Eight qualitative interviews were conducted (five clinicians including neurologists and epileptologists, and three PAs). Key features identified for both conditions were seizures, neurological and motor, behavioral, sleep, and communication (verbal and non-verbal). A combined DEE model identified six key features across both conditions and key impacts on patients, caregivers, and families (Figure 1).
Conclusions: DS and LGS have profound impacts on the lives of patients, caregivers, and families. The DEE model will be used to inform the development of patient-centered outcome measures for clinical trials.
Keywords: Epilepsy/Sleep, Rare Diseases

57. Similar Antiseizure Medication Refill Characteristics in Hispanic and White Pediatric Patients

Baker M(Salt Lake City, UT), Olsen J, Wilkes J, Sweney M, Soisson S, Bonkowsky J

Objective: Previous work has shown that children of Hispanic ethnicity have a reduced likelihood to achieve seizure remission, but it was unknown whether this was related to medication adherence. The purpose of this study was to determine antiseizure medicine (ASM) refill characteristics, comparing Hispanic and non-Hispanic White pediatric patients.
Methods: This was a retrospective population-based cohort study in children between ages 6 months and 15 years at their initial presentation. The cohort was assembled from clinic, emergency department, or hospital visits, in an integrated health care delivery system. Epilepsy outcome was determined at the conclusion of the study period and categorized as seizure free, treatment failure, or undetermined. ASM refill characteristics were determined from an insurance provider.
Results: 247 patients were identified; all patients had 5 or more years of follow-up. 52 (21%) patients were treatment failure; 181 (73%) were seizure free; and 14 (5.7%) were undetermined. ASM prescription refills rates were similar in Hispanic and in White patients (38.2, 32.1, respectively). Hispanic and White patients had similar numbers of different ASMs prescribed, 2.1 and 2.4, respectively. There was not a significant difference in proportion of days covered between Hispanic (0.99) and White (0.95) patients.
Conclusions: We found no differences between pediatric Hispanic and White epilepsy patients, for number of ASM refills, the number of ASMs prescribed, the proportion of days covered, or the lateness of refills. Our findings suggest that the observation of reduced likelihood to achieve seizure remission in pediatric Hispanic patients is not associated with medication adherence.
Keywords: Epilepsy/Sleep, Equity, Diversity, Inclusion

58. Quality of Life and Developmental Outcomes in SCN8A-Related Epilepsy

Xie V (Washington, DC), Kramer Z, Berl M, Schreiber J

Objective: Mutations in the SCN8A gene have been associated with an increasing spectrum of epileptic and

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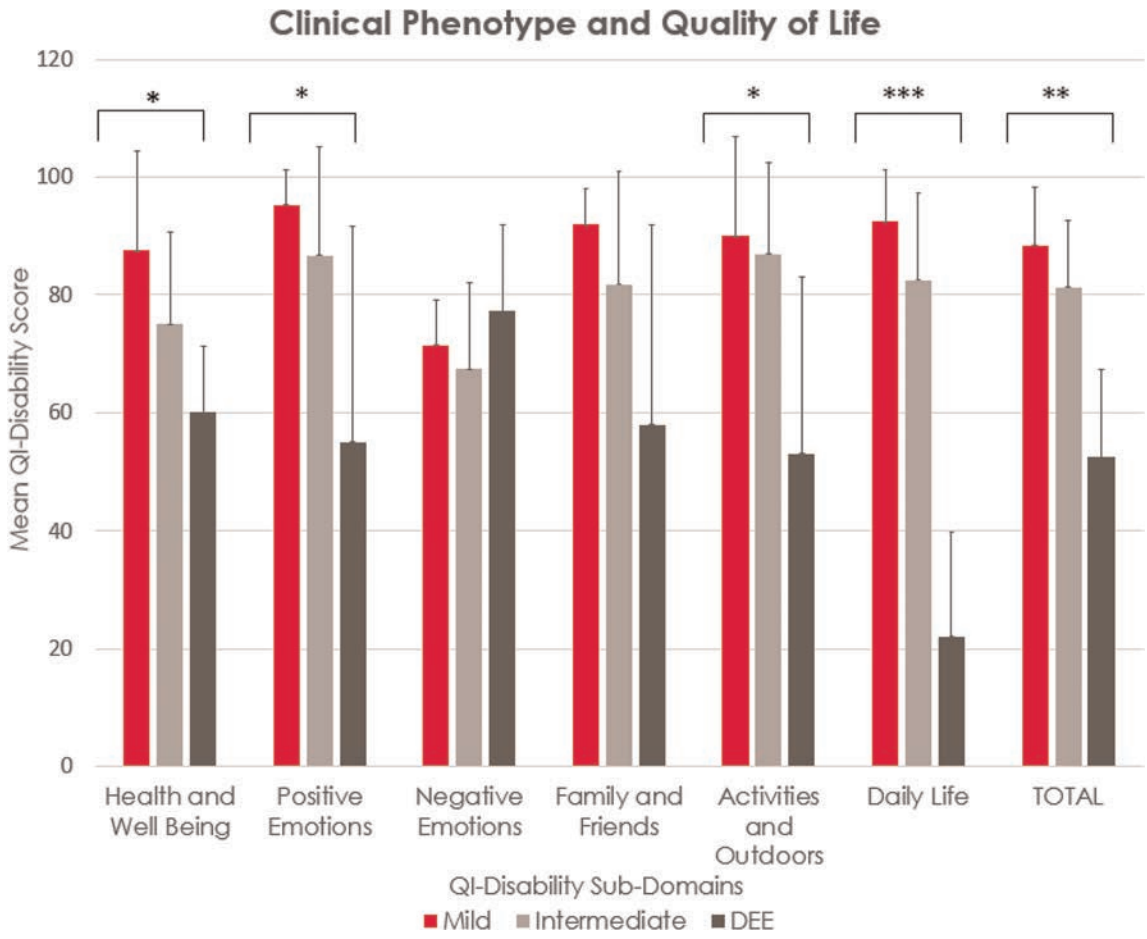

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neurodevelopmental disorders. Non-seizure outcomes, such as quality of life and development, remain poorly understood and lack standardized modalities for investigation. Through an established cohort of patients with SCN8A variants, we sought to characterize these outcomes.

Methods: Clinical histories for participants with SCN8A-related epilepsy were analyzed. The Vineland Adaptive Behavioral Scores-III (VABS-III), Pediatric Quality of Life Inventory (PedsQL) Epilepsy Module, and Quality of Life Inventory-Disability (QI-Disability) forms were administered via parent interviews. VABS-III scores were analyzed for change over time. Quality of life scores were analyzed for association with developmental scores, clinical phenotype, and seizure frequency.

Results: 17 participants ages 2-23 years were included and 10 participants underwent VABS-III administration twice. Participants were differentiated into mild, intermediate, or developmental and epileptic encephalopathy (DEE) phenotypes, and seizure-free >6 months or actively experiencing seizures. There was no significant change in standardized scores in all developmental domains of the VABS-III over time. VABS-III score was positively correlated with multiple subdomains of the QI-Disability and PedsQL forms (p-value <0.001 for total QI-Disability score). Clinical phenotype showed significant differences in more QI-Disability subdomains than seizure frequency phenotype.

Conclusions: Participants demonstrated stable developmental scores over time. Higher developmental scores correlated with a higher quality of life in multiple domains, and there were significant differences in quality of life scores between clinical phenotypes. Emphasis on therapy services such as speech, PT, and OT may contribute to a higher quality of life in patients with SCN8A-related epilepsy.

Keywords: Epilepsy/Sleep, Genetics

59. Long-term treatment with intracerebroventricular cerliponase alfa for children with CLN2 disease: Safety and efficacy after >5 years

de los Reyes E (Columbus, OH), Schulz A, Gissen P, Specchio N, Slasor P, Bondade S, Cohen-Pfeffer J

Objective: A primary open-label study showed that intracerebroventricular (ICV) infusion of 300 mg cerliponase alfa (rhTPP1) biweekly for 48 weeks slowed deterioration in motor and language function in children with CLN2 disease. This extension study assessed long-term safety and efficacy of cerliponase alfa over an additional 240 weeks.

Methods: Subjects completing the primary study continued receiving 300 mg cerliponase alfa biweekly for up to 240 weeks in the open-label extension. Cumulative data from both studies were used to evaluate long-term safety and efficacy.
Results: 24 subjects were treated in the primary study (9 male, 15 female; mean [SD] age 4.9 [1.3] years); 23 subjects enrolled in the extension and received 300 mg cerliponase alfa for a mean (range) of 272 (162–300) weeks. Treated subjects were less likely than natural history (NH) controls to experience to unreversed 2-point decline or score of zero in ML score (HR, 0.14; 95% CI: 0.06, 0.33; p<0.0001). Mean (SD) rate of decline in ML score was 0.38 (0.50) points/48 weeks for treated subjects and 2.13 (0.95) points/48 weeks for NH controls. All subjects experienced ≥1 adverse event (AE); 21 (88%) experienced a serious AE. There were no deaths and no study discontinuations due to AEs. The most common drug-related AEs were pyrexia (46%), hypersensitivity (42%) and seizures (38%); device-related AEs were observed in 20 subjects (83%).
Conclusions: ICV-administered cerliponase alfa for children with CLN2 disease has an acceptable safety profile and sustained treatment effect over >5 years.
Keywords: Epilepsy/Sleep, Rare Diseases, Genetics

60. Pathogenic and Likely Pathogenic Variants in KCNQ2 Underlie a Large Majority of Genetic Epilepsy in Neonates and Infants <6 Months of Age

Grayson C (Burnaby, BC, Canada), Johnson B, Willcock A, DeRienzo L, Butterfield N, Millichap J, Harden C, Sherrington R

Objective: Variants in the *KCNQ2* gene underlie a spectrum of neonatal-onset epilepsies. *KCNQ2*-related epilepsy typically presents during the first week of life, caused by loss of Kv7.2-mediated potassium current. The objective of this analysis was to determine the molecular diagnostic yield and age of diagnosis of patients with *KCNQ2*-related epilepsy in a sponsored pediatric genetic testing program.
Methods: The sponsored testing program uses a next-generation sequencing panel with simultaneous sequence and exonic copy number variant detection in up to 186 genes previously associated with epilepsy. Eligible patients have unprovoked seizures and were 0-48 (Feb/19-Jan/20) or 0-96 months of age (Jan/20-present). Ordering physicians provided a brief clinical history.
Results: Data in children <24 months at testing was analyzed. Causal variants in *KCNQ2* stratified by age accounted for 69.9%(n=109/156) of the positive molecular diagnoses (PosMD) in neonates (<1 month), and 19%(n=109/573) of neonates tested. *KCNQ2* variants were also the most frequent molecular diagnosis at <6 months (32.8%; n=156/475 PosMD). At <24 months, the most frequent PosMD were *PRRT2*(23.7%), *KCNQ2*(15.5%), *SCN1A*(13.9%), *SCN2A* (3.9%), *CDKL5* and *PCDH19*(2.9%). The average age at diagnosis of *KCNQ2*-related epilepsy in patients <24 months (n=176) was 1.9 months.
Conclusions: Variants in *KCNQ2* are the most common cause of genetic epilepsy during early infancy. These data support the early genetic testing of neonates and infants with seizure onset <6 months of age. Early diagnosis of KCNQ2-related epilepsy has important implications for clinical management and for access to therapies in clinical development, such as XEN496 in the Phase 3 "EPIK" study.
Keywords: Epilepsy/Sleep, Genetics, Rare Diseases

61. Findings from the Implementation of a Novel Needs Assessment Survey in Children and Youth with Epilepsy; The Impact of Social Determinants of Health on Utilization of Medical Services

Wilson E (Boston, MA), Sheng H, Mumber H, Camayd C, Alvarado M, Niemann M, Jacobellis S, Sandel M, Garg A, Douglass L

Objective: This study aimed to characterize the relationship between social determinants of health (SDOH) and epilepsy-specific outcomes through the use of a novel needs assessment survey, The Epilepsy Needs Assessment Survey (ENAS).
Methods: This was an observational quality improvement study. A novel screening survey (ENAS) was administered to patients with epilepsy at a large urban hospital. We assessed for the prevalence of various SDOH and the association with independence in activities of daily living, verbal status, prevalence of intractable epilepsy, missed school/work days, missed neurology appointments and emergency department visits.
Results: Forty-nine percent of participants reported at least one insecurity. While disease burden did not appear to differ significantly between families with and without hardships, families who reported any hardship had almost twice the percentage of missed neurology appointments and were significantly more likely to have an ED visit related to seizure (RR = 5.44, CI 2.82-10.48, p < 0.001). Specifically, families with housing insecurity were significantly more likely to have an ED visit related to seizure (RR = 3.13, CI 1.25-7.89, p = 0.015)
Conclusions: Several studies have suggested that social determinants of health (SDOH) impact various patient health outcomes such as developmental concerns, functional limitations and higher healthcare utilization. The impact of SDOH on patients with complex medical conditions in subspecialty clinics has not been well documented, however. This is one of the first studies to assess the effects of SDOH on epilepsy-specific outcomes using a low cost, novel screening tool which can be utilized better understanding this relationship.
Keywords: Epilepsy/Sleep

62. Effect of ganaxolone on behaviors in children with the CDKL5 Deficiency Disorder

Downs J (Perth, Australia), Aimetti A, Busse G, Jacoby P

Objective: CDKL5 deficiency disorder (CDD) is a rare developmental epileptic encephalopathy. A phase 3 randomized, placebo-controlled trial found that ganaxolone, a neuroactive steroid recently approved by FDA for the treatment of seizures associated with CDD, significantly reduced major motor seizure frequency (MMSF) in children with CDD. This post-hoc analysis explored whether ganaxolone was associated with improved behaviors.

Methods: Children (2-19 years) with genetically confirmed CDD and >=16 major motor seizures per month were enrolled. Ganaxolone or placebo was administered TID over a 17-week period. Behavior was measured with the Anxiety, Depression and Mood Scale (ADAMS) in five domains: Manic/Hyperactive Behavior, Depressed Mood, Social Avoidance, General Anxiety, and Compulsive Behavior (decreased scores indicate improvement). Scores were compared using ANCOVA, adjusted for age, sex, number of anti-seizure medications, baseline 28-day MMSF, and baseline developmental skills and behavior scores.
Results: 101 children with CDD (39 clinical sites, 8 countries) were randomized. Median (IQR) age was 6 (3-10) years, 79.2% were female, and 50 received ganaxolone. After 17 weeks of treatment, Manic/Hyperactive scores were on average 1.36 points (95%CI –2.62,-0.11, p=0.034) lower for children in the ganaxolone group than in the placebo group. Post-treatment Compulsive Behavior scores were 0.72 points (95%CI -1.36,-0.09, p=0.027) lower in the ganaxolone group. Depressed Mood, Social Avoidance and General Anxiety scores were similar between the two groups.
Conclusions: Non-seizure outcomes can contribute to the success of anti-seizure interventions. Along with better seizure control, children who received ganaxolone had improved behavioral scores in select domains compared to those receiving placebo.
Keywords: Epilepsy/Sleep, Genetics, Rare Diseases

63. Treatment-response and long-term outcome in patients with Electrical Status Epilepticus in Sleep (ESES)

Weisman H (Ramat Gan, Israel), Tzadok M, Heimer G, Zohar-Dayan E, Bar-Yosef O, Ben-Zeev B

Objective: We describe the etiology, clinical characteristics, treatment-response and long-term outcomes in patients with ESES.
Methods: We reviewed the medical records of children with ESES at the tertiary pediatric epilepsy clinic in Edmond and Lily SAFRA children's hospital between the years 2005-2019. The collected data includes patient characteristics, therapeutic regime, and outcomes.
Results: The average time of follow-up was 82 months. Of the 101 children concluded in the study, 89 (88.1%) of the children had resolution of ESES under treatment. Seventy children (69.3%) were treated with steroids. Among them, 42 (60%) responded to treatment.The majority (71.3%) of the children had functional improvement at last follow up compared to baseline. Nonetheless, 63.4% attend special education programs or have learning disability. Children who had resolution under steroids treatment had less functional improvement at last follow up (p-value<0.03).
Conclusions: We show high resolution rate for ESES and good functional outcome in long term follow up in a broad patient population. Approximately half of the children responded to steroid courses. Children who were treated with steroids often have more refractory ESES and different underlying pathology than the ones responded to AED's, which may partially explain their inferior functional outcome.
Keywords: Epilepsy/Sleep, Cognitive/Behavioral Disorders (including Autism)

64. Measuring Transition Readiness in Adolescents with Epilepsy: Opportunities and Challenges

Krysiak T (Dayton, OH), MacDonald S, Cates S, Kumar G

Objective: Our aim was to create a process to evaluate self-care knowledge and transition readiness in adolescents with epilepsy.
Methods: Quality Improvement Project (QIP) methodology was used to administer the Safety, Awareness, and Familiarity regarding Epilepsy in Teenage Years (SAFETY) questionnaire. Staff education and training was addressed in the first PDSA series. Adolescent epilepsy patients 13-18 years were recruited. Other PDSA cycles included addressing loss of forms and forms without patient identifiers, inclusion exceptions and modifying the scripting to identify the value of the

Table 1 PDSA Summary

Intervention	Key Driver	Cycle 3	Cycle 2	Cycle 3
Staff Education and Training	**Staff Awareness of Self Care Assessment (SCA) Process**	**Plan-Summary**: Educate focus group **Plan-Prediction**: Receptive and helpful in facilitating **Study-Results: ADAPT** **Act:** Include clinic staff who will administer	**Plan-Summary**: Educate clinic staff who will be responsible for administration/collection of SCA **Plan-Prediction**: receptive staff **Study-Results:** Receptive to process, identified possible barriers **Act: ADAPT** Include all department staff to foster commitment	**Plan-Summary**: Further educate providers/dept staff to identify roles and future implications **Plan-Prediction**: receptive staff **Study-Results:** Staff receptive **Act: Adopt**

TABLE 1 (Continued)

Intervention	Key Driver	Cycle 3	Cycle 2	Cycle 3
Initiation of Self Care Assessment (SAFETY)	**Available Self Care Assessment Tools (SAFETY)**	**Plan-Summary**: Initiate SCA process 1 provider 3 clinics **Plan-Prediction**: Assessments completed **Study-Results:** inconsistent introduction, loss of forms **Act: ADAPT-** new location for forms	**Plan-Summary**: Initiate process for all providers at main clinic for 1 week **Plan-Prediction**: Assessments will be completed at not lost **Study-Results:** Unidentified patient completed assessment forms **Act: ADAPT –** all forms will have identified patient registration sticker	**Plan-Summary**: Administer assessment to all patients identified **Plan-Prediction**: Administer SCA to all eligible patients **Study-Results:** Assessments completed by identified patients **Act: ADOPT-** to include new age ranges 13yo through 18yo – AIM was amended
Rationale and Value Incentive for Patient	**Identified Educational Needs**	**Plan-Summary**: Introduction of SCA to patient/family **Plan-Prediction**: Receptive **Study-Results:** SCA was perceived as testing to patient **Act: ADAPT-** Revised Language to be "seeking needs"	**Plan-Summary**: Introduce benefit of SCA to patient **Plan-Prediction**: Receptive family/wary adolescent **Study-Results:** Patient still worried about answers **Act: ADAPT-** Warm hand off when explaining benefits	**Plan-Summary**: SCA introduction with identified benefits **Plan-Prediction**: Patient and family receptive **Study-Results:** Patient and family receptive **Act: ADOPT**

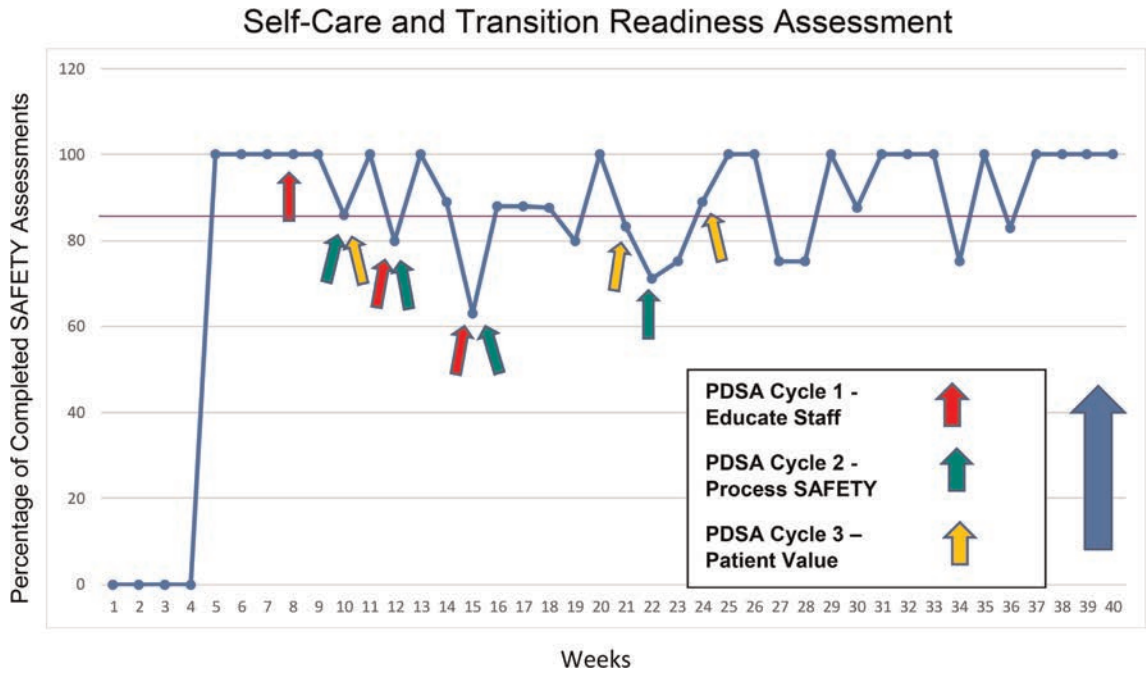


FIGURE 1. Abstract 64

assessment so patients felt more comfortable participating. (Table 1)The outcome measure, percentage of completed self-care assessment tool (SAFETY) was calculated based on the number of adolescent epilepsy patients who kept their appointment in the Neurology clinic and completed the survey. Evaluation of the outcome measure was displayed via an annotated run chart. (Figure1)

Results: The number of self-care assessments completed increased from 0% to above 85% from November 2020 through July 2020 (170 completed assessments out of 193 possible opportunities). Barriers included assessment in cognitively delayed patients, missed appointments and language barriers. The process was firmly adopted in the department continues to be in place two years later. Patients were willing to complete the assessment when the intent and benefit were explained.

Conclusions: Self-care evaluation and transition readiness can be easily assessed and measured in adolescents with epilepsy and facilitates the implementation of additional interventions that address education and transition of our epilepsy patients. Based on these evaluations, we initiated a self-care and transition readiness education plan.

Keywords: Epilepsy/Sleep, Education

65. Optimal duration for recording pediatric EEG: an observational study

Wander A (New Delhi, India), Chakrabarty B, Gulati S, Jauhari P, Pandey R, Upadhyay A, Yadav S, Kumar S

Objective: To evaluate optimal duration for recording pediatric EEG in outpatient settings for children and adolescents aged 1month-18years.

Methods: Setting: Outpatient EEG Laboratory at Department of Pediatrics at a tertiary care teaching centre in north India.Exclusion criteria: Epileptic encephalopathy, non-epileptic indications, seizures within last 24 hours and critical sicknessTwo categories of protocols- *Category A (awake record with activation procedures followed by sleep, 60 minutes)- Category B (55 minutes sleep followed by 5 minutes awake, younger children and those with impaired cognition who cannot undergo detailed awake study)* Prospective EEG reporting at 20, 30, 40, 50 and 60minute time-points with no retrospective changes allowed at previous time-points.

Results: *Population*: 225 cases (category A, n=163, 140.6+/-38.7 months and B, n=62, 90.1+/-48.5 months) with 65% males.*Indications*: Tapering antiseizure medications (54.2%), Diagnostic (35.1%) and breakthrough seizures (10.7%).*Diagnosis within 20 minutes- Indication-wise* (Category A, B): Tapering (85.3%, 77.8%), Diagnostic (68.4%, 95.5%) and Breakthrough seizures (72.7 %, 76.9%)- *Diagnosis-wise* (Category A, B): Generalised nonstructural (90.9%, 100%), generalised structural (100% in both), focal non-structural (71%, 85.7%), and focal structural (77.5%, 66.7%) epilepsy-*Abnormal awake records with and without sleep in category A*: With sleep (55%), only awake (81%) (p=0.03)

Conclusions: Considerable number of EEGs can achieve correct diagnosis within 20 minutes. Recording beyond 20 minutes with sleep is particularly beneficial in newly diagnosed epilepsies, more so for focal epilepsies. If awake

Table 1: Category A detailed data (Awake with activation procedures followed by sleep). Abstract 65

	Within 20 minutes	Beyond 20 minutes	p value
Indication			
Tapering	81	14	0.04
Diagnosis of new onset seizure	39	18	
Breakthrough seizures	8	3	
Final Diagnosis			
NGE	40	4	0.06
SGE	4	0	
NFE	44	18	
SFE	38	11	
With versus without sleep in abnormal records			
Awake only	17	4	0.03
Awake with sleep	38	31	

(NGE: Non-structural generalised epilepsy, SGE: Structural generalised epilepsy, NFE: Non-structural focal epilepsy, SFE: Structural focal epilepsy)

Table 2: Category B detailed data (Sleep only). Abstract 65

	Within 20 minutes	Beyond 20 minutes	p value
Indication			
Tapering	21	6	0.1
Diagnosis of new onset seizure	21	1	
Breakthrough seizures	10	3	
Final diagnosis			
NGE	9	0	0.05
SGE	10	0	
NFE	18	3	
SFE	14	7	

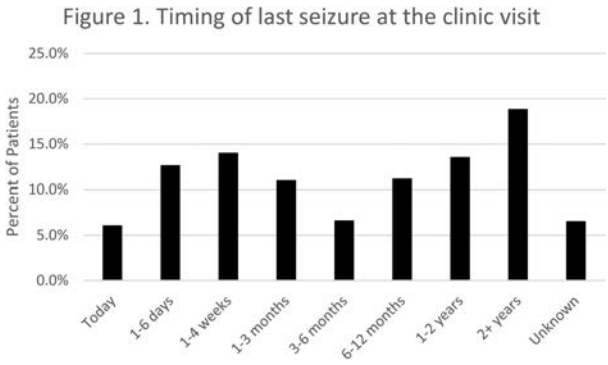
(NGE: Non-structural generalised epilepsy, SGE: Structural generalised epilepsy, NFE: Non-structural focal epilepsy, SFE: Structural focal epilepsy)

recording is extended beyond 20 minutes, inclusion of sleep improves yield of the EEG record.
Keywords: Epilepsy/Sleep

66. Quality Improvement in Epilepsy Care: Characterization of the Population in a Mixed Rural and Small Urban Setting

Trescher W (Hershey, PA), Paudel S, Naik S, Byrnes C, Kandel P, Tariq S, Donahue M, Farrell K, Fureman B, Buchhalter J, Moura L

Objective: National guidelines endorse standardized documentation of seizure frequency and type as quality measures for epilepsy care. Challenges persist in measuring outcomes in clinical practice due to variability of practitioner documentation and capturing results of an entire practice. Clinical practice characteristics need to be defined and outcomes measured uniformly to improve outcomes. The goal of this study was to use a low-cost paper form to collect epilepsy outcomes data in a clinical practice to characterize the clinical population broadly.
Methods: With the Epilepsy Learning Healthcare System (ELHS), we developed a standardized Epilepsy Health Assessment (EHA) form completed by patients and parents/caregivers at each visit and a corresponding Epilepsy Outcomes (EO) form completed by the clinicians providing care for patients with epilepsy. Patients' demographic data were obtained from the Cerner-based EMR. The demographic data and the EHA and EO data from July 2020 to March 2021 were entered into an IRB-approved REDCap database.
Results: The population consisted of 66% white, 7.6% Black, 1.8% Asian, and 24.6% other/unknown, with 19.6% Hispanic, 77.4% Non-Hispanic, and 3% not reported. The clinicians characterized the seizures as Generalized in 41.5%, Focal in 48.7% of patients, and other/unknown in 9.9%. Outcomes were measured by the timing of the seizures (Figure 1) and frequency of the seizures (Figure 2). Eight anti-seizure medications accounted for 83% of medications prescribed. Other measures: side effects, emergency interventions, medication adherence.
Conclusions: This work represents an important step to understanding the outcomes of epilepsy care in a clinical setting and may help guide formatting an EMR.
Keywords: Epilepsy/Sleep



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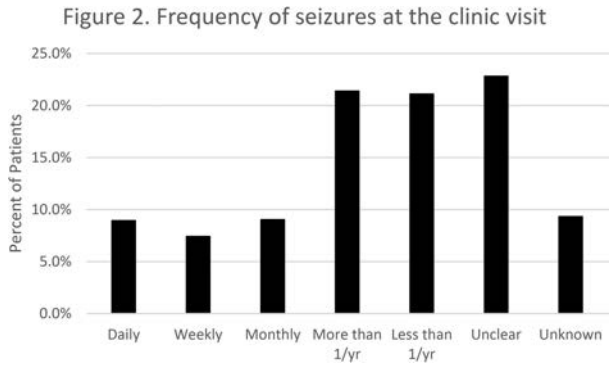

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67. Beyond stopping the 'Fits' ! – Developing and Delivering an Epilepsy Awareness Training

Ohiaeri C (Abuja, Nigeria), Takon I

Objective: To improve Epilepsy awareness and emergency response during a seizure in Health workers, teachers, and parents in Northern Nigeria.
Methods: Epilepsy awareness workshop was conducted to explore the knowledge of attendees and deliver training on epilepsy and improve participants' awareness on epilepsy and improve ability of the participants to give first aid to a child having seizures. Pre-workshop questionnaires were administered to explore the attitudes and knowledge of attendees. Face to face trainings using video's and didactic lectures covering causes, presentation, management of epilepsy and resources available for parents and professionals were covered in the presentation. Post workshop questionnaire evaluation was also administered to the attendees.
Results: 30% of participants felt epilepsy was contagious and most participants(80%) felt lack of awareness, superstitious beliefs, myths, and misconceptions contributed to the stigmatisation seen in children with epilepsy. Above 90% of the participants did not know what first aid to give to children having seizures however most of the participants agreed that the hospital was the best place for managing children with epilepsy. The post-workshop evaluation showed improved knowledge amongst the attendees with all attendees rating the workshop as very good to excellent.
Conclusions: Epilepsy awareness training is an effective way of reducing morbidity and mortality in children with epilepsy. Training health workers, teachers, and parents should be expanded nationally as part of the improvement in services for children with epilepsy.
Keywords: Epilepsy/Sleep, Education

68. Utilization of point of care data entry to provide information regarding rare epilepsy syndromes

Scantlebury M (Calgary, AB, Canada), Buchhalter J, D'Alfonso S, Appendino J, Ho A, Jacobs J

Objective: To demonstrate that data entry into the electronic health record at the point of care for use as a registry is feasible.
Methods: Standardized data elements from 1/1/2016 to 3/18/2022 included in a pediatric epilepsy note (Sunrise

Clinical Manager) at the Alberta Children's Hospital were exported into a data analysis and display platform (Tableau). The data was filtered for Continuous Spike Wave of Sleep (CSWS), Dravet Syndrome (DS) and Lennox Gastaut Syndrome (LGS). Patient numbers for Age at Onset, Seizure Frequency Score (SFS; 0=seizure free, no medications, 1=seizure free on medications, 2=1-3 seizures/year, 3=2-11 seizures/year, 4=1-3 seizures/month, 5=1-6 seizures/week, 6=1-3 seizures/day, 7=4-10 seizures/day, 8>10 seizures/day) and most used (non-rescue) medications are presented.

Results: The database contains 3913 patients comprising 6061 events. 1418 patients had multiple seizure types.CSWS: N=22.Age at onset: 1y<5 y (N= 9), 5y<10y (N=9), 10y<18y (N=3), not specified (N=2). SFS: 0(N=4), 1(N=14), 2 (N=2), 4(N=1), 5(N=1), not specified (N=11). Medications: ethosuximide (N=8), clobazam (N=5), levetiracetam (N=4).DS: N=20.Age at onset- 0-1mo (N=1), 1m<1y (N=12), 1y<5y (N=9), not specified (N=7); SFS: 1(N=1), 2 (N=2), 3(N=4,), 4(N=5), 5(N=5), 6(N=2), 7(N=2). Medications: stiripentol (N=13), clobazam (N=13), valproate (N=7), levetiracetam (N=5).LGS: N=29. Age at onset: 0-1m (N=2), 1m<1y (N=4), 1y<5 y (N=10), 5y<10y (N=4), 10y<18y (N=5). SFS: 1(N=18), 2(N=3), 4(N=3), 5(N=6), 6(N=4), 7(N=5), 8(N=5), not specified (N=2). Medications: lamotrigine (N=12), clobazam (N=7), valproate (N=6), levetiracetam (N=6).

Conclusions: It is possible to record clinically useful information at the point of care without double entry into another platform for analysis.

Keywords: Epilepsy/Sleep, Rare Diseases

69. Challenges of determination in date of onset of infantile spasms: A tertiary health center's experience

Hadjinicolaou A (Boston, MA), Briscoe Abath C, Singh A, Donatelli S, Yuskaitis C, Harini C

Objective: Swift initiation of first-line treatment of infantile spasms (IS), is essential and as little as 1 week treatment delay can affect developmental outcomes. Knowing this, we aimed to compare patients where date of IS onset (DOS) is clearly determined or estimated within 1 week of onset to those in whom DOS could not be estimated to within 1 week. We also set out to examine the reasons for the inability to identify DOS to the nearest week.

Methods: Authors conducted a retrospective chart review of all children with initial diagnosis of IS at a single tertiary care center between 2019-2022. Four independent reviewers collected information regarding DOS to verify accuracy. Two reviewers collected and cross-verified other data points.

Results: DOS could be determined accurately or estimated to the nearest week in 50% (49/98), and DOS was within one month in 78% (77/98). Parental (21/49), physician (14/49), and patient-related (24/49), factors contributed to the difficulties in estimating the DOS to the nearest week and in 12/49 (24%) multiple factors were at play. Lack of adequate documentation contributed to the difficulty in 10% (5/49).

Conclusions: In nearly half of new onset IS cases, DOS determination to the nearest week was not possible. While physician and parent related factors are modifiable to a certain extent, patient factors are challenging to modify despite evaluation at a tertiary care center. We propose interventions that could lead to improvement in DOS determination and thereby delays to treatment, ultimately promoting optimal developmental outcomes.

Keywords: Epilepsy/Sleep

70. Interhemispheric dysynchronization by deep brain stimulation rapidly improves seizure control in Lennox Gastaut Syndrome: a proof of concept case

Marks W (Fort Worth, TX), Keator C, Shahani D, Song Y, Papadelis C, Honeycutt J

Objective: Generalized epilepsy may result from hypersynchronization of interhemispheric neuronal activity. The centromedian nucleus (CMN) and subthalamic nucleus (STN) may serve as propagators of synchronization. Corpus callosotomy results in rapid desynchronization in epileptiform discharges. CMN and STN have demonstrated reduction of seizures in Lennox-Gastaut Syndrome (LGS).We believe that a similar effect can be induced by dys-synchronous stimulation (DSS) of the CMN or STN by DBS.

Methods: A patient with refractory LGS underwent stereotactic EEG monitoring and electrical stimulation with depth electrodes in the CMN and STN. EEG and evoked potential propagation were monitored.

Results: In the 24 months prior to DBS, the patient had 28 hospitalizations for seizure management. During sEEG evaluation synchronous stimulation (SS) at 125 and 185 Hz or dyssynchronous (DSS) at125 Hz/185 Hz of STN and CMN were undertaken. Improved alertness and better speech and motor control were seen with dyssynchronous CMN stimulation. Subsequent placement of permanent leads followed by periods of synchronous and disynchronous stimulation followed. Seizure control was modestly improved with synchronous stimulation, but there were 4 more rescue hospitalizations over 3 months. Change to DSS resulted in dramatic improvement in seizure control, with no hospitalization for seizures in 7 months. Cognition has dramatically improved, gaining nearly two years of academic skills.

Conclusions: Dysynchronous stimulation of the CMN may produce rapid and seemingly sustained seizure reduction in Lennox Gastaut Syndrome. Cognition may also be improved. This may offer a lower morbidity option than corpus callosotomy. Further studies are needed to validate this proof of concept.

Keywords: Epilepsy/Sleep, Translational/Experimental Therapeutics, Movement Disorders (including Cerebral Palsy)

71. Efficacy and safety of perampanel in pediatric patients aged 2–<12 years with seizures associated with Lennox-Gastaut Syndrome

Porter B (Palo Alto, CA), Kira R, Lee J, Aeby A, Patten A, Ngo L

Objective: Lennox-Gastaut Syndrome (LGS) is a severe refractory childhood-onset epilepsy, characterized by various

Table 1. Baseline patient demographics and clinical characteristics (Safety Analysis Set). Abstract 71

	Children (2–<12 years) (n=35)	
	Perampanel (n=16)	Placebo (n=19)
Mean (SD) age, years	6.2 (2.8)	7.2 (2.7)
Female, n (%)	8 (50.0)	8 (42.1)
Mean (SD) weight, kg	21.5 (6.3)	22.7 (8.3)
Mean (SD) time since diagnosis, years[a]	3.4 (3.2)	5.4 (3.1)
Most common seizure types (history) (≥5 patients in any group), n (%)		
Tonic-atonic	15 (93.8)	19 (100)
Atypical absence	8 (50.0)	6 (31.6)
Myoclonic without fall	9 (56.3)	8 (42.1)
Myoclonic with fall	6 (37.5)	5 (26.3)
Focal onset	7 (43.8)	3 (15.8)
Generalized tonic-clonic	5 (31.3)	3 (15.8)

[a]Time from diagnosis to date of informed consent
SD, standard deviation

seizure types, including drop seizures. We report the results of a subgroup analysis in children (aged 2–<12 years) in a Phase III study (Study 338; NCT02834793) that evaluated the efficacy and safety of adjunctive perampanel in patients aged ≥2 years with inadequately controlled seizures with LGS.

Methods: Study 338 consisted of a randomized, double-blind, placebo-controlled Core Study, followed by an open-label Extension Phase. The Core Study comprised 4–8-week Screening/Baseline and 18-week Treatment (6-week Titration; 12-week Maintenance) Periods. Perampanel was initiated at 2 mg/day; up-titrated to ≤8 mg/day based on tolerability/efficacy. The primary endpoint was median percent change in drop seizure frequency/28 days during the Treatment Period (drop seizures included atonic, tonic, or myoclonic seizures with fall or those that could have led to a fall). Secondary endpoints included other efficacy outcomes and safety of perampanel.

Results: The Safety Analysis Set included 35 patients aged 2–<12 years (Table 1). The median percent reduction in drop seizure frequency/28 days from baseline for perampanel vs placebo was 54.3% vs 8.0%, and for total seizures was 27.1% vs 5.2%. The 50% responder rate for drop seizures for perampanel vs placebo was 56.3% vs 31.6%, and for total

Table 2. Overview of TEAEs, most common TEAEs, and perampanel exposure and dosage (Safety Analysis Set). Abstract 71

	Children (2–<12 years) (n=35)	
	Perampanel (n=16)	Placebo (n=19)
All TEAEs, n (%)	13 (81.3)	16 (84.2)
Treatment-related TEAEs,[a] **n (%)**	8 (50.0)	4 (21.1)
Serious TEAEs, n (%)	3 (18.8)	1 (5.3)
Deaths[b]	0 (0.0)	0 (0.0)
TEAEs leading to dose adjustment, n (%)	9 (56.3)	3 (15.8)
TEAEs leading to drug withdrawal	0 (0.0)	0 (0.0)
TEAEs leading to dose increase	1 (6.3)	0 (0.0)
TEAEs leading to dose reduction	8 (50.0)	3 (15.8)
TEAEs leading to dose interruption	0 (0.0)	0 (0.0)
Most common TEAEs (≥2 patients in either group)[c]**, n (%)**		
Upper respiratory tract infection	4 (25.0)	0 (0.0)
Gait disturbance	3 (18.8)	0 (0.0)
Nasopharyngitis	2 (12.5)	2 (10.5)
Somnolence	2 (12.5)	2 (10.5)
Lethargy	2 (12.5)	0 (0.0)
Drooling	2 (12.5)	1 (5.3)
Decreased appetite	2 (12.5)	0 (0.0)
Fatigue	2 (12.5)	0 (0.0)
Hordeolum	2 (12.5)	0 (0.0)
Mean (SD) duration of exposure[d]**, weeks**	18.2 (0.7)	17.3 (2.4)
Mean (SD) modal perampanel dose, mg/day	6.4 (2.0)	–

[a]Includes TEAEs considered by the physician to be related to perampanel or TEAEs with missing causality
[b]Includes all patients with serious AE resulting in death
[c]Only TEAEs with greater incidence in the perampanel group than the placebo group are included
[d]Duration of exposure = (date of last dose of study drug – date of first dose of study drug) + 1
AE, adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event

seizures was 37.5% vs 26.3%. Table 2 summarizes treatment-emergent adverse events, and perampanel exposure and dosage.

Conclusions: Adjunctive perampanel reduced drop- and total-seizure frequency in patients aged 2–<12 years with LGS, and may be beneficial in controlling seizures associated with LGS in children.

Keywords: Epilepsy/Sleep

72. EEG Findings Enhance the Yield of Epilepsy Gene Panel Testing in Children

Nordli III D (Jacksonville, FL), Nordli Jr. D, Sheth R

Objective: Epilepsies with encephalopathy are important to promptly and thoroughly evaluate because of their associated refractory nature and potential for neurologic regression. Genetic causes are increasingly recognized and the presence of certain clinical features such as early age of presentation, developmental delay and normal brain imaging are known to increase the yield of genetic testing, but the role of EEG has not been well studied. We sought to determine the association between EEG findings and informative epilepsy gene panel results in children.

Abstract 72

Category	Name	Spikes	Background
1	Familial Epilepsies	None	Normal
2	Genetic Generalized Epilepsy	Stereotyped and generalized	Normal
3	Self Limited Epilepsy	Focal or multifocal and sterotyped	Normal
4a	Epileptogenic Encephalopathy	Multifocal and pleomorphic	Slowed
4b	Epileptic Encephalopathy	Multifocal and pleomorphic	Slowed, disorganized and discontinuous
5	Focal	Focal pleomorphic	Focal slowing/ attenuation

EEG Category	+ Gene Panel	- Gene Panel	% Yield
4a	12	3	80%
All Others	31	63	33%
Totals	43	66	

Methods: The results of epilepsy gene panel testing were obtained for 109 pediatric patients at Nemours Children's Center in Jacksonville, Florida from 04/2019-02/2021. Results were obtained from *Invitae*^{TM} via the offered *epilepsy gene panel* test and the *Behind the Seizure* program. The EEGs for each patient were independently analyzed and categorized based on the presence or absence of features consistent with an epileptogenic encephalopathy as outlined below. Gene panel results for each patient were reviewed and were deemed positive if a clinically relevant pathogenic variant was present or if a variant of undetermined significance was identified and determined to be responsible for patients clinical picture.

Results: Fisher exact test and percent yield of gene panel: See Figure 1p= 0.0006963

Conclusions: The presence of certain EEG features are associated with a meaningful result obtained from epilepsy gene panel testing. EEG characterization can be incorporated into the evaluation of patients with epilepsy in order to optimize the selection of patients who are likely to benefit from an epilepsy gene panel test.

Keywords: Epilepsy/Sleep

73. Pediatric Epilepsy Gene Panel Results and Long-Term Seizure-Free Status

Bonkowsky J (Salt Lake City, UT), Russell K, Wilkes J, Tidwell T, Porter C, Olsen J, Sweney M

Objective: To determine whether results from epilepsy genetic testing panels correlate with seizure freedom or intractability.

Methods: Prospective and retrospective epilepsy cohorts were evaluated. In the prospective cohort, genetic epilepsy panel testing was performed on patients with over 10 years of follow-up in whom their epilepsy status was known (seizure free or treatment failure). In the retrospective cohort, genetic epilepsy panel results were evaluated in a cohort of patients previously seen and evaluated, and in whom epilepsy outcomes were evaluated by chart review.

Results: Prospectively, 22 patients with over 10 years of follow-up had genetic panel testing performed: 11 seizure-free and 11 treatment failure. Average CADD scores (higher CADD score indicates greater pathogenicity) of variants were similar (22 versus 23, seizure free versus treatment failure); and number of variants identified was lower in treatment failure (15 versus 9). Retrospectively, in 80 patients previously tested, there was no significant statistical correlation with seizure freedom status, using CADD, REVEL, or pathogenicity call by the commercial testing company.

Conclusions: We found that results from epilepsy genetic panel testing do not correlate with long-term seizure outcomes in children. Continued work is needed to delineate the utility of genetic testing in epilepsy; for example, whether it is indicated for certain types of epilepsy; using cost/benefit analyses to understand overall utility of testing; and how epilepsy test result translates into a clinical change that impacts long-term seizure freedom.

Keywords: Epilepsy/Sleep, Genetics

74. Annual/Seasonal Patterns and Somatic Comorbidities of Non-Epileptic Events (NEE) in Pediatric Populations

Stephens T (Cleveland, OH), Zhou Q, Mudd E, Falcone T, Thompson N, Pestana-Knight E

Objective: Non-epileptic events (NEE) are paroxysmal and not correlated with underlying electrical discharges in the brain, which are an associated feature of Functional Neurological Disorder (FND). FND occurs across the lifespan, including children. Objectives include: examining features/patterns of pediatric FND, including seasonal variations, hospital admission patterns, and comorbidities to gain better insight into the unique factors of pediatric FND.

Methods: Retrospective chart review for pediatric patients (8-18yo) admitted to the epilepsy monitoring unit with the presence of psychogenic paroxysmal events. Descriptive, between-group differences, and interaction effect statistics were conducted.

Results: Across 5 years, 322 patients had 325 admissions and 72.0% (n=232) experienced an NEE. Patients who experienced NEE were more likely to be an adolescent and had a higher number of psychiatric disorders. The mean number of admissions ranged from 3.4 (SD=1.0) in July to 7.4 (SD=3.4) in January. The first quarter had the largest mean and median number of admissions, followed by the 4th, 2nd, and 3rd quarters. The interaction between developmental stage and severity of functional impairment was statistically significant (omnibus p-value = 0.022). The effect of functional impairment was greater in children than adolescents, such that children with moderate-severe functional impairment had greater hazard of NEE, compared to children with mild functional impairment.

Conclusions: There are unique features and developmental considerations when working with pediatric NEE/FND, which impact both the patient and provider experiences. Future directions will examine cohort effects (e.g., pre- vs. post-pandemic) and associated factors.

Keywords: Epilepsy/Sleep, Cognitive/Behavioral Disorders (including Autism)

75. Effectiveness, Safety and Tolerability of Perampanel in Pediatric and Adolescent Patients with Focal-Onset and Generalized-Onset Seizures: Evidence from Clinical Practice

Auvin S (Paris, France), Garcia-Ron A, Gil-López F, Shankar R, Yamamoto T, Ngo L, Villanueva V

Objective: To assess the effectiveness, safety and tolerability of perampanel (PER) when used to treat pediatric and adolescent patients in everyday clinical practice.

Methods: Pediatric (<12 years) and adolescent (12–16 years) patients treated with PER for focal-onset or generalized-onset seizures were identified from PERMIT, a pooled analysis of 44 clinical practice studies/work groups. Retention was assessed after 3, 6 and 12 months of PER treatment, and effectiveness was assessed at the last visit (last observation carried forward). Effectiveness assessments included responder rate (≥50% seizure frequency reduction) and seizure freedom rate (no seizures since at least the prior visit). Safety and tolerability were assessed by evaluating adverse events (AEs), psychiatric AEs, and AEs leading to discontinuation.

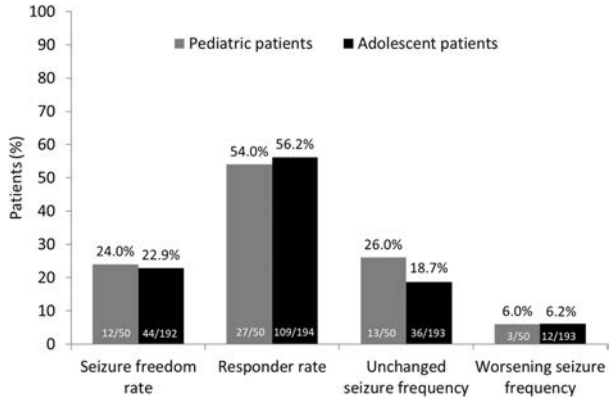


Figure. Summary of effectiveness at the last visit in pediatric and adolescent patients. Response was defined as ≥50% seizure frequency reduction from baseline. Seizure freedom was defined as no seizures since at least the prior visit. Abstract 75

Results: Sixty-four pediatric and 204 adolescent patients were identified. Retention rates at 3, 6 and 12 months were, respectively, 89.6%, 77.8% and 58.8% in pediatric patients, and 90.2%, 81.8% and 60.3% in adolescents. At the last visit, seizure freedom and responder rates were 24.0% and 54.0%, respectively, in pediatric patients, and 22.9% and 56.2%, respectively, in adolescent patients (Figure). AEs were reported for 34.5% of pediatric patients and 42.8% of adolescent patients (Table). Overall, 8.8% of pediatric patients and 15.2% of adolescent patients discontinued due to AEs over 12 months. Psychiatric AEs were reported for 21.8% of pediatric patients and 20.5% of adolescent patients.

Conclusions: PER was effective and generally well tolerated when used to treat pediatric and adolescent patients with focal-onset and generalized-onset seizures under everyday clinical practice conditions.Supported by Eisai

Keywords: Epilepsy/Sleep

Table. Summary of safety and tolerability in pediatric and adolescent patients. Abstract 75

Total patients	Pediatric patients N=55	Adolescent patients N=187
Patients with any AE, n (%)	19 (34.5)	80 (42.8)
Patients with AEs leading to discontinuation, n (%)	3 (8.8)[a]	23 (15.2)[b]
Patients with any psychiatric AE, n (%)	12 (21.8)[c]	38 (20.5)[c]

[a]N=34; [b]N=151; [c]N=185. AE, adverse event

76. Tethered, Online Education Improves Awareness of the Place in Care of New Treatments and Helps Align Patient/Caregiver and Clinician Treatment Goals in Developmental and Epileptic Encephalopathies

Drexel C (Needham, MA), Bixler E, Meskis MA, Jaksha A, Conecker G, Dixon-Salazar T, Kowalski K, Sullivan J

Objective: An emerging concept in developmental and epileptic encephalopathies (DEEs) management is to account for seizure and non-seizure impacts of medication, such as social or functional benefits, in making treatment decisions. We evaluated the impact of aligned, online continuing medical education on healthcare providers' (HCPs') ability to diagnose and treat DEEs and caregivers' ability to engage in care.

Methods: A 5-part HCP and 3-part caregiver series on symptoms, treatments, team-based care, and supportive tools for DEE launched live-online between June 2021 and January 2022; each activity will remain online for one year. Test questions were administered pre, immediate post, and 2 months post activity. Responses were analyzed to determine lessons learned and continuing gaps. Chi-square tests compared pre and post responses ($P<0.05$).

Results: As of March 2022, 1,385 HCPs and 1,238 caregivers participated in at least one activity. Significant increases occurred related to HCPs' awareness of the genetics of DS (+53%, P<0.05), impacts of treatment on seizure and non-seizure outcomes (+70%, P<0.05), and on caregivers' QoL (+70%, P<0.05). HCPs (92%) reported benefits on practice and patient experience (312 write-ins examples). Caregivers reported improved communication with HCPs (61%) and improved ability to control healthcare decisions (100 write-ins examples).

Conclusions: Live-online education for both HCPs and caregivers improves adoption of new treatments for DS and enhances caregivers' engagement in care. Baseline scores highlight the need for ongoing education on the evolving treatment landscape for DEE to build upon acquired knowledge and improve shared decision-making.

Keywords: Epilepsy/Sleep, Education, Rare Diseases

77. Polysomnographic parameters and comparison of academic performance in those with and without sleep disorders, an observational study

Chakrabarty B (New Delhi, India), Zulfiqar L, Gulati S, Jauhari P, Pandey R, Upadhyay A

Objective: To compare in children and adolescents aged 2-18 years- Polysomnographic findings between those with and without sleep disorders- Academic performance in those with and without sleep disorders

Methods: The study was conducted in a tertiary-care teaching hospital in north India. The study population comprised of children and adolescents- attending a public school,- visiting the studyhospital with minor ailments or with Duchenne muscular dystrophy (DMD), spinal muscular atrophy (SMA), asthma and cerebral palsy (CP).They all underwent clinical evaluation and overnight polysomnography (PSG) as part of the CASEQ (Childhood and Adolescent Sleep Evaluation Questionnaire) development and validation study.[1]

Table 1: Distribution of polysomnographic parameters in normal and diseased population. Abstract 77

PSG parameters	Normal	SRBD	SRMD	p value
Sleep efficiency	80.6%	75.5%	81.5%	0.06
AHI	2.2	4.8	1.4	0.0001
AI	5.2	6.8	5.4	0.1

(SRBD: Sleep related breathing disorder, SRMD: Sleep related movement disorder, AHI: Apnea Hypopnea Index, AI: Arousal index)

Table 2: Distribution of academic performance in normal and diseased population. Abstract 77

Academic performance	Normal	SRBD	SRMD	p value
Poor	10%	26.8%	42.1%	0.004
Average	35%	58.9%	36.8%	
Good	55%	14.3%	21.1%	

(SRBD: Sleep related breathing disorder, SRMD: Sleep related movement disorder)

Results: Overall, 100 subjects (minor ailments:77, asthma:12, school:7, CP:2, DMD:2) were evaluated (mean age: 9+/-2 years, 74% males). The final diagnoses were sleep related breathing disorder (SRBD, 56), sleep related movement disorder (SRMD, 19), normal (20) and others (5). Apnea-hypopnea index (AHI) was significantly higher in SRBD (4.8,3.3-10.6) compared to SRMD (1.2,0.8-1.8) and normal (2.2,1.4-3.7) cases (p=0.001). Significant positive correlation (r^2=0.2) was seen for AHI and periodic limb movement index with arousal index (p=0.01 and 0.05). Good academic performers were significantly more prevalent in normal (55%) compared to SRBD (14.3%) and SRMD (21.1%) cases (p=0.004).

Conclusions: Clinical evaluation and PSG play complimentary role in diagnosis of sleep disorders, as isolated PSG may have limitations related to first night effect. Those with common sleep disorders like SRMD and SRBD have significant academic impairment compared to normal children and adolescents

Keywords: Epilepsy/Sleep

Reference

1. Zulfiqar L, Chakrabarty B, Gulati S, Jauhari P, Pandey RM, Tripathi M, et al. The Childhood and Adolescent Sleep Evaluation Questionnaire (CASEQ): Development and validation of an ICSD-3-based screening instrument, a community and hospital-based study. J Sleep Res. 2022;31:e13479.

78. Unusual Presentation of Phosphatidylinositol glycan biosynthesis class A protein (PIGA) deficiency presenting as refractory pediatric epileptic encephalopathy; A mystery solved after 21 years

Sial GZ (Buffalo, NY), Mesha M, Lopez Weinstock A

Objective: To highlight the importance of comprehensive epilepsy panel for diagnosing PIGA related epilepsy. Inherited glycosylphosphatidylinositol (GPI) deficiency is caused by decreased presentation of GPI anchor proteins (GPI-AP). PIGA enzyme facilitates the synthesis of GPI-AP. PIGA deficiency, an X linked recessive disorder, is associated with multiple congenital anomalies. Neurological presentation consist of refractory seizures and intellectual disability.

Methods: We present a 21-year-old male with static encephalopathy and refractory epilepsy, in whom comprehensive epilepsy gene panel confirmed the diagnosis. Review of medical records, electroencephalograms, laboratory, imaging, and genetic testing was performed.

Results: Patient presented with refractory myoclonic epilepsy at age 6 months. There was milestone regression at age 2 years. Childhood evaluation revealed normal karyotype, Fragile X, serum and urine amino acids, urine organic acids, and serum lactate. Seizure semiology consisted of daily prolonged tonic, tonic-clonic and myoclonic seizures in clusters, requiring daily rescue therapy and frequent ER visits. He was on 5 anti-seizure drugs (ASD) and VNS, and had failed multiple ASD and the ketogenic diet. Video-EEG monitoring revealed continuous generalized slowing, multiregional sharp waves, generalized spike-wave complexes, polyspikes, paroxysmal fast activity and myoclonic seizures. MRI brain showed stable mild atrophy. Comprehensive epilepsy panel performed at age 21 revealed hemizygosity for PIGA, c.823C>T (p.Arg275Trp), a diagnostic pathogenic variant.

Conclusions: The diagnosis of PIGA related epilepsy can be challenging based on clinical grounds. A comprehensive gene panel should be considered in adult patients with idiopathic severe childhood epilepsy and intellectual disability.

Keywords: Epilepsy/Sleep, Neurometabolic Disorders

79. Seizure during hemodialysis in a pediatric patient with renal disease requires further neurological workup

Sandweiss A (Houston, TX), Pareek A, Moore M, Gill J

Objective: Seizures are reported as a common adverse event during hemodialysis, thought to occur in approximately 7-10% of all hemodialysis patients. Seizures occur due to an underlying epilepsy disorder or provoked by an external factor such as fluctuating ionic potentials. Though prior reports suggest most seizures are provoked in dialyzed patients, pediatric patients who have a seizure associated with dialysis require a complete neurological workup in order to rule out an underlying epilepsy disorder.

Methods: We present a pediatric patient with end-stage renal disease who had a seizure during his third hemodialysis session that uncovered a previously unknown epilepsy syndrome.

Results: An 8 year-old healthy male presented to the hospital with six weeks of malaise, ultimately found to have a new diagnosis of chronic kidney disease secondary to renal dysplasia. BUN and creatinine were 175 and 7.63 respectively with normal blood pressure. He was admitted and initiated on a hemodialysis regimen; he sustained a focal seizure lasting up to 5 minutes during his third hemodialysis session. Immediate workup included a normal CT head and stable serum electrolytes. Routine EEG revealed 3-4 Hz spike and wave activity potentiated by photic stimulation. History revealed no other red-flag signs for epilepsy, though he had a clear absence seizure during hyperventilation on the neurology exam. He was diagnosed with juvenile myoclonic epilepsy and started on valproic acid, achieving seizure freedom during subsequent hemodialysis four days later.

Conclusions: Seizures are not uncommon during hemodialysis, but all patients require a complete neurological evaluation to unmask a potential underlying epilepsy syndrome.

Keywords: Epilepsy/Sleep

80. Successful treatment of status epilepticus in a patient with a novel phenotype of an ATP1A2 missense mutation known to cause hemiplegic migraines

Trivedi A (San Diego, CA), Yang J, Ladt K, Rho J

Objective: The *ATP1A2* gene on chromosome 1 encodes the alpha-2 polypeptide subunit on the Na/K ATP-ase pump. Mutations in *ATP1A2* have been associated with familial hemiplegic migraine type II. However, the association between a particular mutation in this gene, and epilepsy is not well described and limited literature exists on the related clinical management.

Methods: A 12-year-old male with a history of seizures in infancy and a known hemiplegic migraine-associated *ATP1A2* mutation c.2563G>A , pGly.855Arg, was admitted for status migrainosus, prolonged dysarthria, left sided hemiparesis and sensory loss. His symptoms persisted despite intravenous verapamil, intranasal ketamine, and trials of acetazolamide, topiramate and valproic acid. He gradually improved after 6 days with return of left sided function and speech. However, 24 hours later, he developed epilepsia partialis continua consisting of leftward gaze-evoked nystagmus and clonic movements of the left face and arm. His seizures persisted despite lorazepam and increased valproic acid dosing.

Results: Seizures improved after starting lacosamide and initiating a ketogenic diet. At the last follow up three months after hospitalization, he remained seizure-free and his migraines had been successfully aborted with naproxen and additional lacosamide doses.

Conclusions: We present the case of focal-onset status epilepticus following an episode of hemiplegic migraine in a patient with an *ATP1A2* mutation, a genotype-phenotype correlation that has not been previously described. He was successfully treated with a combination of ketogenic diet and lacosamide, supporting the combined targeting of slow inactivation of voltage-gated sodium channels and altering the metabolic milieu as a therapeutic approach.

Keywords: Epilepsy/Sleep, Genetics, Headache/Migraine

81. Stiripentol for drug-resistant epilepsy treatment in tuberous sclerosis complex

Aungaroon G (Cincinnati, OH), Franz D, Mehta A

Objective: This study assesses the efficacy and tolerability of stiripentol (STP) in tuberous sclerosis complex (TSC) patients with drug-resistant epilepsy (DRE).

Methods: A retrospective review of TSC patients at Cincinnati Children's Hospital from 2011 until 2021 was performed to identify patients with DRE receiving STP. Seizure frequency was assessed 1 month before (baseline) and 1, 3, 6, and 12 months after STP initiation.

Results: Of the 1492 TSC patients, 13 (10 males) received STP. The age range was 3.8 to 40 years (median, IQR = 15.2 years, 6.7 - 22.0). STP was initiated a median of 13.5 years (IQR 5.0 - 20.3) after seizure onset. The median treatment duration was 12.8 months, and a median STP dose was 21.1 mg/kg/day (IQR 12.8 - 34.1). The number of patients with > 50% seizure reduction was 6/13 (46.2%), 4/13 (30.8%), 8/11 (72.7%), and 6/8 (75.0%) at 1, 3, 6, and 12 months. Importantly, 6 patients (46.2%) had persistent seizure reduction from 1 through 12 months, with the mean (±SD) percentage of reduction at 1, 3, 6, and 12 months of 68.1% (±22.0), 71.3% (±23.2), 75.7% (±23.5), and 75.7% (±23.5), respectively. 11/13 patients reported side effects with aggression being the most common and 3 patients discontinued STP due to side effects.

Conclusions: Most TSC patients with DRE treated with STP experienced seizure reduction, with about half having a persistent seizure reduction. This suggests that STP could be an efficacious and tolerable treatment option for this population.

Keywords: Epilepsy/Sleep, Neurocutaneous Disorders, Genetics

82. Higher beta-hydroxybutyrate levels result in decreased neutrophils in children with epilepsy on the ketogenic diet

Gombolay G (Atlanta, GA), Elkins K, Lu S, Holt P, Johnson M, Gedela S

Objective: The ketogenic diet (KD) produces beta-hydroxybutyrate (BHB) which decreases neutrophils in adults but limited studies are available in children. BHB may decrease inflammation by decreasing neutrophils. We compare the relationship of BHB with neutrophils in children with epilepsy on the ketogenic diet.

Methods: IRB approval was obtained. Children at a single KD clinic from 2010-2021 were included. Data collected included age when seizures started, age when KD started, sex, white blood cell count (WBC), and absolute neutrophil counts (ANC). ANC was excluded if obtained in the setting of infection or medications such as steroids. Low normal BHB was defined as BHB < 4 mmol/L and high normal BHB was defined as BHB ≥ 4 mmol/L. Statistical analysis was performed using SAS 16.0 (Cary, N.C.).

Results: Forty-one patients were included and divided into low BHB (N=20) and high BHB (N=21).One-tailed two sample t test to predict whether high BHB results in lower ANC demonstrated that patients with BHB ≥ 4 had on average 34.6% neutrophils (95% 29.3-39.8%) as compared to 41.8% (95% CI 34.9 – 48.6) in BHB < 4 (p = 0.043). However, multivariate logistic regression modeling showed that BHB levels and ANC did not correlate with probability of improvement in seizures at 12 months.

Conclusions: Higher BHB levels are associated with lower ANC in children on KD. Further investigation is needed in larger studies to investigate the effect of BHB on ANC in children.

Keywords: Epilepsy/Sleep

Table 1: Patient characteristics between low normal and high normal BHB levels. Abstract 82

	BHB < 4 N=20	BHB ≥ 4 N=21	p-value
Sex M:F, N (%)	13:7 (65:35)	13:8 (62:38)	1.000
Age started diet, y Mean (SD)	5.1 (4.7)	3.4 (2.5)	0.145
Age seizure started, y Mean (SD)	0.8 (1.2)	1.2 (1.6)	0.347
Number of seizures per week prior to starting KD Mean (SD)	165.9 (235.7)	143.3 (160.7)	0.720
Number of seizures per week at 12 mo, mean (SD)	16.9 (23.3)	31.2 (46.8)	0.213
Type of seizure N (%)			
GTC	3 (15)	3 (14)	1.000
Focal seizures	6 (30)	6 (29)	0.920
Absence	3 (15)	1 (5)	0.343
IS	8 (40)	10 (48)	0.623
Myoclonic seizure	8 (40)	5 (24)	0.266
Drop	2 (10)	6 (29)	0.238
Tonic	10 (50)	4 (19)	**0.039**
ESES	1 (5)	0 (0)	0.488
WBC, 10^6/ml, mean (SD)	7.6 (3.6)	6.8 (2.6)	0.461
Neutrophil %, mean (SD)	41.8 (14.6)	34.6 (11.5)	**0.043**
Lymphocyte %, mean (SD)	47.4 (14.1)	53.8 (11.3)	0.057

83. Cognitive and Behavioral Effects and Tolerability of Adjunctive Brivaracetam in Children and Adolescents with Focal Seizures: Pooled Interim Analysis

Little A (Smyrna, GA), Elshoff J-P, Fleyshman S, De La Loge C, Nondonfaz X, Reichel C, Floricel F, Smeyers P

Objective: Evaluate cognitive/behavioral effects and tolerability of long-term adjunctive brivaracetam in children/adolescents with focal seizures.

Methods: Interim post-hoc analysis (cut-off 14-Jul-2020) of pooled data from Phase IIa, open-label trial (N01263/NCT00422422; patients aged ≥1 month-<16 years) and ongoing, Phase III, open-label, long-term follow-up (N01266/NCT01364597; direct enrollers aged ≥4-<17 years). Cognitive/behavioral outcomes assessed with Achenbach CBCL (1.5-5/6-16 years) and BRIEF-P/BRIEF (<5/5-16 years).

Results: 140 patients analyzed (mean age: 9.5 years; 57.1% male). Mean changes from baseline to final visit (raw subscale scores): CBCL 1.5-5 aggressive behavior/anxious&depressed/attention problems/emotionally reactive/sleep problems/somatic complaints/withdrawn/other problems: -1.4/-1.5/-0.5/-1.0/-1.1/-0.9/-0.7/-3.2; CBCL 6-18 aggressive behavior/anxious&depressed/attention problems/rule-breaking behavior/social problems/somatic complaints/thought problems/

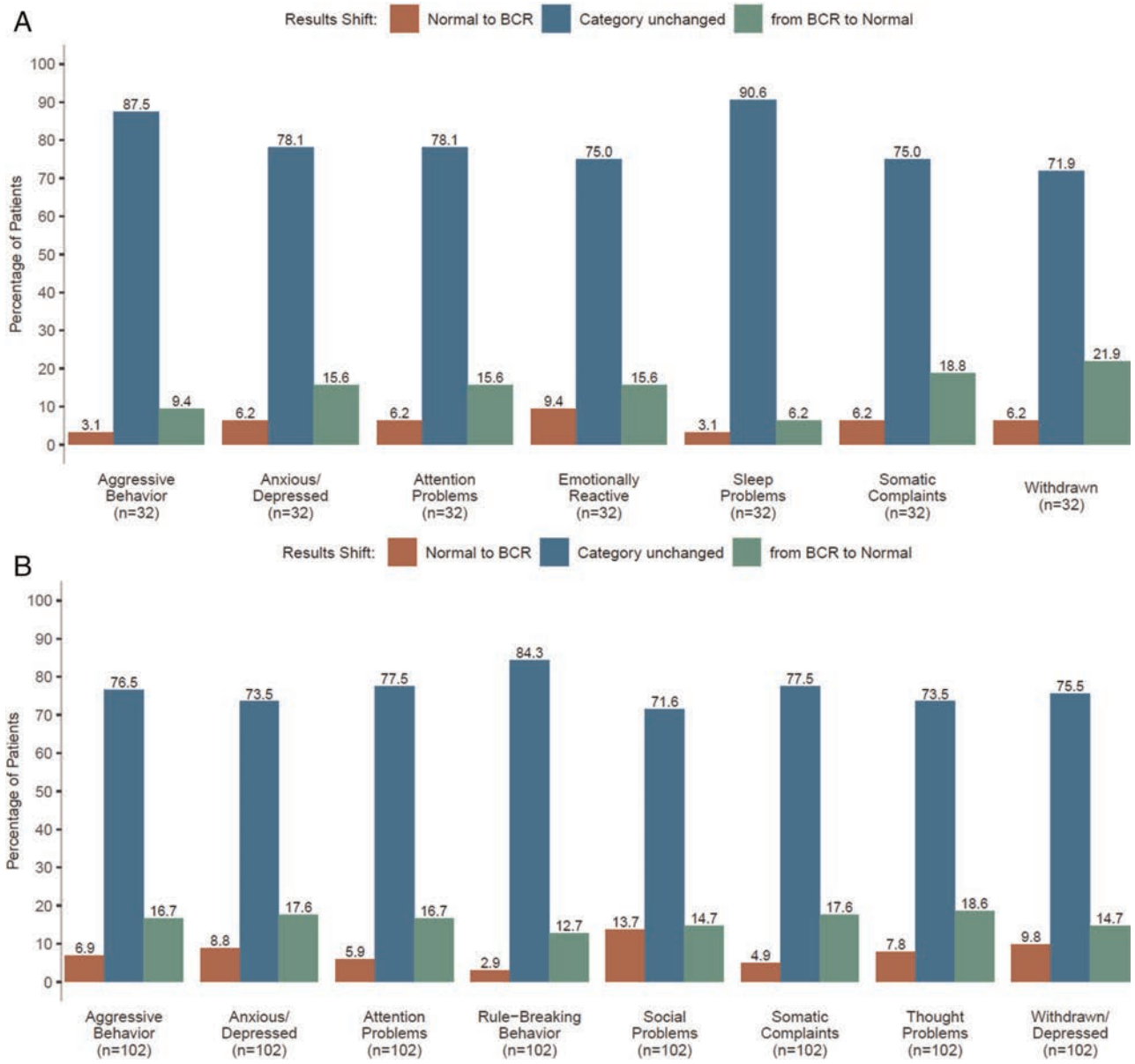


FIGURE 1. Shifts in T-score categories (normal[a], borderline or clinical range[b]) in Achenbach Child Behavior Checklist (CBCL) subscales from Baseline to last evaluation in patients with focal seizures: (A) Achenbach CBCL 1.5-5 years of age; (B) Achenbach CBCL 6-18 years of age. BCR: Borderline or clinical range. Only patients providing CBCL data at both Baseline and last evaluation were included. Baseline data were obtained from the core trial Screening Visit. Median time to last CBCL evaluation: 295.5 days (patients 1.5-5 years of age, n=32), 1043.0 days (patients 6-16 years of age, n=102). [a]Normal: T-score <65; [b]BCR: T-score ≥65. Abstract 83

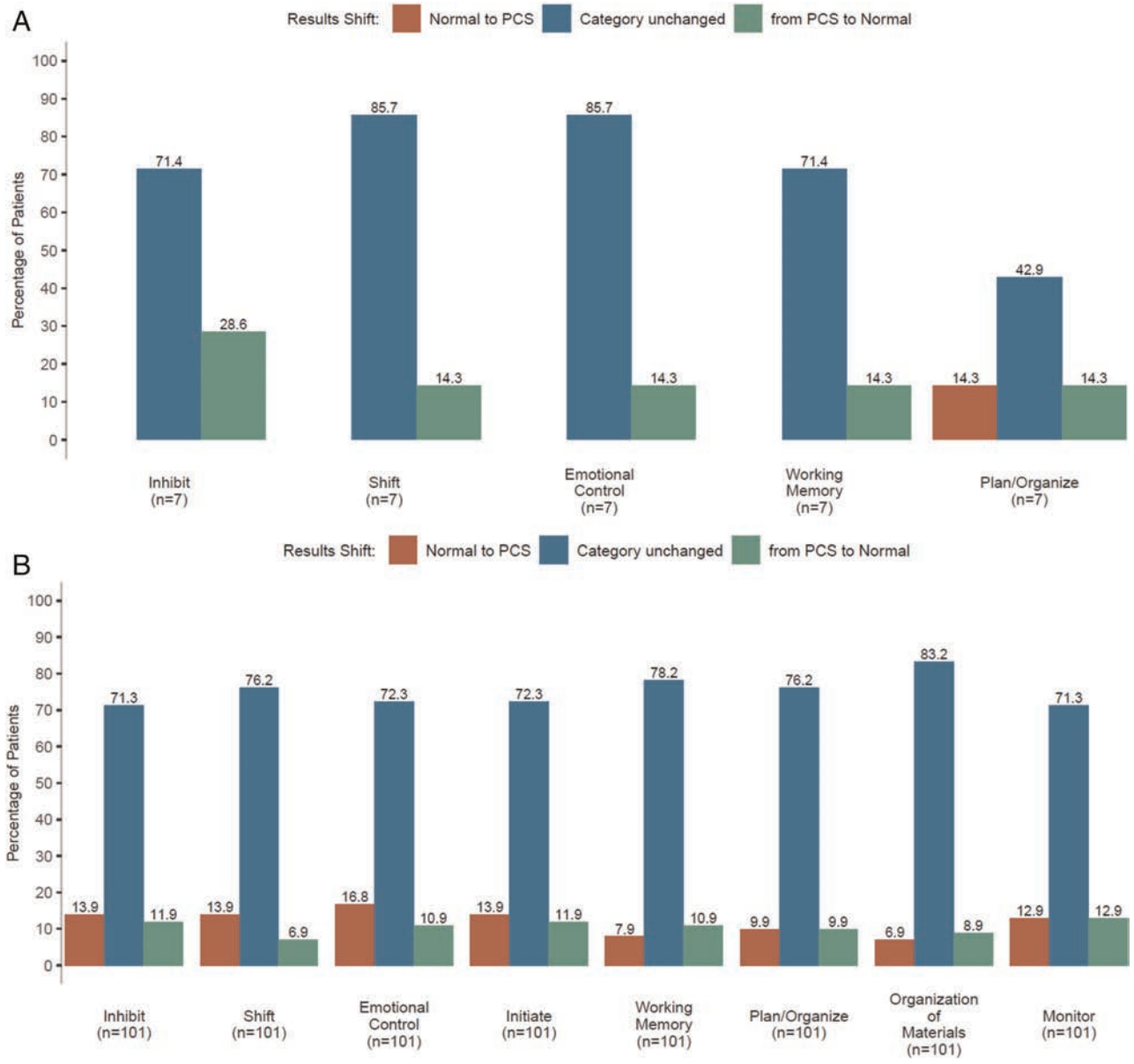


Figure 2. Shifts in T-score categories (normal[a], potential clinical significance[b]) in Behavior Rating Inventory of Executive Function (BRIEF) subscales from Baseline to last evaluation in patients with focal seizures: (A) BRIEF-Preschool Version (BRIEF-P) <5 years of age; (B) BRIEF 5-18 years of age. PCS: Potential clinical significance. Only patients providing BRIEF-P/BRIEF data at both Baseline and last evaluation were included; some patients may have had missing subscale scores, and in such cases, the sum of the proportion of patients in the results shift groups is <100%. Baseline data were obtained from the core trial Screening Visit. Median time to last BRIEF-P/BRIEF evaluation: 204.0 days (patients <5 years of age, n=7), 1220.0 days (patients 5-16 years of age, n=101). [a]Normal: T-score <65; [b]PCS: T-score ≥65. Abstract 83

withdrawn&depressed: -1.8/-1.4/-1.2/-0.7/-0.5/-1.2/-0.8/-0.1; BRIEF-P inhibit/shift/emotional control/working memory/plan&organize: -6.6/-2.1/-4.9/-4.0/-3.0; BRIEF inhibit/shift/emotional control/initiate/working memory/plan&organize/organization of materials/monitor: -1.6/-0.5/-1.0/-0.6/-1.8/-1.4/-0.8/-0.9. Most patients in both age groups had no shift in T-score category from baseline to last evaluation for each CBCL subscale (between normal and borderline or clinical range [BCR], Fig. 1) and BRIEF-P/BRIEF subscale (between normal and potential clinical significance [PCS], Fig. 2). For all CBCL subscales, more patients changed from BCR to normal than normal to BCR. Changes across BRIEF-P subscales were mostly from PCS to normal. Across BRIEF subscales, similar proportions of patients changed from normal to PCS and PCS to normal. Incidences of treatment-emergent adverse events (TEAEs): overall (1.5-5/6-16 years: 100%/95.4%); drug-related (40.6%/34.3%); serious (18.8%/26.9%); discontinuations due to TEAEs (6.3%/7.4%); deaths (3.1% [n=1]/0.9% [n=1]).

Conclusions: In this pooled interim analysis, cognitive/behavioral functioning scores in children/adolescents with focal seizures under long-term adjunctive brivaracetam were generally stable or slightly improved compared with baseline. Brivaracetam was generally well tolerated.Funding: UCB Pharma

Keywords: Epilepsy/Sleep

84. Isoflurane controls Super Refractory Status Epilepticus secondary to a Monoallelic DNM1L Mutation: A Case Report

Park C (Fort Worth, TX), Luke R, Perry M

BACKGROUND: Variants in DNM1L are reported as rare causes of refractory epilepsy and frequently present as super refractory status epilepticus (SE). Specifically, the monoallelic R403C variant can present with epilepsia partialis continua (EPC), a form of focal SE which lacks definitive treatment options. We report a patient with an R403C DNM1L mutation successfully treated with isoflurane for super refractory EPC on two separate occasions.

Methods: N/A

Case Information: A 14-year-old male presented with super refractory SE manifest as EPC secondary to a monoallelic R403C variant in DMN1L. Failed therapies included multiple loading doses of antiseizure medications in addition to continuous midalozam, pentobarbital, propofol, ketamine, and lidocaine infusions. Adminstration of 0.9% isoflurane for 12 hours achieved burst suppression and resolution of status with the ability to wean off all continuous infusions over the following week. He returned over two years later with a similar presentation and failed interventions prior to initiation of isoflurane for 30 hours, which again aborted SE. Unfortunately, SE returned 3 weeks later and he failed isoflurane as the initial treatment.

Conclusions: DNM1L frequently presents with super refractory SE rarely responding to conventional treatments. Short-term administration of inhaled isoflurane aborted SE in two of three instances for our patient and may represent an efficacious treatment that should be considered earlier in the treatment strategy to shorten duration of SE in this condition. The reason for failure of this therapy when used as initial intervention is unclear and may be secondary to progression of disease, though further investigation is warranted.

Keywords: Epilepsy/Sleep, Genetics, Rare Diseases

85. Novel missense variant in the SLC2A1 c.1162T>C (p.Trp388Arg) causing childhood onset intractable generalized epilepsy, microcephaly and cognitive impairment

Abdul Hamid O (Memphis, TN), Patterson A, Caron E, Weatherspoon S

Objective: Glucose transporter 1 deficiency syndrome (GLUT1-DS) is a rare inborn error of metabolism caused by impaired glucose transport through blood brain barrier due to mutation in SLC2A1 gene, encoding a glucose transporter protein. Clinical symptoms, ranging from severe epileptic encephalopathy, microcephaly and movement disorders. The diagnosis of GLUT1-DS requires hypoglycorrhachia in the presence of normoglycaemia with a reduced cerebrospinal fluid (CSF):plasma glucose ratio.

Methods: In this case, we describe a child who developed generalized tonic-clonic seizures and absence seizures at age 6. Epilepsy gene panel identified a novel missense variant of undetermined clinical significance in exon 9 of the SLC2A1 gene c.1162T>C (p.Trp388Arg). The clinical features of this patient include intractable epilepsy and epileptic encephalopathy with severe language delay. Her head conference was in the 10th percentile for age. The ictal electroencephalogram (EEG) was characterized by generalized paroxysmal 3.5 Hz spike-slow wave complexes.

Results: She continued to have very frequent clinical and electrographic seizures despite therapeutic serum levels of Depakote, Ethosuximide and Keppra. Brain MRI was unremarkable. Metabolic screening labs were normal. A chromosomal MicroArray was normal. Only the mother was available for parental testing and she did not harbor the patient's variant. Allele frequency is extremely low in all databases. A lumbar puncture demonstrated a reduced CSF: plasma glucose ratio consistent with GLUT1-DS.

Conclusions: Treatment with modified Atkins diet showed clinical improvement with the reduction of clinical seizures and improvement in EEG. Given phenotypic overlap with previously reported individuals, we propose the pathogenicity of this variant.

Keywords: Epilepsy/Sleep, Genetics, Cognitive/Behavioral Disorders (including Autism)

86. Patient Outcomes During Transition from Pediatric to Adult Care for Epilepsy

Nurre E (Cincinnati, OH), Brothers S, Olson J, Hornbach A, Fong S

Objective: To collect clinical outcomes data for patients with epilepsy during and after transition from pediatric to adult healthcare

Methods: For this retrospective chart review, in the University of Cincinnati electronic health record database, we collected data for patients who transitioned from Cincinnati Children's Hospital Medical Center to University of Cincinnati (UC) Health neurology department for epilepsy care. We collected patient information including age, sex, ethnicity, comorbidities, substance abuse history and insurance type as well as imaging and EEG data for diagnosis. We gathered clinical outcomes data for these patients including healthcare utilization measures (emergency department visits, outpatient clinic visits, patient telephone calls, hospital admissions) as well as laboratory testing, anti-epileptic drug information and surgical discussions if medically refractory epilepsy. The results of this analysis will be used to identify gaps in care during transition and target areas to improve clinical outcomes in this process.

Results: Preliminary results revealed patients identified (N=139) with a wide range of ages and comorbidities.

Conclusions: Patients transitioning from pediatric to adult care in epilepsy have poor clinical outcomes and gaps in care. There may be target areas to improve clinical outcomes in this process.

Keywords: Epilepsy/Sleep

EQUITY, DIVERSITY, INCLUSION

87. Implementation of a Provider-to-Provider 24-7 Hotline for Angelman Syndrome Improves Access to Expert Care

Duis J (Aurora, CO), Nangia S, Walleigh D, Berry-Kravis E

Objective: We have implemented a provider-to-provider consultation hotline available 24-7 with access to expert providers across the United States to improve health equity and access to care for all individuals with Angelman Syndrome (AS). Our goal was to develop evidence-based algorithms for the management of common urgent and emergent concerns and to demonstrate novel methods for expert access for management of rare disorders to improve health outcomes and standards of care.

Methods: The infrastructure for an on-call service for individuals with AS was coordinated at Children's Hospital Colorado for access to an on-call Angelman specialist. Together with key opinion leaders in the field, we developed clinical pathways for the management of AS. We are collecting prospective data to understand outcomes with these standards of management. Calls are accepted nationally and internationally with interpreter services available.

Results: Since July 1, 2020, we have received consultations from across the world including Italy, France, and Australia. The primary concerns include seizure management, poor sleep, behavior concerns, motor changes, and non-epileptic myoclonus. Outcomes have been positive with shared information on existing data and clinical pathways. Phone calls are more often from trainees than attending providers. Acceptance of the emergency line by providers is a barrier to receipt of actionable calls.

Conclusions: Consensus management convened by a group of key opinion leaders and implementation of an infrastructure to receive calls from providers to assist in local management of Angelman Syndrome has been successful. We have a met some barriers regarding acceptance and use of line.

Keywords: Diversity, Equity, Inclusion, Rare Diseases, Genetics

88. Differential National Trends in Child Neurology

Ramsy N (Champaign, IL), Peterman N, Yeo E, Kaptur B

Objective: There is a significant gap between the need for child neurology and the number of available child neurologists. This work utilized geospatial analysis to identify the communities where this gap is the highest and the demographics of those most affected.

Methods: US Census and Center for Medicare Services databases from 2015-2019 were utilized to obtain the socioeconomic demographics of each US county and the corresponding number of practicing and child neurologists. Counties without neurologists were excluded. Physician race was estimated using name-based predictive algorithms. Cluster analysis was conducted to classify countries as statistically significant, $p < 0.05$, hotspots (High-High), coldspots (Low-Low), and geospatial outliers (Low-High and High-Low) of child neurology using Moran's I analysis. Clusters were then compared across socioeconomic variables using ANOVA.

Results: 22,533 practicing neurologists, 70.94% white and 36.14% female, and 2,378 child neurologists, 71.03% white and 50.25% female, were included. Southern California and the Mid-Atlantic were child neurology hotspots with 110.63 neurologists and 12.34 child neurologists per county. Coldspots were predominantly located in Appalachia with an average of 4.30 neurologists and 0.09 child neurologists per county. Compared to coldspots, hotspots were statistically significantly less impoverished, less white, more urbanized, and had higher median income.

Conclusions: Quantifying the gap in child neurology is critical for properly allocating resources. Although Appalachia has the lowest access in the nation, even locations with high access to child neurology had what would be considered poor access compared to general neurology.

Keywords: Diversity, Equity, Inclusion

89. Race and Gender-Associated Disparities in Acute Headache Management in a Pediatric Emergency Department

Shiswawala N (Cleveland, OH), Gao C, Goldstein J, Rose J, Bass N, Wyllie K, Malay S, Grube A

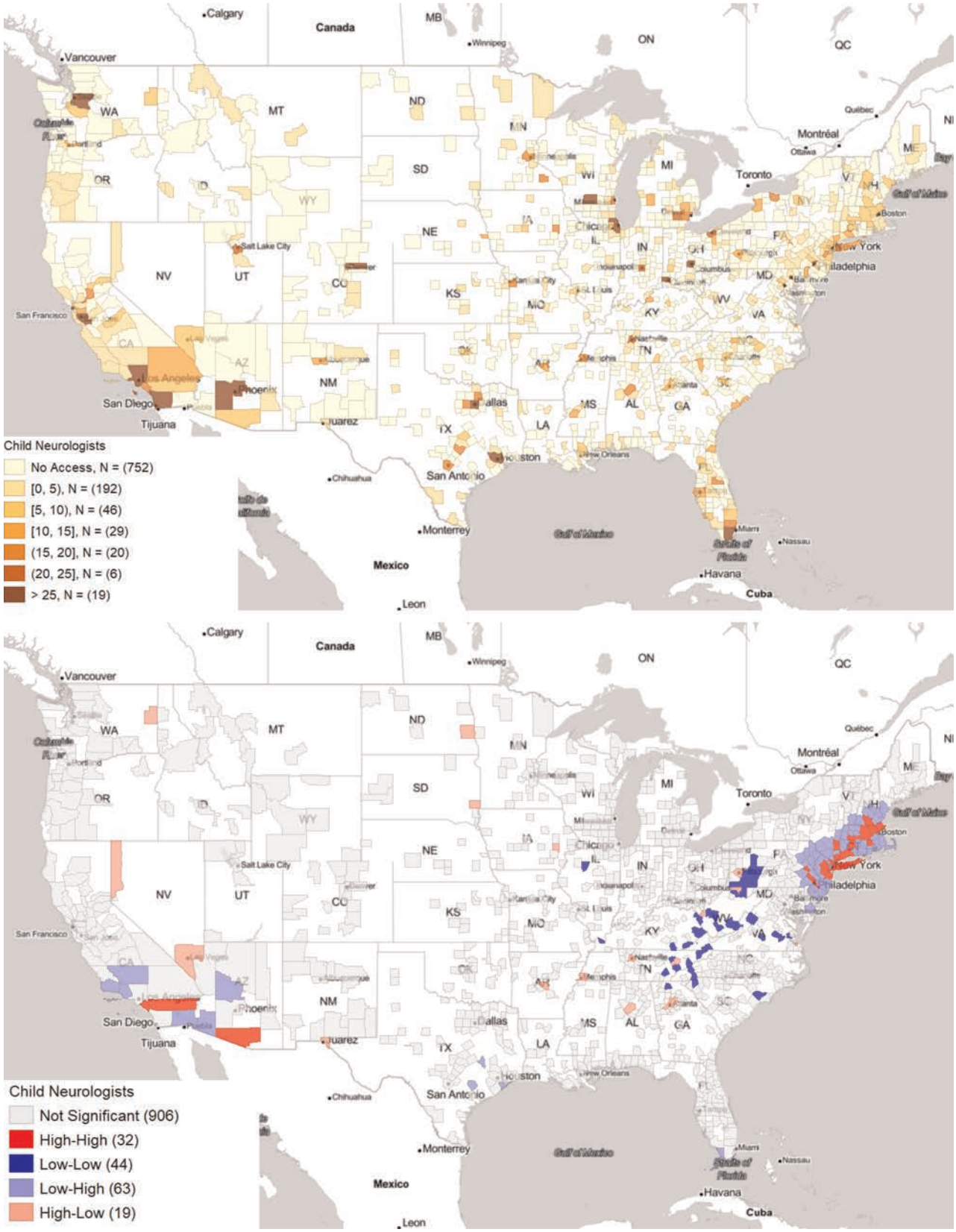
Objective: Racial and gender healthcare disparities in analgesic use for headaches in emergency departments (ED) have been previously documented[1]. Literature is scarce for pediatric populations. This study's aim was to evaluate for differences in the acute management of headaches in a pediatric ED.

Methods: A retrospective cohort study of children within a single hospital ED system with headaches during a 3-year period was completed. Headache medications were grouped into 3 categories: 1 (oral), 2 (first-line IV), and 3 (second-line IV). Association of race and gender with multiple clinical variables were included. Assessment was performed using univariable Chi-squared tests.

Results: 607 children were included; 269 White children (44%), 321 Black children (53%) and 17 children of other races (3%). Statistically significant differences in time to initial analgesic were not observed based on race or gender. A race-associated difference in the category of treatment was noted; black children received Category 1 medications more than white children (31% vs 9.4%, $p<0.0001$). More white children received Category 3 medications (15% vs 2.6%, $p <0.0001$). Females had a statistically significant greater reduction in pain compared to males (4 vs 6, $p=0.025$).

Conclusions: We observed a race-associated difference in the analgesic agent category used and a greater reduction in pain scores following treatment for females compared to males. No significant differences in time to initial analgesic for gender or race. These findings highlight the need for further research in pediatric headache healthcare disparities to address racial and gender disparities in this population.

Keywords: Diversity, Equity, Inclusion, Headache/Migraine


Child Neurologists
No Access, N = (752)
[0, 5), N = (192)
[5, 10), N = (46)
[10, 15], N = (29)
(15, 20], N = (20)
(20, 25], N = (6)
> 25, N = (19)
Child Neurologists
Not Significant (906)
High-High (32)
Low-Low (44)
Low-High (63)
High-Low (19)
Canada
Mexico
Cuba
Calgary
Vancouver
Winnipeg
Toronto
Montréal
Ottawa
Québec
Boston
New York
Philadelphia
Baltimore
Washington
Salt Lake City
San Francisco
Los Angeles
San Diego
Phoenix
Las Vegas
Tijuana
Juarez
Chihuahua
San Antonio
Houston
New Orleans
Dallas
Atlanta
Miami
Nassau
Havana
Monterrey
Leon
MB
ON
QC
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ME
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CA
ID
NV
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90. Reducing Implicit Bias and Promoting DEI Efforts in Child Neurology Residency Recruitment- An Update from 2020

Kumar I (Ann Arbor, MI), Gottlieb-Smith R, Leber S, Behnke T, McCaffrey H, Shellhaas R, McNamara N, Cartwright K, Fedak Romanowski E

Objective: The Michigan Medicine Pediatric Neurology Division used quality-improvement (QI) methodology to reduce unconscious bias and increase objectivity by implementing interventions during the selection process of residency applicants. The goal was to increase diversity of interviewed applicants by 2022 while sustaining foundational principles for success in child neurology.

Methods: We examined baseline demographic data from 2019 recruitment season focusing on gender, self-identified race, hometown, degree, USMLE scores, and participation in minority interest groups. Our first intervention included an implicit bias self-assessment and review of education modules on hiring bias by faculty. For further PDSA cycles, we introduced new interventions: 1) removing candidate photograph, name, and gender; 2) changing our objective scoring system by broadening the definition of scholarly work and putting more weight on interpersonal skills; 3) adding standardized questions to interviews.

Results: As previously reported, baseline data (2019) suggested unconscious biases to interview more female, white, Midwest/Michigan, MD (vs. DO) candidates with minimal participation in minority interest groups as previously reported. After two PDSA cycles, there was reduction of biases related to sex and geographic location (Tables 1 and 2).

TABLE 1: P values calculated by Wald's test of each independent variable, and then of the interaction of year with each variable in logistic regression models of interviewed status. Abstract 90

	2019	2020	2021	Year interaction
Gender (Female vs Male)				
Eligible*	.054	.839	.111	.425
Invited	<.001	.338	.022	.037
Interviewed	.002	.198	.180	.177
Race (white vs nonwhite)				
Eligible	.002	.170	.123	.425
Invited	.001	.026	.003	.681
Interviewed	.005	.012	<.001	.707
Region				
Eligible	<.001	<.001	<.001	.025
Invited	<.001	<.001	<.001	.273
Interviewed	<.001	<.001	<.001	.136
Degree (MD vs DO vs MD/PhD vs Other)				
Eligible	<.001	<.001	<.001	.981
Invited	<.001	<.001	<.001	.736
Interviewed	.002	<.001	<.001	.779
Step 1				
Eligible	<.001	.511	<.001	.107
Invited	<.001	<.001	<.001	.683
Interviewed	<.001	.001	<.001	.683
Step 2				
Eligible	<.001	.018	<.001	.609
Invited	<.001	<.001	<.001	.417
Interviewed	<.001	<.001	<.001	.495
Minority interest group (No vs Yes)				
Eligible	<.001	<.001	.008	.049
Invited	.033	<.001	<.001	.242
Interviewed	.074	<.001	.003	.330
Age group				
Eligible	<.001	.001	.001	.182
Invited	<.001	.011	<.001	.021
Interviewed	<.001	.012	<.001	.086

*Applicants who graduate from US/Canadian medical schools, and have successfully passed the USMLE are eligible for our program, as determined by the MM Pediatrics Department, thus the number of eligible applicants is lower than the total number of applicants.

TABLE 2: Demographics from all applicants, all eligible applicants, all applicants invited to interview, and all interviewed applicants of all three recruitment years. Abstract 90

Applicant characteristics	2019 (Baseline)				2020 (after one PDSA cycle)				2021 (after two PDSA cycles)			
	All Applicants N=144	Eligible Applicants* N=83	Invited to Interview N=47	Interviewed N = 39	All Applicants N=137	Eligible Applicants N=81	Invited to Interview N=51	Interviewed N = 45	All Applicants N = 147	Eligible Applicants N = 111	Invited to Interview N = 60	Interviewed N = 52
Sex	91 (63%)	58 (70%)	41 (87%)	33 (85%)	87 (64%)	52 (64%)	35 (69%)	32 (71%)	94 (64%)	75 (68%)	45 (75%)	37 (71%)
Female	53 (37%)	25 (30%)	6 (13%)	6 (15%)	59 (36%)	29 (36%)	16 (31%)	13 (29%)	53 (36%)	36 (32%)	15 (25%)	15 (29%)
Male												
Self-identified Race	54 (38%)	40 (48%)	27 (57%)	22 (56%)	61 (45%)	40 (49%)	29 (57%)	27 (57%)	57 (39%)	47 (42%)	32 (53%)	31 (60%)
White	75 (52%)	39 (47%)	18 (38%)	15 (38%)	71 (52%)	39 (48%)	20 (39%)	16 (36%)	82 (56%)	57 (51%)	26 (43%)	19 (37%)
Non-white	15 (10%)	4 (5%)	2 (4%)	2 (4%)	5 (4%)	2 (2%)	2 (4%)	2 (4%)	8 (5%)	7 (6%)	2 (3%)	2 (4%)
Not answered												
Age	3 (2%)	1 (1%)	0 (0%)	0 (0%)	4 (3%)	4 (5%)	1 (2%)	1 (2%)	4 (3%)	4 (4%)	4 (7%)	4 (8%)
<25	81 (56%)	58 (70%)	36 (77%)	35 (90%)	93 (68%)	62 (77%)	43 (84%)	38 (84%)	91 (62%)	78 (70%)	51 (85%)	43 (83%)
26-30	41 (28%)	23 (28%)	11 (23%)	4 (10%)	20 (15%)	10 (12%)	6 (12%)	5 (12%)	35 (24%)	21 (19%)	3 (5%)	3 (6%)
31-35	14 (10%)	1 (1%)	0 (0%)	0 (0%)	9 (7%)	2 (2%)	0 (0%)	0 (0%)	12 (8%)	6 (5%)	1 (2%)	1 (2%)
36-40	2 (1%)	0 (0%)	0 (0%)	0 (0%)	4 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
41-60	30 (21%)	0 (0%)	0 (0%)	0 (0%)	7 (5%)	3 (4%)	1 (2%)	1 (2%)	4 (3%)	2 (2%)	1 (2%)	1 (2%)
Not answered												
Hometown region	14 (10%)	11 (13%)	8 (17%)	8 (21%)	4 (3%)	3 (4%)	2 (4%)	2 (4%)	10 (7%)	9 (8%)	6 (10%)	6 (12%)
Michigan	24 (17%)	21 (25%)	12 (26%)	12 (31%)	19 (14%)	18 (22%)	9 (18%)	9 (20%)	25 (17%)	20 (18%)	11 (18%)	9 (17%)
Midwest	23 (16%)	17 (20%)	10 (21%)	8 (21%)	26 (19%)	17 (21%)	14 (27%)	14 (33%)	19 (13%)	18 (16%)	14 (23%)	12 (23%)
Northeast	15 (10%)	12 (14%)	6 (13%)	3 (8%)	34 (25%)	26 (32%)	17 (33%)	12 (27%)	40 (27%)	34 (31%)	19 (32%)	18 (35%)
South	20 (14%)	17 (20%)	9 (19%)	6 (15%)	19 (14%)	14 (17%)	7 (14%)	6 (16%)	18 (12%)	17 (15%)	9 (15%)	6 (12%)
West	2 (1%)	2 (2%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1 (2%)	1 (2%)
Puerto Rico	30 (21%)	2 (2%)	1 (2%)	1 (3%)	30 (21%)	2 (2%)	2 (4%)	2 (4%)	34 (23%)	12 (11%)	0 (0%)	0 (0%)
International	16 (11%)	1 (1%)	1 (2%)	1 (3%)	4 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
No information												
Degree	107 (40%)	76 (92%)	45 (96%)	37 (95%)	93 (68%)	72 (89%)	49 (96%)	43 (96%)	100 (68%)	89 (80%)	53 (88%)	47 (90%)
MD	12 (8%)	7 (8%)	2 (4%)	2 (5%)	13 (10%)	10 (12%)	2 (4%)	2 (4%)	21 (14%)	16 (14%)	7 (12%)	5 (10%)
DO	23 (16%)	0 (0%)	0 (0%)	0 (0%)	31 (23%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Other	2 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	25 (17%)	6 (5%)	0 (0%)	0 (0%)
No information												
USMLE Step 1	17 (12%)	4 (5%)	1 (2%)	1 (3%)	9 (7%)	4 (5%)	1 (2%)	1 (2%)	11 (7%)	3 (3%)	0 (0%)	0 (0%)
<200	46 (32%)	25 (30%)	4 (9%)	2 (5%)	51 (37%)	27 (33%)	10 (20%)	9 (20%)	52 (35%)	42 (38%)	11 (18%)	9 (17%)
200-220	46 (32%)	30 (36%)	22 (47%)	19 (49%)	47 (34%)	30 (37%)	21 (41%)	20 (44%)	52 (35%)	41 (37%)	29 (48%)	25 (48%)
221-240	10 (7%)	23 (28%)	6 (13%)	17 (44%)	26 (19%)	18 (22%)	17 (33%)	15 (33%)	27 (18%)	25 (23%)	20 (33%)	18 (35%)
>240	5 (3%)	0 (0%)	0 (0%)	0 (0%)	4 (3%)	2 (2%)	2 (4%)	0 (0%)	5 (3%)	0 (0%)	0 (0%)	0 (0%)
No information												
USMLE Step 2	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)
<200	27 (19%)	6 (7%)	0 (0%)	0 (0%)	19 (14%)	7 (9%)	3 (6%)	3 (7%)	25 (27%)	12 (11%)	1 (2%)	1 (2%)
200-220	54 (38%)	32 (39%)	10 (21%)	8 (21%)	54 (39%)	30 (37%)	9 (18%)	9 (20%)	47 (32%)	35 (32%)	12 (20%)	8 (15%)
221-240	54 (38%)	43 (52%)	36 (77%)	30 (77%)	54 (39%)	40 (49%)	38 (75%)	32 (71%)	66 (45%)	60 (54%)	47 (78%)	43 (83%)
>240	8 (6%)	2 (2%)	1 (2%)	1 (3%)	9 (7%)	4 (5%)	1 (2%)	1 (2%)	8 (5%)	3 (3%)	0 (0%)	0 (0%)
No information												
Minority Interest Group Involvement	37 (26%)	12 (14%)	7 (15%)	6 (15%)	34 (25%)	6 (7%)	3 (6%)	3 (7%)	54 (37%)	34 (31%)	12 (20%)	11 (21%)

**Applicants who graduate from US/Canadian medical schools, and have successfully passed the USMLE are eligible for our program, as determined by the MM Pediatrics Department, thus the number of eligible applicants is lower than the total number of applicants.

Conclusions: In the past two application cycles, gender bias was reduced in 2020, and among those interviewed in 2021, but not in the 2021 invited group. We broadened our geographic reach to the South likely influenced by virtual interviews. Further interventions will focus on specifically reducing biases in race, degrees, and age. We continue to invite and interview applicants with higher USMLE scores though shifting focus to interpersonal skills, QI and medical education.

Keywords: Diversity, Equity, Inclusion

91. Telephone vs Video Visits in Pediatric Neurology during the COVID-19 Pandemic: Outcomes and Access

Grefe A (Winston-Salem, NC), Ip E, Chen S-H, Kirkendall E, Nageswaran S

Objective: During the COVID pandemic, health insurance companies allowed reimbursement for both telephone and video telehealth services in North Carolina (NC), on par with in-person visits. Parity for telephone visits is now being reversed. This study intended to evaluate the effects of video versus telephone visits on children's access to outpatient neurology.

Methods: Using Electronic Health Record data, we collected information about children who had outpatient pediatric neurology telehealth appointments in a tertiary care children's hospital. Inclusion criteria were: Age < 18 years, NC residence, and at least one pediatric telehealth neurology appointment between 3/10/20 and 3/9/21. Appointment outcomes (completion, cancelation, and no-show rates) were calculated. We used *the General-Estimating Equation (GEE)* to compare outcomes for video and telephone visits.

Results: A total of 1,250 children had at least one neurology telehealth visit scheduled during the study period (607 telephone only, 517 video only, 126 mixed). Telephone users,

TABLE 1. Demographic Characteristics of Children. Abstract 91

	All Telehealth Users (n=1250)	Phone Users (n=607)	Video Users (n=517)	Mixed (n=126)	p value*
Age (mean), *years*	9.9 (5.1)	10.4 (5.1)	9.4 (5.1)	10.0 (5.1)	0.0045
Public Insurance (%)	62.6	69.4	55.3	59.5	<0.0001
Private Insurance (%)	37.1	30.3	44.5	39.7	
Missing (%)	0.3	0.3	0.8	0.8	
Race categories	67.1	60.3	73.9	72.2	<0.0001
White (%)	16.6	18.5	14.1	17.5	
Black (%)	15.9	21.1	11.2	10.3	
American Indian/Pacific Islander, Asian and Other (%)	0.4	0.2	0.8	0	
Missing (%)					
Hispanic ethnicity (%)	10.9	15.2	6.6	7.9	<0.0001
Rural residence (%)	35.4	35.6	35.4	34.1	0.952
Distance from the children's hospital (mean), *miles*	31.3 (30.4)	31.7 (29.4)	31.1 (31.2)	30.5 (32.2)	0.896

*Chi-square tests for categorical variables and t-tests for continuous variables comparing telephone and video users and those using both modalities

TABLE 2. Pediatric Neurology Telehealth Appointment Outcomes for Telephone versus Video Visits. Abstract 91

Appointment Outcomes	All Telehealth Visits (n=2,014)	Phone Visits (n=1,043)	Video Visits (n=971)	p value*
Completed	1,519 (75%)	834 (80%)	685 (71%)	<0.0001
Cancelled	294 (15%)	125 (12%)	169 (17%)	0.00023
No Show	201 (10%)	84 (8%)	117 (12%)	0.0023

*Based on GEE to adjust for correlation between repeated visits from the same individual

compared to video users, were more likely to be of minority race/ethnicity and to have public health insurance (Table 1). Of the 2,014 neurology telehealth visits scheduled, completion rates were higher for telephone visits compared to video (telephone 80%; video 71%; p<0.0001). The cancellation and no-show rates were significantly lower for telephone visits (8% and 12%, respectively) compared to video (17% and 12%, respectively) (Table 2).

Conclusions: Telephone visits improved access to outpatient pediatric neurology, especially for children of minority race/ethnicity and with public health insurance. Reversal of policies to reimburse telephone visits could deepen the socioeconomic divide for children's access to neurology services.

Keywords: Diversity, Equity, Inclusion, COVID-19

92. Missed Appointments and Socioeconomic Trends Among Child Neurology Patients

Albor L (Cincinnati, OH), Ritter D, Venkatesan C

Objective: The purpose of the study is to assess the relationship between socioeconomic factors and missed appointments among children who receive their outpatient neurology care in resident continuity clinic at a tertiary care academic medical center.

Methods: This study is a retrospective study of child neurology patients seen in resident continuity clinic from 2018-2019. The prevalence of no-shows was determined; no-shows were defined as child neurology visits missed by the patient without notification of cancellation. Patient demographics were then analyzed including race, insurance, median household income, and distance from hospital.

Results: The prevalence of no-shows among resident clinic encounters was 14% (312 missed appointments of 2257 scheduled encounters). Black patients were disproportionately overrepresented in the no-show population; while they comprised 22% of scheduled patients, they represented 41% of the no-show population. However, white patients were underrepresented in the no-show group; while they comprised 69% of scheduled patients, they represented only 47% of no-shows (p<.001). Patients with private insurance were more likely to complete appointments than patients with public insurance. Median household income was inversely correlated with no-show rate. Patients who lived closer to the hospital (less than 10 miles) were more likely to miss their appointment. The no-show rate for Black patients remained higher regardless of insurance status, median household income, or distance from the hospital.

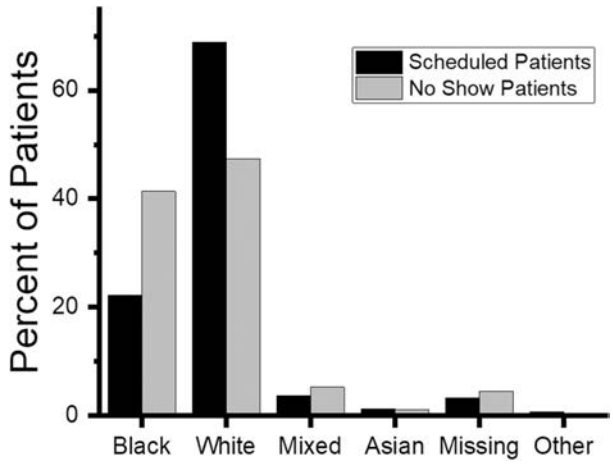

FIGURE 1: No Shows by Race. Abstract 92

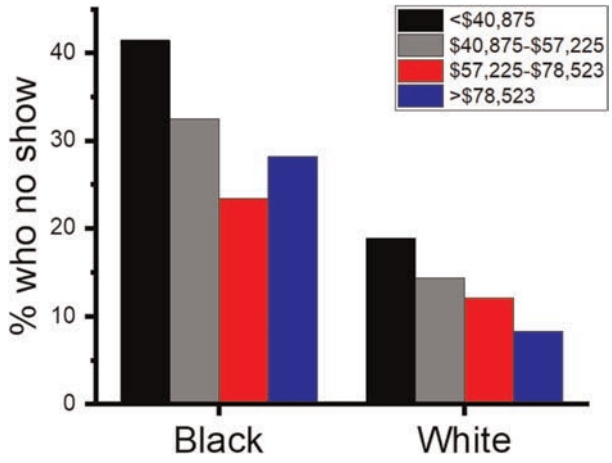

FIGURE 2: No Shows by Race and Median Household Income. Abstract 92

Conclusions: Racial and socioeconomic disparities are present in access to outpatient pediatric neurology care. Future studies are needed to determine the effect on health outcomes and reasons for these disparities to inform potential interventions.

Keywords: Diversity, Equity, Inclusion, Education

93. Cure SMA Patient Data Collection: Comparing the Cure SMA Clinical Data Registry, Membership Database and US SMA Population

Belter L (Elk Grove Village, IL), Whitmire S, Monk A, Schroth M

Objective: Evaluate if two Cure SMA-managed databases (the spinal muscular atrophy [SMA] membership database and the clinical data registry [CDR]) are representative of the US SMA population.

Methods: A descriptive analysis evaluated similarities/differences between the membership database, CDR, and the US SMA population based on published literature and US Census data. Proportions of sex, race/ethnicity, age, and treatment status with a SMA disease modifying therapy (DMT) were compared across all cohorts. Patients with an unknown SMA type or non-5q-SMA, international, or deceased patients were removed from the analysis. Significance testing was not performed.

Results: The breakdown of males was 46.5%, 51.4% and 49.0% for the membership database, CDR, and US SMA population, respectively. There was a greater percentage of Whites in the membership database compared with the CDR and US SMA populations: 75.2% vs 62.4% and 70.0%, respectively. There was a greater proportion of children (< 18 years old) in the CDR vs the membership database and

US SMA populations: 73.1% vs 51.1% and 43.2%. Finally, the CDR reported greater use of DMTs 82.7% vs 62.0% than the US SMA population. Additional analyses will be presented.
Conclusions: The Cure SMA managed databases closely represent the gender breakdown of the US SMA population, but there is an over representation of pediatric individuals in the Cure SMA managed databases and White race in the membership database. Future outreach efforts from Cure SMA will be tailored to close gaps including supporting underserved populations and adding adult care centers to the Cure SMA Care Center Network.
Keywords: Diversity, Equity, Inclusion, Neuromuscular Disorders

GENETICS

94. Genetic Causes and Biological Pathways Elucidated by Exome Sequencing in Patients with Cerebral Palsy

Srivastava S (Boston, MA), Chopra M, Gable D, Poduri A

Objective: Although there are known risk factors for cerebral palsy (CP), in many cases the cause is unclear (cryptogenic). To characterize the breadth of biological pathways implicated in CP, we conducted exome sequencing (ES) in a large cohort of CP.
Methods: We performed detailed phenotyping on individuals with a CP diagnosis and classified them as acquired (meets criteria for CP; known risk factors), cryptogenic (meets criteria for CP; no risk factors), or masqueraders (diagnosed with CP, but has regression/progression). We performed ES on the probands/parents.
Results: We enrolled 147 probands, comprising acquired (69), cryptogenic (69), and masquerader (9) groups. 32/147 (22%) had pathogenic/likely pathogenic variants in 28 unique clinically relevant genes. The CP masquerader group had the highest yield (67%, 6/9) followed by cryptogenic (32%, 22/69) and acquired (6%, 4/69) CP. In logistic regression model, the presence of a genetic disorder related to classification ($p=0.002$), but not primary motor phenotype, multiple comorbidities, and MRI pattern (normal/non-normal). The genes identified were related to diverse biological functions, including metabolism, transcription, translation, G-protein/GTPases, and ion channels. The most common biological functions of the associated genes were metabolism-related (5 genes) and transcriptional regulation (5 genes) in patients with various motor phenotypes. Additionally, 4 were G-protein/GTPases (*ATL1*x2, *GNAO1*, *GNB1*), and all patients with variants in these genes had spastic di/quadriplegia.
Conclusions: A substantial portion of CP without risk factors have Mendelian disorders related to diverse biological functions. Our data suggest emerging gene category-phenotype correlations. As more patients with CP undergo genetic testing, the genetic landscape of CP will expand.
Keywords: Genetics, Movement Disorders (including Cerebral Palsy)

95. Pathogenic Variants in SPTSSA Dysregulate Sphingolipid Synthesis and Cause a Complicated Form of Hereditary Spastic Paraplegia

Srivastava S (Boston, MA), Shaked H, Gable K, Gupta S, Somashekarappa N, Han G, Gotkine M, Cope H, Goldenberg P, Tan Q, Elpeleg O, Lee C-H, Shimon E, Eichler F, Dunn T

Objective: *SPTSSA* (*Serine Palmitoyltransferase Small Subunit A*) encodes an activating subunit of serine palmitoyltransferase (SPT), the enzyme that catalyzes the rate-limiting step of sphingolipid (SL) synthesis. Neurological disorders associated with defects in SL degradation have been recognized for decades, but only recently have disorders resulting from pathogenic variants in SL biosynthetic genes been discovered.
Methods: We establish *SPTSSA* as a human disease gene, reporting two different pathogenic variants in *SPTSSA* causing a complicated form of HSP in three unrelated patients. We provide functional evidence supporting pathogenicity of both variants including assessment of *in vivo* SPT activity and ORMDL-mediated inhibition of SPT.
Results: Two of the patients (Pt 1, female, 4y; Pt 2, female, 8y) have a recurrent *de novo* heterozygous missense variant (p.Thr51Ile), and one of the patients (Pt 3, male, 22y) has a homozygous frameshift variant (p.Gln58AlafsTer10). All three exhibited progressive appendicular spasticity, motor dysfunction, and epileptiform activity. Pt 1 has language impairment, Pt 2 has cognitive impairment, and Pts 1, 3 have sensorineural hearing loss. The pathogenicity associated with both variants is due to excessive SL synthesis resulting from impaired regulation of SPT by the ORMDL proteins. The ORMDLs, which bind to SPT, feedback inhibit SPT when SL levels become excessively high and thereby play a crucial role in the maintenance of SL homeostasis and the elaboration of myelin membranes.
Conclusions: Our evidence indicates that pathogenic variants in *SPTSSA* interfere with ORMDL regulation, supported by the recently solved structures of the SPT/ORMDL3 complex, which shows that domains of SPTSSA directly contact ORMDL3[1,2].
Keywords: Genetics, Movement Disorders (including Cerebral Palsy)

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96. Demonstrating the Value of Genome Sequencing in a Pediatric Neurology Cohort: A Successful Partnership Between a Patient Organization and Industry

Snyder H (San Diego, CA), Salz L, Cohen J, Hughes I, Helbig K, Park K, Koehn M, Poduri A, Patel A, Schmidt S

Objective: Evidence demonstrating utility of whole-genome sequencing (WGS) in rare disease continues to grow. In

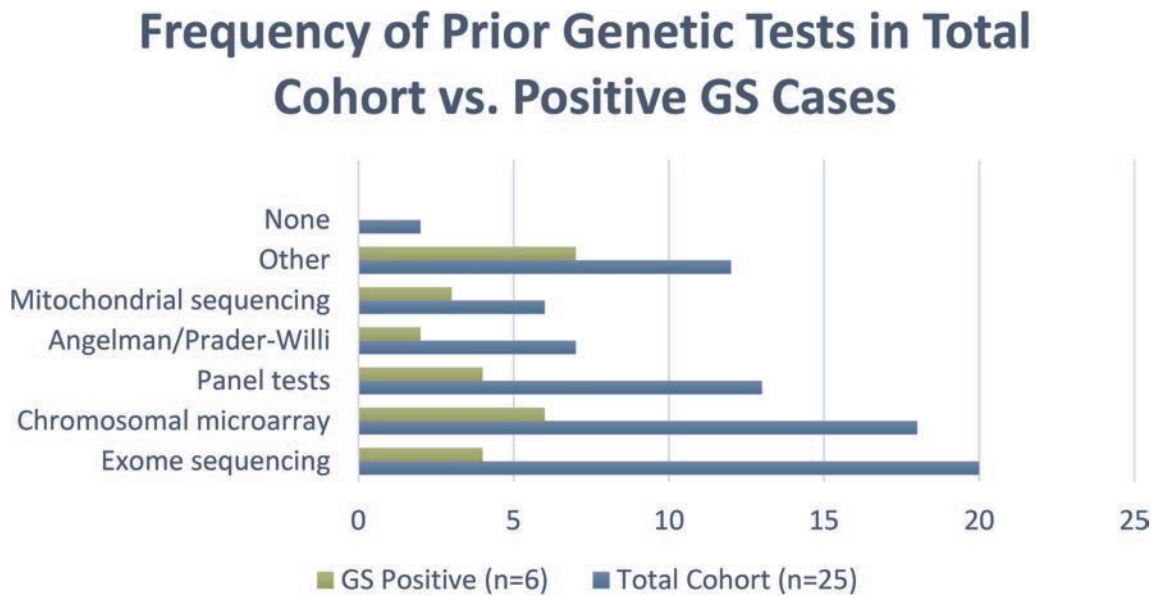

FIGURE 1. Abstract 96

TABLE 1. Abstract 96

Demographics	N=25
Gender (Male; Female)	12; 13
Average Age (range)	9.04 years (1.6-21.7)
Ethnicity	
White	20 (80%)
African American	1 (4%)
Asian American or Pacific Islander	1 (4%)
Middle Eastern	1 (4%)
First Nation American/Native American	1 (4%)
Not reported	1 (4%)
Prior genetic testing	
No prior genetic testing	2 (8%)
One genetic test	2 (8%)
Two genetic tests	4 (16%)
Three genetic tests	4 (16%)
Four or more genetic tests	13 (52%)
Types of prior genetic tests	
Whole-exome sequencing (WES)	20
Chromosomal microarray (CMA)	18

2020, the Child Neurology Foundation (CNF) adopted an initiative focused on shortening the diagnostic odyssey. To aide in this initiative, industry partner Illumina, Inc., sponsored a WGS project for a small cohort of probands with suspected rare disease.

Methods: An expert panel of neurologists selected by CNF developed inclusion criteria for case submission. WGS was completed by one of two CAP/CLIA approved laboratories. Clinical reports were sent directly to the ordering provider. IRB exemption was obtained retrospectively.

TABLE 1 (Continued)

Demographics	N=25
Panel test	13
Angelman/Prader Willi	7
Mitochondrial sequencing	6
Other (ie. single gene, karyotype, telomeres)	13
Genome sequencing results	
Positive	6 (24%)
Negative	9 (36%)
Variant of uncertain significance (VUS)	8 (32%)
Incidental finding*	3 (12%)

*G6PD variants in 2 probands; CLNC1 variant in 1 proband

Results: A total of 104 applications were received from 39 sites. The panel selected 25 cases from five geographically diverse sites in the U.S. with an average age of 9.04 years. (Table 1) All probands had multiple phenotypes, the most common being: seizures (18/25), global delay (17/25), hypotonia (13/25), and cognitive impairment (12/25). Prior genetic testing was reported in 23/25 (92%) probands, including 20 probands with prior whole-exome sequencing. (Figure 1) The overall diagnostic yield for WGS was 24% (6/25). Information on medical management changes was available for a limited number of cases and included cessation of unnecessary imaging, introduction to support groups, and altered health screening. Clinician interviews conducted by CNF revealed positive feedback on the experience and perceived value of WGS.

Conclusions: This experience demonstrates a unique way that industry and patient organizations can collaborate to engage patients and providers. Continued follow up on the impact of results on medical management is necessary to further highlight the value of WGS.

Keywords: Genetics, Rare Diseases

97. Precision diagnostics for GLUT1 disorders using deep mutational scanning

Tayebi N (St. Louis, MO), McCall K, Leon Ricardo B, Gurnett C

Objective: Accurate genetic diagnosis is critical, particularly as effective therapies become available for neurological disorders. The accumulation of variants of uncertain significance (VUS) creates a growing crisis that negatively influence the ability to implement precision therapies. The goal of this research is to demonstrate the utility of a growth assay to quantify the functional impact of variants in *SLC2A1,* the gene responsible for GLUT1 deficiency syndrome.

Methods: 55 variants across three exons were evaluated using a growth assay in HAP1-Lig4KO cell line. We created a donor library consisting of 15 variants for exon 10, 22 variants for exon 2 and 18 variants for exon 3 in pathogenic, benign, and VUS categories. Variant libraries were introduced into the HAP1-lig4KO cell line using exon specific CRISPR/Cas9. Cell populations were harvested and sequenced at days 5 and 11.

Results: By sequencing pools of cells at days5 and 11, we could quantitative determine the impact of variants on cell viability. As proof of principle, Nonsense and known pathogenic variants in all three exons dropped out of the population, while known benign variants were not depleted. In addition, *SLC2A1* missense variants in exon 10 (p.R458P) and exon 3 (p.W65R and G76S) identified in the patients with childhood onset epilepsy had intermediate functional effects in this assay.

Conclusions: Our quantitative functional data correlated with clinical phenotypes, suggesting that it can also be clinically useful for prognosis. Future work is needed to scale the assay such that every possible variant in *SLC2A1* can be quantitatively determined.

Keywords: Genetics

98. PTC Pinpoint CP Spectrum: A sponsored no-charge to patients 265-gene panel for patients with symptoms suggestive of CP and absence of risk factors for an acquired brain injury

Miller R (Liverpool, NY), Kopesky J, McLaughlin H

Objective: Cerebral palsy (CP) is one of the most common neurodevelopmental disorders affecting 2-3/1,000 livebirths. Studies find that 10-30% of cases have a genetic etiology. Diagnostic yield is suspected to be increased in patients without an environmental cause, such as an acquired brain injury. Identifying a genetic etiology has a significant impact on clinical management decisions. We report the utilization patterns and molecular diagnostic yield of a targeted, no-charge to patients sponsored gene panel program, PTC Pinpoint CP Spectrum.

Methods: Eligibility criteria: (I) symptoms suggestive of CP, (II) absence of risk factors for an acquired brain injury. Gene curation focused on genes associated with clinical phenotypes consistent with cerebral palsy. Physician-reported clinical history was collected. Diagnostic yield was calculated from results of tests ordered for 1683 individuals between 9/15/2020 (program inception) and 12/15/21.

Results: 166/1683 (10%) individuals had a definitive genetic cause of CP identified. There were causative variants identified in 59 different genes, with *SPAST* and *CTNNB1* being the most common cause in 19 patients and 18 patients, respectively. Providers from over 18 different specialties have utilized the panel. Age at testing varied greatly (ages 0-74) but the average age was 8 years.

Conclusions: PTC Pinpoint CP Spectrum is a valuable tool utilized by a variety of providers that can identify the underlying genetic cause for patients with CP of unknown etiology. The diagnostic yield is expected to improve with continued gene curation. This no-charge to patients sponsored gene panel program can be part of a tiered diagnostic approach for patients with CP.

Keywords: Genetics, Movement Disorders (including Cerebral Palsy), Rare Diseases

99. Exome Sequencing in 18,911 Individuals Affected by Autism Spectrum Disorder Suggests Broad Based Testing Approach

Lindy A (Gaithersburg, MD), Torene R, Mullegama S, McGee S, Retterer K, Kruska P

Objective: Evaluate the time to diagnosis and diagnostic outcome of exome analysis for individuals with autism, with and without comorbidities, and highlight genes not previously associated with autism spectrum disorders (ASD).

Methods: Retrospective analysis of exome data was performed on 13,024 trios (proband and parents), 2,989 duos, and 2,898 singletons (2.4 Male:Female ratio) affected by ASD, as designated by referring physician, from a commercial laboratory. Individuals were grouped as isolated ASD or syndromic. Syndromic autism was defined as having two or more comorbidities (dysmorphic features, seizures, developmental delay, muscle or skeletal abnormality).

Results: Positive findings were identified in 698 genes, 417 of which were absent from the Simon Foundation

Autism Research Initiative (SFARI) list. Individuals with syndromic and isolated ASD had a positive rate of 21% (3,147/14,957) and 7.9% (313/3,954), respectively. Only 17% of positive cases utilized exome analysis as a first tier test, whereas 83% of individuals with a positive finding had prior negative testing that included *FMR1* analysis (46%; 1,585/3,460), array CGH (78%; 2,684/3,460), or *FMR1* and CGH (41%; 1,405/3,460). Findings were identified in 1337 emerging genes not previously associated with ASD.

Conclusions: This large study demonstrates the genetic heterogeneity of ASD and the advantage of exome sequencing. Exome sequencing allows for gene discovery and new gene associations with ASD by using an agnostic approach. Reversing the current testing strategy to utilize exome analysis before more focused genetic testing would reduce the time to diagnosis for 83% of individuals, and especially for individuals with a syndromic presentation.

Keywords: Genetics, Cognitive/Behavioral Disorders (including Autism)

100. Natural History of Childhood Neurodegeneration in UBTF-Related Disease

Nagy A (Boston, MA), Molay F, Becker C, Gupta A, Eichler F

Objective: A specific variant in *UBTF* has recently been implicated in childhood-onset neurodegeneration characterized by an initial period of typical or mildly delayed development followed by regression. Affected individuals frequently experience movement disorders, including ataxia and dystonia, as well as epilepsy. This study aims to clarify the natural history of this rare disorder.

Methods: A REDCap survey of families of patients with a pathogenic variant in *UBTF* was conducted. Between March 2021 and February 2022, 52 surveys were started. Duplicate and incomplete responses were excluded. Ten unique responses were fully submitted, and these were included for analysis.

Results: The median age of the 10 subjects was 12.5 years (range 5-20 years). Symptom onset occurred at a median of 2.5 years. Six individuals received neurologic diagnoses, including autism, epilepsy, cerebral palsy, developmental delay, and ADHD, prior to their genetic diagnosis. Sleep difficulties (80%), adverse reactions to temperature extremes (50%), and chronic pain (40%) were commonly reported. Three respondents were diagnosed with seizures, while a fourth had clinical concern for seizures without a definitive diagnosis.All participants reported both motor and language regression (median age 3.75 years at onset, range 2-5 years). Of the eight participants who had undergone a procedure under anesthesia, three experienced subsequent regression. Three participants also reported regression following an illness.

Conclusions: This study involves the largest cohort with *UBTF*-related disease to date. Developmental regression was universal and in some cases was provoked by anesthesia or illness, highlighting the importance of provider and patient education and stressor avoidance when feasible.

Keywords: Genetics, Rare Diseases, Movement Disorders (including Cerebral Palsy)

101. A Cross-Sectional Study of the Neuropsychiatric Phenotype of CACNA1C-Related Disorder

Levy R (Palo Alto, CA), Timothy K, Bernstein J, Pasca S

Objective: *CACNA1C* encodes the L-type calcium channel Cav1.2. Specific gain of function pathogenic variants in *CACNA1C* cause Timothy syndrome (TS) with cardiac long QT, syndactyly, and neurologic and psychiatric symptoms. Recent publications highlight a broader spectrum of *CACNA1C*-related disorder (CRD) that includes isolated cardiac disease, isolated neurologic deficits, and TS. We found that Cav1.2 is involved in activity-dependent signaling and neuronal migration, but it is unknown how this leads to neuropsychiatric symptoms. We surveyed individuals with CRD to define the neuropsychiatric and developmental phenotype and thus guide research into the role of calcium channels in neural development.

Methods: Caregivers of and individuals with CRD completed an IRB-approved online survey of developmental milestones, neuropsychiatric symptoms, and diagnoses.

Results: 20 participants with germline variants completed the survey. The most common neuropsychiatric symptoms were developmental delay in 90%, incoordination in 70%, hypotonia in 65%, autism spectrum disorder in 50% (autistic features in 90%), epilepsy in 45%, and depression or anxiety in 15% of participants. There were no significant differences in most symptoms between participants with TS or non-cardiac CRD.

Conclusions: In our CRD cohort there was an increased incidence of multiple neuropsychiatric symptoms. These findings indicate the key role of Cav1.2 in brain development and the clinical importance of screening and therapeutically addressing neuropsychiatric symptoms in CRD. Future directions include deep phenotyping of neuropsychiatric symptoms and organoid and assembloid models of *CACNA1C* variants to elucidate shared molecular mechanisms and identify therapeutic targets.

Keywords: Genetics, Cognitive/Behavioral Disorders (including Autism), Rare Diseases

102. Muscle RNA sequencing facilitates detection of a pathogenic LAMA2 variant not identified by routine whole genome sequencing

Roose J (Akron, OH), Okur V, Owen N, Liu P, Moore S, Ginsberg M

Objective: RNA sequencing (RNA-seq) of muscle tissue has recently been demonstrated in the research setting to aid in diagnosis of inherited myopathies. We aimed to identify the molecular diagnosis in a patient with merosin-deficient congenital muscular dystrophy (MDC1A) following a negative trio whole genome sequencing (WGS) using commercially available RNA-seq.

Methods: This is a case report of a single patient. She presented shortly after birth with hypotonia, weakness, talipes eqinovarus and dysphagia. Creatine kinase levels exceeded 3,000 U/L (ULN: 190 U/L). Brain MRI at 3 months of age was normal, and muscle ultrasound demonstrated diffusely increased muscle echogenicity. A next generation sequencing panel revealed a single, maternally inherited pathogenic

variant in the *LAMA2* gene (NM_000426.3), c.2049_2050del (p.Arg683Serfs*21). Muscle biopsy with immunofluorescence staining confirmed the MDC1A diagnosis. Clinical WGS did not initially reveal a second pathogenic variant in the *LAMA2* gene, and RNA-seq of muscle tissue was performed.

Results: RNA-seq of muscle for the *LAMA2* gene revealed reduced expression of exons 38-65. Targeted WGS data reanalysis identified a paternally inherited, approximately 8Mb balanced inversion disrupting the *LAMA2* gene, Chr6:g.[129393858-137420408inv], in trans with the aforementioned pathogenic variant. The inversion was confirmed via fluorescence in situ hybridization.

Conclusions: Despite clinical access to WGS, patients with conditions including inherited myopathies may fail to obtain a molecular diagnosis. Clinical RNA-seq may lead to diagnoses in these challenging cases. We demonstrate the clinical utility of commercially available RNA-seq in identifying a pathogenic mutation in the *LAMA2* gene, not easily detected by conventional DNA sequencing technologies.

Keywords: Genetics, Neuromuscular Disorders

103. Use of exome sequencing in the evaluation of developmental delay/intellectual disability among child neurologists: Current practices, perspectives, and barriers

Cole J (St. Louis, MO), Aravamuthan B

Objective: Per American College of Medical Genetics 2021 guidelines, exome sequencing (ES) should be a first or second-line diagnostic test in people with developmental delay or intellectual disability (DD/ID). Noting this recent shift in diagnostic recommendations, we evaluated child neurologists' perspectives on ES for diagnostic evaluation for DD/ID.

Methods: Select members of the Child Neurology Society (CNS) and American Academy of Neurology (AAN) (based on relevant special interest group membership) were surveyed online from July-September 2021 on their perspectives regarding the use ES for diagnostic evaluation of people with DD/ID. Demographic predictors of their perspectives were assessed using logistic regression. Conventional content analysis was used to determine the barriers they cited to the use of ES in clinical practice.

Results: Of 184 respondents, 27% rarely include ES as part of their diagnostic evaluation for DD/ID (<5% of the time). However, 64% stated insurance should cover ES as a first-tier test for DD/ID. Longer duration of practice and higher percentage of patients seen with DD/ID were significant predictors of increased use of ES for DD/ID evaluation ($p<0.001$). The most commonly cited barriers to obtaining ES were lack of access to geneticists/counselors and lack of insurance approval.

Conclusions: We demonstrate a gap between clinical guidelines and clinical practice regarding the use of ES for DD/ID evaluation potentially due to systems-level access barriers. These results pose advocacy targets for our field, particularly with regards to insurance coverage for ES.

Keywords: Genetics, Cognitive/Behavioral Disorders (including Autism)

104. Phenotypic and Genotypic Heterogeneity Related to Gene Defects in TBL1XR1

Nagy A (Boston, MA), Molay F, Brito Pires C, Grant N, Becker C, Neumeyer A, Eichler F

Objective: Genetic causes for autism and other common neurologic disorders are increasingly recognized. *TBL1XR1* is implicated in Pierpont Syndrome (PS), a disorder of developmental delay, poor growth, and dysmorphism, and in non-PS autism, epilepsy, and neurodevelopmental delay. *TBL1XR1*-related disease has not been fully characterized in the literature. This study examines the spectrum of *TBL1XR1*-related disease.

Methods: A REDCap survey of families of patients with *TBL1XR1*-related disease was conducted. Between January 2021 and February 2022, 105 caregiver surveys were started with 35 completed and submitted.

Results: The median age of the 35 subjects with completed and unique surveys was 8 years (range 1-25 years). Twenty-six individuals received a neurologic diagnosis, most commonly autism (31.4%), prior to genetic diagnosis. Thirteen were diagnosed with PS, despite genetic heterogeneity not previously reported in PS. Development ranged from near-normal to severe delay. A minority experienced regression (14.3% reporting motor regression, 22.9% language regression, 8.6% social regression). Twelve experienced seizures (median age at onset 2.5 years, range 0.4-23.2 years). Over half of those with language regression also experienced seizures. Chiari malformations, hearing and vision issues, and ADHD were commonly reported. Twenty-six respondents provided their genetic variants, the majority of which were not previously reported in the literature.

Conclusions: This study reports the largest cohort of patients with *TBL1XR1*-related disease to date. Respondents describe developmental delay, with some reporting regression. Seizures, regardless of type, were associated with language regression. The interplay between seizures and developmental regression is not fully explained and remains an area for future exploration.

Keywords: Genetics, Rare Diseases, Cognitive/Behavioral Disorders (including Autism)

105. The phenotypic spectrum of GTPBP3 mutation related disease: a case series

Bhayana K (Cleveland, OH), Parikh S

Objective: GTPBP3 is an evolutionarily conserved multidomain protein, involved in posttranscriptional modification of mt-tRNA. Prior studies identified individuals with cardiomyopathy, hypotonia, developmental delay, seizures, visual impairment, and/or lactic acidosis. Most patients had decreased mitochondrial complex (I, IV) activity on muscle biopsy. We described a case series of 8 patients with novel presentations of GTPBP3 mutation.

Methods: Clinicians were notified of the project via a genetic and metabolic disease message board. 8 new patients with this ultra-rare disorder were identified. Data was collected from 5 institutions via retrospective chart review.

Results: 62.5% patients presented with developmental delay and/or fatigue, 37.5% had seizures, 25% had hypotonia,

12.5% had vision or hearing impairment. Other neurologic symptoms included sleep disorders and headaches. 12.5% had a history of consanguinity. The inheritance was recessive. All patients were diagnosed by 18 years of age. 87.5% patients are alive. MRI showed T2-signal abnormality with restricted diffusion in bilateral thalami in 62.5% patients; 75% had elevated lactic acid, and 62.5% underwent muscle biopsy showing decreased complex I, IV activity. 75% patients had LVH on ECHO.

Conclusions: The clinical features in this cohort were similar to those described previously. Sleep difficulties, headaches and hearing impairment were some additional symptoms.

The findings are often similar to Leigh syndrome, which can be expected, based on defective mitochondrial energy production. Prior studies reported deaths in ~50% patients (cardiac causes majorly), however, most patients in our cohort are alive (one status-post cardiac transplant). Continued reporting for this gene is essential in determining long-term prognosis and potential for treatment.

Keywords: Genetics, Rare Diseases

106. Qualitative studies on SMN1 gene and genetic couselling of spinal muscular atrophy

Bouayed Abdelmoula N (Sfax, Tunisia), Abdelmoula B

Objective: Spinal muscular atrophy (SMA) is one of the most common autosomal recessive diseases, affecting approximately one in 10,000 live births. SMA is caused by a deficit of the survival of motor neuron protein (SMN), which is encoded by two genes, SMN1 and SMN2 at 5q13. Due to a specific SNP, SMN2 produces a transcript that cannot completely prevent neuronal cell death at physiologic gene dosages. Whereas, PCR-RFLP analysis can detect the homozygous absence of SMN1 in approximately 95% of patients with clinically typical SMA, carrier testing for SMA is relatively complex and requires quantitative PCR to determine SMN1 copy number. The aim of this study was to report our SMA genetic testing experience, combined with appropriate genetic counselling.

Methods: DNA extraction was carried out using standard procedures (Phenol-Chloroform method). A PCR technique was developed in our department, to amplify SMN1 exon 7 and SMN1 exon 8. Upstream and downstream primers were designed using PCR in silico platform. Restriction enzyme digestion with respectively DraI and DdeI was used to detect SMN1 deletions and to differentiate between the highly homologous SMN1 and SMN2 genes. Ten SMA patients and their parents were analyzed.

Results: All patients were detected positive with apparent homozygous SMN1 exon 7 deletion. Additional exon 8 deletion was detected in 75% of cases. A comprehensive genetic counselling was delivered to the families and molecular prenatal diagnosis was considered for two families.

Conclusions: We conclude that PCR-RFLP of SMN remains an accurate and reproducible method for detection of SMA patients with a SMN1 deletion.

Keywords: Genetics, Neuromuscular Disorders, Neonatal & Fetal Neurology

107. Hypocitrullinemia on Newborn Screening as an early indicator of Leigh Syndrome due to homoplasmic m.8993T>G variant

Treitel R (New York, NY), Moore E, McLaughlin J, Frigeni M

Objective: Leigh Syndrome (LS) caused by homoplasmic m.8993T>G variant has been previously associated with hypocitrullinemia and multiple carboxylase deficiency-like biochemical phenotypes. This case report further supports the crucial role of Newborn Screening (NBS) as a potential early indicator of LS.

Methods: The authors report on a male infant with hypocitrullinemia on NBS diagnosed with m.8993T>G associated LS after developing intractable seizures at age 2 months.

Results: The patient's first and second NBS were notable for borderline hypocitrullinemia. A third NBS was obtained and normal, thus no workup was pursued. At age 2 months, he was hospitalized in the setting of perioral cyanosis and lactic acidosis (5.3 mmol/L). During hospitalization, he developed seizures of left temporal origin refractory to treatment. Brain MRI demonstrated large generalized region of non-enhancing signal abnormality without significant diffusion restriction. Metabolic workup and rapid whole exome sequencing with mitochondrial DNA analysis were obtained. Results demonstrated hypocitrullinemia (5.7 mcmol/L), elevated 3-hydroxyisovalerylcarnitine (0.18 mcmol/L) and propionylcarnitine (0.98 mcmol/L), and urinary lactate and pyruvate excretion. Mitochondrial DNA testing demonstrated a homoplasmic m.8993T>G pathogenic variant in the MT-ATP6 gene, consistent with a diagnosis of LS.

Conclusions: Hypocitrullinemia and elevation of 3-hydroxyisovalerylcarnitine and propionylcarnitine have been previously reported in association with homoplasmic m.8993T>G variant [1, 2, 3]. In line with other reported cases, patient was started on citrulline and biotin supplements, but passed away at age 4 months in the setting of a severe upper respiratory tract infection. Hypocitrullinemia and 3-hydroxyisovalerylcarnitine elevation should prompt evaluation for LS, as early diagnosis and prompt management may improve outcome.

Keywords: Genetics, Rare Diseases

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HEADACHE/MIGRAINE

108. The Efficacy of Nerve Block Injections in the Pediatric Population

Kravitz A (Washington, DC), McCracken E, DiSabella M, Strelzik J

Objective: Migraine is a common disorder in the population. The use of nerve block injections to treat migraine has been studied in adults however their evidence in pediatrics is limited. This study aims to evaluate the efficacy of nerve block injections in pediatric patients with migraine.
Methods: Patients who presented at the Headache Clinic at Children's National Hospital between 2020 and 2022 and were treated with occipital, supra-orbital, supratrochlear or auriculotemporal nerve block injections were asked to complete a survey about their symptoms before and after the procedure.
Results: Sixteen patients were included in the study who ranged in age from 10 to 19 years of age with a mean age of 15. Participants were 75% female (n=12) and 25% male (n=4). The majority of patients treated were diagnosed with migraine without aura (62%, n=10) or occipital neuralgia (44%, n=7). Headaches were reported to be most common in the frontal (50%, n=8) and parietal (81%, n=13) head regions. The majority of patient's received a greater occipital (N=13) or a lesser occipital nerve block injection (N=5). Pain scores were significantly decreased after the injection for all participants (p-value= .003, N=16), and those with occipital neuralgia had the most significant reduction in pain (p-value= .007, N= 10).
Conclusions: Nerve block injections are effective in reducing pain in pediatric patients with migraine without aura and occipital neuralgia. Future large-scale studies including children and adolescents with primary and secondary headache disorders would help to gain a better understanding of response rates and indications for the procedure.
Keywords: Headache/Migraine

109. An Unusual Presentation of Cerebrospinal Fluid Leak Due to the Rupture of an Occult Myelomeningocele in a Typically Developing Adolescent.

Avasarala P (Woodbridge, VA), Nasr L, Lateef T

Objective: Headaches presenting to pediatric emergency departments are mostly attributable to common self-limited conditions such as upper respiratory illnesses or migraine and imaging is typically reserved for cases that may require prompt specific management.Objective: We present a case of a 17-year-old male with acute onset, severe positional headache that was alleviated by lying down.
Methods: Case Report.
Results: While his headache was suggestive of an internal spinal fluid leak, there was no obvious cause for a leak, such as a spinal tap, spinal surgery or trauma to the head or neck. Brain and spine imaging revealed abnormal intraspinal extrathecal fluid collection extending from the cervical through lumbar regions and a large sacral meningocele with scalloping of the sacral bone suggesting chronic, slow, growth. The meningocele had likely ruptured during reported strenuous exercise, as CSF was tracking throughout the spinal canal in the extradural space. Myelogram with serial imaging demonstrated a connection between the inferior thecal sac and the meningocele, as well as escapement of contrast dye through the wall of the meningocele into the epidural space. Surgery was successfully completed and included sacral laminectomies, exploration/ ligation of sacral meningocele and closure of the congenital neural tube defect. Since surgery, his headches have completely resolved.
Conclusions: This is the first reported case where a CSF leak developed due to rupture of an undiagnosed myelomeningocoele. This case highlights the importance of taking a good history and pursuing emergent MR imaging, especially if the history suggests a secondary headache that might require prompt intervention.
Keywords: Headache/Migraine, Neuroimaging

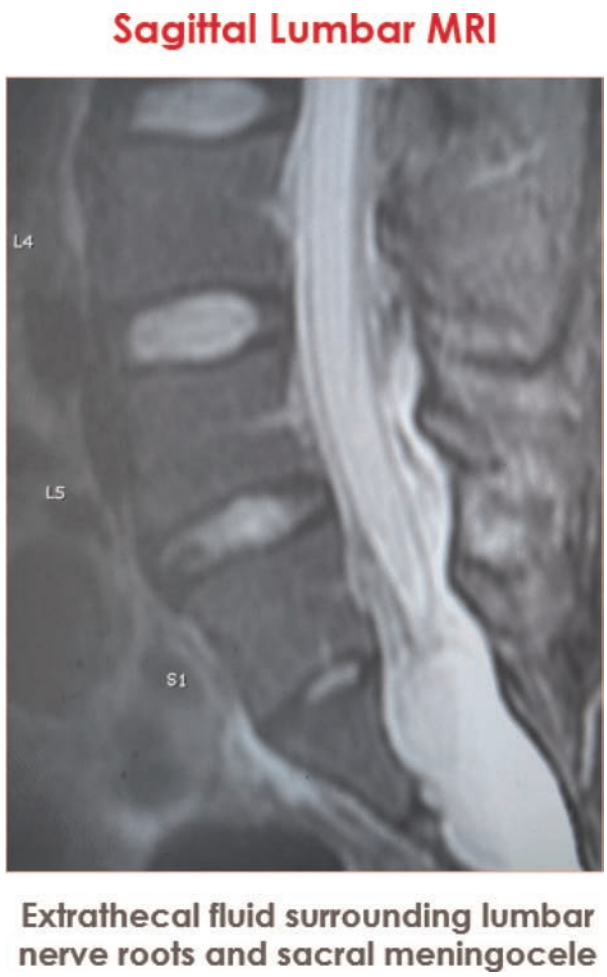


FIGURE 1. Abstract 109

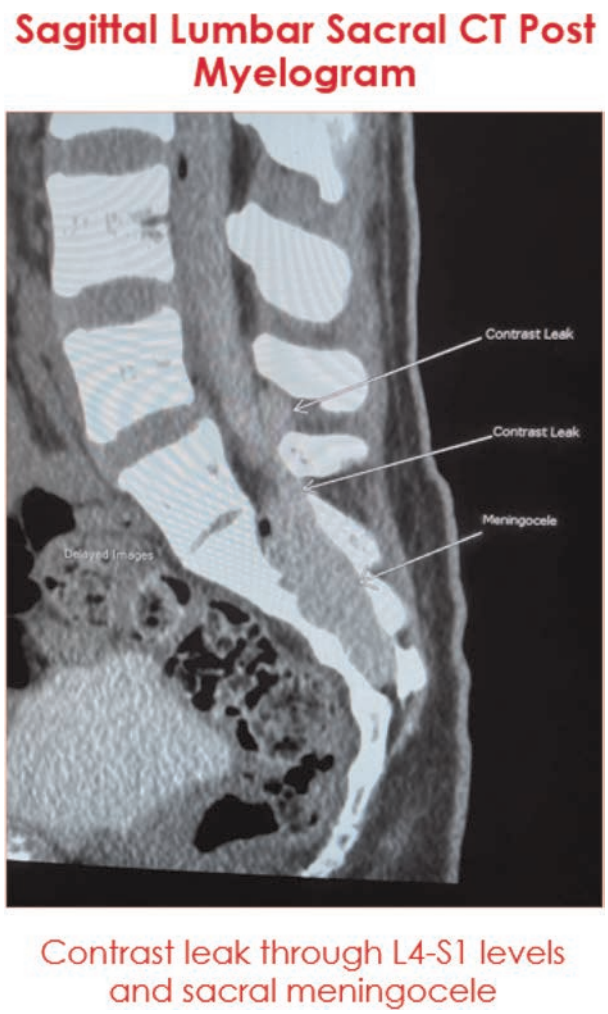


FIGURE 2. Abstract 109

INFECTIONS/ NEUROIMMUNOLOGY

110. Acute Flaccid Myelitis: role for enterovirus-induced nuclear pore complex dysfunction in pathogenesis

Elrick M (Baltimore, MD), Jayaram M, Rothstein J

Objective: Acute flaccid myelitis (AFM) is a polio-like infectious disorder of children linked to Enterovirus D68 (EV-D68) characterized by motor neuron toxicity resulting in paralysis. The mechanisms underlying selective motor neuron toxicity are unknown, and effective therapies are lacking. Dysfunction of the nuclear pore complex (NPC) has been implicated in promoting neurotoxicity in multiple neurodegenerative disorders of motor neurons. Enterovirus proteases are known to cleave the nucleoporins that comprise the NPC. We therefore aim to determine the extent to which this NPC disruption contributes to motor neuron toxicity in AFM.

Methods: We determined the impact of EV-D68 proteases on nucleoporin levels and cleavage in cell lines and in vitro, respectively. In addition, we utilized reporters of protein and RNA transport to evaluate the impact of these deficits on nucleocytoplasmic transport in iPS-derived motor neurons. Further, we assayed the impact of EV-D68 protease expression on iPS motor neuron toxicity.

Results: The expression levels of 18 out of 30 nucleoporins was altered by EV-D68 proteases. A subset of these were direct protease substrates. These deficits resulted in perturbations of protein and RNA transport, and decreased survival of motor neurons.

Conclusions: NPC disruption is a feature of EV-D68 infection of human motor neurons and causes toxicity that may contribute to the pathogenesis of AFM. Further work to evaluate the NPC as a therapeutic target for neuroprotection in AFM is warranted.

Keywords: Infections/Neuroimmunology, Neuromuscular Disorders

111. Sleep Characteristics in Pediatric Anti-NMDA Receptor Encephalitis

Gombolay G (Atlanta, GA), Morris M, Loerinc L, Blackwell L, Howarth r

Objective: Discuss sleep dysfunction, its association with one-year outcomes and sleep/sedation medications used in pediatric anti-NMDA receptor encephalitis (pNMDARE).

Methods: Institutional Review Board approved retrospective data collection at Children's Healthcare of Atlanta (2010-2021). Inclusion criteria were: positive CSF anti-NMDA receptor antibodies. One-year outcomes were assessed with the pediatric modified Rankin score (mRS). Statistical analyses were performed (SAS 16.0: Cary, N.C.).

Results: Thirty-nine/forty-one (95.1%) had sleep problems (insomnia: 87.8% and hypersomnia: 7.3%). The most common sleep medications were melatonin, trazodone, and diphenhydramine. The most common sedating medications included midazolam, fentanyl, and propofol, but no differences were observed in sedating medication type and poor outcomes at one year.Thirty had one-year outcomes with good (mRS ≤ 2) in 63.3% and poor outcomes (mRS ≥ 3) in 36.7%. Twenty-two percent reported sleep problems at one year. Zolpidem was more commonly used in poor (45.5%) compared to good outcomes (5.3%) at one year (p=0.0156). Sleep problems at onset did not associate with one-year outcomes, but sleep complaints at one year was the only significant predictor for poor mRS at one year (Odds ratio 5.8, 95% confidence interval: 1.2, 29.4) in a backwards elimination logistic regression model. This model included sleep complaints at onset, sleep complaints at one year, and risk factors for poor outcomes (abnormal EEG/MRI, treatment delay, second-line therapy, and ICU admission).

Conclusions: Sleep problems are common in pNMDARE and one-year sleep problems may predict poor outcomes. Further investigation should investigate if sleep disturbance at one year reflects disease severity versus contributes to poor outcomes.

Keywords: Infections/Neuroimmunology

TABLE 1: Demographic and clinical characteristics of pediatric anti-NMDA receptor encephalitis patients from 2010 to 2021 (N=41). Sleep and sedation medications are also included. Abstract 111

		mRS at one year (N=30)	
	Total (N=41)	**mRS good (N=19)**	**mRS poor (N=11)**
Age in years, Mean (SD)	11.1 (5.2)	12.0 (4.5)	11.5 (5.9)
Sex M:F, N (%)	12:29 (29.3:70.7)	5:14 (26.3:73.7)	3:8 (27.3:72.7)
Race N (%)			
White	11 (26.8)	6 (31.6)	2 (18.2)
Black	21 (51.2)	8 (42.1)	8 (72.7)
Black/White	1 (2.4)	1 (5.3)	0 (0)
American Indian/Alaska Native	0 (0	0 (0)	0 (0)
Asian	0 (0)	0 (0)	0 (0)
Unknown	8 (19.5)	4 (21.1)	1 (9.1)
Ethnicity N (%)			
Hispanic	13 (31.7)	8 (42.1)	1 (9.1)
Non-Hispanic	26 (63.4)	11 (57.9)	10 (90.9)
Unknown	2 (4.9)	0 (0)	0 (0)
MRI abnormal, N(%)	18 (43.9)	8 (42.1)	7 (63.6)
EEG abnormal, N(%)	35 (85.4)[1]	15 (79.0)	11 (100.0)
CSF WBC per mm^3, median (IQR)	8 (3, 38)[4]	8 (3, 38)[1]	6 (2, 57)
Sleep problems at onset, N (%)	39 (95.1)	18 (94.7)	10 (90.9)
Sleep problems at one year, N (%)	9 (22.0)[13]	4 (21.1)[2]	5 (55.6)
First line treatment[a] N (%)	41 (100.0)	19 (100.0)	11 (100.0)
Second line treatment[b] N (%)	30 (73.2)	12 (63.2)	11 (100.0)
Hospital LOS in days, median (IQR)	23 (14, 40)	16 (12, 23)	31 (17,57)
Rehab LOS in days, median (IQR)	36 (23, 47)	24.5 (14.0, 35.5)[3]	51 (28, 64)
ICU admit, N (%)	29 (70.7)	10 (52.6)	10 (90.9)
Intubated, N (%)	19 (46.3)	7 (36.8)	6 (54.6)
Time to first line[c] in days, median (IQR)	13 (6, 16)[8]	13 (6, 15)[4]	19 (7, 24)[2]
Time to second line[d] in days, median (IQR)	29 (21, 39)[16]	25.5 (21.0, 31.0)[9]	29 (17, 41)[2]
Tumor present, N (%)	5 (12.2)	1 (5.3)	2 (18.2)
Time to improvement[e] in days, median (IQR)	16 (7, 39)[6]	8 (5, 18)[4]	33 (5, 57)[1]
Did not improve in 4 weeks[f]	11 (26.8)	1 (5.3)	5 (45.5)
Medications used for sleep			
Melatonin	36 (87.8)	16 (84.2)	10 (90.9)
Zolpidem	10 (24.4)	1 (5.3)	5 (45.5)

TABLE 1 (Continued)

	Total (N=41)	mRS at one year (N=30)	
		mRS good (N=19)	mRS poor (N=11)
Amitriptyline	4 (9.8)	1 (5.3)	3 (27.3)
Mirtazapine	4 (9.8)	1 (5.3)	2 (18.2)
Ramelteon	0 (0)	0 (0)	0 (0)
Chloral hydrate	6 (14.6)	2 (10.5)	3 (27.3)
Clonidine	13 (31.7)	6 (31.6)	3 (27.3)
Diphenydramine	14 (34.1)	6 (31.6)	5 (45.5)
Doxepin	0 (0)	0 (0)	0 (0)
Eszopiclone	2 (4.9)	0 (0)	1 (9.1)
Gabapentin	2 (4.9)	0 (0)	2 (18.2)
Guanfacine	1 (2.4)	0 (0)	1 (3.3)
Quetiapine	10 (24.4)	4 (21.1)	3 (27.3)
Trazodone	26 (63.4)	9 (63.3)	9 (81.8)
Risperidone	3 (7.3)	1 (5.3)	0 (0)
Ziprasidone	2 (4.9)	1 (5.3)	1 (9.1)
Medications used for sedation			
Dexmedetomidine	20 (48.8)	5 (26.3)	6 (54.6)
Fentanyl	23 (56.1)	11 (57.9)	8 (72.7)
Ketamine	8 (19.5)	2 (10.5)	2 (18.2)
Midazolam	25 (61.0)	13 (68.4)	7 (63.6)
Propofol	21 (51.2)	9 (47.4)	6 (54.6)
Sevoflurane	0 (0)	0 (0)	0 (0)

mRS: modified Rankin score, SD: standard deviation, M: male, F: female, MRI: magnetic resonance imaging, CSF: cerebrospinal fluid, WBC: white blood cell count, LOS: length of stay, ICU: intensive care unit

[a]First line treatment included steroids, intravenous immunoglobulin, plasmapheresis

[b]Second line treatments included: rituximab, cyclophosphamide

[c]Time to first line treatments defined as number of days from symptom onset to initial date for first line treatments

[d]Time to second line treatments defined as number of days from symptom onset to initial date for second line treatments

[e]Time to improvement defined as numbers of days from the initial date of first treatment administered to date that patient began to improve

[f]Defined as improved after 4 weeks of treatment onset

[1]1 missing datapoint

[2]2 missing datapoints

[3]3 missing datapoints

[4]4 missing datapoints

[6]6 missing datapoints

[8]8 missing datapoints

[9]9 missing datapoints

[13]13 missing datapoints

[16]16 missing datapoints

112. Application of Optimization Methods to Distinguish between Definite Pediatric Infectious and Autoimmune Encephalitis within One Week of Symptom Onset

Kammeyer R (Aurora, CO), Pointon T, Ward R, Piquet A, Yeshokumar A, Schreiner T

Objective: To apply an optimization algorithm to distinguish between cases of definite infectious (IE) and autoimmune encephalitis (AE) within the first week after neuropsychiatric (NP) symptom onset

Methods: Patients presenting with encephalitis to Children's Hospital Colorado between Jan 2000 and Feb 2021 were identified through retrospective chart review. Patients were included if a definite infectious etiology was determined or meeting Cellucci criteria for pediatric AE, and if presenting with seizure or AMS. Detailed temporal data for onset of each constitutional and NP symptom was recorded. The proportion of patients with individual symptoms/diagnostic findings at day 3 after NP symptom onset were compared using a Z-test; day 3 was chosen as a focus given a goal for rapid antibiotic / immunotherapy decisions after initial presentation. A brute force optimization algorithm was created in Matlab, set to optimize accuracy in identification of AE.

Results: A total of 47 patients (25 AE and 22 IE) were identified. Given the size of the data cohort, only the 4 most significant parameters were entered into optimization. The combination of two of negative infectious rapid PCR testing, absence of fever, or personality/behavioral change gave an accuracy of 96% and specificity of 100% for identifying AE at day 3 after NP symptom onset.

Conclusions: A combination of clinical and paraclinical factors may be useful in discerning between AE and IE in early stages of illness and allow early treatment initiation for AE. However, validation with a separate cohort will need to be performed to confirm utility.

Keywords: Infections/Neuroimmunology, Critical Care

113. Initial Disease Severity Predicts Executive Functioning in Children with anti-N-methyl-d-aspartate receptor encephalitis (ANMDARE)

Semerjian C (Washington, DC), Kahn I, Suslovic W, Doslea A, Matuska E, Fleming M, Wells E, Sepeta L

Objective: Executive functioning (EF) and memory deficits are primary cognitive concerns following anti-N-methyl-d-aspartate receptor encephalitis (ANMDARE) in adults and children, although predictors of cognitive outcomes remain poorly understood. Delay in treatment is predictive of worse outcomes for adults (Finke et al., 2012), but this has not been reported with children (deBruijn et al., 2018). We aim to fill this gap by investigating predictors of memory and EF in children with ANMDARE.

Methods: We retrospectively identified 12 pediatric patients (mean age=11.6, SD=4.2) with ANMDARE who underwent neuropsychological evaluation including measures of memory and EF (mean time since diagnosis=21.1 months). Linear regression models examined several predictors of outcome: premorbid neurodevelopmental concerns, length of hospital stay (LOS), modified Rankin Scale (mRS at admission), and other disease-related factors (e.g., abnormal MRI at admission).

Results: Approximately one-third of parents reported elevated everyday EF concerns, while mean scores were broadly average across objective memory and EF measures. MRS predicted ratings of daily EF overall, accounting for 60% of the variance (p=.01, n=10), as well as metacognitive skills at the trend level (p=.056, R^2=.427, n=10). LOS predicted EF across objective and parent-report measures (BRIEF-2 ERI, p=.02; TOL-Dx, Total Correct, p=.04), accounting for 55-68% of variance respectively. Interestingly, history of premorbid neurodevelopmental concerns also predicted higher-order executive planning (TOL-Dx Total Correct, p=.03, R^2=.629). No variables predicted memory performance.

Conclusions: Initial disease severity is helpful in predicting EF and self-regulation in children with ANMDARE. Further study with additional patients will be important to determine its utility in informing prognosis.

Keywords: Infections/Neuroimmunology, Cognitive/Behavioral Disorders (including Autism)

114. Refractory Pediatric NMDA Receptor Encephalitis: A Case Series

Rospigliosi D (Houston, TX), Kannan V, Adeseye V, Lotze T, Lai Y-C, Muscal E, Shukla N

Objective: Management protocols for pediatric NMDA receptor encephalitis (NMDARE) increasingly recommend anti-CD-20 agents following first-line anti-inflammatory therapy. Even with early, aggressive treatment, some patients exhibit refractory disease or recurrences. Our objective is to characterize clinical features of these patients to identify potential predictive risk factors and treatment escalation targets.

Methods: We performed IRB-approved retrospective, descriptive review of patients in our institutional NMDARE database (2011-2021). Refractory disease was defined as lack of neurological improvement within 1-3 months, or recurrent relapse, after standardized treatment protocol (steroids, IVIg, pheresis for ICU patients, and two doses of rituximab 500mg/m^2). Demographics, clinical information, and diagnostic results from refractory patients were collected.

Results: 8/73 (10.9%) patients met criteria for refractory NMDARE (median age 10.0 years, IQR 8.3-14.0. 2 male, 6 female). Median days from symptom onset to first treatment was 12.5 (IQR 8.5-18.8), to detection of +NMDA Ab was 20.5 (17.8-24.0), and to rituximab was 27.5 (26.5-31.0). All were critically ill with seizures and respiratory failure. 2 (25%) had associated ovarian teratoma. Oligoclonal bands were tested in 6, with 4 resulting positive (67%). 7 had confirmed B-cell depletion after rituximab. Post-rituximab NMDA titers persisted in serum in 5 (63%) and CSF in 8 (100%). Immune therapy escalation is summarized in Table 1.

Conclusions: Severe initial presentation is consistent among our refractory patients. The contribution of other factors such as oligoclonal bands and time to diagnosis/treatment are less clear, and warrant inter-group comparison with non-

Table 1. Timing and modalities of immune therapy escalation. Abstract 114

Patient	Days from 1st rituximab to immune therapy escalation	Immune therapy agents	Dosing
1	192	Repeat rituximab Mycophenolate	500 mg/m^2 x2 1000 mg BID
2	143	Cyclophosphamide	500 mg/m^2 monthly
3	377	Repeat rituximab	500 mg/m^2 x2
4	234	Repeat rituximab	500 mg/m^2 x2
5	49	Tocilizumab Cyclophosphamide	8-12 mg/kg monthly 500 mg/m^2 monthly
6	44	Tocilizumab Cyclophosphamide	8 mg/kg monthly 500 mg/m^2 monthly
7	95	Tocilizumab	8 mg/kg monthly
8	393	Repeat rituximab Tocilizumab Mycophenolate	500mg/m^2 x2 10 mg/kg monthly 500mg BID

refractory patients. Persistence of serum and CSF titers despite B-cell depletion may inform future treatment escalation choices.

Keywords: Infections/Neuroimmunology, Critical Care

115. Number of clinical seizures during hospitalization is associated with long-term neurologic and neurocognitive outcomes in pediatric cerebral malaria

Clark D (Columbus, OH), Andrews A, Muller D, Bond C, Opoka R, Idro R, Bangirana P, Witten A, Sausen N, Birbeck G, John C, Postels D

Objective: Cerebral malaria (CM) incidence is highest in children less than 5 years old. Clinical seizures are common. Mortality is 15 – 50%. At hospital discharge, 10 – 30% of survivors have neurologic abnormalities; 25 – 50% have neurodevelopmental impairment. We evaluated the association between the number of clinical seizures during hospitalization with long-term neurologic and neurocognitive sequelae in CM survivors.

Methods: We enrolled children 6 months to 12 years old with CM at Mulago Hospital (Kampala, Uganda) between 2008 and 2013. Trained hospital personnel counted seizures. We performed neurological examinations and/or neurocognitive testing at hospital discharge, one week later, and 6-, 12-, and 24-months. We assessed neurocognitive outcomes using age-appropriate standardized neuropsychological tests.

Results: We evaluated 144 CM survivors. The mean number of seizures in children with and without neurologic deficits at hospital discharge was similar (1.6 vs. 1.2, respectively, p=0.35). Children with more seizures had higher odds of persistent neurologic abnormalities. Children with 6-month neurologic deficits had a mean of 4.9 seizures (OR 1.44; p=0.004). Those with 24-month deficits had a mean of 8.6 seizures (OR 1.76; p=0.001). Seizures were associated with

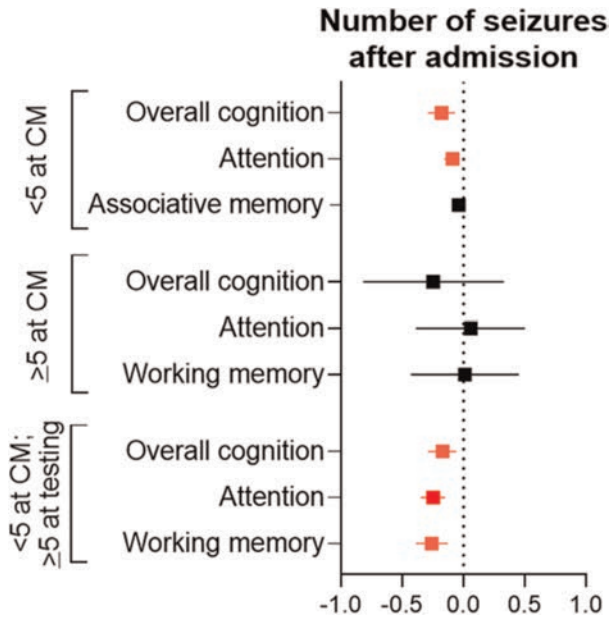


FIGURE 1: Relationship of clinical seizures with cognitive outcomes over a 24-month follow-up period in Ugandan children with cerebral malaria (CM) aged <5 years and ≥5 years. Plots represent beta coefficients (95% CI) from linear mixed-effects models adjusted for age, socioeconomic status, and home environment z-score. Red indicates significant result. Abstact 115

Table 1: Association of number of clinical seizures during hospitalization with the presence of neurologic deficits at various time-points. Abstract 115

	Number of clinical seizures during admission			
Neurologic Deficit (ND)	**ND, mean (SD) (n)**	**No ND, mean (SD) (n)**	**OR (95% CI)**	**P-value[a]**
Discharge	1.6 (3.3) (55)	1.2 (1.6) (93)	1.07 (0.93, 1.23)	0.35
6 months	4.9 (6.6) (10)	1.1 (1.5) (133)	1.44 (1.13, 1.85)	**0.004**
12 months	7.2 (7.8) (6)	1.1 (1.5) (138)	1.59 (1.19, 2.13)	**0.002**
24 months	8.6 (7.8) (5)	1.1 (1.5) (138)	1.74 (1.25, 2.43)	**0.001**

[a]Binary logistic regression

worse cognition in children <5 years: each additional seizure changed overall cognitive z-score by -0.18 (95% CI -0.29 to -0.07; p=0.001).
Conclusions: Increasing number of clinical seizures during hospitalization is associated with long-term neurologic deficits and adverse neurocognitive outcomes in children with CM. To improve neurological and neurocognitive outcomes in CM survivors, consideration should be given to developing novel methods to decrease clinical seizure burden in these gravely ill children.
Keywords: Infections/Neuroimmunology, Cognitive/Behavioral Disorders (including Autism)

116. Clinical and Demographic Characteristics of Pediatric anti-NMDAR Encephalitis

Sandweiss A (Houston, TX), Jiang Y, Erickson T, Muscal E, Murray K

Objective: Anti N-methyl-d-aspartate receptor (NMDAR) encephalitis is a specific autoimmune CNS disorder that decouples electrochemical synapses from their neuronal network, causing seizures, neuropsychiatric symptoms, movement problems, and autonomic dysfunction. Although well studied in the adult population, the clinical characteristics and potential triggers in pediatric cases of anti-NMDAR encephalitis are not well understood. Our objective is to characterize the patients with anti-NMDAR encephalitis and identify the most common presenting symptoms and etiologies.
Methods: We retrospectively analyzed patients with anti-NMDAR at Texas Children's Hospital (TCH) between 2010 and 2021.
Results: Of the 65 pediatric cases at TCH, our cohort is 65% female and 62% Hispanic, which is 1.6 times higher than the demographics of our TCH patient population and that of the Houston Metropolitan area at large (Harris County, 39% Hispanic). The average age of onset in our pediatric cohort was 7.2 years (range 3 months to 17.9 years). Post-herpetic NMDAR encephalitis and ovarian teratoma associated encephalitis made up 12.3% and 4.6% respectively. Among the idiopathic NMDAR encephalitis group, the most common presenting symptom was focal weakness associated with altered gait and speech regression. Within our cohort, 100% had behavioral/cognitive symptoms, 79% had seizures, 73% had speech problems, 67% had movement disorder, and 61% had memory deficits.
Conclusions: Our study describes the clinical characteristics which help define the presenting symptoms and potential etiologies in a heterogenous population from the largest single center pediatric cohort of anti-NMDAR encephalitis to date.
Keywords: Infections/Neuroimmunology

117. Steroid Un-Responsive Encephalopathy Associated with Autoimmune Thyroiditis (SUEAT) in Pediatric Patients.

Rathore G (Omaha, NE)

Objective: Steroid Responsive Encephalopathy associated with autoimmune thyroiditis (SREAT) is a rare condition, with only a few isolated cases reported in children. Marked clinical improvement following treatment with steroids, is a hallmark of SREAT. We report a series of children with encephalopathy associated with thyroid antibodies who are refractory to steroid monotherapy.
Methods: An IRB approved chart review was conducted on patients <18 years diagnosed with autoimmune encephalitis. A retrospective analysis of clinical features, diagnostic tests, response to therapy and long term follow up was conducted on patients positive for Thyroperoxidase (TPO) antibodies.
Results: 52 patients <18 years were diagnosed with autoimmune encephalitis, 10 (19.2%) of these were positive for TPO antibodies. Median age at disease onset was 14.5 years (range 6-18 years) with only 1 male patient being. Mental status (90%) and behavior changes (100%) were most common presentations, seizures were detected in only 1 patient. MRI (20%) and EEG (30%) abnormalities were uncommon, and only 1 patient had evidence of inflammation in cerebrospinal fluid (CSF). Autoimmune encephalitis and paraneoplastic antibody panels were negative besides 2 (20%) patients having concomitant Thyroglobulin (TG) antibodies. All patients needed additional IVIG after steroids treatment, 7(70%) patients received Rituximab and 3(30%) patients needed Plasmapheresis. All patients recovered at an average of 4.4 years follow up.
Conclusions: Encephalopathy associated with thyroid antibodies can be steroid unresponsive in the pediatric

population. Further immune therapy, including plasmapheresis, should be considered in these patients, even in the absence of other para-clinical evidence of inflammation.
Keywords: Infections/Neuroimmunology, Cognitive/Behavioral Disorders (including Autism)

118. The Role of Plasmapheresis in Children with Antibody- Negative Autoimmune Encephalitis

Rathore G (Omaha, NE)

Objective: Plasmapheresis is well established therapy for antibody mediated autoimmune encephalitis (AIE). In patients with no identified antibody, the role of plasmapheresis is unclear. Starting plasmapheresis becomes even more controversial in children with antibody negative AIE. We show the efficacy and relative safety of plasmapheresis as a treatment option for antibody negative AIE in children.
Methods: An IRB approved chart review was conducted on patients <18 years diagnosed with autoimmune encephalitis. A retrospective analysis of response to plasmapheresis and long term follow up was conducted on patients that did not have an identified antibody.
Results: 52 patients <18 years were diagnosed with autoimmune encephalitis, 14 (26.9%) of these tested negative for antibodies. 2 (14%) patients received only steroids, while all others received Steroids plus IVIG. 7 (58%) patients received rituximab for poor response/relapse following Steroids plus IVIG. Of these, 3 (43%) patients further underwent plasmapheresis for presumed refractory AIE. All patients had improvement after plasmapheresis and remained symptom free, including seizure freedom, at 2 year follow up. One patient needed repeat plasmapheresis for presumed relapse. No adverse effects reported.
Conclusions: Several studies have shown that timely delivery of immunotherapies is crucial and delay in treatment due to negative autoantibodies can lead to poorer outcomes. Plasmapheresis is safe and should be considered for refractory/relapsing AIE in children, even in the absence of an identified antibody. Larger studies in future can help solidify the findings from our cohort.
Keywords: Infections/Neuroimmunology, Cognitive/Behavioral Disorders (including Autism)

119. CASPR2 Autoimmune Encephalitis Triggered by Acute Mercury Toxicity

Mwangi M (St. Louis, MO), Ahmadi S, Garvey-Whatley M, Tabatabai G

Objective: Autoimmune encephalitis is a disease with variable clinical presentations including seizures and neuropsychological disorders. Infectious, paraneoplastic etiologies are among the common causes, and rarely, mercury toxicity is a potential cause.The postulated mechanism is autoimmunity through a mercury-induced immunomodulatory effect causing a defect in apoptosis, leading to a Th2-mediated humoral response. Prior cases describe patients presenting with hypertension, rash, musculoskeletal pain, paresthesia's and myokymia. Diagnosis is based on clinical history, elevated mercury levels and autoimmune panel. Treatment is generally responsive to immunomodulation.
Methods: Case details were obtained through hospital medical records system. Appropriate IRB approval and consent was obtained.
Results: Patient presented with rash and fever. Initially, a tick-born illness work-up was unremarkable. Persistent musculoskeletal and gastrointestinal pain led to admission and treatment with empiric steroids for a potential inflammatory condition. Shortly after admission her course was complicated by generalized tonic-clonic seizures in the setting of PRES and hypertension. CSF studies were notable for elevated protein, and an autoimmune encephalitis panel was positive for CASPR2 autoantibodies. Retrospectively, mercury exposure was established. She was first treated with rituximab and methylprednisolone, though continued seizures led to daily oxcarbazepine. Given symptoms refractory to rituximab, steroids, and chelation therapy she underwent plasmapheresis with gradual improvement.
Conclusions: Acute mercury toxicity causing CASPR2 autoimmune encephalitis is rare but treatable. Previous cases described responsiveness to chelation therapy, IV steroids and rituximab. We describe a case of canonical symptoms of acute mercury toxicity with additional complication of seizures with PRES, refractory to standard treatment but ultimately responsive to plasmapheresis.
Keywords: Infections/Neuroimmunology

120. The Utility of the Neutrophil-to-Lymphocyte ratio in Aquaporin-4 Neuromyelitis Optica Spectrum Disorder

Devlin L (Atlanta, GA), Gombolay G

Objective: The Neutrophil-to-Lymphocyte ratio (NLR) is an inflammatory biomarker that may predict disease course in neuroinflammatory diseases. We examine whether NLR at time of symptom onset predicts longitudinal disease

Table 1: Summary of Patient Characteristics. Abstract 120

Aquaporin-4 positive, N (%)	7 (100)
Sex (Female:Male)	7:0
Age, years, Mean (SD)	12.3 (2.5)
WBC at onset, Median (IQR)	6.7 (5.7, 13.2)
Treatment within 6 weeks of onset	
Steroids, N (%)	5 (71.4)
Intravenous Immunoglobulin, N (%)	4 (57.1)
Plasmapheresis, N (%)	3 (42.9)
Disease Modifying Therapy	
Rituximab, N (%)	7 (100)
Mycophenolate mofetil, N (%)	2 (28.6)
Cyclophosphamide, N (%)	1 (14.3)

SD: Standard deviation, IQR: interquartile range

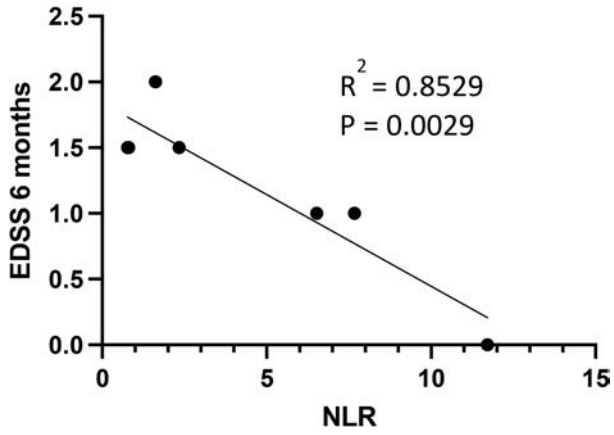


FIGURE 1: Linear regression of NLR at onset versus EDSS at 6 months. Abstract 120

outcomes in pediatric (Neuromyelitis Optica Spectrum Disorder) NMOSD.

Methods: Institutional Review Board approval was obtained. Clinical data was collected retrospectively from patients at a single institution between January 1, 2010 to November 1, 2021. The NLR was calculated as the ratio of percent neutrophils to percent lymphocytes of a pre-treatment complete blood count. The Expanded Disability Status Scale (EDSS) score, a clinical measure of disability, quantified disease severity. Statistical analysis was performed using SAS 9.4 (Cary, NC). Descriptive statistics were reported including mean and standard deviation or median and interquartile range (IQR). Linear regression models were performed with EDSS at 6 months as the outcome variable and NLR as the primary predictor variable.

Results: Seven patients were included, all were female and all were aquaporin-4 positive. Linear regression models demonstrated a relationship between NLR at presentation and EDSS at 6 months ($R^2 = 0.8529$, $p = 0.0029$). Age at presentation ($p = 0.2415$) and BMI ($p = 0.5749$) were not significantly associated with EDSS at 6 months. NLR remained significant in a multivariate linear regression model even when adjusting for age at presentation, as age can affect NLR.

Conclusions: In our cohort, a higher NLR at presentation was associated with greater disease severity at 6 months as evidenced by EDSS. The NLR in pediatric patients at first presentation of NMOSD may predict disease course.

Keywords: Infections/Neuroimmunology

121. A case of refractory status dystonicus due to anti-NMDA receptor encephalitis responsive to intrathecal rituximab

Zolno R (St. Louis, MO), Mwangi M, Gaudioso C, Gilbert L, Super C, Tomko S, Mar S

Objective: We report the rapid cessation of intractable status dystonicus with the use of intrathecal (IT) rituximab in a case of pediatric anti-NMDA receptor (NMDAR) encephalitis.

Methods: A 2-year-old female presented with seizures and developmental regression, followed by mutism, orofacial dyskinesias, status dystonicus, and autonomic instability, requiring intubation. CSF panel returned positive for anti-NMDAR antibodies. Despite treatment with high dose IV steroids, plasmapheresis, IV rituximab, Intravenous Immunoglobulin (IVIG), and IV continuous precedex infusion with multiple blouses of IV Valium for weeks, she continued to have status dystonicus. She was subsequently treated with IT rituximab plus IT hydrocortisone 12 mg weekly for five total doses. The IT rituximab dose started at 3 mg, with the subsequent four doses at 6 mg, 6 mg, 10 mg, and 10 mg respectively.

Results: Initial treatment with IT rituximab resulted in complete rapid resolution of dystonia, within 48 hours. Following IT rituximab, the patient was able to be transferred out of the ICU. The patient then received a course of IV cyclophosphamide, after finishing 4 doses of IT rituximab for prolonged neurological recovery.

Conclusions: This case demonstrates rapid efficacy of IT rituximab with IT hydrocortisone in treating severe status dystonicus resistant to standard therapy in severe refractory anti-NMDA encephalitis. The role of IT rituximab in the treatment of status dystonicus in this condition warrants additional consideration.

Keywords: Infections/Neuroimmunology, Critical Care, Movement Disorders (including Cerebral Palsy)

122. Unusual presentation of transiently multiphasic pediatric MOGAD with CSF eosinophilia and histiocytosis

Moehlman M (Washington, DC), Genser I, Tochen L, Kahn I, Kornbluh A

Objective: Describe an unusual pediatric case of myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) presenting as transient multiphasic neurologic symptoms over a one-month span associated with atypical CSF composition including eosinophilia and histiocytosis.

Methods: Chart Review

Results: A 5-year-old boy initially presented with 9 days of low-grade fever, vomiting, and headache. Lumbar puncture showed CSF pleocytosis (WBC 35/μL with 67% lymphocytes, 8% neutrophils, 6% eosinophils), and he was diagnosed with presumed aseptic meningitis. He experienced rapid recovery, but two days later returned with a focal seizure and encephalopathy. MRI of the brain revealed diffuse leptomeningeal enhancement with cortical and subcortical edema. He received antibiotics with meningitic coverage for 2 days and again returned to neurologic baseline. Two weeks later he developed right leg weakness, abnormal gait, and recurrent headaches. Repeat MRI showed new multifocal cerebral white and grey matter hyperintensities, multilevel gray matter-predominant cervicothoracic cord hyperintensities, and cauda equina enhancement. Evaluation showed CSF pleocytosis of 28/μL, with 18% eosinophils, 15% histiocytes, and serum eosinophilia of 14%. He was treated with intravenous immunoglobulin (IVIG) and pulse methylprednisolone for 3 days with complete neurologic recovery. Extensive infectious work-up was negative. Serum myelin oligodendrocyte glycoprotein antibody (MOG-IgG) via fluorescence activated cell sorting assay was positive (titer 1:100), confirming a diagnosis of MOGAD.

Conclusions: We present an interesting clinical presentation of pediatric MOGAD with a transiently multiphasic encephalomyelitis course and an atypical CSF and peripheral inflammatory profile. Eosinophilia in the CSF of patients with MOGAD is rare and CSF histiocytosis has not been previously documented.

Keywords: Infections/Neuroimmunology

MOVEMENT DISORDERS (INCLUDING CEREBRAL PALSY)

123. GABA and Glutamate Levels in Supplementary Motor Area Modulate Lateralization of Motor Cortex Excitability in Tourette Syndrome

Larsh T (Cincinnati, OH), Huddleston D, Horn P, Cecil K, Jackson H, Edden R, Wu S, Mostofsky S, Gilbert D

Objective: Atypical lateralization of hemispheric function as well as alterations in prefrontal control of motor function may underlie symptoms of Tourette Syndrome(TS). We aimed to evaluate lateralization of motor circuits by comparing physiological properties of left and right motor cortex(M1) and evaluating associations of each with supplementary motor area(SMA) neurotransmitter levels in children with TS and typically developing controls(TDC).

Methods: We recruited thirty-three 8-12-year-old right-handed children(17 TS, 16 TDC) and performed left and right M1 single pulse Transcranial Magnetic Stimulation(TMS), with motor evoked potentials(MEPs) measured in contralateral first dorsal interosseous(FDI) muscles, to quantify global excitability(MEP amplitudes). We used edited 3 Tesla magnetic resonance spectroscopy(MRS) to quantify GABA and Glx(glutamate + glutamine) levels in a bilateral SMA voxel.

Results: *Lateralization of M1 excitability:* In both TS and TDC children, MEPs evoked by TMS in right M1 were significantly smaller than those evoked in left M1($p<0.0001$). *Influence of SMA GABA and Glx on M1:* Neurotransmitter effects on hemispheric excitability asymmetries differed between TS and TDC(both $p<0.0001$). For TS, greater levels of both SMA GABA and Glx were associated with lesser hemispheric asymmetry, which was driven by less excitability in the non-dominant hemisphere; whereas, for TDC, hemispheric motor excitability was similar across SMA GABA and Glx levels.

Conclusions: In children with TS, GABA and glutamate levels in SMA may differentially influence lateralization of motor cortex excitability. These results support further investigation of the mechanistic roles of SMA GABAergic and glutamatergic neurotransmission and hemispheric lateralization in motor physiology in TS.

Keywords: Movement Disorders (including Cerebral Palsy), Neuroimaging, Translational/Experimental Therapeutics

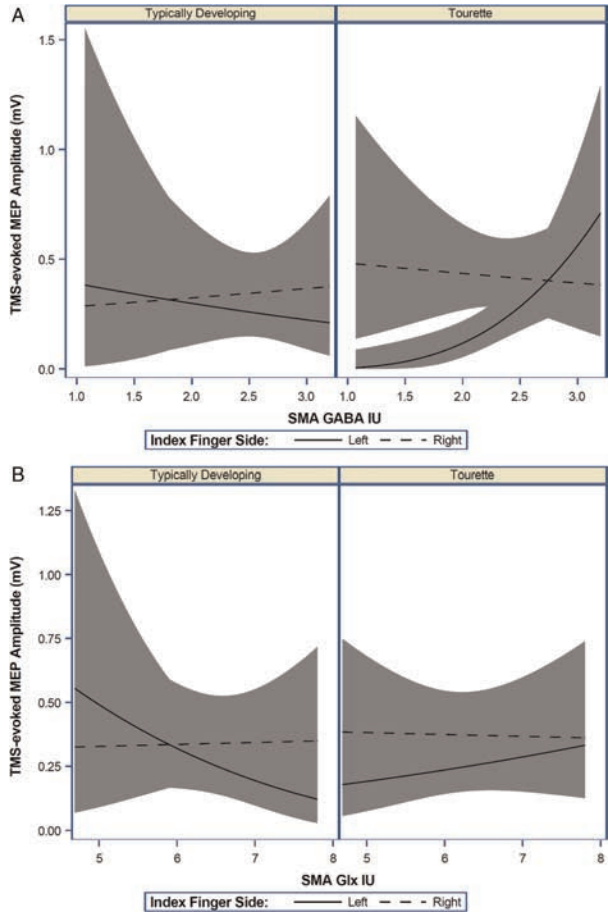


FIGURE 1. Single Pulse MEP Amplitudes for TDC (Left Panels) and TS (Right Panels) Plotted Against A.) SMA GABA Levels and B.) SMA Glx Levels. Abstract 123

124. Prevalence of mental health symptoms within the caregiver-child dyad of pediatric patients with cerebral palsy

Clark G (Portland, OR), Crowder D

Objective: Assess the prevalence of concurrent mental health symptoms in the caregiver-child dyad of children with cerebral palsy (CP) and their caregivers (CG).

Methods: We queried the EHR of an academic medical system for patients aged ≥2 and ≤17 years with presence of ICD codes for CP and paralysis. We emailed subjects a survey that queried demographics and the PedsQL and Family Impact Module, a validated survey, and data was anonymized on export to REDCap. Respondent dyads were sorted into four groups based on negative mental health (MH) or quality of life (QoL) impacts: G1 (both impacted), G2 (child-only impacted), G3 (CG-only impacted), and G4 (neither impacted). Demographics and CP characteristics were compared by groups.

Results: 39 completed surveys met inclusion criteria. Group distribution was G1 (53.84%), G2 (0%), G3 (30.76%), and G4 (15.38%). Most caregivers felt at least somewhat supported (46.2% Yes, 41% Somewhat, 12.8% No). A majority in G1 and G3 reported 'Somewhat' or 'No'

support compared to G4 (0% No). G4 CP severity was mild compared to G1 and G3 (majority moderate to severe). CP types included spastic (51.3%), mixed-type (12.8%), ataxic (2.5%), and "unknown" or "not listed" (30.8%). The most common health insurance was Medicaid (48.1%). The largest age group was 8-12 years (38.5%); 35.9% were girls and 64.1% were boys.

Conclusions: Caregiver-child dyads with CP have congruent, negative MH and QoL impacts in >50% of cases. Child MH or QoL impacts were only seen if the caregiver was impacted; thus, positive caregiver screening should trigger child screening.

Keywords: Movement Disorders (including Cerebral Palsy)

125. Altered Pain Network Structure and Functional Connectivity in Children with Bilateral Cerebral Palsy

Gorny N (Baltimore, MD), Damiano D, Hoon A, Jantzie L, Lindquist M, Pekar J, Robinson S, Stashinko E, Vaconcellos Faria A, Ye X, Chin E

Objective: A majority of individuals with cerebral palsy (CP) report chronic pain, but functional brain networks responsible for pain processing have not been examined. Our objectives were 1) to characterize structural and functional alterations of the pain network in children with CP and 2) to determine if alterations were associated with reported pain levels.

Methods: As baseline assessment for a clinical exercise trial, 22 children with bilateral CP and 19 typically-developing children underwent MRI (MPRAGE and 7-minute resting state BOLD-fMRI). Scans with artifact, excessive head motion, or malformation obscuring gyral patterns were excluded, leaving 30 children included in analyses; 13 of these children had CP (Age(mean±SD):12.0±3.2) and 17 were typically-developing (13.6±3.2).Within the canonical acute pain network, group differences in regional volume and functional connectivity (FC) were examined using non-parametric rank sum tests corrected for multiple comparisons (Figure 1). For connections with significant group differences, correlations versus caregiver-rated comfort/pain scores were examined for children with CP.

Results: Children with CP had significant volume loss only within somatosensory network regions (Figure 2). FC was increased between the insula and post-central gyrus (PoCG; corrected p=0.049). Gray matter volumes did not correlate with pain, but greater insula-PoCG FC trended toward a correlation with more pain (negative correlation with comfort, ρ=-0.58, CI:[-0.85;0.02]).

Figure 1. Study Design

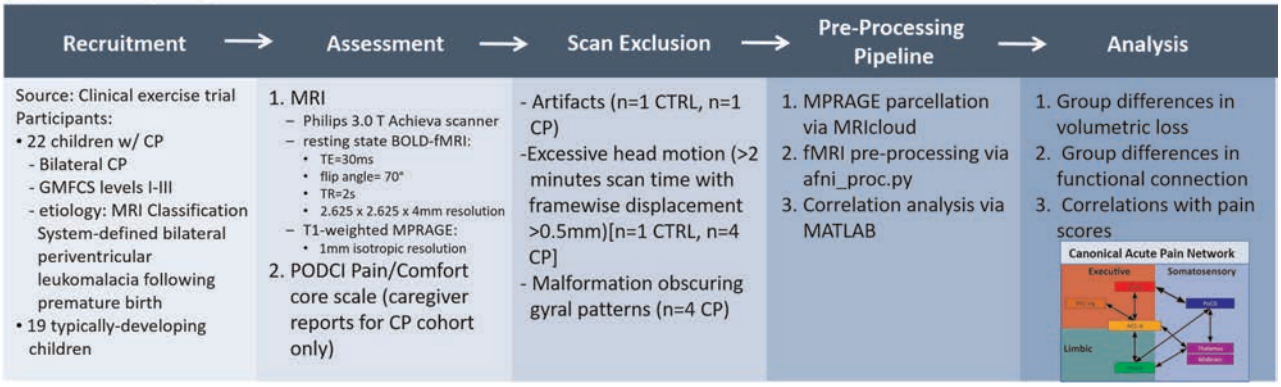


Figure 2. Volumes and Functional Connectivity

A

Region	Difference in Volume in participants w/ CP (compared to CTRLS as percentage loss)	Corrected p value	Volume in participants w/ CP correlated with PODCI comfort/pain
Superior Frontal Prefrontal Cortex	-2.5%	p>0.5	ρ=-0.33 95%CI [-0.77;0.44]
Lateral Frontal Orbital Gyrus	-2.7%	p>0.5	ρ=-0.10 95%CI [-0.68;0.50]
Post Central Gyrus	-9.1%	p=0.1	ρ=0.27 95%CI [-0.43;0.77]
dorsal Anterior Cingulate Cortex	-1.7%	p>0.5	ρ=-0.14 95%CI [-0.70;0.46]
Insula	-6.4%	p=0.31	ρ=0.24 95%CI [-0.52;0.73]
Thalamus	-30.3%	p<0.001*	ρ=-0.43 95%CI [-0.83;0.23]
Midbrain	-13.5%	p<0.01*	ρ=-0.02 95%CI [-0.65;0.63]

*indicates significance

B

Functional Connectivity between Regions	CTRL (median ± IQR)	CP (median ± IQR)	Corrected p value	FC in CP correlated with PODCI comfort/pain
Post Central Gyrus (PoCG) to Thalamus	0.33 ± 0.42	0.10 ± 0.39	p=0.29	ρ=0.22 95%CI [-0.41;0.70]
PoCG to Insula	0.52 ± 0.35	0.31 ± 0.28	p=0.05*	ρ=-0.58*, 95%CI [-0.85;0.02]
PoCG to Lateral Frontal Orbital Gyrus (LFOG)	0.13 ± 0.20	0.09 ± 0.19	p>0.5	ρ=-0.50 95%CI [-0.83;0.02]
Thalamus to Insula	0.36 ± 0.28	0.23 ± 0.29	p>0.5	ρ=0.14 95%CI [-0.43;0.71]
Thalamus to dorsal Anterior Cingulate Cortex (dACC)	0.25 ± 0.29	0.30 ± 0.30	p>0.5	ρ=-0.02 95%CI [-0.59;0.65]
Insula to dACC	0.55 ± 0.52	0.55 ± 0.27	p>0.5	ρ=-0.47 95%CI [-0.86;0.22]
dACC to Superior Frontal Prefrontal Cortex (SF PFC)	0.08 ± 0.46	0.07 ± 0.37	p>0.5	ρ=-0.02 95%CI [-0.64;0.58]
dACC to LFOG	0.04 ± 0.23	0.20 ± 0.23	p=0.15	ρ=-0.20 95%CI [-0.68;0.42]

Conclusions: Children with CP showed volume loss in somatosensory regions and increased resting FC between somatosensory and affective networks; FC trended higher in children with pain. Further examination of these systems may help clarify chronic pain mechanisms.
Keywords: Movement Disorders (including Cerebral Palsy), Neuroimaging, Neuroscience

126. Further Evidence for Early-Onset, Severe Complex Hereditary Spastic Paraplegia Caused by De Novo Variants in SPAST

Mo A (Boston, MA), Saffari A, Soldatos A, Alter K, Strelko O, Jordan C, Srivastava S, Sahin M, Fink J, Smith L, Toro C, Blackstone C, Christie M, Ebrahimi-Fakhari D

Objective: Individuals with familial SPG4 (HSP-*SPAST*), the most common form of autosomal-dominant hereditary spastic paraplegia (HSP), typically present in young adulthood with slowly progressive motor disability, consistent with pure HSP. A recent study, however, raised the question whether *de novo SPAST* variants can lead to complex HSP. The present study aims to delineate the clinical and molecular spectrum of children with *de novo* SPG4.
Methods: Cross-sectional data from 19 children with *de novo* SPG4 (range: 1.2-17 years) enrolled in our Registry for Early-Onset HSP (NCT04712812).
Results: The molecular spectrum encompassed 12 unique *SPAST* variants, with 7/19 individuals carrying the p.-Arg499His mutation. Symptom onset was in early childhood (median: 9.8 months, 7.5 months IQR). All affected individuals presented with significant motor delay and ascending lower extremity spasticity and weakness, with 4/19 having upper extremity involvement as well. Cerebellar dysfunction and extrapyramidal movement disorders were common (11/19), the latter mostly consisting of focal or segmental dystonia (7/19). Most individuals had intellectual disability (9/11) of variable severity, and 3/19 remained non-verbal. Epilepsy was present in 4/19. Neurogenic bladder dysfunction and gastrointestinal dysmotility were common. The mean Spastic Paraplegia Rating Scale score was 27.1±9.3 (SD). The mean SPATAX disability level was 5±1.34 (SD), indicating that most children are wheelchair-dependent. Motor disability increased over time.
Conclusions: Our results confirm that *de novo* variants in *SPAST* lead to a childhood-onset and severe form of complex HSP that differs from classic familial SPG4. Clinicians should be aware of this syndrome in the differential diagnosis for cerebral palsy.
Keywords: Movement Disorders (including Cerebral Palsy), Genetics, Rare Diseases

127. A Comparison of Comorbidities between Preterm and Term Children with Cerebral Palsy and Periventricular White Matter Injury

Marefi A (Montreal, QB, Canada), Husein N, Oskoui M, Shevell M

Objective: This study aims to look at the differences in frequencies in comorbidities in children with cerebral palsy (CP) & periventricular white matter injury (PVWMI) born preterm or term.
Methods: Participants were extracted from the Canadian Cerebral Palsy Registry (CCPR) from 1999 to 2021. Term participants with PVWMI (n= 147) were compared to preterm participants with PVWMI (n=269) regarding non-independent ambulation, lack of functional hand use, epilepsy, tube feeding dependence, cognitive impairment, cortical visual impairment, severe auditory impairment, and non-verbal communication. A chi-square analysis with Yates' continuity correction comparing frequencies was utilized.
Results: Comorbidities were more frequent in children with PVWMI born term vs preterm for epilepsy (25.3% vs 10.5%; $p<0.1$), tube feeding dependence (4.8% vs 0.007%; $p<0.1$), visual impairment (19.0% vs 9.3%; $p<0.1$) and non-verbal communication (69.2% vs 56.4%; $p<0.1$). No statistical significance was reached with differences in cognitive impairment (63.3% vs 59.4%), auditory impairment (10.1% vs 11.5%, non-ambulatory status [GMFCS Level IV-V] (29.5% vs 25.5%) and lack of functional hand use [MACS Level Iv-V] (26.7% vs 18.1%). Twenty-nine percent of term children with PVWMI had the SD subtype compared to 44.3% in preterm children.
Conclusions: Comorbidities, such as epilepsy, tube feeding dependence, visual impairment, and non-verbal communication occur more frequently in term children with PVWMI compared to preterm children and the CP subtype also differs based on gestational age. These findings suggest a more pervasive and extensive injury in term children with PVWMI compared to preterm children despite a common radiologic pattern of injury.
Keywords: Movement Disorders (including Cerebral Palsy)

128. Development of a self-assessment questionnaire to identify dystonia in people with cerebral palsy

Rust A (St. Louis, MO), Jaleel F, Cheung S, Pearson T, Ueda K, Viehoever A, Leger K, Wilson J, Guez-Barber D, Shusterman M, Aravamuthan B

Objective: To develop a self-assessment questionnaire for dystonia in people with cerebral palsy (CP): a debilitating but under-recognized condition.
Methods: Young people with CP and their caregivers were recruited at in-person CP clinic visits at two large tertiary care hospitals. Via a paper survey, we asked 2 questions based on the consensus definition of dystonia and asked respondents to provide supportive examples:1) When moving one body part, does A DIFFERENT BODY PART start moving unintentionally?2) When others handle their body, do body parts NOT BEING HANDLED BY OTHERS start moving unintentionally?Respondent-given examples were consolidated into a questionnaire and given to a new set of people with CP and caregivers. Responses were compared between people with and without dystonia as identified by CP clinic practitioners.
Results: 116 people with CP (58 with dystonia) or their caregivers responded to the two initial questions. A 'yes' answer to both questions was 40% sensitive and 97% specific for dystonia. Respondent-given examples included statements

like: "she stiffens up on transfers" and "when moving one leg, the other leg wants to move". These examples were consolidated into a 22-item questionnaire administered to 89 people with CP (32 with dystonia) or their caregivers. 'Yes' answers to >22% of items yielded 84% sensitivity and 70% specificity for dystonia.

Conclusions: These results demonstrate the potential viability of a self-assessment questionnaire for identifying dystonia in people with CP. Such auxiliary dystonia identification methods could help address the important problem of dystonia under-recognition in people with CP.

Keywords: Movement Disorders (including Cerebral Palsy)

129. White Matter Injury Predominates in People with Dystonia and Cerebral Palsy Following Premature Birth

Chintalapati K (St. Louis, MO), Pearson T, Ueda K, Aravamuthan B

Objective: Dystonia in people with cerebral palsy (CP) is classically associated with deep grey matter injury at term gestation. However, dystonia also occurs in people with CP following premature birth without clear grey matter injury on MRI. Our objective was to determine MRI patterns of brain injury associated with dystonia in people with CP following premature birth.

Methods: Subjects were people with CP following premature birth (gestational age <37 weeks), evaluated at a tertiary care multi-disciplinary CP clinic with clinically-available MRIs. Subjects were assessed for dystonia in-person by a pediatric movement disorders specialist, with video confirmation in a subset by two other movement disorders specialists blinded to subject identities. MRI T1 weighted scans were assessed in tandem by two investigators blinded to subjects' motor phenotypes for size markers of the basal ganglia, corpus callosum, lateral ventricles, and cerebellum, normalized to markers of total brain size.

Results: 137 subjects were evaluated (ages 0-17 years). Compared to subjects without dystonia (N=96), subjects with dystonia (N=41) had greater thalamic size / total brain size (0.22 vs 0.24, P = 0.005) and lateral ventricular size / total brain size (0.12 vs 0.14, P=0.001, ANOVA), suggestive of comparatively diminished white matter volume in subjects with dystonia.

Conclusions: In people with CP after premature birth, our results suggest increased white matter injury best correlates with the presence of dystonia. Therefore, white matter injury may be a significant contributor to dystonia pathogenesis in people with CP following premature birth.

Keywords: Movement Disorders (including Cerebral Palsy), Neuroimaging

130. Clinical and molecular phenotype of PTRHD1-associated juvenile parkinsonism

Tavani J (Phoenix, AZ), Marchetto A, Stoffels J, Darvish H, Zech M, Shoukier M, Kruer M

Objective: Although Parkinson's Disease is the most common movement disorder in adults, juvenile parkinsonism (occurring in children and adolescents) is comparatively rare. Juvenile parkinsonism is often dominated by rigidity, hypokinesia, and postural instability and less commonly features a resting tremor. Despite its rarity, several important scientific insights have come from studies of early-onset parkinsonism. We describe 5 previously unreported patients with mutations in *PTRHD1*, an orphan gene of unknown function. Although mutations in this gene have recently been reported in a few families with juvenile parkinsonism and intellectual disability, clinical phenotypes have been incompletely characterized. We sought to identify genotype-phenotype correlations in patients with homozygous missense or genomic loss of function mutations in *PTRHD1*.

Methods: Each family provided written informed consent for participation according to local ethics guidelines. Clinical phenotypes, MRI images, patient photographs, and videos were collected from 5 patients with homozygous mutations in the *PTRHD1*gene. When possible, blood and/or skin punch biopsies were also performed for transcriptomic and proteomic analysis.

Results: Clinical presentations included dysarthria, rigidity, postural instability, gait dysfunction, and mild intellectual disability. Resting tremor was observed in several patients. There was no evidence of oculomotor abnormalities. Anatomic MRI imaging was normal. Patients responded to carbidopa-levodopa but developed peak-dose dyskinesias and wearing-off effects early in the treatment course.

Conclusions: Biallelic *PTRHD1* mutations represent a newly-recognized form of parkinsonism that should be considered in patients presenting in childhood or adolescence.

Keywords: Movement Disorders (including Cerebral Palsy), Genetics

131. Spectrum of Pediatric to Early Adulthood POLR3A-Associated Movement Disorders

Zea Vera A (Washington, DC), Bruce A, Larsh T, Jordan Z, Espay A, Brüggemann N, Gilbert D, Wu S

Objective: POLR3A mutations cause hypomyelination, hypodontia, hypogonadism, and cerebellar ataxia. We aim to describe the range of other movement disorders seen in a cohort of patients with POLR3A-related disorders.

Methods: Six patients with POLR3A mutations evaluated in specialized movement disorder centers were included.

Results: Age of onset ranged from birth to early adulthood (Table 1). Four patients were females. Patient 1 presented at birth with a progeroid syndrome. At 23 years she has pseudobulbar affect, parkinsonism, dystonia, ataxia, and spasticity. Patient 2 presented in infancy with rapidly progressive chorea, dystonia, and myoclonic seizures. She required ventilatory support/G-tube and died at 2 years 11 months. Patient 3 presented at age 5 years with mild dystonia, ataxia, and spasticity. Patient 4 presented at 15 years old with slowly progressive cervical and arm dystonia with no additional symptoms up to 20 years old. Patients 5 and 6 developed spastic ataxia and peripheral neuropathy at age 20 years old that slowly progressed over more than 10 years. Patient 5 also had segmental dystonia. Vertical gaze palsy or slowed vertical saccades were identified in 4 patients. Cognitive involvement varied. Dentition abnormalities and short stature or amenorrhea each occurred in 2 patients.

TABLE 1. Phenotypic characteristics of the POLR3A patient cohort. Abstract 131

ID	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Gender	Female	Female	Female	Female	Male	Male
Age of onset	Birth	<6 months	5 years	15 years	20 years	20 years
Last follow up	23 years	2 year 11 months (deceased)	10 years	20 years	59 years	30 years
Cognitive Symptoms	Yes	Severe global developmental delay	No	No	No	No
Independent walking	Achieved but lost at 13 years	Never achieved	Achieved and maintained	Achieved and maintained	Achieved and maintained	Achieved and maintained
Pyramidal signs	Yes	Yes	Yes	No	Yes	Yes
Cerebellar signs	Gait ataxia, intention tremor, dysmetria	No	Mild gait ataxia, intention tremor, and dysmetria	No	Gait ataxia, and dysmetria	Gait ataxia
Dystonia	Oromandibular Dystonia	Severe generalized dystonia	Mild lower extremity dystonia	Cervical and right arm dystonia	Multifocal dystonia	No
Chorea	No	Severe generalized chorea	No	No	No	No
Tremor	Rest and intention tremor	No	Intention tremor	Dystonic tremor	Intention tremor	No
Parkinsonism	Yes	No	No	No	No	No
Eye movements	Impaired down-gaze and limited up-gaze	Impaired vertical up gaze	Round-the-house sign, nystagmus on lateral gaze, saccadic pursuit movements	Normal	Normal	Saccadic pursuit, slow vertical saccades
Sensory symptoms	Sensory neuropathy	None	Hyporeflexia, but no sensory symptoms	None	Sensory neuropathy	Sensory neuropathy
Other neurologic symptoms	None	Axial hypotonia, dysautonomia, myoclonic seizures	Mild axial hypotonia	None	None	Dysarthria
Dentition abnormalities	No	No	Yes	Yes	No	No
Endocrinologic abnormalities	Growth failure, amenorrhea	No	Short stature	No	No	No
	Yes	No	Yes	No	No	No

TABLE (Continued)

ID	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Myopia or Hyperopia						
Other symptoms	Progeroid syndrome	Required ventilatory support and G-tube feeds	No	No	No	No
Brain MRI	Polymicrogyria	Ventriculomegaly, and abnormal signal and volume loss in the bilateral caudate and putamen.	T2 hyperintensity of dentate, superior cerebellar peduncles, midbrain, thalamus, and posterior limb of internal capsule	Subtle T2/FLAIR hyperintensity in the posterior pons (in the region of the superior cerebellar peduncles)	Cerebellar Atrophy	Bilateral symmetric FLAIR hyperintensity in the midbrain (directly underneath red nucleus), and superior cerebellar peduncles

Conclusions: POLR3A mutations exhibit significant phenotypic pleomorphism, often including dystonia and ataxia. Vertical gaze impairment, a feature seldom reported in POLR3A-related disorders, was seen frequently in our cohort and may be explained by the involvement of midbrain structures (riMLF or interstitial nucleus Cajal).

Keywords: Movement Disorders (including Cerebral Palsy), Genetics, Rare Diseases

132. Dysphagia is a strong risk factor in predicting low bone density in adults with cerebral palsy

Jung SH (Seoul, Republic of Korea),

Objective: Dysphagia is a common medical problem suffered by persons with cerebral palsy (CP). Although dysphagia has been linked to elevated risk of osteoporosis in the general population, there has been no quantitative study focusing on dysphagia in persons with CP and its impact on low bone density.

Methods: This cross-sectional study investigated the relationship between dysphagia in the CP population and its effect on bone mineral density (BMD), *T*-score, and *Z*-score, adjusted for possible confounding risk factors.

Results: Ninety-seven adults with CP were divided into two groups: dysphagia and no dysphagia. The dysphagia group showed significantly lower BMD, *T*-score, and *Z*-score at every anatomical site explored. Adjusted for age, sex, body mass index, and physical activity, dysphagia was significantly negatively correlated with BMD. Subjects with dysphagia showed significantly higher odds ratio of age-adjusted low BMD and osteopenia than those without dysphagia. This study found dysphagia to be an important risk factor in predicting low BMD and osteopenia in adults with CP.

Conclusions: In the presence of dysphagia in adults with CP, it may be beneficial to screen for low BMD for appropriate clinical intervention. This study was supported by the Translational R&D Program on Smart Rehabilitation Exercises (#TRSRE-PS01), National Rehabilitation Center, Ministry of Health and Welfare, Korea.

Keywords: Movement Disorders (including Cerebral Palsy), Neurorehabilitation

133. Reduced dominant motor cortex inhibition is associated with increased tic severity in children with Tourette syndrome

Batschelett M (Baltimore, MD), He J, Crocetti D, Horn P, Puts N, Huddleston D, Mostofsky S, Gilbert D

Objective: Tourette syndrome (TS) is characterized by chronic motor and/or vocal (phonic) tics, often preceded by premonitory urge perceptions. Hypotheses regarding TS pathophysiology suggest dysregulation within striatal-thalamic-cortical circuits, contributing to disrupted signaling within motor circuits (primary motor [M1] and premotor). The objective of this study was to identify how patterns of M1 inhibition or excitation associate with TS symptom severity.

Methods: Using Transcranial Magnetic Stimulation (TMS), we measured the physiology of resting left M1 innervating right intrinsic hand muscle in sixty 8-12-year-old children: 30 TS (including 15 with comorbid ADHD) and 30 typically developing (TD). Additionally, standard clinical scales for tic and premonitory urge severity (TS) and ADHD (all) were performed. We used repeated measures mixed model regressions to compare TMS measures between diagnostic groups and to examine dimensional associations with TS symptoms (tics and urges).

Results: There were no diagnostic differences (TS vs. TD) for any of the TMS measures. However, after accounting categorically for comorbid ADHD, among TS children, reduced short interval cortical inhibition (SICI) was associated with greater severity of tics (p=0.002), but not urges. Comparisons of single and paired pulse TMS-evoked potentials suggests distinctive physiological correlates of more severe motor vs. phonic tics.
Conclusions: In children with TS, more severe tics, but not urges, are strongly associated with less SICI in left M1. These results demonstrate a potential link between M1 physiology in TS and tic symptomology. Taken together, these findings provide support for SICI as a biomarker for the targeted treatment of TS symptoms.
Keywords: Movement Disorders (including Cerebral Palsy), Neuroimaging, Neuroscience

134. Comorbidities of children with cerebral palsy born at term compared to preterm in the Canadian Cerebral Palsy Registry

Pekeles H (Montreal, QB, Canada), Husein N, Kirton A, Oskoui M, Shevell M

Objective: Comorbidities may be a bigger challenge than neuro-motor impairment for individuals with cerebral palsy (CP) and their caregivers. We set out to compare the comorbidity spectrum of children with CP who were born term or later compared to those who were born preterm as these populations have different causal mechanisms leading to the CP phenotype.
Methods: Using data from the Canadian Cerebral Palsy Registry (CCPR) of 2217 children with CP, we compared the comorbidity spectrum of term children (37 weeks and above GA, n=1263) to preterm children (born below 37 weeks GA, n=954) with CP. A chi-square analysis with Yates' continuity correction comparing frequencies was utilized.
Results: We found significant differences in comorbidities in children with cerebral palsy born preterm vs term for epilepsy (10.7 % vs 21.7%), visual impairment (11.2% vs 18.2%), auditory impairment (13.2% vs 8.0%), communication impairment (58.0% vs 67.5%) and lack of functional hand use [MACS Level IV-V] (22.1% vs 27.9%) (p value < 0.05). No significant difference based on GA was found for tube feeding dependence, cognitive impairment, or non-ambulation [GMFCS Level IV-V], all of which were more frequent in term children approaching significance (p value 0.08-0.1).
Conclusions: With the exception of auditory impairment, CP children born term had more frequent comorbidities compared to children born preterm. This suggests that the causal mechanisms leading to CP in term children are more widespread. This also suggests that both populations should have similar surveillance mechanisms in place longitudinally.
Keywords: Movement Disorders (including Cerebral Palsy), Neonatal & Fetal Neurology

135. Stereotactic EEG evaluation aids decision making in patients with complex dystonia undergoing deep brain stimulation

Marks W (Fort Worth, TX), Acord S, Honeycutt J, Song Y, Papadelis C

Objective: Deep Brain Stimulation (DBS) of the globus pallidus (GPi) has been effectively utilized for dystonia. For complex or refractory patients, especially with hyperkinesis, secondary targets have been investigated. The use of depth electrode recording has been implemented by Sanger et al. We report our experience in seven patients with dystonia using stereotactic EEG (sEEG) depth electrode stimulation and recording to guide DBS decision making.
Methods: Review of patients that have undergone sEEG recordings as part of their DBS evaluation. sEEG electrodes were implanted using robotic guidance. Targets were selected based on clinical symptoms. GPi was always included unless previously implanted with permanent DBS leads. STN and VOA of thalamus are generally done using a single sEEG electrode passing through both nuclei. Each contact is stimulated in bipolar fashion with monitoring of efficacy and adverse events. Prolonged stimulation is accomplished using an external generator system.
Results: Seven patients with dystonia underwent sEEG evaluation for DBS lead placement. Five patients had a confirmed or presumed genetic etiology. Two were evaluated for initial DBS placement; five for lead modification. Four of the five secondary evaluations underwent placement of additional leads. Lead sites included GPi (7), Thalamus (24) and STN (8). Negative side effects related to stimulation aided in ultimate target selection. Monitoring time was 3-11 days. There were no surgical complications related to the placement of sEEG leads.
Conclusions: Stereotactic EEG testing of selected patients can aid in the decision making process for DBS placement or revision.
Keywords: Movement Disorders (including Cerebral Palsy), Translational/Experimental Therapeutics, Rare Diseases

136. Characteristics of children with cerebral palsy secondary to intrapartum asphyxia in the post therapeutic hypothermia era

Pekeles H (Montreal, QB, Canada), Al Amrani F, Perez-Morgui M, Wintermark P, Shevell M

Objective: To explore the profile of children with cerebral palsy (CP) secondary to intrapartum asphyxia (IAP) treated with therapeutic hypothermia (TH) after birth and to compare characteristics of children treated with TH with mild vs. severe CP outcome.
Methods: We identified all children treated with TH for IAP in a single-center tertiary level neonatal intensive care unit from 2008 to 2018 with a CP outcome. We collected perinatal and outcome measures from patient charts. We searched the literature for characteristics of children with CP prior to TH (historical cohort) to compare to our cohort. We subdivided our cohort into mild vs. severe CP and compared neonatal characteristics to identify predictors of severe phenotype.
Results: 30 out of 355 cooled neonates (8%) developed CP. More children had spastic quadriparesis and epilepsy, and fewer had visual impairment in the post-TH era compared to the historical cohort, but had similar Gross Motor Function Classification System scores. In our cohort, more children had severe (19/30, 63%) compared to mild CP (11/30, 37%). The severe group had higher mean birth

weight, lower 5- and 10-minute Apgar scores, and more often white matter injury with associated deep gray matter injury or near-total injury pattern ($p<0.05$).

Conclusions: Our data demonstrated more infants with severe rather than mild CP in our cohort treated with TH. Birthweight, 5- and 10-minute Apgar scores and MRI findings were significantly different between mild vs. severe phenotype groups. Our findings can guide clinicians how to better weigh these factors, when counselling parents in the neonatal period.

Keywords: Movement Disorders (including Cerebral Palsy), Neonatal & Fetal Neurology

137. PEDiDBS: The international registry of pediatric patients undergoing deep brain stimulation

Marks W (Fort Worth, TX), Sankpal U, Bailey L

Objective: Deep brain stimulation is being used with increasing frequency in pediatric patients with dystonia and now epilepsy. Multiple devices from several manufacturers are in clinical use worldwide. There are differences in patient selection, surgical techniques, perioperative postoperative management. These questions can best be addressed by collaborative data sharing.

Methods: PEDiDBS is the result of the collaborative efforts of an international team of investigators working over the last several years to develop a secure method of data sharing regarding children undergoing DBS. PEDiDBS is a REDCap-based secure multi-center database that meets the compliance and international privacy laws.

Results: Four centers are now fully enrolled and beginning data entry. Approximately 2 dozen more sites have requested information and in start-up. Subjects are entered utilizing a de-identified limited data set and is stored on a secure REDCap cloud server. Privacy is assured through the use of site numbers and a limited data set for patient information in accordance with applicable privacy laws. Each site enters their own data and is responsible for ensuring accuracy. Individual sites retain access to their own data. Requests for aggregate data for analysis by participating sites are reviewed by the data sharing committee.

Conclusions: PEDiDBS is a vehicle for information sharing between all interested centers implanting pediatric patients with DBS. The data sharing allows for better utilization of this complex technology. Participation and enrollment information is available on the website www.PEDiDBS.org.

Keywords: Movement Disorders (including Cerebral Palsy), Genetics, Translational/Experimental Therapeutics

138. Prevalence of Genetic Disease in Patients with Cerebral Palsy

Brooks A (Rootstown, OH), Mawby I, Rossman I

Objective: Cerebral palsy (CP) is a heterogenous disorder resulting from early brain injury or aberrant neurodevelopment, causing motor disability and a myriad of other neurologic sequelae. Genetic mutations have been identified in some patients with CP; however, the prevalence of causal genetic disorders in CP is unknown. We aimed to identify the prevalence of genetic disorders and the most common genetic mutations in pediatric patients with CP.

Methods: Using the EPIC SlicerDicer tool, the Akron Children's Hospital patient population was sliced into two groups: 1) the term "cerebral palsy" as diagnosis or medical history, between January 1, 2021 and December 31, 2021, and 2) the slice of group 1 with "genetic disease" as diagnosis or medical history. Patients with genetic diseases unrelated to CP were manually removed and subgroups of genetic diseases were quantified.

Results: We identified 2,633 CP patients treated in 2021. Of these patients, 170 (6.5%) were identified as having a genetic disease. Within this group, three siblings shared a *COL4A1* mutation; further identification of additional genetic mutations is ongoing.

Conclusions: Considering genetic etiologies is critical when CP patients present without pre- or perinatal trauma or lack brain malformations or injury on neuroimaging. We identified 6.5% of a CP population to have a genetic disorder, but the prevalence may vary across populations. Early genetic diagnoses in patients with CP may alter clinical management and identify CP risk for future pregnancies. Clinical genetic testing may help to define the pathophysiology of CP and offer targets for treatment in some patients.

Keywords: Movement Disorders (including Cerebral Palsy), Genetics

139. Geographical Knowledge Disparities in Cerebral Palsy Epidemiology

Avila-Soto F (St. Louis, MO), Aravamuthan B

Objective: Noting dramatic differences in CP prevalence and etiology across geographical regions, we aimed to identify geographical disparities in the published knowledge of CP epidemiology.

Methods: We conducted a PRISMA-style systematic review of primary literature on CP prevalence using the search terms: "cerebral palsy"[title] AND (rate OR prevalence OR epidemiology) in PubMed and Web of Science. We excluded studies not published in English.

Results: Of 2720 studies, 91 met inclusion/exclusion criteria. 68/91 (74.7%) studies reported CP prevalence in Europe, North America, and Australia (Region 1) and are cited an average of 7.3 times/year since publication. The remaining 24/91 (26.4%) studies reported CP prevalence in Asia, the Middle East, and Africa (Region 2) and are cited significantly less often, 3.3 times/year since publication ($p=0.01$, t-test). No studies from Latin America were identified. Geographical citation disparities persist even when accounting for journal impact. Normalized to a journal's CiteScore (number of citations in one year for a journal's articles published in the previous 3 years), Region 1 papers are cited 1.6x more often than typical for the corresponding journal, while Region 2 papers are cited only 0.5x as often ($p<0.001$, t-test). Region 1 papers were written exclusively by Region 1 authors (100%) while Region 2 papers significantly less frequently included Region 2 authors (84.4%) ($p<0.0001$, comparison of proportions).

Conclusions: Our results show geographical disparities in our published knowledge of CP epidemiology. Understanding CP globally requires increased global support of all CP

researchers, particularly in regions where CP prevalence remains under-studied or unknown.
Keywords: Movement Disorders (including Cerebral Palsy), Equity, Diversity, Inclusion

140. A Two-Part, International, Real-World, Observational Registry of Participants Diagnosed with Aromatic L Amino Acid Decarboxylase Deficiency (AADC-d) With or Without Treatment With Eladocagene Exuparvovec

Giugliani R (Porto Alegre, Brazil), Vincenzo V, Pearl P, Roubertie A, Johnson S, Li J, Lupo P, Penematsa V, Tang T

Objective: Aromatic L-amino acid decarboxylase deficiency (AADC-d) is a very rare autosomal-recessive neurotransmitter disorder resulting in severe neurodevelopmental impairment; information about clinical presentation, prognostic factors, and treatment patterns is limited. AADCAware is a 2-part study; Part A aims to describe the natural history of AADC-d in patients receiving standard of care. Part B aims to assess long-term safety and effectiveness of eladocagene exuparvovec on motor function. Demographics and baseline characteristics of patients in Part A of AADCAware, up to March 10, 2022, are described.
Methods: AADCAware is an international, multicenter, longitudinal, real-world, observational registry of patients with AADC-d. In Part A, participants will be followed up annually for a minimum of 5 years.
Results: Nineteen participants (10 male and 9 female) have been enrolled; their median (min, max) age was 4 (1, 41) years. Median (min, max) ages at: onset of first symptoms, genetic molecular diagnosis and AADC enzymatic activity diagnosis were 3 (0, 6), 11.5 (5, 384) and 24 (4, 384) months, respectively. Of 18 participants with AADC-d severity data available at enrollment; 13 (72.2%) had severe disease; three (16.7%) had moderate disease and two (11.1%), mild disease. Motor development status was assessed using the Peabody Developmental Motor Scale-2. Of 12 participants with available data, nine (75.0%) had not developed full head control, the ability to sit unassisted or stand or walk with support. Only 3 (25.0%) participants mastered all 4 motor milestones.
Conclusions: The majority of participants presented with severe illness (72.2%) and failed to achieve the 4 measured motor milestones (75.0%).
Keywords: Movement Disorders (including Cerebral Palsy)

NEONATAL & FETAL NEUROLOGY

141. Neonatal encephalopathy treated with therapeutic hypothermia: is absence of cord blood acidosis a marker for causes other than hypoxic-ischemic encephalopathy (HIE)?

Cornet M-C (San Francisco, CA), Kuzniewicz M, Forquer H, Hamilton E, Newman T, Scheffler A, Murtha A, Wu Y

Objective: To determine the prevalence of cord acidosis among infants with presumed HIE, and to compare risk factors and outcomes in infants with and without cord acidosis.
Methods: We identified all neonates who received therapeutic hypothermia (TH) for presumed HIE within Kaiser Permanente Northern California between 2011 to 2019. Cord acidosis was defined as pH <7.00 or base deficit ≥12. We abstracted maternal demographics, prenatal and perinatal conditions and brain MRI findings from electronic records. We reviewed charts to confirm the presence of encephalopathy and seizures.
Results: Of 426 infants with presumed HIE (population incidence 0.14%), 394 (92%) underwent cord gas analysis. Cord acidosis was present in 196 of 394 (50%). Compared to infants with acidosis, infants without cord acidosis were more likely to have exposure to magnesium (12 vs 6% p=0.049), chorioamnionitis (37% vs. 19%, P<0.001), and epidural analgesia (69% vs. 51%, P<0.001). They were less often born by emergency cesarean section, had more respiratory needs, and less end-organ injury (Table). The rates of moderate/severe encephalopathy, seizures, diffusion restriction on MRI, and length of stay were similar in the two groups. Infants without cord acidosis were more likely to have a diagnosis of acute ischemic stroke (20% vs 5%; p=0.02).
Conclusions: Half of all infants undergoing TH for HIE had no evidence of cord acidosis. These infants may have distinct underlying etiologies including stroke or chorioamnionitis. Further studies are needed to assess the efficacy of neuroprotective treatments for NE based on the underlying pathophysiology.
Keywords: Neonatal & Fetal Neurology

142. Seizure Burden, EEG Background, and Outcome in Neonates with Acute Intracranial Infections: A Prospective Multicenter Cohort Study

Mehta N (San Francisco, CA), Shellhaas R, McCulloch C, Chang T, Wusthoff C, Abend N, Lemmon M, Chu C, Massey S, Franck L, Thomas C, Soul J, Rogers E, Numis A, Glass H

Objective: To characterize the association between seizure burden, EEG background, and neurodevelopmental outcome among neonates with acute symptomatic seizures due to intracranial infection.
Methods: This was a prospective, multicenter cohort study of neonates enrolled in the *Neonatal Seizure Registry* with seizures due to intracranial infection. Continuous EEG monitoring was performed based on ACNS guidelines. EEG background was categorized using standardized terminology. High seizure burden was defined *a priori* as >7 EEG confirmed seizures. Primary outcome was neurodevelopment at 24-months corrected age using Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA-FS). Secondary outcomes were post-neonatal epilepsy and motor disability.
Results: Twenty-seven of 303 neonates (9%) had seizures due to intracranial infection, including 16(59.3%) bacterial, 5(18.5%) viral, and 6(22.2%) unknown. Twenty-three

	No cord acidosis	Cord acidosis	p-value
	N=194	N=196	
Demographics and Pregnancy			
Maternal age	30 (27-34)	32 (28-35)	0.015
Maternal race			0.38
Asian/PI	48 (24.7%)	43 (21.9%)	
Black	17 (8.8%)	21 (10.7%)	
Hispanic	30 (15.5%)	37 (18.9%)	
White	86 (44.3%)	74 (37.8%)	
Multiracial, other, missing	13 (6.7%)	21 (10.7%)	
Preeclampsia	32 (16.5%)	23 (11.7%)	0.18
In utero drug exposure	14 (7.6%)	12 (6.5%)	0.67
SSRI exposure	7 (3.6%)	9 (4.6%)	0.62
Delivery characteristics			
Magnesium exposure	23 (12.4%)	12 (6.5%)	0.049
Epidural analgesia	127 (68.6%)	94 (50.5%)	<0.001
Chorioamnionitis	71 (36.6%)	38 (19.4%)	<0.001
Maternal fever in labor	43 (22.2%)	23 (11.7%)	0.006
Sentinel events (Uterine rupture, cord prolapse, shoulder dystocia)	27 (13.9%)	19 (9.7%)	0.20
Emergency Caesarean	86 (44.3%)	131 (66.8%)	<0.001
Neonatal			
Male sex	123 (63.4%)	120 (61.2%)	0.66
Gestational age	40 (38-41)	40 (38-40)	0.53
1min Apgar score	1 (1-2)	2 (1-3)	0.019
5min Apgar score	4 (2-5)	4 (3-6)	<0.001
Intubation in DR	125 (64.4%)	90 (45.9%)	<0.001
In utero growth restriction	28 (14.4%)	32 (16.3%)	0.60
Moderate to severe encephalopathy	157 (80.9%)	158 (80.6%)	0.94
Seizures	53 (27.3%)	53 (27.0%)	0.95
Peak lactate	7.3 (5.19-11.4)	7.21 (4.355-12.44)	0.85
Creatinine >=1mg/dl in first 3 days of life	72 (37.1%)	96 (49.0%)	0.018
ALT>=60U/L	39 (20.1%)	57 (29.1%)	0.040
INR >=1.7	84 (43.3%)	104 (53.1%)	0.054
Arterial ischemic stroke	12 (20%)	3 (5%)	0.019
Restricted difusion on MRI	54 (31.2%)	47 (27.8%)	0.49
Lenght of stay (hours)	223 (169-321)	226 (154-330)	0.75
Death	9 (4.6%)	10 (5.1%)	0.83

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.

TABLE. Clinical characteristics of neonates with and without cord acidosis (pH <7.00 or base deficit ≥12) among neonates treated with TH for suspected HIE. Abstract 141

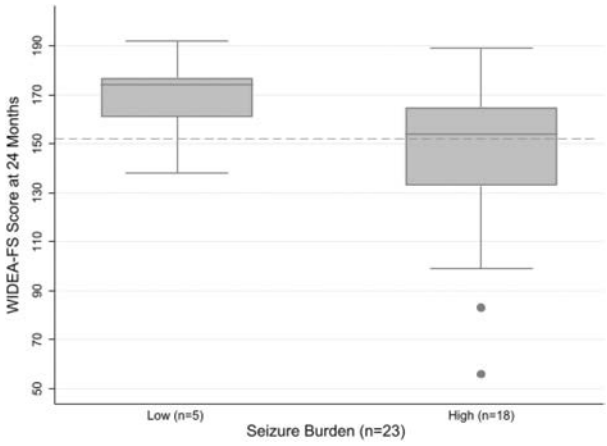


FIGURE: Distribution of WIDEA-FS scores among 23 neonates with low and high seizure burden. Mean (SD) WIDEA-FS score for typically developing population is 172 (10). Dashed line represents WIDEA-FS score of functional impairment (2 SD below the mean). Abstract 142

patients (85.2%) had subclinical seizures. Among 23 infants with 24-month follow-up, the WIDEA-FS was, on average, 23 points lower in infants with high compared to low seizure burden (95% CI [-45,-0.6], p=0.04, *Figure*). After adjusting for gestational age and etiology of infection, the association no longer remained significant (p= 0.09); however, the effect size remained unchanged(β=-23), and the potential confounders were not significantly associated with outcome. EEG background was not significantly associated with WIDEA-FS. All infants with post-neonatal epilepsy (n=4, *Table*) and motor disability (n=6) had high seizure burden, although the association between high seizure burden, EEG background, and secondary outcomes was not significant.

Conclusions: EEG monitoring in neonates with intracranial infection may provide useful management and prognostic information. High seizure burden may be associated with worse neurodevelopmental outcomes in this population.

Keywords: Neonatal & Fetal Neurology, Infections/Neuroimmunology, Critical Care

143. Relationship between blood and cerebral glucose concentration - an in-vivo investigation of glycemic status in newborns with hypoxic-ischemic encephalopathy

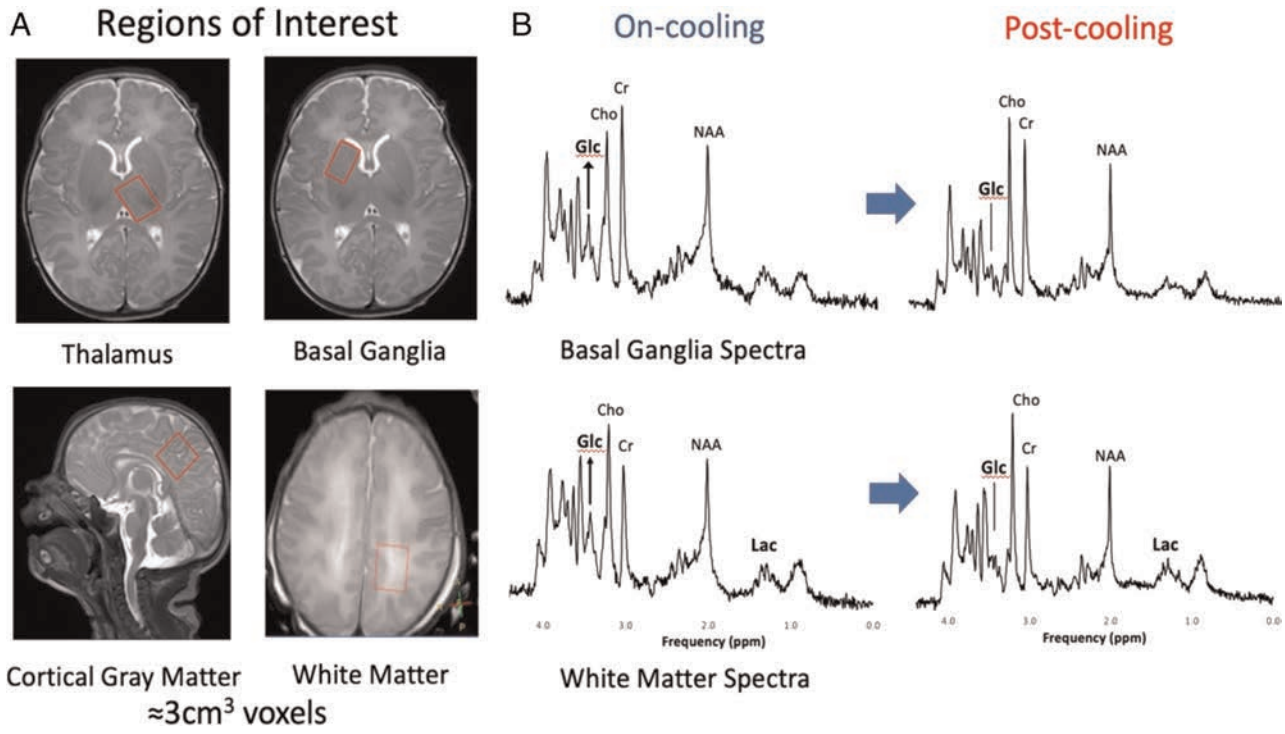
Geyer Winkler Santos E (Los Angeles, CA), Tetarbe M, Wisnowski J, Blüml S, Wu T-W

Objective: To determine regional cerebral glucose concentration (Glc) in relation to glucose infusion rate (GIR) and blood glucose concentration (BG) during therapeutic hypothermia (TH) in newborn hypoxic-ischemic encephalopathy, and to assess whether Glc is affected by injury severity and pattern or by sedative use.

TABLE: Clinical characteristics of neonates with acute symptomatic seizures secondary to acute intracranial infections who developed post-neonatal epilepsy by 24 months. Abstract 142

Patient	Sex	Gestational Age (weeks)	Etiology of infection (Organism)	Additional seizure etiologies	EEG background	Seizure burden	Epilepsy diagnosis	Epilepsy management	WIDEA-FS Score	GMFCS Score
1	F	38.5	HSV	N/A	Mild/ moderately abnormal	High	Focal epilepsy	LEV, PHB	56	5
2	M	31	E. Coli	IVH	Mild/ moderately abnormal	High	Unknown	OXC	112	3
3	M	39	GBS	N/A	Mild/ moderately abnormal	High	Focal epilepsy	LEV, OXC	148	0
4	F	40.3	GBS	Ischemic stroke	Mild/ moderately abnormal	High	Focal epilepsy	LEV	99	4

E. Coli Escherichia coli
GBS Group B Streptococcus
IVH Intraventricular hemorrhage
LEV Leviteracetam
PHB Phenobarbital
OXC Oxcarbazepine
WIDEA- FS Warner Initial Developmental Evaluation of Adaptive and Functional Skills Score at 24 months corrected age
GMFCS Gross Motor Function Classification System Score



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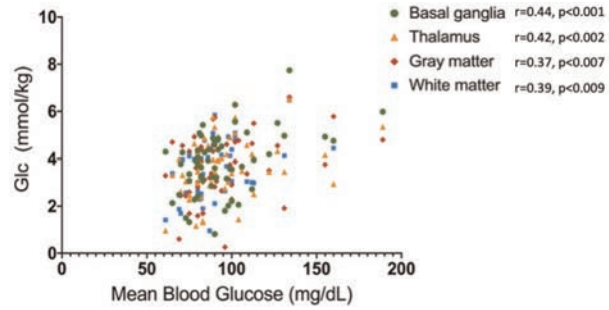

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Methods: Standard T1, T2, DWI and MR spectroscopy (MRS) were performed *during* and *after* TH. Glc measurements were derived from MRS in 4 regions of interest (Figure 1). BG, GIR and sedative use data were abstracted from the chart ± 12 hours from time of MRS acquisition. Brain injury severity was scored by a neuroradiologist and dichotomized into normal-mild and moderate-severe based on Barkovich scoring system. Paired and unpaired t-test, Pearson correlation, repeated measures ANOVA, and multiple regression were performed.

Results: 59 patients were prospectively enrolled. Excluding missing or poor-quality imaging, 404 MRS from 54 patients (30 female) were analyzed. 43 and 11 had moderate and severe encephalopathy on Sarnat exam, respectively. GIR and BG during TH was 6.0±1.3 mg/kg/min and 95±25 mg/dL, respectively. There was no significant difference among Glc in the different regions during TH (RM-ANOVA, F (1.96,105.5)=0.57, p=0.6). There was a significant correlation between BG and Glc in all regions (Figure 2). On multiple regression analysis accounting for sex, gestational age, birthweight, injury severity and pattern, and sedative use, BG remained most predictive of Glc in all four regions (R^2 0.2-0.3, p<0.05).

Conclusions: During therapeutic hypothermia, blood glucose moderately affects cerebral glucose concentration. Injury severity-pattern and sedatives did not influence cerebral glucose concentration.

Keywords: Neonatal & Fetal Neurology, Neuroimaging, Critical Care

144. Prenatal Neurologic Diagnosis: Challenges in Neuroimaging, Prognostic Counseling, and Prediction of Neurodevelopmental Outcomes

Patel V (Philadelphia, PA), Tarui T, Venkatesan C, Agarwal S

Objective: Prenatal diagnosis of fetal brain abnormalities is rapidly evolving with the advancement of neuroimaging techniques, thus adding value to the prognostic counseling and perinatal management. However, challenges and uncertainties persist in prenatal counseling due to limitations of prenatal imaging, continued development and maturation of the brain structure, and the heterogeneity and paucity of outcome studies. This case series highlights prenatally diagnosed brain abnormalities that challenged prognostic counselling and perinatal management.

Methods: A multi-centered retrospective chart review was conducted, focusing on complex and challenging fetal neurologic consultations. This case series was exempt from IRB-

approval due to low case numbers. Charts were reviewed for neuroimaging, genetic workup, prenatal prognostic discussion, postnatal imaging and testing, and infant outcome.
Results: A series of cases with their perinatal course are presented. This case series highlighted the variability in prenatal testing and counseling which leads to challenges in accurately determining postnatal outcomes. Results showed that fetal MRI is critical to determining the full extent of anomalies, however, some anomalies may not be recognizable until later gestation or postnatally.
Conclusions: These cases challenged various diagnostic and management discussions and led to complexity in the prognostic counseling process. Advocating for a national collaborative fetal neurologic registry to help guide the ever-expanding world of prenatal diagnostics and counseling is critical to this field. Study of large-scale outcomes data from such a registry may help better counsel families and provide better-informed multidisciplinary planning from an early age.
Keywords: Neonatal & Fetal Neurology, Neuroimaging

145. Multivariate Approach to Predicting Developmental Delay Among Children with Hypoxic-Ischemic Encephalopathy

Story J (Los Angeles, CA), Gang M, Rao L

Objective: Neonatal hypoxic-ischemic encephalopathy (HIE) is a significant source of neurological morbidity, though neurodevelopmental outcomes are difficult to predict. Prior investigations relating HIE with early development, as measured through the Bayley Scales of Infant Development (BSID), show inconsistent results. Selection of risk factors for analysis may contribute to these discrepancies. Our study aims to compare clinical, laboratory, radiological, and electrographic markers of HIE severity to cognitive, language, and motor development in full-term neonates that underwent therapeutic hypothermia (TH) for HIE.
Methods: Neonates that underwent TH for HIE between 2008 and 2014 were included in analysis. Chart review was performed to obtain clinical information regarding their NICU admission and BSID composite scores from clinic follow-up. Cord blood pH and 10-minute APGAR were compared to BSID scores using Pearson's correlation coefficient. Independent samples *t*-tests were used to compare BSID scores based on specific MRI, MRS, or cEEG findings.
Results: Evidence of hypoxia on MRI (hyperintensities or abnormal diffusion-weighted imaging) was associated with cognitive delays, but not with language or motor delays, and lactate peaks on MRS were associated with motor delays. Excessive sharps and background attenuation on cEEG did not predict BSID differences, though electrographic seizures were associated with both cognitive and motor delays (Fig. 1). Arterial cord blood pH and 10-minute APGAR did not correlate with BSID scores (Fig. 2).
Conclusions: Risk of developmental delay after HIE cannot be adequately assessed using any single risk-stratification modality. A holistic approach involving both imaging and cEEG may better predict long-term effects on multiple developmental domains.
Keywords: Neonatal & Fetal Neurology

146. Correlations between fetal sulcal brain developmental patterns and postnatal neurodevelopmental outcomes in children with prenatally diagnosed isolated cerebral ventriculomegaly

Reid S (Boston, MA), Lee P, Madan N, Yun H, Graham G, Samura O, Kitano R, Akiyama S, Takeoka E, Craig A, Grant P, Im K, Tarui T

Objective: Isolated cerebral ventriculomegaly (IVM) is the most diagnosed fetal brain anomaly, but its significantly variable neurodevelopmental outcomes (normal to moderate developmental delays) are difficult to predict. We determined whether the fetal brain's regional growth or sulcal pattern correlates with their 18-24 month neurodevelopmental outcomes.
Methods: Twenty-three fetuses with fetal MRI diagnoses of IVM (atrial diameter 10-15 mm) (17.7-37.7 gestational weeks) were prospectively recruited. We obtained their postnatal neurodevelopmental outcomes at 18-24 months after birth through medical record review. We performed post-acquisition MRI processing of regional volumetrics and sulcal pattern analyses. In sulcal pattern analysis, each fetal case was quantitatively compared with normal template brains to calculate the similarity indices of sulcal position, depth, basin area and their combination. We compared regional volume growth trajectories and sulcal patterns between fetuses with abnormal (n=9) and normal neurodevelopment (n=14) using non-linear/linear regression models and unpaired t-tests ($p<0.05$).
Results: Regional volumetric analyses found no significant group differences. Sulcal pattern analyses found lower similarity indices in the delayed neurodevelopment group for the left intersulcal relationship of combined features ($p=0.0125$), left whole pattern area ($p=0.0184$), right intersulcal relationship of position ($p=0.0281$), right whole pattern area ($p=0.0286$), right corresponding basins area ($p=0.0500$) and right intersulcal relationship of area ($p=0.0332$).
Conclusions: In fetuses with IVM, abnormal patterns of sulcal position and basin area in the second to third trimester were significantly correlated with abnormal neurodevelopment at 18-24 months old, indicating the potential use for the sulcal pattern index as a quantitative neurodevelopmental outcome predictor.
Keywords: Neonatal & Fetal Neurology, Neuroimaging

147. Metabolic reprogramming in a piglet model of mild neonatal hypoxic ischemic encephalopathy (HIE)

Lammert D (Baltimore, MD), Fernandez R, Liu X, Koehler R, Scafidi S, Scafidi J

Objective: Neonatal hypoxic ischemic encephalopathy (HIE) remains a leading cause of long-term neurologic morbidity. Emergent evidence demonstrates that up to 25% of children with mild HIE suffer motor and developmental delay by 18 months. There is a paucity of understanding regarding the extent, duration and compensatory metabolic adaptation in the brain following mild neonatal HIE. We sought to investigate the nature of this metabolic reprogramming.

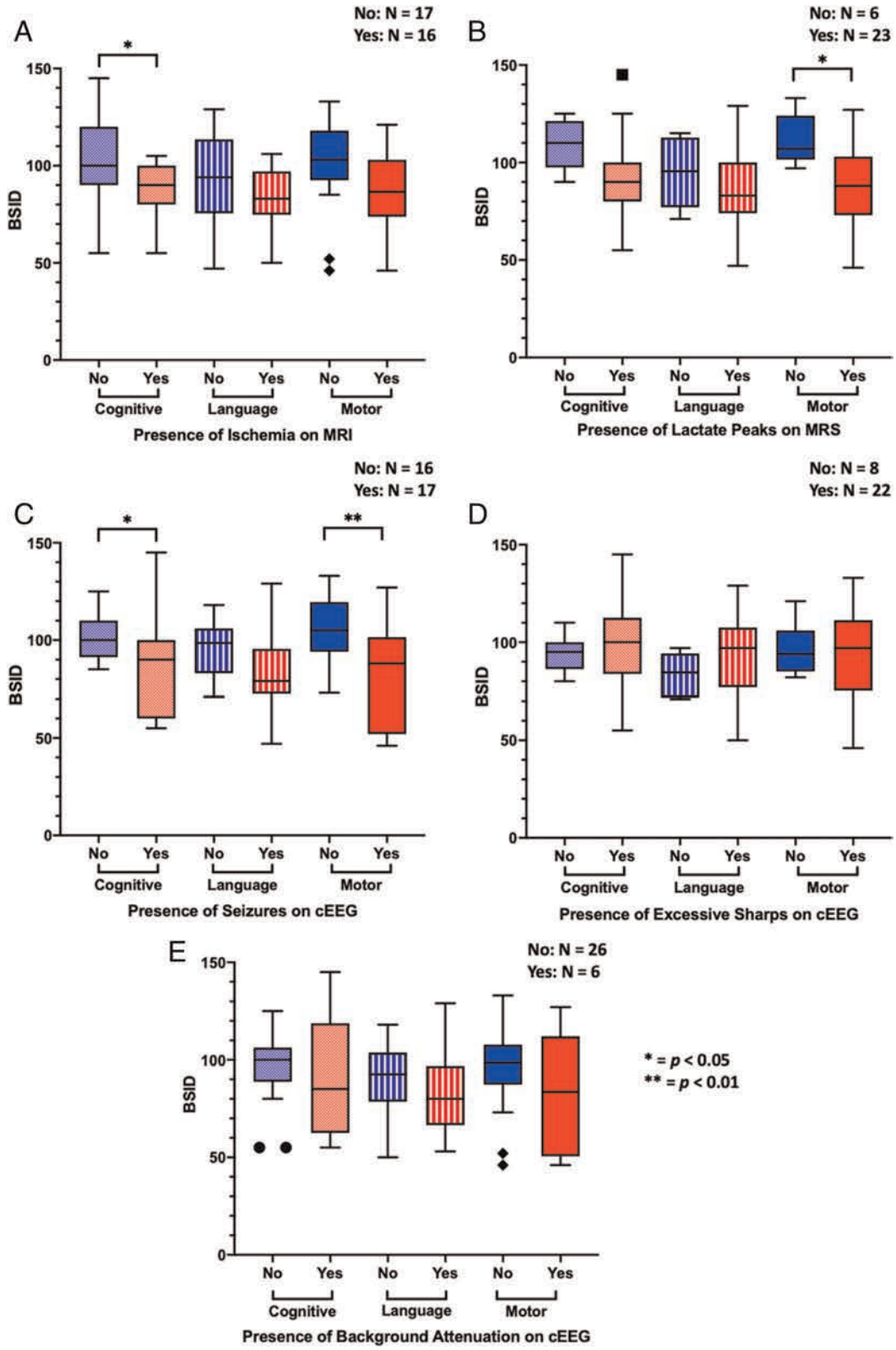


FIGURE 1. BSID Scores Based on MRI, MRS, and cEEG Findings. BSID scores <85 are typically considered abnormal. A. BSID scores based on the presence of ischemia on MRI. Cognitive development is decreased when ischemia was observed. B. BSID scores based on the presence of lactate peaks on MRS. Motor development is decreased when lactate peaks were observed. C. BSID scores based on presence of seizures on cEEG. Cognitive and motor development was decreased when electrographic seizures were detected. D. BSID scores based excessive sharps on cEEG. E. BSID scores based on background attenuation on cEEG. Abstract 145

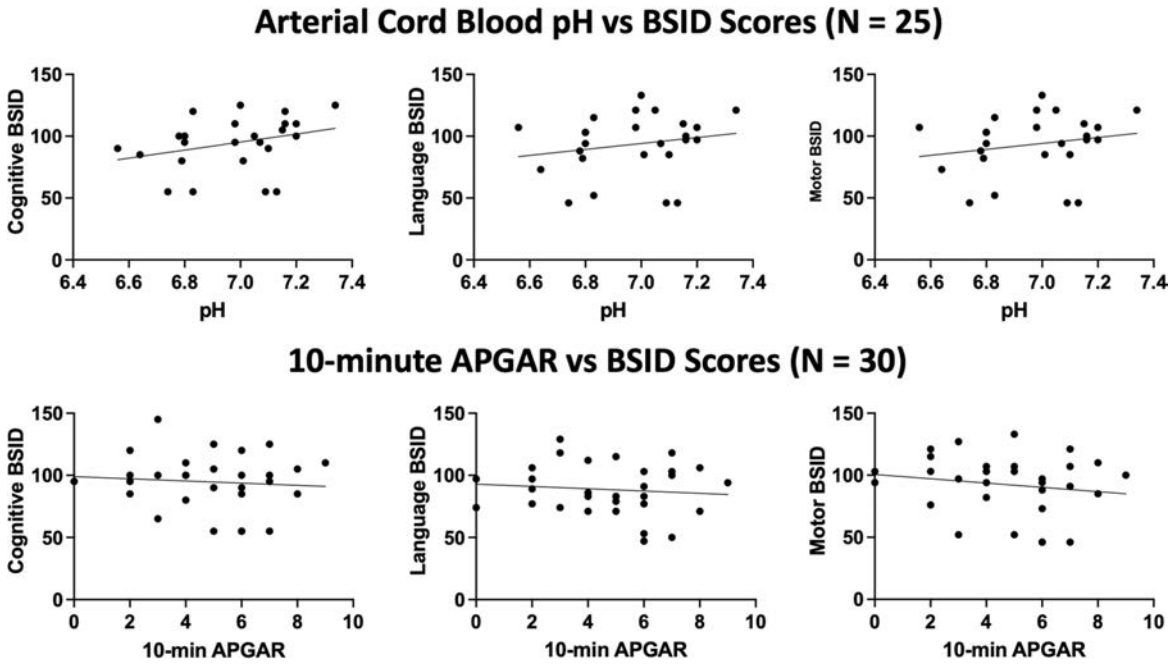


FIGURE 2. Arterial Cord Blood pH and 10-minute APGAR scores vs BSID scores. Neither cord blood pH nor 10-minute APGAR scores showed significant correlation with the cognitive, language, or motor domains of the BSID score. Abstract 145

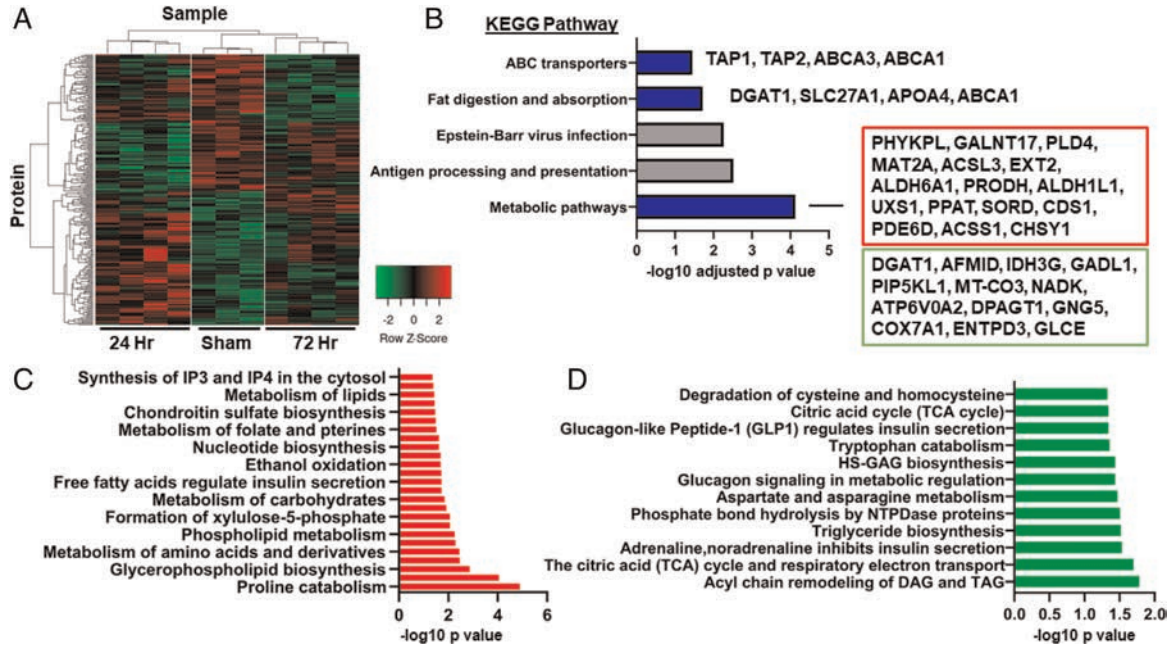


FIGURE 1. Unbiased proteomics screen of piglet mild neonatal asphyxia. (A) Heatmap (heatmapper.ca) of scaled abundances of proteins identified through 11-plex TMTpro labelling of peptides and LC-MS/MS. Proteins were identified as significantly increased or decreased at either 24 or 72 hours post recovery compared to sham if p value was <0.1, accepting a 10% false positive rate to enable discovery. The heatmap shows this subset of proteins. (B) Significantly changed proteins were then analyzed for common pathways using g:Profiler (https://biit.cs.ut.ee/gprofiler/gost). KEGG terms with $p<0.05$ are shown. Gene symbols for proteins associated with each of these KEGG terms are included to the right of the corresponding bar. Relevant energy-associated terms are highlighted in blue. The Epstein-Barr virus infection KEGG term is representative of immune and inflammation pathway enrichment. (C, D) Proteins included in the KEGG metabolic pathways were divided by those increased or decreased at 24 or 72 hours. Reactome (reactome.org) was then used to analyze the types of metabolic pathways. Metabolic pathways enriched in the increased protein expression set are represented in red (C) and decreased in green (D). Abstract 147

Methods: Methods were approved by JHH ACUC. Piglet (*sus scrofa*) brain gross anatomy, time to peak brain growth, and growth patterns are more consistent with human development than other animal models. Term neonatal asphyxia was modeled in 3-day old piglets. Animals were intubated, subjected to whole-body hypoxia for 45 minutes to reach an SaO2 of 30-35%, after which the endotracheal tube was occluded for 7 minutes. No piglets demonstrated clinical seizures, and all were able to walk and eat after resuscitation. Piglets were sacrificed at 24 or 72 hours after recovery, and hippocampi were microdissected. Samples were analyzed using TMTpro peptide labelling and LC-MS/MS and QRT-PCR.
Results: Pathway analysis of protein expression demonstrated the pathways involved in carbon metabolism from glucose were upregulated, while down-regulated pathways were most significantly associated with oxidative metabolism. At the mRNA level, *GAPDH, PDHA1,* and *LDHA* were significantly decreased at both 24 and 72 hours. Taken together our data suggest differential regulation of glucose metabolism and a shift away from oxidative phosphorylation.
Conclusions: Even in mild HIE, metabolic perturbations are present up to 72 hours after insult.
Keywords: Neonatal & Fetal Neurology, Neuroscience

148. Radiographic Hypoxic-Ischemic Injury without Clinical Signs of HIE in Term Neonates

Abbott M (Denver, CO), Nazario Malave M, Stence N, Neuberger I, Dingman A

Objective: To describe the imaging and outcomes for neonates without clinical neonatal hypoxic ischemic encephalopathy (HIE) but with imaging consistent with HIE, referred to here as radiographically isolated HIE.
Methods: We conducted a search of neonatal MRIs at our hospital 2009-2019 using the following terms: hypoxic-ischemic injury, global hypoxia, anoxic, and neonatal encephalopathy. We included patients who presented within one week of life, and excluded patients who met criteria for clinical HIE/therapeutic hypothermia or had other clear cause of injury. MRIs were scored using the Weeke injury score based on DWI and T1 sequences (scale of 0-28).
Results: Of 193 patients reviewed, 29 met inclusion criteria (15%). MRI's were done at a median age of 2 days of life (range 0-6 days). Median injury score was 17.5(IQR 10.5-23.5). T1 changes were present in 79%. A definitive diagnosis was reached in 3 patients: NKH, hyperinsulinism, and VLFA deficiency in one patient each. Outcome data was available in 26 patients, with a mortality rate of 19%. Remote epilepsy occurred in 42%, and 4 patients developed infantile spasms. Of surviving patients, 38% have cortical visual impairment, 33% are non-verbal and 33% require a g-tube.
Conclusions: Our cohort of neonates with radiographically isolated HIE have a guarded prognosis, with a substantial mortality rate and developmental challenges. Radiology data demonstrates these are severe injuries, with T1 changes already present despite early MRI, suggesting likely antenatal, rather than perinatal timing of injury. Antenatal timing of injury may help explain this cohort's unique presentation and outcomes.
Keywords: Neonatal & Fetal Neurology, Neuroimaging

149. Heart rate variability at term is associated with Central Autonomic Network connectivity in premature neonates

Christoffel K (Washington, DC), Cruz J, Govindan R, Cook K, Niforatos-Andescavage N, Basu S, Limperopoulos C, du Plessis A

Objective: The autonomic nervous system (ANS) of a premature neonate develops in an abnormal extrauterine environment. ANS dysfunction may contribute to development of neuropsychiatric disorders, which are more prevalent in prematurity survivors. The mature ANS is modulated by the Central Autonomic Network (CAN), but has not been studied in premature infants. To explore the relationship between ANS tone and CAN connectivity, we measured heart rate variability (HRV) and resting state functional MRI (rsfMRI), respectively, in premature neonates at term-corrected age (TCA).
Methods: We prospectively enrolled 34 premature neonates (mean gestational age at birth: 27.9 +/- 2.5 weeks) who underwent rsfMRI at TCA (39.5 +/- 1.9 weeks) and had

Brainstem segment	ROI Laterality	Precuneus	Anterior Cingulate	Medial PFC	Thalamus	Cerebellum	Amygdala	Insula	Hippocampus
Midbrain	R	0.06	-0.042	0.016	0.504**	0.4*	0.273	0.491**	0.413*
	L	0.014	-0.119	0.173	0.351*	0.487**	0.437**	0.187	0.43*
Pons	R	-0.171	-0.095	0.129	0.452*	0.508**	0.442*	0.464*	0.37*
	L	-0.247	0.132	0.253	0.314	0.492**	0.267	0.083	0.436*
Medulla	R	-0.362*	0.006	-0.178	0.39	0.21	0.576**	0.581**	0.507**
	L	-0.149	0.155	0.038	0.187	0.214	0.193	0.197	0.56**

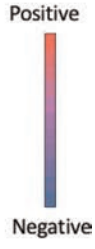


FIGURE 1. Heat map of Pearson correlation values for 37-week RMS1 with each ROI pairing. Starred values are statistically significant on exploratory analysis. A single asterisk (*) represents a p-value less than .05, two asterisks (**) represent a p-value less than .01. No relationships remained significant after adjustment for multiple comparisons. Abstract 149

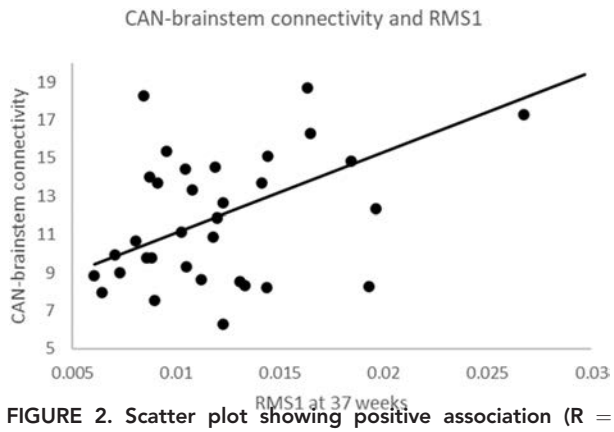


FIGURE 2. Scatter plot showing positive association (R = .561, p = .001) of CAN-brainstem connectivity and HRV metrics at TCA, where each dot represents one subject. Abstract 149

continuous HRV data recorded over 37 weeks postmenstrual age. RMS1 was the primary HRV metric. Medulla, pons, midbrain, and total brainstem connectivity was assessed to 8 other ROIs pertinent to the CAN: anterior cingulate, medial prefrontal cortex, precuneus, hippocampus, amygdala, insula, thalamus, and cerebellum.

Results: Univariate linear regression revealed associations between RMS1 and numerous ROI pairings, but none remained significant after Bonferroni correction for multiple comparisons. RMS1 was positively associated with CAN-medulla connectivity (R = .520, p = .002), CAN-pons connectivity (R = .483, p = .004), and CAN-midbrain connectivity (R = .522, p = .002). Association with total CAN-brainstem connectivity (R = .561, p = .001), is shown in figure 2.

Conclusions: In premature neonates, term HRV is associated with connectivity between brainstem and the CAN. Further work is needed to elucidate the development of CAN and its relationship to ANS tone among prematurity survivors.**Keywords:** Neonatal & Fetal Neurology, Neuroscience

150. Neonatal Tetanus Still Remains a Differential Diagnosis for Seizures in Developed Countries: Case Report

Zhu Z (Hershey, PA), Bolt E, Paudel S, Paul D, Naik S

Objective: Neonatal tetanus presents clinically as muscular rigidity and spasms. Moderate to severe cases are associated with a mortality rate of 58-92%. $MgSO_4$ used early in the disease course improves survival by reducing ventilation time. Limited studies exist on the safety and efficacy of $MgSO_4$.

Methods: A 10-day-old term Amish female was hospitalized for a 3-day history of spasms, poor feeding with trismus, rigidity, opisthotonos and risus sardonicus. She was born at home without prenatal immunization. Essential oils were used for umbilical stump hygiene.

Results: The patient had episodes of rigidity and persistent muscle spasms with no EEG correlates. Suspecting grade III neonatal tetanus, she received TIG. Testing for the BRAT1 gene mutation, IEM and the CP panel were negative. CSF, blood and urine culture were sterile. She was treated with midazolam, pancuronium, morphine and antimicrobials while under ventilation. She was then transitioned to IV $MgSO_4$, oral diazepam and oral baclofen. IV magnesium was infused at 40mg/kg/hr, and increased as needed, with monitoring of serum magnesium and calcium and urine calcium. Patient was weaned off pancuronium, morphine and midazolam and was extubated. Diazepam and baclofen were subsequently discontinued, treating with only MgSO4.

Conclusions: $MgSO_4$ and diazepam have been reported to be effective in treating tetanus, particularly in older patients >1 year old. $MgSO_4$ works by causing muscle relaxation and is useful in alleviating autonomic symptoms. This protocol proved safe and advantageous in treating neonatal tetanus by reducing the use of paralytics and sedatives, while shortening ventilation time to avoid complications secondary to prolonged ventilation.

Keywords: Neonatal & Fetal Neurology, Infections/Neuroimmunology, Neuromuscular Disorders

151. Ante-natal and post-natal factors affecting the rate of growth of corpus callosum in preterm infants, a retrospective study.

Angappan D (Beaverton, OR), Morales M, Murali D, Parimi P

Objective: The primary objective was to determine the effect of ante-natal steroids, post-natal narcotic/opiate use and prolonged total parenteral nutrition on the rate of growth of corpus callosum in premature infants. The secondary objective was to examine the effect of IVH, BPD and NEC on corpus callosal growth.

Methods: Premature infants ≤ 32 weeks of gestation and ≤1500 grams admitted to an academic level III NICU between January 2010 to December 2020 were included in this retrospective study. Inner and outer lengths of corpus callosum (CC) and diagonal measurements of globo-thalamic-ovoid (GTO) were measured serially on day 3,10, 30, 60 and 90 days of life using cranial ultrasonogram. Preterm infants were stratified into <26 weeks (n=47), 26-28 weeks (n=38), and 29-32 weeks (n=66) gestational age to examine the clinical factors responsible for perturbations in growth.

Results: The inner and outer measurements of CC (cm) in preterm infants <26 weeks gestational age was significantly different (p<0.001) compared to infants in 26-28 week and 29–32-week category. The GTO measurements were also significantly different between gestational age categories during the same time intervals (p<0.001). While the CC measurements in <26-week preterm infants at 32 weeks corrected age are not different compared to preterm infants born at 32 weeks, the GTO measurements were significantly different (p <0.01).

Conclusions: Stepwise regression analysis demonstrated that only birth weight and gestational age explained 70% of variation in the measurements of corpus callosum at birth. Neither pre-natal nor post-natal factors negatively impacted the post-natal corpus callosal growth.

Keywords: Neonatal & Fetal Neurology, Neuroscience, Neurorehabilitation

152. Implementation of a Neonatal Hypoxic-Ischemic Encephalopathy Neurocritical Care Protocol: Improved Compliance with Management Guidelines and Decreased Antiseizure Medications at Discharge

Hunter S (Chapel Hill, NC), Broman-Fulks J, Shiloh-Malawsky Y

Objective: Evaluation of the impact of implementing a neurocritical care protocol for neonatal hypoxic-ischemic encephalopathy (HIE)

Methods: A multidisciplinary team (neonatologists, pediatric neurologists, epileptologists) developed a neurocritical care protocol for neonates with HIE; incorporating electroencephalography (EEG) monitoring practice guidelines, data driven recommendations for MR imaging, and expert opinions for antiseizure medication management. Local protocol consensus was achieved by discussions among team members and their respective divisions. The protocol implementation process required updating and educating neonatology, pediatric neurology, and neurophysiology teams. All neonates admitted with moderate to severe HIE were studied retrospectively 18 months before and 18 months after protocol implementation. Primary outcomes: protocol adherence of EEG monitoring and imaging acquisition. Secondary outcomes: EEG and MRI abnormalities detected, length of stay and antiseizure medication use.

Results: Of the 60 patients with HIE, 28 were in the pre-protocol and 32 in the post-protocol groups. The groups were similar in demographics and clinical presentation characteristics. Post-protocol adherence for MRI acquisition in the first 5 days of life was 77%; a significant increase from the pre-protocol group (4%). EEG monitoring increased from 33 to 84%, and the mean age at start of EEG decreased by a mean of 24.3 hours. In the post-protocol group, there was a statistically significant decrease in antiseizure medications prescribed on discharge. There was no significant change in other outcome measures.

Conclusions: Implementation of a neonatal HIE neurocritical care protocol was associated with a significant increase in EEG monitoring, earlier EEG monitoring, earlier MRI acquisition, and decreased antiseizure medications at discharge.

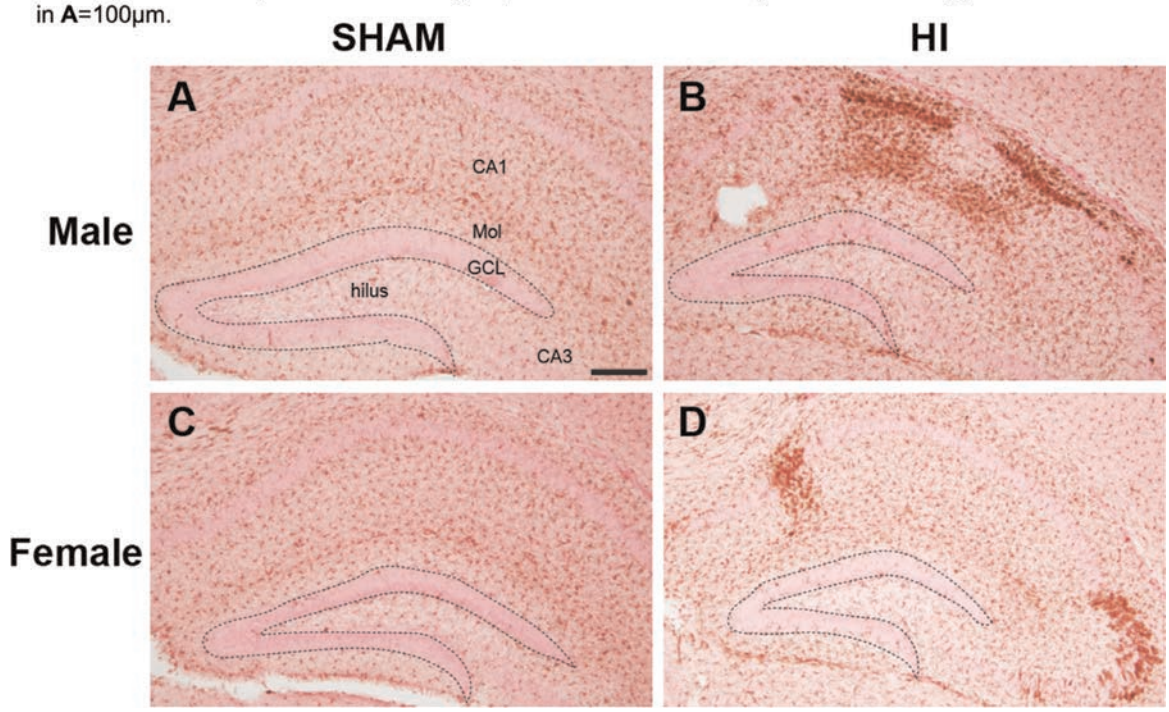
Keywords: Neonatal & Fetal Neurology, Critical Care, Epilepsy/Epilepsy

153. Male mice have larger lesions and more variable macrophage response than females 3 days after P10 hypoxia-ischemia

Guez-Barber D (Philadelphia, PA), Gillis S, Kiffer F, Yun S, Eisch A

Objective: In rodent models of hypoxia-ischemia (HI), males show larger anatomic injuries, distinct motor deficits, and worse cognition after HI relative to females. Microglia, the brain's resident macrophages, have sex-dependent developmental trajectories and gene expression patterns. Lesion and transplantation studies show microglia play different roles in

Figure 1: Hypoxia-Ischemia increases macrophage response in the hippocampus. (A-D) Representative images of anterior hippocampal sections from male and female mice after HI or Sham. Hypoxia-ischemia or Sham was induced at P10, mice were euthanized at P13. Brains were sectioned and immunohistochemistry was performed using an antibody against Iba1, which labels both brain resident microglia and monocyte-derived macrophages that infiltrate the brain from the peripheral blood. GCL = granule cell layer of the dentate gyrus, Mol = molecular cell layer of the dentate gyrus. Scale bar in A=100μm.



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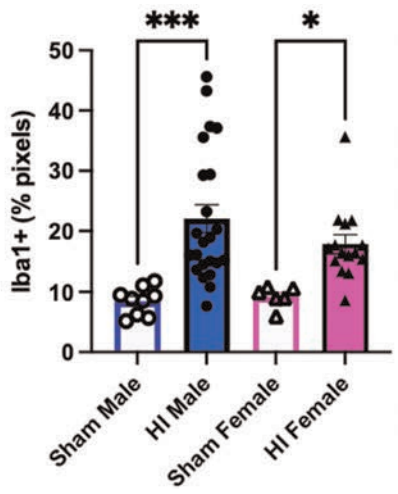

Figure 2: Hypoxia-Ischemia increases macrophage response in the hippocampus of male and female mice. Quantification of data from hippocampal sections from male and female mice after HI or Sham. Hypoxia-ischemia or Sham was induced at P10, mice were euthanized at P13. Brains were sectioned and immunohistochemistry was performed using an antibody against Iba1. Image analysis described in Methods. Sham Male n=9, HI Male n=23, Sham Female n=6, HI Female n=15. Data were not normally distributed so nonparametric statistics were used. Kruskal-Wallis, ***p<0.0001, *p<0.05. The following comparisons are not significant: Sham Male vs. Sham Female, HI Male vs. HI Female.

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male and female brains after HI or stroke. We examined the macrophage response 3 days after postnatal day 10 (P10) HI in the hippocampus, a hypoxia-sensitive brain region critical for learning.

Methods: We used a modified Vannucci model with P10 right carotid artery ligation followed by hypoxia at FiO2 8% for 45 minutes. At P13, mice were euthanized and lesion size, if present, was measured. Brains were fixed then sectioned for immunohistochemistry with Iba1 antibody. Images were analyzed in ImageJ for % area of Iba1+ pixels.

Results: Of 95 mice treated with HI, 12 (27%) male HI mice and 7 (18%) female HI mice had a grossly visible pale lesion on the surface of the brain. Of these mice, the lesion size was significantly larger in males (mean 12.3mm2) than females (mean 5.5mm2); this is consistent with the literature. Iba1 in the hippocampus was increased after HI in both male and female mice compared with Sham mice, but the variance in Iba1 response among HI Males was notably higher than the variance among HI Female mice.

Conclusions: Next steps include differentiating in both male and female mice how much of the Iba1 response is due to brain resident microglia vs. macrophages infiltrating from the periphery.

Keywords: Neonatal & Fetal Neurology, Neuroscience, Infections/Neuroimmunology

154. Short-term Treatment Response and Long-term Outcome in a Retrospective Neonatal Seizure Cohort Initially Treated with Levetiracetam or Phenobarbital

Knox A (Madison, WI), Jordan E

Objective: In a previous study, we characterized several different outcome measures in a retrospective cohort of neonates with seizures who were monitored on video EEG before initial treatment. Here we study how these short-term measures correlate with long-term neurodevelopmental outcomes.

Methods: Long-term outcomes for a previously described retrospective cohort of 25 patients were determined by chart review of their most recent office visit. Outcome was defined as either abnormal (a diagnosis of developmental delay,

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Association Between Demographics, Short-term Treatment Response and Normal Long-term Outcome

Long-term outcome		Normal		Abnormal			
	Variable	**Yes**	**No**	**Yes**	**No**	**Accuracy**	**P-value**
Pre-treatment variables	Etiology other than HIE	9	7	3	6	0.60	0.41
	Normal imaging	4	8	2	11	0.60	0.37
	Initial treatment with levetiracetam	9	3	8	5	0.56	0.67
	Pre-treatment seizure burden < 10%	9	3	7	6	0.60	0.41
Post-treatment measures	Seizure burden <10% after treatment	9	3	7	6	0.60	0.41
	Seizure free after treatment	4	8	4	9	0.52	1.00
	20% decrease in seizure burden	3	10	6	7	0.38	0.41

intellectual disability, cerebral palsy, epilepsy, or death) or normal. We correlated long-term outcome with both short-term outcome measures and pretreatment variables. Comparisons were made using Fisher's exact test.
Results: Patient had been followed a median of 3.4 years (interquartile range 2.4 - 4.1 years). 38% had developmental delay, 38% had cerebral palsy, 8% had epilepsy, and 48% were normal. There were no statistically significant associations; neither outcome measures nor pretreatment variables showed good accuracy for predicting long-term outcomes. Sustained seizure burden < 10% better associated with normal long-term outcomes than seizure freedom and decrease in seizure burden (accuracy 0.6, 0.52 and 0.38 respectively). Pretreatment seizure burden < 10%, initial treatment with levetiracetam, normal imaging and an etiology other than HIE also better associated with good long-term outcomes (0.6, 0.56, 0.6, and 0.6 respectively).
Conclusions: Sustained low seizure burden after initial treatment with neonatal seizures may be a better surrogate of long-term neurodevelopmental outcomes than seizure freedom after initial treatment. Pretreatment seizure burden and etiology remain important predictors of long-term outcomes. A larger cohort is necessary to confirm these associations.
Keywords: Neonatal & Fetal Neurology, Epilepsy/Sleep

NEUROCUTANEOUS DISORDERS

155. Variation in neuroimaging and outcomes in patients with SWS type III

Hadjinicolaou A (Boston, MA), Quinlan A, Prabhu S, Pinto A

Objective: Sturge-Weber Syndrome (SWS) is a life-long neurovascular condition present in roughly one out of every 20,000 live births. SWS Types I and II involve cutaneous and ophthalmological findings, in addition to neurological involvement in Type I, whereas Type III is exclusive to brain stigmata. Our study aims to describe the characteristics of brain MRI findings in patients with SWS Type III. We hypothesize that SWS Type III has a unique radiological phenotype and resultant different clinical manifestations. We will correlate neuroradiological features with seizure and cognitive outcomes in eleven patients with SWS Type III.
Methods: This is a retrospective case series examining the clinical, radiological and cognitive characteristics of patients referred to the Comprehensive SWS Clinic at Boston Children's Hospital with a diagnosis of SWS Type III. We analyzed MRI findings based on vascular and brain parenchymal features. The clinical and cognitive outcomes were based on a validated assessment tool in this population (Neuroscore).
Results: This is the largest case series of patients with Type III SWS from a single center. Eleven patients were identified. Stroke-like events and atypical headaches are likely to occur in conjunction predominantly with deep venous anomalies, whereas seizures are likely to be associated with brain parenchymal abnormalities such as atrophy and calcifications.
Conclusions: Preliminary results indicated that predominant imaging features can predict neurological outcomes.
Keywords: Neurocutaneous Disorders, Neuroimaging

NEUROIMAGING

156. Quantitative Volumetric Analysis of Brain MRI from Infants and Children with Neuronopathic Mucopolysaccharidosis type II (MPS II) using FreeSurfer

Roche F (Lyon, France), Clark K, Phillips D, Hagood J, Cho Y, Vincent F, Holland S, O' Leary D

Objective: To develop a semi-automated method to quantify brain volumes in children with neuronopathic MPS II, a disease caused by a deficiency of iduronate-2-sulfatase leading to an accumulation of glycosaminoglycans. Radiologically, numerous cerebral abnormalities can be present in MPS II, but important hallmarks of the neuronopathic phenotype are atrophy and white matter changes.
Methods: Brain structures were quantified using MR 3D-T1 weighted images, processed with FreeSurfer (FS) and Infant FreeSurfer (IFS). IFS was required in patients younger than 2 years old due to age-related inverted T1 contrast. A semi-automated preprocessing step was developed to handle enlarged perivascular spaces and to improve FS segmentation accuracy. Total brain, ventricular and brain parenchymal volumes were calculated for all patients. 53 images were processed from 12 patients, ranging from 5 to 76 months of age. Intraclass correlation coefficients (ICC) were determined from a mixed model with Patient as random effect and Method as a fixed effect.
Results: 7 patients were successfully processed with both FS and IFS. 3 infants could only be processed using IFS and 2 patients with enlarged ventricles could only be processed on FS. Lesions greater than 3x3x3 mm were successfully segmented. Total brain and ventricular volumes were comparable between FS and IFS (ICC=1.0 and ICC=0.99, respectively).
Conclusions: MPS II studies often include a wide patient age range and may necessitate a combination of MRI analytical approaches. A strong relationship was demonstrated between IFS and FS for brain and ventricular volumes, providing support for a mixed analysis strategy with MPS II.
Keywords: Neuroimaging, Rare Diseases

157. Development of Wearable Magnetoencephalography for Detection and Localization of Brain Activation during Movements for Pediatrics

Xiang J (Cincinnati, OH)

Objective: Conventional magnetoencephalography (MEG) systems are very bulky and immobile. This study was to develop a new wearable MEG system, which is based optically pumped magnetometer (OPMs) and advanced noise cancellation techniques.
Methods: A wearable MEG prototype was developed with commercial OPMs and a custom helmet. The OPMs were divided into primary sensors and reference sensors. For each primary sensor, a synthetic gradiometer (SG) was constructed by computing a secondary sensor that simulated noise with

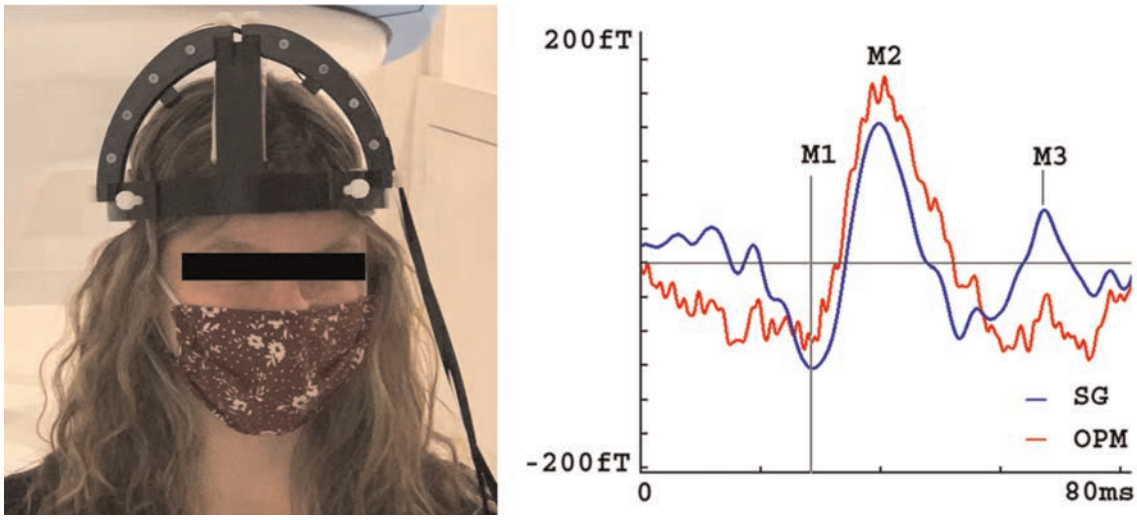


Fig.1.A Photo of Our New Wearable OPM MEG Prototype and MEG Waveforms from a Participant during Finger Tapping. The synthetic gradiometer (SG) waveform shows three components (M1, M2 and M3), while the optically pumped magnetometer (OPM) waveform shows predominately M2. The waveform patterns in SG (OPMsg) are consistent with the waveform patterns revealed by SQUID MEGs in previous reports. All signals are processed with a band-pass filter of 1- 100 Hz. Abstract 157

signals from the reference sensors. Magnetic noise was removed with spatial filtering by using SG. MEG data from a phantom with known source signals and six human subjects were used to assess the efficacy of SGs.

Results: In comparison to conventional MEG, OPM MEG showed higher signal amplitude and lower variations among subjects. SGs in OPMs significantly reduced magnetic noise ($p < .01$), enhanced signal-to-noise ratio (SNR) ($p < .001$) and improved the accuracy of source localization ($p < .02$). OPM MEG precisely revealed movement-evoked magnetic fields in MEG data recorded from human subjects.

Conclusions: Wearable OPM MEG supports all head anthropometrics, which is particularly beneficial for the applications of MEG in pediatric settings. SGs in wearable MEG provided an effective method to enhance SNR and improve the accuracy of source localization by suppressing noise. Software simulated SGs may bring new opportunities to use OPM measurements in various clinical and research applications. Pediatric patients, who cannot keep still for conventional MEG recordings, typically require sedation/anesthesia. Those patients can have wearable OPM MEG tests without sedation/anesthesia.

Keywords: Neuroimaging, Neuroscience

NEUROMETABOLIC DISORDERS

158. The viral exposome is marked by repertoire constraints in children with primary mitochondrial dysfunction

Gordon-Lipkin E (Bethesda, MD), Kruk S, Thompson E, McGuire P

Objective: Viral infection is a significant cause of metabolic decompensation and neurologic decline in children with mitochondrial disease (MtD), yet there is limited information regarding the the repertoire of viruses to which they are exposed and which viruses pose more or less of a threat. Building a compendium of the "viral exposome" in children with MtD may help elucidate the relationship between the viral immune response and MtD for, ultimately, more targeted therapy.

Methods: In a cross-sectional serology study, we characterized the viral exposome in 19 children with MtD and 16 controls using phage display and immunoprecipitation sequencing (PhIPseq) to define the antiviral antibody repertoire. All MtD patients had a known pathogenic variant.

Results: As a group, children with MtD recognized fewer viral proteins, and antiviral antibodies displayed less robust fold changes, as well as limited polyclonality. Using a deconvolution algorithm to determine viral exposures, both children with MtD and controls experienced about 14 different viral exposures. Comparable viral species were identified. However, unlike controls, children with MtD failed to show a relationship between viral exposures and age. Finally, human alphaherpesvirus 1 (HSV-1) exposures were only seen in children with MtD.

Conclusions: Our findings suggest that while children with MtD have similar numbers and types of viral exposures, their antiviral antibody responses are qualitatively distinctive. Additional longitudinal studies combining clinical data on infectious illnesses, neurologic function scores, and PhIPseq, will be important steps in characterizing host-pathogen interactions in this vulnerable population.

Keywords: Neurometabolic Disorders, Infections/ Neuroimmunology

159. Small Molecule and Energy Deficiency Neurometabolic Disorders in Pediatric Intensive Care Unit– Children's National Experience over 10 Years

Sen K (Washington, DC), Pariseau N, Zhang A, Harrar D, Gropman A

Objective: Metabolic crises in inborn errors of metabolism (IEMs) are life-threatening emergencies which result in admission to pediatric intensive care units (PICUs). Among the relatively common IEMs; urea cycle disorders (UCD), organic acidemias (OA), Maple syrup urine disease (MSUD) and mitochondrial diseases (MD) constitute majority of these admissions.
Methods: Data was collected by retrospective chart review for patients with afore-mentioned disorders who were admitted at our institution from 2008-2018 and information was analyzed in REDCap.
Results: Our cohort included 40 patients (8 UCD, 7 OA, 3 MSUD and 22 MD) with 153 admissions. Presenting symptoms included altered mentation (36%), seizures (41%), focal weakness (5%), and emesis (28%). Biochemical aberrations included hyperammonemia (37%), lactic acidosis (55%), and elevated leucine (6%). Continuous EEG was performed during 40% of these admissions for fluctuating mentation, prolonged seizures, and raised intracranial pressure monitoring. EEG background demonstrated slowing - mild (20%), moderate (52%), severe (14%); and 45% of recordings showed seizures (46% clinical and 83% electrographic). Neuroimaging was ordered in 25% of admissions, revealing edema (2.4%) as well as cortical and basal ganglia injury (20% and 2.4%). Mean length of stay was 5.11 days and 4% had in-hospital mortality. 8% had iatrogenic complications, most commonly hyperglycemia or hypotension. Mean pediatric overall and cerebral performance score at discharge were 3.32 and 3.39 respectively.
Conclusions: This is the largest study till date which investigates recognition, stabilization and mortality in patients with neurometabolic disorders admitted to PICUs. This data can be used to form standardized protocols to improve the neurological care in IEMs.
Keywords: Neurometabolic Disorders, Critical Care, Rare Diseases

160. CANinform, a Retrospective and Prospective Natural History Study of Canavan Disease: Status and Initial Analyses

Eichler F (Boston, MA), Andonian H, Nagy A, Kirby K, Laforet G, Shaywitz A, Balser J, Bley A

Objective: Canavan disease (CD) is an ultra-rare leukodystrophy caused by mutations in the *ASPA* gene leading to elevated brain N-acetylaspartate (NAA) and profound early-onset impairment of psychomotor development. CD has no approved therapies and longitudinal natural history data are sparse. CAN*inform* was initiated in 2019 to rigorously collect CD patient data to define meaningful clinical endpoints and provide robust control data for interventional trials.
Methods: Data are compiled via retrospective medical record review and prospective patient assessments. After rigorous training, developmental specialists apply a systematized data extraction process to medical record review and expert physiotherapists perform a battery of standardized developmental assessments. COVID-19 required adaptation of in-person assessments to remote conduct via video. A novel CD-specific scale is used to map disease progression. Data analysis uses descriptive statistics according to a statistical analysis plan.
Results: To date, data spanning age 3m-20.75y (median age at enrollment 32m) have been collected from 46 participants. While variability occurs, early analysis suggests that some basic motor milestones such as head control and independent sitting are almost never achieved, while other milestones (e.g. rolling over) are sometimes achieved but delayed. In addition, a subset of patients gain certain skills (e.g. voluntary grasp) that are subsequently lost. A small minority of patients are outliers with relatively higher function across multiple motor domains.
Conclusions: Developmental and disease state parameters and patterns from the natural history study create a frame of reference for guiding patient stratification, defining clinical endpoints and discerning a meaningful treatment effect in the CAN*aspire* gene therapy trial.
Keywords: Neurometabolic Disorders, Rare Diseases

161. Mitochondrial disease patients admitted to the ICU have more severe neurologic phenotypes

Doerfler M (Chicago, IL), Mithal D

Objective: Neurologic symptoms affect at least half of patients with mitochondrial disease but how many of these patients require critical care remains unclear. Stroke-like lesions, status epilepticus, metabolic decompensation and more diffuse organ dysfunction can acutely alter neurologic function. With limited published literature on the frequency and severity of neurocritical illness in mitochondrial disease the present study aims to compare mitochondrial disease patients that spent time in the ICU as compared to those that did not.
Methods: A single center retrospective cohort of 102 children with mitochondrial disease was divided into patients admitted to the ICU and those admitted to the hospital but never to the ICU. Charts were reviewed and clinical and genetic characteristics were extracted.
Results: 67 out of 102 patients (66%) were admitted to the hospital for at least one day. 45 patients (44%) were admitted to the ICU for at least 1 day. In addition to significantly higher neurologic disease burden, the ICU cohort had more concern for sepsis and a higher burden of multi-organ disease. Lifespan was not different between the cohorts and duration of ICU stay was not associated with mortality. There was no difference in the distribution of nuclear v. mitochondrial DNA variants.
Conclusions: Two thirds of mitochondrial disease patients who are admitted to the hospital will have an ICU admission with high mortality rates. Those who survive may have long ICU admissions with more severe neurologic disease burden. Further studies are required to understand which patients are at highest risk and what treatments might improve outcomes.
Keywords: Neurometabolic Disorders, Critical Care, Rare Diseases

NEUROMUSCULAR DISORDERS

162. An Open-label, Phase 1/2a, AAV9-CLN3 Gene Transfer Clinical Trial For Juvenile Neuronal Ceroid Lipofuscinosis

de los Reyes E (Columbus, OH), Aylward S, Islam M, Meyer K, Stefanelli E, Jiang H, Weimer J, Goldman M

Objective: *CLN3* mutations cause Juvenile Neuronal Ceroid Lipofuscinosis (JNCL), a severe childhood onset neurodegenerative disorder with urgent unmet treatment needs. Our study is an open-label, dose-escalation, phase 1/2a study (NCT03770572) evaluating safety and efficacy of AT-GTX-502, an adenovirus-associated virus serotype 9 (AAV9)-mediated gene therapy.

Methods: The trial includes subjects aged 3 to 11 years with JNCL genetic confirmation and Unified Batten Disease Rating Scale (UBDRS) physical subscale impairment score of ≤7. Four subjects received a single intrathecal injection, three patients at 6 $x10^{13}$ vector genomes (vg) (low-dose) and one patient at 1.2 x 10^{14} vg (high-dose). Subjects are evaluated at screening, days 7, 14, 21, and 30; and months 3, 6, 9, 12, and every 6 months through month 60.

Results: Low-dose subjects included two males and one female aged 114, 105, and 71 months at enrollment, respectively. The high-dose subject was a male aged 120 months. Durations of follow-up was 38.6, 34.7, 33.5, and 26.6 months. Treatment was generally well tolerated and most treatment-emergent adverse events were mild or moderate and unrelated to AT-GTX-502.Interim efficacy results show lack of disease progression in 3 out of 4 as compared to natural history which reports a gain of +2.86 points/year on the UBDRS physical impairment scale. In contrast, our patient cohort UBDRS physical impairment scores were -2 (36 months), +7 (24 months), -2 (30 months), 0 (24 months) respectively.

Conclusions: Interim results demonstrate safety and suggest efficacy in 3 out of 4 patients, warranting further evaluation in a larger patient cohort.Sponsor: Amicus Therapeutics.

Keywords: Neuromuscular Disorders, Translational/ Experimental Therapeutics, Rare Disesases

163. Comparing the change in 6-minute walk distance in nmDMD patients receiving ataluren: STRIDE Registry compared with phase 3 clinical trial

Muntoni F (London, United Kingdom), Tulinius M, Buccella F, Desguerre I, Kirschner J, Nascimento Osorio A, Johnson S, Werner C, Jiang J, Li J, Trifillis P, Wing J, Mercuri E

Objective: We investigated whether ataluren-treated nonsense mutation Duchenne muscular dystrophy (nmDMD) patients in real-world practice (STRIDE Registry; NCT02369731) experienced a similar decline in 6-minute walk distance (6MWD) vs ataluren-treated patients in a phase 3 clinical trial (Study 020; NCT01826487). The 6-minute walk test is a motor function assessment that allows progressive loss of ambulation to be recorded.

Methods: STRIDE patients (n=42) were assessed by their first 48-week change (difference between their first '48-week assessment' [between 40 and 72 weeks] and first assessment); Study 020 patients (ataluren [n=45] and placebo [n=50]) were assessed by change over 48 weeks. Only patients with a 6MWD of ≥300 to ≤400 metres (m) at first assessment were assessed. For patients who lost ambulation, 6MWD was imputed as 0 m the day ambulation was lost.

Results: Mean (95% CI) first baseline 6MWD assessment for STRIDE patients (349.7 [341.4, 358.0] m, n=42) was comparable to that for patients in Study 020 (ataluren, 356.7 [348.9, 364.5] m, n=47; placebo, 354.5 [346.3, 362.8] m, n=52). Mean (SD) age at first assessment was also comparable (STRIDE ataluren, 9.6 [3.1], n=42; 020 ataluren, 8.9 [1.8], n=47; placebo, 9.0 [1.5], n=52).STRIDE patients experienced a mean (95% CI) decline in 6MWD of −3.5 (−20.9, 13.8) m, performing better than ataluren-treated Study 020 patients (−28.3 [−45.1, −11.5] m). Placebo-allocated patients experienced a greater decline in 6MWD (−75.5 [−105.7, −45.3] m).

Conclusions: In both the real-world and clinical trial setting, ataluren delays motor function decline in nmDMD patients vs placebo, thus delaying disease progression.

Keywords: Neuromuscular Disorders, Rare Diseases

164. Safety and Effectiveness of Onasemnogene Abeparvovec (OA) Alone or with Other Disease-Modifying Therapies (DMTs): Findings from RESTORE

Raju D (Bannockburn, IL), Servais L, Benguerba K, De Vivo D, Kirschner J, Muntoni F, Proud C, Tizzano E, Saito K, Faulkner E, LaMarca N, Sun R, Anderson F, Finkel R

Objective: We aimed to describe real-world safety and effectiveness of OA alone or with other DMTs for patients with SMA.

Methods: RESTORE is an ongoing, prospective, multicenter, multinational, observational SMA patient registry. We evaluated patients with two or three *SMN2* gene copies receiving OA alone or with any other DMTs.

Results: As of Nov. 23, 2021, data were available for 247 patients who received OA: 121 (49.0%) received OA alone (Group 1); 48 (19.4%) received OA before (Group 2); and 78 (31.6%) received OA after (Group 3) another DMT. All patients in Group 3 received nusinersen, and none received risdiplam. Clinical characteristics are presented by treatment in Table 1. Of patients with ≥two milestone assessments (≥one post-OA administration; n=112), 71 (63.4%) achieved new milestones: 35 (49.3%) in Group 1, 15 (21.1%) in Group 2, and 21 (29.6%) in Group 3. Time to first milestone achievement after OA administration was similar between groups (p=0.2). Median changes in milestone assessment scores for Groups 1, 2, and 3 are detailed in Table 2. Any-grade treatment-emergent AEs were recorded in Groups 1, 2, and 3 for 51 (42.2%; 23 [19.0%] with Grade ≥3), 28 (58.3%; 15 [31.3%] with Grade ≥3), and 49 (62.8%; 26 [33.3%] with Grade ≥3) patients, respectively. No new safety signals were identified.

Conclusions: Real-world effectiveness was observed for patients receiving OA monotherapy, for patients who

Table 1. Clinical characteristics of the study patients by treatment regimen. Abstract 164

	Group 1 (OA monotherapy) n=121	Group 2 (Add-on to OA) n=48	Group 3 (Switch to OA) n=78	*p* value
Sex (n, %)				
Male	61 (50.4)	17 (35.4)	29 (37.2)	0.09
Female	60 (49.6)	31 (64.6)	49 (62.8)	
SMN2 copy number (n, %)				
Two	71 (58.7)	44 (91.7)	59 (75.6)	<0.0001
Three	50 (41.3)	4 (8.3)	19 (24.4)	
SMA type (n, %)				
Presymptomatic	32 (26.4)	2 (4.2)	9 (11.5)	<0.0001
1	60 (49.6)	42 (87.4)	56 (71.8)	
2	23 (19.0)	2 (4.2)	11 (14.1)	
3	1 (0.8)	2 (4.2)	0 (5.0)	
Missing	5 (4.2)	0 (0.0)	2 (2.6)	
Age at diagnosis, months (median, IQR)	1 (0–6.5)	2 (0–5)	3 (1–8)	0.046
Age at first treatment, months (median, IQR)	3 (1–9)	3 (2–6.5)	4.5 (2–11)	0.19
Interval between diagnosis to treatment, months (median, IQR)	0.7 (0.5–1.2)	0.6 (0.4–1)	0.7 (0.4–1.2)	0.26

IQR, interquartile range; OA, onasemnogene abeparvovec; SMA, spinal muscular atrophy; *SMN2*, *survival motor neuron 2* gene.

Table 2. Change in motor milestone assessment scores by measure. Abstract 164

	Group 1	Group 2	Group 3
Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), median (range)	11 (IQR, 6–16) (n=43)	11 (IQR, 5–21) (n=19)	4 (IQR, 1–11) (n=33)
Hammersmith Functional Motor Scale—Expanded (HMFSE), median (range)	13.5 (IQR, 4.5–17.8) (n=12)	5 (IQR, 1–14) (n=9)	4 (IQR, 2–8) (n=10)
Hammersmith Infant Neurological Examination (HINE), median (range)	6.5 (IQR, 2–12.25) (n=14)	6.5 (IQR, 0.75–9.25) (n=6)	3.5 (IQR, 0.5–5.5) (n=8)

IQR, interquartile range.

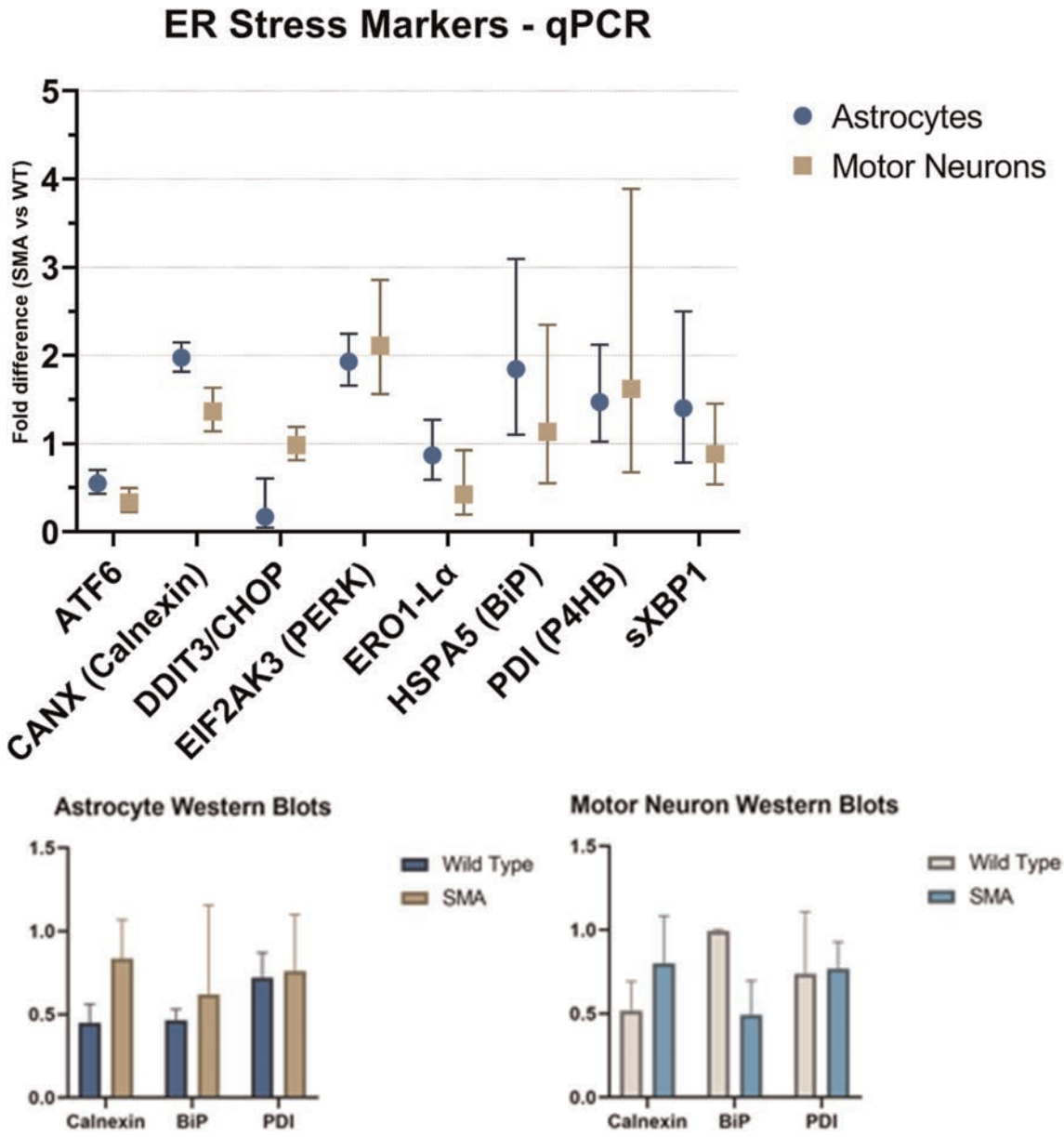
switched to OA from nusinersen, and for patients who received add-on DMT. In this patient cohort, those who switched from nusinersen to OA experienced more frequent and severe AEs.

Keywords: Neuromuscular Disorders,

165. Endoplasmic reticulum (ER) stress in a cellular model of spinal muscular atrophy

Whitinger J (Milwaukee, WI), Welby E, Allison R, Ebert A

Objective: To explore the mechanism of ER stress within a motor neuron and astrocyte cellular model.



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Methods: Induced pluripotent stem cells (iPSCs) previously generated from SMA and healthy control individuals were grown in cell culture. They were then differentiated into spinal cord motor neurons and astrocytes; both in monoculture and co-culture systems. Cells were harvested and markers of ER stress examined using RT-qPCR and Western blotting.

Results: Several markers of the adaptive pathway of ER stress were elevated in both motor neurons and astrocytes (Calnexin, PDI and BiP) in RNA expression levels with similar trends on a protein level. Fold difference in motor neurons was 1.37, 1.62, and 1.14 respectively. In astrocytes fold difference was 1.96, 1.47 and 1.85 respectively. A major marker of the apoptotic pathway, CHOP, was downregulated in astrocytes (fold difference: 0.17) but was equivocal in motor neurons (fold difference 0.98). Other factors were equivocal or showed mixed trends. Similar trends were seen in co-culture RNA data.

Conclusions: While variability is present there is a general trend towards upregulation of the ER Stress pathway. This upregulation does not appear to be specific to cell type (astrocyte or motor neuron), and is consistent when cells are grown together. The response does seem to favor the activity of the adaptive pathway of ER stress. More work is needed to further characterize the response as well as other pathways of cellular stress which may induce an SMA phenotype.

Keywords: Neuromuscular Disorders, Translational/ Experimental Therapeutics

166. Caregiver or Patient Rationale for Pursuing Multiple SMA SMN-dependent Therapies – Data from the 2021 and 2022 Cure SMA Community Update Surveys

Belter L (Elk Grove Village, IL), Curry M, Schroth M, Jareck J

Objective: The objective of this analysis was to describe the opinions and perceptions of caregivers and patients with SMA leading to combination or sequential therapy.

Methods: Data was provided from the Cure SMA annual community update surveys (CUS).

Results: The 5th annual CUS closed in June 2021 with 633 completed surveys. Those on treatment, US residents, and non-duplicated surveys were included within analysis (n=386). The final sample size included 154 (39.9%) affected SMA adults and 232 (60.1%) caregivers of affected individuals. 148 (38.3%) indicated they have been treated with more than one FDA-approved therapy. Respondents' rationale for pursuing multiple SMN-dependent therapies included: 37.5% indicated not gaining function as expected, 8.3% indicated losing motor function, and 80% indicated they wanted all possible SMA treatments. The final sample size, description, and rationale for use of multiple therapies from the 6thannual CUS will be provided after the survey closes in May 2022. Results between 2021 and 2022 will be compared.

Conclusions: There is growing interest in the SMA community for the use of multiple SMA treatments. Data from the annual CUS highlight that, despite a lack of safety or efficacy evidence, combination therapy is seen in clinical practice. This survey helps to identify caregivers' and patients' rationales for pursuing combination treatment. Furthermore, these results emphasize the importance of data collection to analyze safety and effectiveness.

Keywords: Neuromuscular Disorders

167. Phase 1/2a Trial of Delandistrogene Moxeparvovec in Patients with DMD: 4-year Update

Mendell J (Columbus, OH), Sahenk Z, Lehman K, Lowes L, Reash N, Iammarino M, Alfano L, Lewis S, Church K, Shell R, Potter R, Griffin D, Pozsgai E, Hogan M, Hu L, Mason S, Darton E, Brandl K, Rodino-Klapac L

Objective: Delandistrogene moxeparvovec (SRP-9001) is an investigational gene transfer therapy developed for targeted skeletal and cardiac muscle expression of micro-dystrophin in patients with Duchenne muscular dystrophy (DMD). This Phase 1/2a, single-dose, open-label clinical trial (NCT03375164) evaluates the safety of systemic delivery of delandistrogene moxeparvovec in patients with DMD.

Methods: Four ambulatory patients with DMD (≥4 to ≤8 years old) were enrolled. Patients received an intravenous infusion of delandistrogene moxeparvovec at a dose of 2.0x1014 vg/kg (supercoiled qPCR, linear plasmid standard equivalent of 1.33x1014 vg/kg) and prednisone (1 mg/kg/day) 1 day pre- to 30 days post-gene delivery. The primary outcome measure is safety. Secondary outcome measures include micro-dystrophin expression in pre- and post-muscle biopsies (Week 12 post-infusion) by western blot and immunofluorescence. Key efficacy measures include North Star Ambulatory Assessment (NSAA) and timed function tests.

Results: Data from 3 years post-treatment were previously presented. Treatment-related adverse events (AEs) were mild-to-moderate, occurred mostly in the first 90 days of treatment, and resolved. No serious AEs, study discontinuations, or AEs associated with clinically relevant complement activation were reported. All patients demonstrated clinically meaningful improvement on NSAA. Patients generally maintained muscle strength and demonstrated improvement in ambulation ability from baseline to Year 3.

Conclusions: The observed safety profile and enduring response following treatment provide proof of concept for the continuation of clinical trials assessing single-dose gene therapy with delandistrogene moxeparvovec in patients with DMD. We present the latest long-term (4-year) safety and functional data from this study. This study is funded by Sarepta Therapeutics.

Keywords: Neuromuscular Disorders, Translational/Experimental Therapeutics, Rare Diseases

168. Improving Bone Health Screening in Patients with Spinal Muscular Atrophy: A Quality Improvement Initiative

McCoy E (Louisville, KY), Hiers P, Lakhotia A, Rogers A

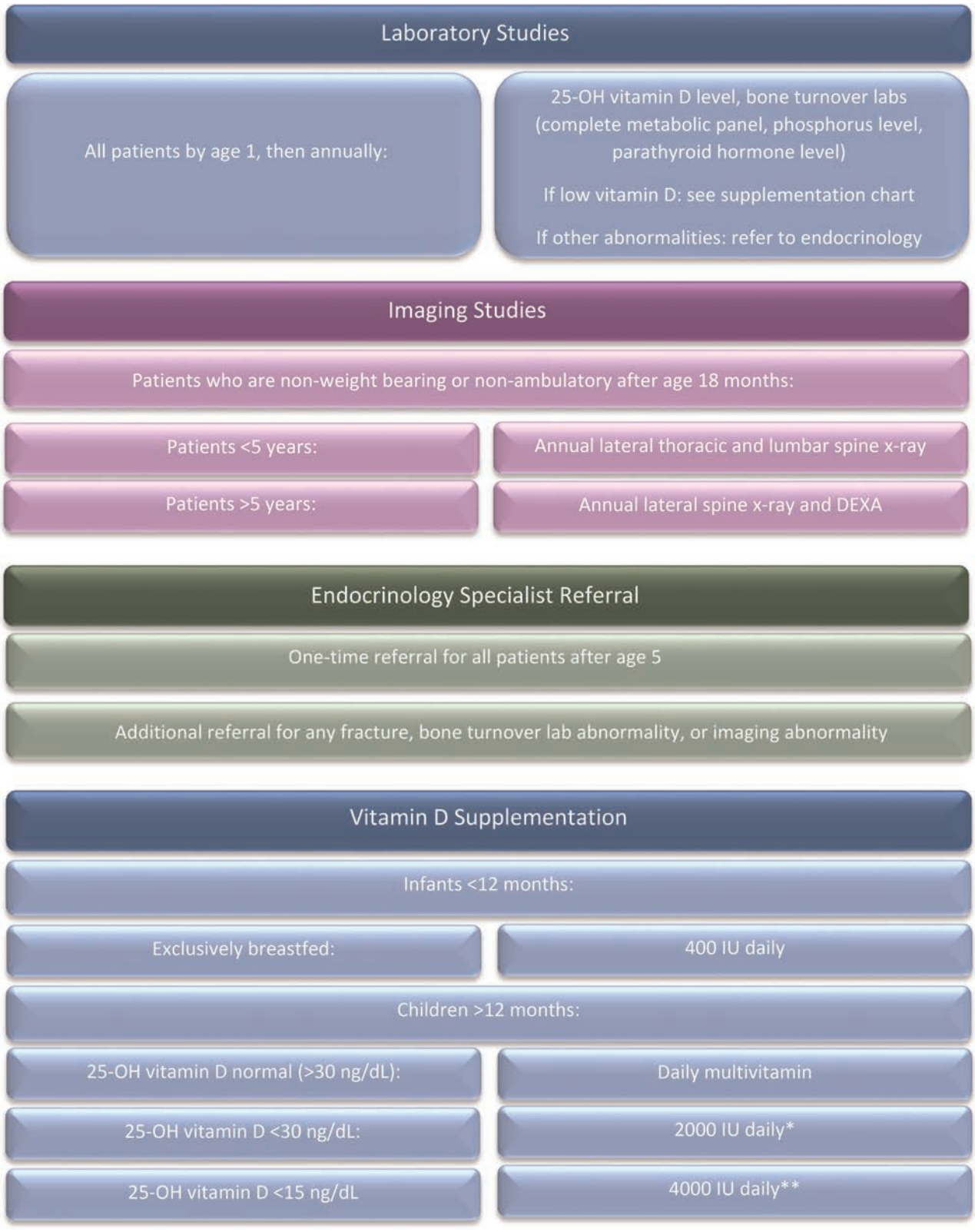
Objective: Poor bone health and fractures are frequent comorbidities of neuromuscular disorders, but are underrecognized in patients with spinal muscular atrophy (SMA). In one study, as many as 85% of SMA patients were found to have low bone mineral density, yet there is limited literature on measures to improve bone health in this population. We conducted a 5-year retrospective review of baseline bone health screening practices before implementing a quality improvement initiative.

Methods: A retrospective chart review was conducted of SMA patients up to age 21 seen at our pediatric neuromuscular clinic from February 2016 to February 2022. Baseline bone health screening practices were assessed. Multidisciplinary input between the divisions of Child Neurology and Pediatric Endocrinology was sought to create a guideline for optimizing bone health, including protocols for laboratory studies, dual-energy X-ray absorptiometry (DEXA), vitamin D supplementation and endocrinology referrals (see Addendum).

Results: Twenty-five living patients were identified; all were included in review. Zero patients had previously undergone screening comparable to that recommended in the proposed guideline. Only two eligible patients (10%) had previously undergone DEXA; both had Z-scores indicative of low bone mineral density. Ten patients (47%) had a previous vitamin D level, and zero had other labs to assess bone turnover. Two patients had a history of fracture.

Conclusions: We found that low bone mineral density is likely under-recognized in our SMA patients, emphasizing the importance of a standardized screening protocol. Following implementation, we predict an increase in overall bone health screening and in the detection of low bone mineral density.

Keywords: Neuromuscular Disorders



University of Louisville/Norton Children's Medical Group Muscular Dystrophy Association (MDA) Clinic Guideline for Optimization of Bone Health in Spinal Muscular Atrophy (SMA) * Re-check 25-OH vit D level after 3 months. If normal (>30 ng/mL), decrease to 1000 IU daily. If remains abnormal, refer to Endocrinology. **Re-check 25-OH vit D level after 3 months. If normal (>30 ng/mL), decrease to 2000 IU daily. If remains abnormal, refer to Endocrinology. Abstracr 168

169. Casimersen in Patients with Duchenne Muscular Dystrophy Amenable to Exon 45 Skipping: Interim Results from the Phase 3 ESSENCE Trial

Iannaccone S (Dallas, TX), Phan H, Straub V, Muntoni F, Wolf D, Malhotra J, Chu R, Darton E, Brandl K, Mercuri E

Objective: Casimersen is FDA approved for treatment of Duchenne muscular dystrophy (DMD) in patients with *DMD* gene mutations amenable to exon 45 skipping. ESSENCE is an ongoing, double-blind, placebo-controlled, Phase 3 trial (NCT02500381) evaluating the efficacy and safety of casimersen and golodirsen. We report results from a prespecified interim analysis of 48-week muscle biopsy data in casimersen- and placebo-treated patients.

Methods: Eligible patients (aged 7–13 years, on stable dose of corticosteroids) were randomized 2:1 to casimersen 30 mg/kg or placebo IV once weekly.

Results: In the interim biopsy analysis, casimersen- but not placebo- treated patients demonstrated significant increases in exon 45 skipping assessed by droplet digital PCR compared with baseline (n=27, $P<0.001$ and n=16, $P=0.808$ respectively). Western blot analysis showed significantly increased mean dystrophin levels from baseline after 48 weeks of casimersen (0.93% vs 1.74% of normal; $P<0.001$) and compared with placebo (mean difference=0.59%; $P=0.004$). Increased dystrophin positively correlated with exon skipping (Spearman rank correlation=0.627; $P<0.001$), demonstrating mechanistic association between de novo dystrophin production and exon 45 skipping. Patients treated with casimersen had significantly increased mean percent dystrophin-positive fibers from baseline to Week 48 (6.46% vs 15.26%; $P<0.001$) and compared with placebo (mean difference=8.29%; $P=0.002$) as shown by immunofluorescence; mean fluorescence intensity was also significantly increased in the casimersen- compared with placebo- treated patients at Week 48 ($P=0.003$). Casimersen was well tolerated; most adverse events were mild and unrelated to casimersen, with no suggestion of kidney toxicity.

Conclusions: The safety and efficacy of casimersen will continue to be evaluated.

Keywords: Neuromuscular Disorders, Rare Diseases

170. Treatments and Outcomes for Patients with Spinal Muscular Atrophy (SMA) Type 2: Findings from RESTORE Registry

Raju D (Bannockburn, IL), Servais L, Benguerba K, De Vivo D, Kirschner J, Mercuri E, Muntoni F, Proud C, Tizzano E, Quijano-Roy S, Saito K, Faulkner E, LaMarca N, Sun R, Anderson F, Finkel R

Objective: We aimed to describe real-world treatment patterns and outcomes for patients with SMA type 2.

Methods: RESTORE is an ongoing SMA patient registry. We analyzed changes in motor milestones and disability scores and assessed treatment-emergent adverse events (TEAEs) for patients who received one or more disease-modifying treatments (DMTs; gene therapy [onasemnogene abeparvovec (OA)] or *SMN2* modulator [nusinersen/risdiplam]).

Results: As of Nov. 23, 2021, RESTORE included 48 patients with SMA type 2. Clinical characteristics for patients with SMA type 2 are presented in Table 1. Of 26 patients with two or more motor milestone assessments (one or more post-DMT administration), all but four (OA only [n=3], nusinersen only [n=1]) maintained or achieved new milestones: 13 (59.1%) received OA monotherapy; 6 (27.3%) switched from nusinersen to OA; 1 (4.5%) received add-on treatment to OA; and 2 (9.1%) received nusinersen only. Median HFMSE score change was 5.5 (n=10), with median monthly change of 0.6 (n=10) for all patients, and 11.0 (n=5), with median monthly change of 0.7 (n=6) for patients receiving OA monotherapy. Any-grade TEAEs were recorded for 12/24 (50%) patients who received OA monotherapy, 7/11 (63.6%) who switched from nusinersen to OA, and 1/2 (50%) who received add-on treatment to OA. Of patients who received OA, three required non-oral feeding support and two required BiPAP

Table 1. Clinical characteristics of patients with SMA type 2 in RESTORE. Abstract 170

	SMA type 2 patients (n=48)
Sex, n (%)	
Female	29 (60.4)
SMN2 copy number, n (%)	
Two	8 (16.7)
Three	37 (77.1)
Four	2 (4.2)
More than four	1 (2.1)
Median age at SMA diagnosis, months (range, IQR)	14.0 (9.5–19.25)
Median age at first DMT administration, months (range, IQR)	16.0 (10.5–20.5)
Median age at first treatment, months (range, IQR)	
Onasemnogene abeparvovec monotherapy (n=24)	16.5 (10.5–19.5)
Nusinersen monotherapy (n=10)	25.0 (19–81)
Risdiplam monotherapy (n=1)	8.0
Switching to onasemnogene abeparvovec (n=11)	12.0 (9.0–16.0)
Add-on therapy to onasemnogene abeparvovec (n=2)	15.5 (8.0–23.0)

DMT, disease-modifying treatment; IQR, interquartile range. Median interval between diagnosis and first DMT was 1 month. Median age at first DMT differed between groups ($p=0.0033$).

ventilation. AEs in RESTORE are consistent with OA experience. No new safety signals were identified.
Conclusions: These data suggest that OA is effective and has an acceptable safety profile for patients with SMA type 2.
Keywords: Neuromuscular Disorders

171. Clinical Utility of Serial CMAPs in Spinal Muscular Atrophy

Deng S (Rochester, NY), Ferguson M, Logigian E, Ciafaloni E, Lee B

Objective: Compound muscle action potential (CMAP) amplitude may be a useful biomarker in spinal muscular atrophy (SMA). We reviewed serial CMAP amplitudes in a cohort of patients with SMA in the newborn screening and treatment era.
Methods: Retrospective chart review from March 2019 to March 2022 of infants with SMA receiving care at the University of Rochester was performed.
Results: 14 infants were diagnosed with SMA (n = 9 with 2 *SMN2* copies; n = 4 with 3 *SMN2* copies, n = 1 with 4 *SMN2* copies). All infants received treatment. Mean pre-treatment ulnar and peroneal CMAPs were 1.7 and 1.6 mV for 2-copy infants (n = 8); 5.4 and 3.0 mV for 3-copy infants (n = 2); 6.1 and 4.2 mV for one 4-copy infant. Mean post-treatment CMAPs were 1.8 and 2.7 mV for 2-copy infants (n = 9); 6.0 and 6.6 mV for 3-copy infants (n = 4); 7.5 and 9.0 mV for one 4-copy infant. Two premature 2-copy infants had notably higher initial CMAPs (mean 5.7 and 3.9 mV) compared to full-term 2-copy infants (n = 6, mean 1.3 and 1.4 mV). One of these infants became symptomatic and had a significant drop in CMAPs to 1.2 and 0.8 mV prior to receiving treatment.
Conclusions: CMAP amplitudes correlate with predicted disease severity, with lower pre-treatment CMAP amplitudes seen in 2-copy infants compared to 3- or 4-copy infants. These findings illustrate that routine CMAP exams may help detect pre-clinical decline, monitor treatment response, and potentially guide treatment strategies.
Keywords: Neuromuscular Disorders

172. Comparison of timed function test results in nmDMD patients receiving ataluren: STRIDE Registry vs phase 3 clinical trial

Mercuri E (Rome, Italy), Muntoni F, Tulinius M, Buccella F, Desguerre I, Kirschner J, Nascimento Osorio A, Johnson S, Werner C, Jiang J, Li J, Wing J, Trifillis P

Objective: We investigated whether ataluren-treated nonsense mutation Duchenne muscular dystrophy (nmDMD) patients in real-world practice (STRIDE Registry; NCT02369731) performed similarly in timed function tests (TFTs) vs ataluren-treated patients in a phase 3 clinical trial (Study 020; NCT01826487). TFTs included time to: run/walk 10 metres (m), climb four stairs, descend four stairs and stand from supine; each measuring progressive loss of function.
Methods: STRIDE patients were assessed by their 'first 48-week change' (difference between their '48-week assessment' [between 40 and 72 weeks] and first assessment); Study 020 patients were assessed by change over 48 weeks. Patients who lost ambulation had time to perform TFTs imputed as 30 seconds (s).
Results: Ataluren-treated Study 020 patients experienced smaller mean increases in time (s) to perform TFTs vs placebo-allocated patients (run/walk 10m [95% CI]: ataluren, 2.3 [1.3, 3.3], n=109; placebo, 3.5 [2.3, 4.7], n=110; climb four stairs: ataluren, 2.7 [1.6, 3.7], n=105; placebo, 4.5 [3.0, 5.9], n=103; descend four stairs: ataluren, 2.2 [1.1, 3.2], n=106; placebo, 4.0 [2.4, 5.5], n=100; stand from supine: ataluren, 3.8 [2.7, 5.0], n=101; placebo, 3.9 [2.5, 5.3], n=96). STRIDE patients experienced smaller mean increases in time (s) to perform TFTs vs placebo-allocated Study 020 patients (run/walk 10m [95% CI]: 1.3 [0.6, 2.0], n=113; climb four stairs: 0.4 [−0.3, 1.0], n=73; descend four stairs: 0.3 [−0.1, 0.8], n=59; stand from supine: 1.7 [0.6, 2.8], n=93).
Conclusions: In the real-world and clinical trial setting, ataluren delays decline in TFT performance in nmDMD patients vs placebo, indicating that ataluren delays disease progression.
Keywords: Neuromuscular Disorders, Rare Diseases

173. Integrated Analyses of Data from Clinical Trials of Delandistrogene Moxeparvovec in DMD

Zaidman C (Washington, MO), Shieh P, Proud C, McDonald C, Day J, Mason S, Guridi M, Hu L, Yu L, Reid C, Darton E, Wandel C, Richardson J, Malhotra J, Singh T, Rodino-Klapac L, Brandl K, Mendell J

Objective: Delandistrogene moxeparvovec (SRP-9001) is an investigational gene transfer therapy developed for targeted skeletal and cardiac muscle expression of micro-dystrophin in patients with Duchenne muscular dystrophy (DMD). We analyzed 1-year functional data from ambulatory patients (≥4–≤8 years old) with DMD who received the target dose (1.33x1014 vg/kg by linear qPCR) of delandistrogene moxeparvovec in clinical studies. These data were compared with a propensity-score-weighted external comparator (EC) cohort (N=103) of patients with DMD from a natural history study and two clinical trials.
Methods: The dataset included patients with DMD who received delandistrogene moxeparvovec clinical process material during Study 101 (Phase 1/2a; NCT03375164) or Study 102 (Phase 2; NCT03769116), and patients who received commercially representative delandistrogene moxeparvovec material during ENDEAVOR (Phase 1b; NCT04626674). The primary endpoint is 1-year change from baseline in North Star Ambulatory Assessment total score. Exploratory endpoints include 1-year change from baseline in timed function tests.
Results: Patient functional data (N=53) from Study 101 (n=4), Study 102 (n=29 patients who received the target dose in Part 1 or 2), and ENDEAVOR (Cohort 1 [n=20]) have been assessed. In this analysis, data from all treated patients will be compared with the propensity-score-weighted EC cohort to contextualize the results of the three ongoing delandistrogene moxeparvovec clinical studies.

Conclusions: Collective safety data (latest data-cut) from all patient cohorts in Study 101, Study 102, and ENDEAVOR will be presented. Studies 101 and 102 and ENDEAVOR are sponsored and funded by Sarepta Therapeutics. ENDEAVOR is funded by F. Hoffmann-La Roche.

Keywords: Neuromuscular Disorders, Translational/ Experimental Therapeutics, Rare Diseases

174. Onasemnogene Abeparvovec (OA) Treatment Outcomes by Patient Weight at Infusion: Initial Findings from the RESTORE Registry

Raju D (Bannockburn, IL), Servais L, Benguerba K, De Vivo D, Kirschner J, Mercuri E, Muntoni F, Proud C, Tizzano E, Saito K, Faulkner E, LaMarca N, Sun R, Anderson F, Finkel R

Objective: Interventional trials of OA demonstrated safety and efficacy for infants typically weighing <8.5 kg at infusion. We aimed to describe real-world outcomes for patients with SMA according to weight at time of OA infusion.

Methods: We compared baseline characteristics, effectiveness (measured by CHOP INTEND), and safety of OA for patients weighing <8.5 kg or ≥8.5 kg at the time of infusion in RESTORE (a prospective, multinational SMA patient registry).

Results: As of Nov. 23, 2021, RESTORE included 221 patients with available data on weight at OA infusion: 165 patients weighed <8.5 kg (Group 1); 56 weighed ≥8.5 kg (Group 2). Clinical characteristics for these patients are presented in Table 1. Monotherapy with OA was greater in Group 1 (60.6%) vs. Group 2 (37.5%), and different polytherapy regimens were observed in both groups. Of 75 Group 1 patients evaluable for CHOP INTEND, 70 (93.3%) improved/maintained score, and 63 (84.0%) achieved increases of ≥4 points. All 14 evaluable patients in Group 2 improved/maintained score. Eight (57.1%) achieved ≥4-point increases. In Group 1, 79/165 (47.9%) patients experienced ≥1 treatment-emergent AEs (TEAEs) of any grade, and 41 (24.8%) reported ≥1 serious AEs. In Group 2, TEAEs of any grade were reported in 34/56 (60.7%) patients, and 12 (21.4%) reported ≥1 serious AE. No deaths or unexpected OA-related serious adverse events were reported.

Conclusions: These results suggest patients weighing ≥8.5 kg at OA infusion may benefit from treatment. We did not observe a difference in incidence of TEAEs or serious AEs based on patient weight at OA infusion.

Keywords: Neuromuscular Disorders

Table 1. Clinical characteristics of study patients by weight. Abstract 174

	Group 1: weight <8.5 kg (n=165)	Group 2: weight ≥8.5 kg (n=56)
SMN2 copy number, %		
One	1.3	1.8
Two	72.7	42.9
Three	20.6	48.2
Four	2.4	7.1
More than four	2.4	0
Unknown	0.6	0
SMA type, %		
1	66.1	44.6
2	5.5	39.3
3	1.2	1.8
Unknown	1.7	5.4
Presymptomatic	25.5	8.9
Age <6 months at onasemnogene abeparvovec infusion, n (%)	105 (63.6)	3 (5.4)
Age ≥6 months at onasemnogene abeparvovec infusion, n (%)	60 (36.4)	53 (94.6)

175. Assessment of Transition Plan Implementation and Provider Engagement Amongst Adults Affected by Spinal Muscular Atrophy (SMA)

Colegrove L (Chicago, IL), Curry M, Eisenman L, Belter L, Jarecki J, Schroth M

Objective: Access to novel therapies and improvements in supportive care have increased life expectancy and more individuals affected by spinal muscular atrophy (SMA) are entering adulthood. The transition planning process helps patients and families prepare for the shift from pediatric to adult care. This research explores perceptions and experiences of SMA affected adults upon transition to adult care.

Methods: Cure SMA, an SMA patient advocacy organization, distributed a survey from August through October 2021 to affected adults aged 18-29 within the Cure SMA database.

Results: 52.5% (n=73) respondents had fully transitioned to adult care, 22.3% (n=31) had partially transitioned but still see pediatric providers, 13.7% (n=19) were preparing to transition, and 11.5% (n=16) had not initiated the process. 48.8% of partially/fully transitioned respondents reported pediatric providers assessed their transition readiness, 43.9% discussed transition process and/or development of a transition plan, 16.7% received the plan. 27.6% of partially/fully transitioned respondents reported "self-transitioning" to adult care with no assistance. Suggestions on how providers can improve the process were "have discussions about differences

between pediatric and adult care" (91.9%), and "encourage greater involvement of adolescents/families in transition planning process" (91.1%).

Conclusions: This research provides insight into barriers experienced by SMA affected adults as they transition to adult care. Providers are encouraged to collaborate with individuals to initiate early planning discussions, identify adult providers, arrange pretransition consults, and provide a transition plan. Development of resources/guidelines detailing how best to devise and implement the transition process may alleviate variation in execution among pediatric providers.

Keywords: Neuromuscular Disorders, Rare Diseases

176. Associations between deflazacort vs prednisone/prednisolone and disease progression markers in subgroups of patients with Duchenne muscular dystrophy

McDonald C (Davis, CA), Wing J, Powell A, Mastrandrea N, Signorovitch J, Marden J, Lane H, Zhang A, Nguyen H

Objective: To compare clinical outcomes in Duchenne muscular dystrophy (DMD) by steroid type stratified by baseline age, ambulatory function, and steroid duration.

Methods: Placebo arms from four DMD clinical trials with assessments of 48-week change in six-minute walk distance (6MWD) as the primary outcome were studied. Mean changes in 6MWD and secondary ambulatory outcomes were compared between patients receiving daily deflazacort vs. daily prednisone, adjusting for baseline age, steroid duration, 6MWD, and rise time.

Results: A total of 328 patients were available across placebo arms, with 231 receiving daily steroids (n=127 deflazacort; n=104 prednisone). Stable steroid use for ≥6 months pre-baseline was required in all but one study; all had mean prior steroid use > 1.5 years. Baseline characteristics were balanced across steroid groups. In the overall study population, deflazacort was associated with preservation of 35.4 meters of 6MWD over 48 weeks vs prednisone (P<0.01). When assessing by subgroups, differences between deflazacort vs. prednisone were most pronounced among boys with the following baseline characteristics: aged ≥8 years (+44.5m, P<0.01), rise time ≥5 seconds (+41.3m, P<0.01) and steroid duration >3 years (+57.5m, P<0.01). Overall differences between steroid groups in timed function tests and in the linearized North Start Ambulatory Assessment were numerically consistent.

Conclusions: Benefits of daily deflazacort vs daily prednisone for preserving ambulatory function in DMD were most evident among patients who were older, had been on steroids longer, or were at a more progressed disease stage. These results supplement the evidence for a potential cumulative benefit of deflazacort versus prednisone.

Keywords: Neuromuscular Disorders, Rare Diseases

177. Gene variant and neuromuscular findings from a Long-Chain Fatty Acid Oxidation Disorder gene panel program

Simmons K (Novato, CA), Miller V, Baker II P, Japalaghi O, Longo N, Marsden D, McLaughlin H, Yong J, Miller N

Objective: Long-chain fatty acid oxidation disorders (LC-FAOD) are rare, life-threatening, autosomal recessive conditions that may present with hypoglycemia, cardiomyopathy, cardiac arrhythmias, and neuromuscular symptoms. This abstract summarizes findings from a molecular testing program for individuals who may have undiagnosed LC-FAOD.

Methods: Patients with a clinical diagnosis or suspicion of LC-FAOD are eligible for this no-charge, next-generation sequencing gene panel which includes 6 genes associated with LC-FAOD plus 18 genes associated with disorders that cause abnormal acylcarnitine profiles.

Results: As of 28 October 2021, LC-FAOD gene variants were identified in 153 (37%) of 417 patients tested, including 83 variants of uncertain significance (VUS), 8 likely pathogenic (LP), and 102 pathogenic (P) variants. Twenty-three patients had positive (2 P/LP) LC-FAOD results and 19 had potential positive (2 variants, at least 1 VUS) results. VUS resolution analysis led to the reclassification of 6 variants from VUS to LP or P. Five patients had variants in ≥ two LC-FAOD genes and 22 had variants in one LC-FAOD gene and ≥ one non-LC-FAOD genes. Fifty-one patients had only one LC-FAOD gene variant identified. The most common neuromuscular symptoms among patients ages ≥13 (76 reported) were myopathy (42), elevated creatine kinase (36), and rhabdomyolysis (30), and among patients <13 years (83 reported) were elevated creatine kinase (22), and myopathy (12).

Conclusions: Program results demonstrate the diverse composition of gene variants in patients referred for LC-FAOD genetic testing. Approaches to resolve VUS and identify previously undetected variants in patients with suspected LC-FAOD are important and necessary.

Keywords: Neuromuscular Disorders, Genetics, Rare Diseases

178. Associations Between Daily Deflazacort or Prednisone and Ages at Disease Progression Milestones Among Patients with Duchenne Muscular Dystrophy

McDonald C (Davis, CA), Wing J, Powell A, Mastrandrea N, Signorovitch J, Marden J, Frean M, Lane H, Zhang A, Nguyen H

Objective: This study compared ages at disease progression milestones between patients on daily regimens of prednisone and deflazacort.

Methods: A cohort of DMD patients was identified from two natural history studies. Associations between daily steroid treatment (deflazacort or prednisone) and disease progression milestones representing progressive loss of ambulatory function were assessed using Kaplan-Meier analyses and Cox proportional hazards models adjusted for data source and age at steroid initiation. Milestones included timed rise from floor (RFF) >=5 seconds, RFF >=10 seconds, inability to RFF, inability to complete 4-stair climb (4SC), and loss of ambulation.

Results: 463 patients (mean age 9.86 years; n=288 deflazacort; n=175 prednisone) were identified. At baseline, patients on deflazacort were slightly older (mean age 10.34 vs. 9.08 [prednisone]; p<0.01); however, dose, duration of steroid therapy and baseline functional status were similar

between steroid groups. Relative to prednisone, deflazacort was associated with significant delays in median age at all progression milestones. Deflazacort patients experienced a delay in timed RFF >=10 seconds and RFF >=5 seconds of 0.88 years (log-rank p<0.01) and 0.94 years (p<0.05), respectively. Delays in progression were also observed for inability to RFF (+1.61 years, p<0.001) and inability to complete 4SC (+1.87 years; p < 0.01) for patients receiving deflazacort vs. prednisone. Median age at loss of ambulation was also older for deflazacort (15.92 vs. 14.89 years; p<0.001).

Conclusions: Use of daily deflazacort was associated with delayed progression of multiple ambulatory milestones in patients with DMD.

Keywords: Neuromuscular Disorders, Rare Diseases

179. Associations between steroid treatment and clinical outcomes among non-ambulatory patients with Duchenne Muscular Dystrophy (DMD)

Mayer O (Philadelphia, PA), McDonald C, Hor K, Wing J, Mastrandrea N, Powell A, Signorovitch J, Marden J, Freimark J, Lane H, Zhang A, Frean M

Objective: Compare outcomes by steroid treatment among non-ambulatory (NA) DMD patients.

Methods: NA DMD patients were identified from a prospective, observational study of DMD disease progression (PRO-DMD-01). Associations between steroid treatment (prednisone, deflazacort, or no steroids) were assessed, including changes in forced vital capacity [FVC] %-predicted, left ventricular ejection fraction [LVEF], performance of upper limb [PUL] score, and loss of hand-to-mouth function. Kaplan-Meier analyses and Cox proportional hazards models assessed outcomes for milestones, and mixed models with repeated measures for longitudinal outcomes. Models adjusted for selected baseline characteristics.

Results: 86 NA patients (mean age 13.4 years; n=40 deflazacort; n=29 prednisone; n=17 no steroids) were included. Relative to no steroids, both steroids were associated with delays in median age at FVC %-predicted<60% (+0.9 [prednisone]; +2.3 [deflazacort]; log-rank p<0.01). Median ages at LVEF<55% were numerically prolonged, but non-significant (+2.7 [prednisone]; +0.8 [deflazacort]; p=0.65). While median ages at loss of hand-to-mouth function were not consistently reached, higher proportions of steroid patients maintained function at age 15 (85%-deflazacort; 83%-prednisone; 78%-no steroids; p<0.001). In *adjusted Cox models*, both steroids showed a significant delay in all three milestones relative to no steroids. In *longitudinal models* for change in PUL, prednisone patients had significantly slower decline compared to no steroids (+2.5 points/year; p=0.03), and deflazacort patients were significantly slower than prednisone (+1.5 points/year; p=0.04). Changes in FVC %-predicted and LVEF indicated significantly slower decline for both steroids relative to none.

Conclusions: Steroid use after loss of ambulation was associated with delayed progression of important pulmonary, cardiac and functional deficits in DMD.

Keywords: Neuromuscular Disorders, Rare Diseases

180. A Retrospective Chart Review Assessing the Effect of the COVID-19 Pandemic on the Quality of Life of Myasthenia Gravis Patients Seen at CHLA

Sosa N (Los Angeles, CA), Ramos-Platt L

Objective: This study sought to evaluate the effect of the COVID-19 pandemic on quality of life (QOL) of pediatric Myasthenia Gravis (MG) patients followed at Children's Hospital Los Angeles. Changes in MG-QOL and MG-ADL scores were compared to documented changes in physical exam and other motor measures.

Methods: Chart review was performed to identify all MG patients who had MG-QOL and MG-ADL documented between March 2020 and December 2021 as well as at least one prior MG-QOL and MG-ADL score documented between January 2019 and February 2020. QOL scores, grip/pinch strength on physical examination, physician impressions, disease duration, treatment history, and demographic information were collected. Scores were analyzed using paired T-tests.

Results: Out of 35 patients seen in the multidisciplinary MG clinic, 8 were found to meet inclusion criteria. While there was no statistically significant difference in MG-QOL score, MG-ADL score, or grip/pinch strength between the two timepoints on paired T-testing, MG-QOL scores trended upward on visits conducted in March 2020 or afterward (t= 2.31, p=.054).

Conclusions: Given findings in adult populations showing worsening QOL scores during the pandemic, and a similar trend in our data, our data is suggestive of a similar worsening subjective QOL in pediatric patients with MG following pandemic onset, although physical examination and motor measures did not suggest a decline in function. The study is limited by the small sample size of 8 patients meeting inclusion criteria. Further investigation into the effects of the pandemic on pediatric populations is warranted.

Keywords: Neuromuscular Disorders, COVID-19

181. Childhood Onset Hereditary Spastic Paraplegia (HSP): A case series and review of literature

Panwala T (Boca Raton, FL), Garcia-Santibanez R, Vizcarra J, Gonzalez Garcia A, Verma S

Objective: Hereditary spastic paraplegia (HSP) is characterized by progressive lower extremity spasticity and weakness caused by corticospinal tract degeneration. In this study, the authors highlight the clinical heterogeneity of neurological comorbidities in pediatric HSP patients and emphasize the utility of whole exome sequencing in increasing diagnostic yield of HSP.

Methods: We conducted a retrospective review of childhood-onset HSP cases followed in the neuromuscular clinics at Children's and Emory Healthcare in Atlanta. Clinical presentation, physical examination, electrodiagnostic data, neuroimaging, genetic test results, comorbidities, and treatment were recorded.

Results: Sixteen HSP patients (8 males, 8 females) with a mean age of 19 years ± 15.7 years were included. Ten (66%) presented with gait difficulty. Seven (44%) were

TABLE 1: Clinical, electrophysiological and genetic profile of Atlanta HSP cohort. Abstract 181

#	Age (years)/ sex	Age (years) at onset, age (years) at diagnosis	Ambulatory (Yes or No) mRS score	Clinical manifestations	Affected gene/ mutation	HSP type	NCS/ EMG findings
1	10/M	4, 10	Yes, 3	Leg spasticity, brisk tendon jerks, Babinski+, ADHD	*REEP1* Deletion exon 6	SPG 31	Normal
2^	10/M	8, 9	Yes, 2	Leg spasticity and weakness, brisk tendon jerks, Babinski+	*SPAST* c.631G>A (p.V211I)	SPG4	Normal
3^	14/M	7, 14	Yes, 3	Leg spasticity and weakness, brisk tendon jerks, Babinski+, scoliosis	*SPAST**	SPG4	Not available
4	43/F	12, 41	No, 4	Leg spasticity and weakness, incontinence	*SPAST* Deletion of exon 1	SPG4	Normal
5	33/M	17, 30	Yes, 2	Arm and leg spasticity and weakness, Babinski+, clonus	*SPAST* c.1116 A>C (p.R372S)	SPG4	Not available
6	19/F	5, 6	No, 5	Arm and leg weakness incontinence, developmental delay, autism, epilepsy	*MT-ATP6* c. 8612T>C (p.L29P)	mt SPG	SMAN
7[1]	13/F	5, 11	No, 4	Arm and leg weakness, Babinski+, developmental delay, scoliosis, epilepsy	*PNPT1* c.448A>G (p.T150A) c.688G>C (p.E230Q) *In trans*	mt SPG	SAN
8	14/M	10, 14	No, 4	Arm spasticity, weakness, brisk tendon jerks, scoliosis	*SPG7* c.1A>G (p.M1?)	SPG7	SMAN
9	19/F	13, 19	Yes, 2	Arm and leg spasticity and weakness, Babinski+, developmental delay, epilepsy, autism	*KIF1A* c.1A>G (p.M1V)	SPG 30	SMAN
10	18/M	9, 16	Yes, 3	Leg spasticity, brisk tendon jerks, Babinski+, clonus	*KIF5A* c.839G>A (p.R208H)	SPG 10	SMAN
11	8/M	2, 8	Yes, 3	Arm and leg spasticity and weakness, brisk tendon jerks, Babinski+, developmental delay, ADHD	*KIF1A* c.38G>A (p.R13H)	SPG 30	SMAN
12[1]	38/F	1, 37	No, 3	Leg spasticity and weakness, brisk tendon jerks, Babinski+, dysmetria, developmental delay	*SACS* c.434C>G (p.S14X) 2 bp deletion c.2439_2440	ARSACS	SMAN
13	58/M	12, 19	No, 3	Leg spasticity and weakness, brisk tendon jerks, Babinski +, urinary urgency, developmental delay, scoliosis	*MARS* c.31 G>A (p.G11S)	SPG 70	Not available
14^	5/F	6 months, 1	No, 4	Leg spasticity and weakness, brisk tendon jerks, Babinski +, tremors, incontinence autism, developmental delay	*MARS* c.2671 C>G (p.E453G)	SPG 70	Not available

TABLE 1 (Continued)

#	Age (years)/ sex	Age (years) at onset, age (years) at diagnosis	Ambulatory (Yes or No) mRS score	Clinical manifestations	Affected gene/ mutation	HSP type	NCS/ EMG findings
15^	3/F	6 months, 1	No, 4	Leg spasticity and weakness, brisk tendon jerks, Babinski +, incontinence, autism, developmental delay	*MARS**	SPG 70	Not available
16	4/F	3 months, 1	No, 4	Leg spasticity and weakness, brisk tendon jerks, Babinski +, tremors, incontinence autism, developmental delay	*ATL1* c.2671 C>G (p.E453G)	SPG 3A	Not available

^=non-twin siblings; *=presumptive; ADHD=attention deficit hyperactivity disorder; M=male; MRS=Modified Rankin Score; mt=mitochondrial; SAN=sensory axonal polyneuropathy; SMAN=sensorimotor axonal polyneuropathy
[1]Cerebellar atrophy on MRI of the brain

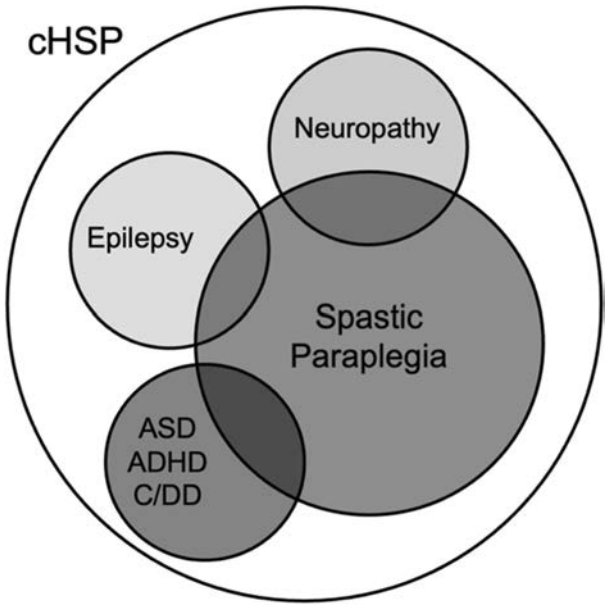


FIGURE 1: Complex Hereditary Spastic Paraplegia Spectrum. Abstract 181

ambulatory at the last clinic follow-up visit with an average disease duration of 7.4 years. Genetically confirmed etiologies included *SPAST* (3 patients), *MARS* (2), *KIF1A* (2), *KIF5A* (1), *SACS* (1), *SPG7*(1), *REEP1* (1), *PNPT1* (1), *MT-ATP6* (1), *ATL1* (1). Sensory motor axonal polyneuropathy (SMAN) was found in seven patients and two exhibited cerebellar atrophy on magnetic resonance imaging (MRI) of the brain. Neurological comorbidities included developmental delay (n=9), autism (n=5), epilepsy (n=3), and attention deficit hyperactivity disorder (n=2).

Conclusions: In our study, a significant proportion (70%) of childhood-onset HSP subjects had co-morbid neuro-cognitive deficits, polyneuropathy with or without neuroimaging abnormalities, and rare genetic etiology. In our cohort, genetic diagnosis was established either through inherited genetic neuropathy panel or whole exome sequencing, which supports the utility of whole exome sequencing in aiding in HSP diagnosis.

Keywords: Neuromuscular Disorders, Rare Diseases, Genetics

182. Beyond Becker and Duchenne: a Novel Phenotype in Dystrophin Gene Mutation - A Case Report

Taskin B (Detroit, MI), Serajee F, Huq A

Objective: The dystrophin gene (DMD) is the largest gene in the human genome, and encodes dystrophin, which bridges the inner cytoskeleton and extracellular matrix. Missense pathogenic mutations in DMD gene are causes of dystrophinopathies including Duchenne/Becker Muscular Dystrophies, or DMD-associated dilated cardiomyopathy.

Methods: 10 year old boy, with mildly elevated liver enzymes, and a CPK level of 1225, was referred to Neurology for fatigue after exertion. His medical history was significant for ADHD with appropriate development. His family history was negative. Physical examination elicited some difficulty with hopping on a single leg and forced gait on heel-walking.Whole exome sequencing was reported a missense point mutation, c.1724T>C (p.L575P) alteration, that results in a T to C substitution at nucleotide position 1724, causing the Leucine at amino acid position 575 to be replaced by a proline (P). The proband was hemizygous for this mutation.

Results: c.1724T>C (p.L575P) alteration has been described in a single paper with three unrelated subjects who presented with fatigue and exertion-induced rhabdomyolysis and

myoglobinuria. This variant is also reported in Clinvar in one patient with BMD. dBSNP suggests a population frequency of 0.002%. Our patient presented solely with complaints of fatigue and elevated serum CPK levels.
Conclusions: This case widens the clinical spectrum of dystrophinopathies and furthermore shows that a patient with a missense point mutation, c.1724T>C (p.L575P) alteration can develop a very mild phenotype only with fatigue after exertion.
Keywords: Neuromuscular Disorders

183. Rapid Exome/Genome Sequencing in the Diagnosis of Congenital Myasthenic Syndromes in Two Hypotonic Infants

Abdul Hamid O (Philadelphia, PA), Gross B, Yum S

Objective: Congenital myasthenic syndromes (CMS) are challenging diagnoses to make in neonates. Due to their clinical heterogeneity, which ranges from fetal akinesia deformation sequence (FADS) to hypotonia and feeding difficulties, suspicion for CMS can be elusive. We present two infants in which rapid exome or genome provided a quick diagnosis and initiation of treatment.
Methods: One infant had a rapid onset of hypotonia and feeding difficulties in the first days of life and found to have compound heterozygous variants in the receptor associated protein of the synapse (RAPSN) gene (maternal nonsense pathogenic p.Q21X (c.60C>T) and paternal missense pathogenic p.N88K (c.264C>A)). Electromyography (EMG) showed evidence of electrodecrement. The second infant had rapid onset of respiratory failure and axial hypotonia at 3 weeks of life requiring tracheostomy. Rapid whole genome resulted in biallelic variants of uncertain significance in the muscle-specific kinase (MuSK) gene (maternal missense c.2365G>A (p.Gly789Ser) and paternal frameshift c.909dup (c.909dupA) p.Ala304fs). This infant's deceased older sibling harbored the same variants and twin sibling harbored only one. EMG demonstrated myopathic features with motor units of decreased amplitude, duration and increased polyphasia with an early recruitment pattern. Muscle ultrasound and biopsy were normal.
Results: Both infants identified by rapid sequencing were trailed on agents targeting neuromuscular junction within the first 2 months of life and had significant clinical improvements in their symptoms.
Conclusions: These cases highlight how rapid genetic sequencing can greatly shorten the diagnostic odyssey for families and lead to rapid initiation of treatment when initial constellation of symptoms may not be obvious for CMS.
Keywords: Neuromuscular Disorders, Genetics, Neonatal & Fetal Neurology

184. Chronic recurrent multifocal osteomyelitis, an uncommon cause of weakness masquerading as a neuromuscular disorder in a child

Pareek A (Houston, TX), Sandweis A, Lotze T

Objective: Chronic, progressive lower extremity weakness and pain in children includes a heterogeneous differential diagnosis, most frequently suggestive of a myopathic or neuropathic disorder. One underrecognized group of lower extremity pain with objective weakness on neurologic exam is orthopedic in nature and may be secondary to a rheumatologic process such as chronic recurrent multifocal osteomyelitis (CRMO). We present a patient who was referred to neurology for neuromuscular evaluation who ultimately had CRMO.
Methods: We present a pediatric patient with neuromuscular deficits who had a primary orthopedic disorder.
Results: A 14-year old male presented to neurology clinic with six years of fluctuating, progressive pain described as "cramping" in the thighs and knees that radiated to the calves bilaterally. Pain was associated with progressive weakness of his lower extremities causing abnormal gait and significant limitations in mobility. Notably, the pain was worse in the morning and triggered by cold weather. His family history of multiple rheumatologic disorders prompted a rheumatology evaluation—which was unrevealing. Due to the chronic and progressive nature of the debilitating symptoms, he had an extensive workup including MRI spine (normal), EMG (non-specific possibly myopathic changes) CK (normal multiple times), chromosomal evaluation and genetic sequencing which were unrevealing. We obtained MRI of the lower extremities with the intent of evaluating for dermatomyositis, but revealed extensive multifocal bony edema of the ischial bones, proximal femoral intertrochanteric regions, and at multiple muscle-bone insertion sites.
Conclusions: CRMO is an uncommon orthopedic cause of muscle weakness and pain, but must remain on a pediatric neurologists' differential diagnosis.
Keywords: Neuromuscular Disorders

185. Novel Therapies in Spinal Muscular Atrophy: Experience from tertiary care center in India

Gulati S (New Delhi, India), Kabra M, Sinha R, Singh S, Chowdhury S, Wander A, Meena A, Choudhary P, Tiwari R, Sharma R, Ojha S, Ghanghoriya P, Aakash M, Kamila G, Gupta V

Objective: Novel therapies in spinal muscular atrophy(SMA) have shown promising short-term outcomes in terms of motor function scores and life expectancy. The drugs that have been approved by the US-FDA for SMA are Nusinersen, Zolgensma and Risdiplam. These are being mostly provided to SMA patients under humanitarian access programs due to their prohibitive exorbitant costs. We present our data of children who have received these medications at our center over the last 2 years and 3 months.
Methods: Two groups of patients(12 and 35) have been receiving intrathecal Nusinersen and are under follow-up. Change in the Modified Hammersmith functional motor scale extended version(HFMSE) is being evaluated. Nine patients(humanitarian-access-7) received intravenous Zolgensma and are under follow-up. Nine children (humanitarian-access-7) have been receiving Risdiplam, out of which 3 have a follow-up of more than 1-year.

Results: Twelve children have been receiving Nusinersen for >2 years, out of which 11 have shown improvement in HFMSE scores(non-compliance: 1). 35 children have a follow up of <6 months. Nine children who have received Zolgensma, showed significant improvement in motor function (those with SMA-II can now stand with orthoses and those with SMA-I can sit independently without support). There has been reduction in the incidence of lower respiratory tract infections. Three children who have been receiving Risdiplam for > 1 year, have shown significant improvement in HFMSE scores, with gain in motor milestones.
Conclusions: Novel therapies in SMA have shown promising results in improving the short-term functional outcome.
Keywords: Neuromuscular Disorders

NEUROOPTHALMOLOGY

186. Development of a pediatric papilledema protocol

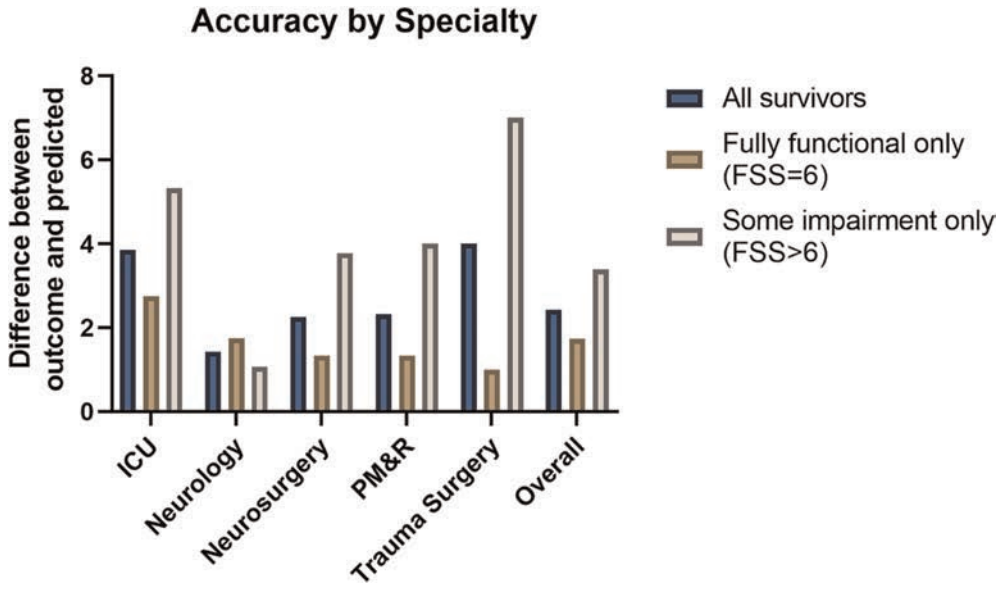
Lax D (Cincinnati, OH), Kaur Dhillon P, Drakou E, Borda M, Ballaban-Gil K

Objective: A papilledema guideline was introduced to our tertiary care pediatric emergency department (ED) with a goal of streamlining evaluation and management of suspected intracranial hypertension. We describe an interim analysis of initial cohorts to guide interdisciplinary development of a formal protocol.
Methods: After IRB approval, we searched ATLAS, our research platform for health data, for "papilledema," "idiopathic intracranial hypertension" and related ICD-10 diagnoses. All patients under 21-years-old presenting to our ED from 01/2015 through 06/2021 for initial workup of suspected papilledema were included.
Results: Of 175 unique records, 102 presented with suspected papilledema of which 13 were diagnosed with pseudopapilledema. Eighty-nine patients required workup, 32 prior to and 57 after introduction of pathway. Initial imaging was performed within 1 day on average though type of imaging was inconsistent. After pathway introduction, venous imaging increased from 81.2% to 94.7%, computed tomography decreased from 9.4% to 3.5%, admissions decreased from 70% to 63% and mean time to successful lumbar puncture (LP) increased from 2.3 to 5.6 days which was not statistically significant (independent sample t-test $p = 0.197$). Time to initial visual field testing improved from 35 to 26 days and time to ophthalmology follow-up improved from 5.96 to 3.61 weeks. No avoidable clinically significant adverse visual outcomes were reported.
Conclusions: Initial workup was inconsistent. Specific targets for improvement include type of imaging, time to LP, visual testing and ophthalmology follow-up. Quality improvement team will include representatives from emergency medicine, neurology, neuro-ophthalmology, radiology, neuro-interventional radiology and neurosurgery departments.
Keywords: Neuroopthalmology, Headache/Migraine, Neuroimaging

NEUROREHABILITATION

187. Accuracy of neuro-prognostication in pediatric severe traumatic brain injury (sTBI)

Sampat V (Wauwatosa, WI), Whitinger J, Flynn-O'Brien K, Kim I, Balakrishnan B, Mehta N, Sawdy R, Zvara K, Nallamothu R, Rehborg R, Farias-Moeller R



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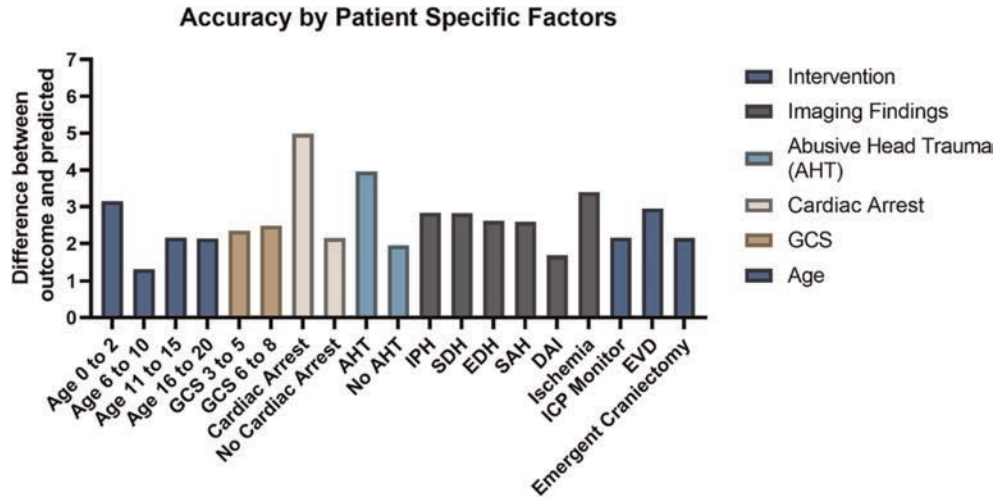

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Objective: To assess accuracy of neuro-prognostication for pediatric sTBI by providers across multiple specialties.
Methods: Surveys were administered to providers of sTBI patients who had neither died nor returned to baseline 4-7 days post-injury. Providers were asked to predict neurologic outcome six months post-injury using the Functional Status Scale (FSS). Patient data included: demographics, injury mechanism, initial GCS, complications, and interventions. Provider data included: specialty and years of practice. Predicted FSS was compared to actual FSS.
Results: 108 surveys were collected on 24 patients. Median age was 8 years [IQR1-14], Median initial GCS was 5 [IQR3-7], 5 had abusive head trauma (AHT). Two died before follow-up. Average FSS score was 8.5 (SD=4). Surveys were collected from critical care (n=23), neurology (n=32), neurosurgery (n=26), physical medicine (n=21), trauma surgery (n=5). Average predicted FSS was 11.7 (SD=6.7). Provider data associated with more accuracy included: complete recovery at follow-up (FSS=6), neurology specialty, and 0-5 years of practice. Patient data associated with less accuracy included: 0-2 years, cardiac arrest, AHT, ischemic brain injury, and FSS>6 at follow-up. No differences were statistically significant.
Conclusions: Neuro-prognostication for children with sTBI is subject to inaccuracies; particularly in young children with AHT and complications of cardiac arrest and/or ischemia, and less so in children with full recovery. Providers predicted a more pessimistic outcome. Neurologists and junior faculty were the most accurate groups. Caution is needed when predicting neurologic outcome for children with sTBI. More data is necessary to assess factors associated with outcome prediction.
Keywords: Neurorehabilitation, Critical Care, Trauma (including Concussion)

188. Withdrawn

NEUROSCIENCE

189. Anti-seizure effects of acute fasting are dependent on intact DEPDC5-mediated mTORC1 signaling
Yuskaitis C (Boston, MA), Modasia J, Schroetter S, Rossitto L-A, Groff K, Morici C, Mithal D, Chakrabarty R, Chandel N, Manning B, Sahin M

Objective: Caloric restriction and acute fasting are known to reduce seizures but through unclear mechanisms. mTOR signaling has been suggested as a potential mechanism for seizure protection from fasting. The upstream mechanistic regulation of mTOR complex 1 (mTORC1) by nutrients and energy has been largely studied outside of the nervous system.
Methods: Fasting for 24h was performed in neuronal specific *Depdc5* knockout (*Depdc5*cc+) and littermate control mice followed by analyzing response to pentylenetetrazol(PTZ)-induced seizures, mTORC1 activity by phosphorylation of S6 (pS6), and metabolomic data. To determine the upstream regulation of mTORC1 in neurons, mTORC1 response to growth factor and/or amino acid withdrawal was assessed in primary cortical neuron cultures with or without shRNA knockdown of *Depdc5* and/or *Tsc2*.
Results: Brain mTORC1 signaling is reduced after acute 24hr fasting of mice. We confirm that neuronal mTORC1 integrates GATOR1 complex-mediated amino acid and Tuberous Sclerosis Complex (TSC)-mediated growth factor signaling. Neuronal mTORC1 is most sensitive to withdrawal of leucine, arginine, and glutamine, which are sensed through signals dependent on DEPDC5, a component of the GATOR1 complex. Metabolomic analysis revealed *Depdc5* neuronal specific knockout mice are resistant to sensing significant fluctuations in brain amino acid levels after fasting. *Depdc5* neuronal specific knockout mice were resistant to the protective effects of fasting on seizures or seizure-induced death.
Conclusions: These results establish that acute fasting reduces seizure susceptibility in a DEPDC5-dependent manner.

Modulation of nutrients upstream of GATOR1 and mTORC1 could offer a rational therapeutic strategy for epilepsy treatment.
Keywords: Neuroscience, Epilepsy/Sleep, Genetics

RARE DISEASES

190. Systemic Complications of Aicardi-Goutières Syndrome

Isaacs D (Philadelphia, PA), Arici S, Dixit A, D'Aiello R, Flores Z, Gavazzi F, Muirhead K, Slattery B, Sherbini O, Shults J, Vincent A, Vanderver A, Adang L

Objective: Aicardi-Goutières Syndrome (AGS) is a heritable interferonopathy arising from abnormal nucleic acid metabolism. This leads to neurologic disability and severe systemic complications. While most cases have a neonatal onset, approximately 20% of individuals present with atypical or late onset disease. This emerging spectrum challenges our understanding of the course of AGS. The characterization of genotype-phenotype correlation and potential systemic sequelae is critical for anticipatory guidance and future clinical trial design.
Methods: Our cohort included 126 individuals with molecularly-confirmed AGS. Detailed information was extracted from medical records and entered into an annotated REDcap database along with source documentation. Key variables included demographics, genotype, and onset of clinical complications (including neurologic, visual, cardiopulmonary, gastrointestinal, hematologic, endocrine, musculoskeletal, and dermatologic). This was used to characterize genotype-phenotype relationships and generate Kaplan-Meier curves for the onset of systemic complications.
Results: We found genotype-specific differences of age at onset, time to diagnosis, and systemic complications. Among the 5 most common genotypes (*TREX1*, *RNASEH2B*, *SAMHD1*, *ADAR1*, and *IFIH1)*, *TREX1* was associated with the youngest onset. Across the population, the most commonly involved organ systems were neurologic, gastrointestinal, cardiopulmonary, and hematologic. In particular, *SAMHD1*-related disease was associated with an increased risk of neutropenia.
Conclusions: We found systemic dysfunction is more prevalent than previously appreciated and that certain genotypes are associated with delayed onset and time to diagnosis. With a better understanding of AGS-related dysfunction, we can better guide clinical care and monitoring through future clinical trials.
Keywords: Rare Diseases

191. Efficacy and safety of trofinetide for the treatment of females with Rett syndrome: results from the randomized, double-blind, phase 3 LAVENDER study

Neul J (Nashville, TN), Percy A, Benke T, Berry-Kravis E, Glaze D, Marsh E, Bishop K, Stankovic S, Youakim J

Objective: To investigate the efficacy and safety of trofinetide in females with Rett syndrome (RTT), a debilitating neurodevelopmental disorder that lacks an approved treatment.
Methods: Females aged 5–20 years with RTT were randomized 1:1 to twice-daily oral trofinetide (n=93) or placebo (n=94) for 12 weeks. Coprimary efficacy endpoints: Rett Syndrome Behaviour Questionnaire (RSBQ) and Clinical Global Impression–Improvement (CGI-I) scale. Key secondary endpoint: Communication and Symbolic Behavior Scales Developmental Profile™ Infant-Toddler Checklist-Social (CSBS-DP-IT Social) composite score. Participants could enroll in a 40-week open-label extension study (available data will be presented).
Results: Trofinetide showed significant difference from placebo after 12 weeks' treatment for the coprimary (Figures 1 and 2) and key secondary endpoints. Mean change from baseline to Week 12 in the RSBQ for trofinetide vs. placebo

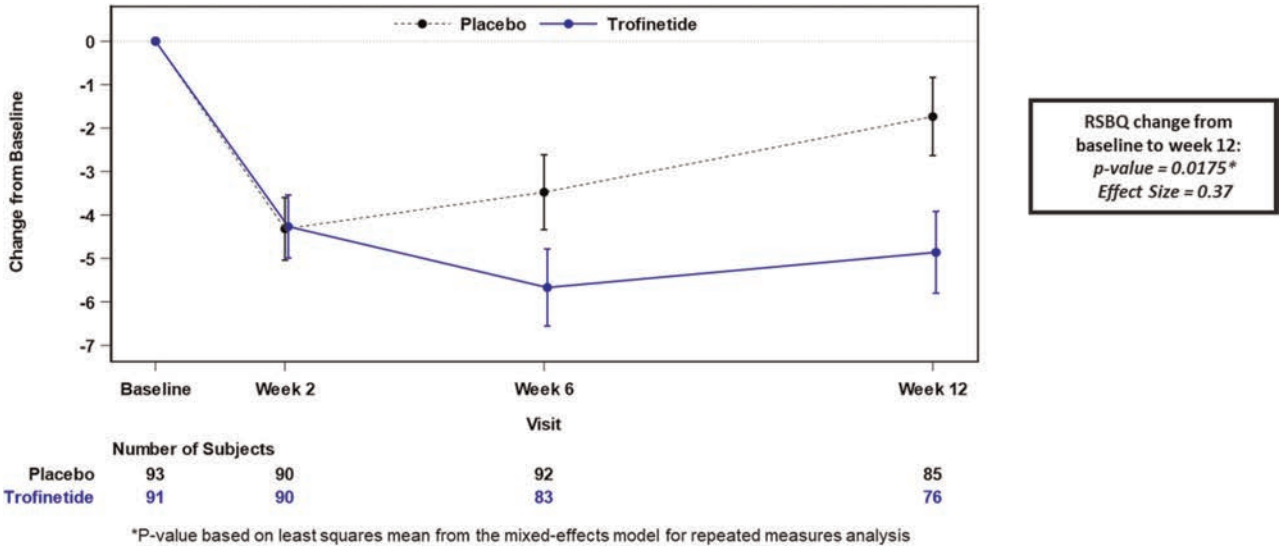

FIGURE 1. Mean (standard error of the mean [SE]) change from baseline in the RSBQ total score at each study visit (Full Analysis Set). Abstract 191

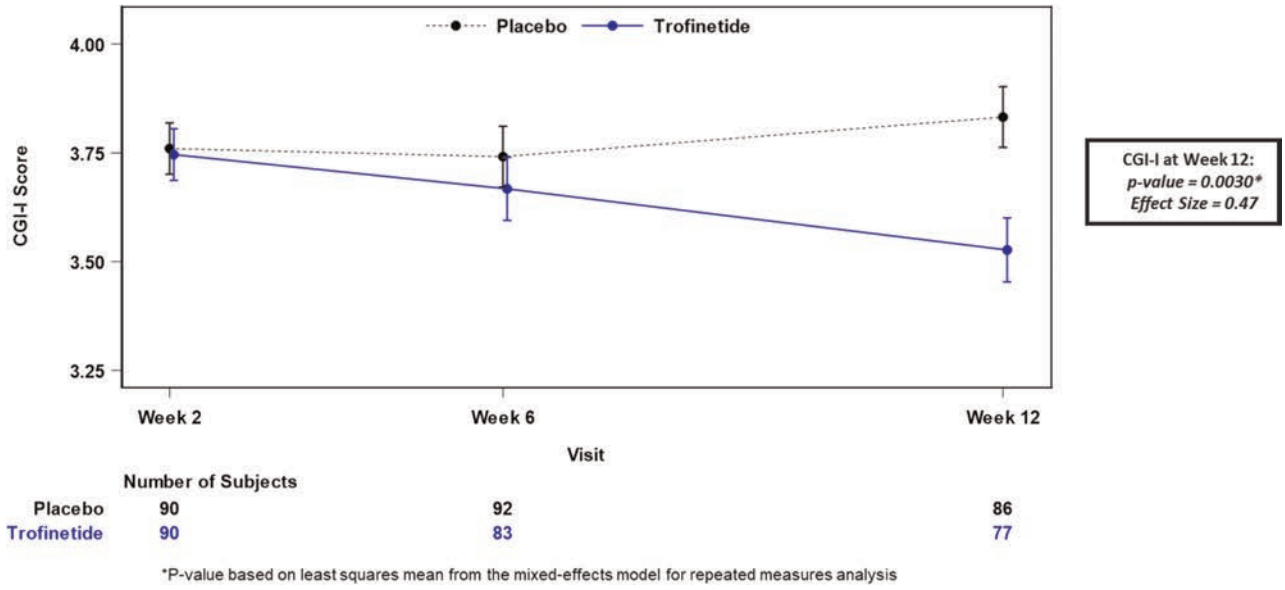

FIGURE 2. Mean (standard error of the mean [SE]) CGI-I score at each study visit (Full Analysis Set). Abstract 191

was -5.1 vs. -1.7 (p=0.0175 for least squares mean [LSM]; Cohen's *d* effect size = 0.37), mean CGI-I scores at Week 12 were 3.5 vs. 3.8 (p=0.0030 [LSM]; Cohens' *d* effect size = 0.47), and mean change from baseline to Week 12 in the CSBS-DP-IT Social composite score was -0.1 vs. -1.1 (p=0.0064 [LSM]; Cohen's *d* effect size = 0.43). Serious treatment emergent adverse events (TEAEs) were reported in 3.2% of participants in both groups. Diarrhea was the most common TEAE (80.6% [trofinetide], 19.1% [placebo]); 98% of all cases were mild-to-moderate in severity.

Conclusions: In this phase 3 study in RTT patients, statistically significant differences between trofinetide and placebo were observed for efficacy endpoints relevant to RTT; no safety concerns were identified.

Keywords: Rare Diseases

192. A Phase 1/2 Open-label, Multiple-dose, Dose-escalation Clinical Trial of the Safety and Tolerability of GTX-102 in Pediatric Patients with Angelman Syndrome

Sell E (Ottawa, ON, Canada), Servais L, Harijan P, Stromatt S, Brandabur M, Berry-Kravis E

Objective: Determine the safety and clinical activity of GTX-102, an antisense oligonucleotide that targets the *UBE3A* antisense transcript, and allows transcription of paternal *UBE3A* in cynomolgus macaques.

Methods: This is a Phase 1/2 open label, dose finding study with intra-patient and inter-cohort dose escalation. Patients receive 3-4 monthly intrathecal injections followed by maintenance dosing every 3 months.

Results: Eighteen children have been treated with doses from 2 mg to 36 mg. The study was initially stopped for lumbosacral radiculopathy in the first 5 patients, treated at doses of 20 mg or 36 mg. The majority of symptoms resolved within 2-4 weeks, and all 5 children had a full clinical recovery. A transient adverse event (AE) of ataxia occurred 2-6 hours after the injection of GTX-102, resolved in 24-72 hours after onset, and appeared to be dose-dependent, starting at doses ≥ 10 mg. Clinical activity for these 5 patients was assessed; all patients were "much improved" or "very much improved" by the Clinical Global Impression-Improvement scale across multiple functional domains. Positive changes were also observed with other measures. The study was amended and lower starting doses (2 mg, 3.3 mg and 5 mg) have been tested in 13 additional patients. Radiculopathy or ataxia has not been reported.

Conclusions: GTX-102 appears to have clinical activity with improvement in several functional domains. Adverse events of radiculopathy and ataxia appear dose related. Results from a planned interim analysis will be presented.

Keywords: Rare Diseases, Genetics, Translational/ Experimental Therapeutics

193. Stress Granules and Staufen1 Mediate Pathophysiology of Vanishing White Matter Disease

Bonkowsky J(Salt Lake City, UT), Shih H-Y, Stevenson T, Scholl E

Objective: Leukodystrophy with Vanishing White Matter (VWM) is caused by mutations in the EIF2B1-5 genes and activation of the integrated stress response (ISR), although mechanisms of disease are unclear. Our objective was to characterize disease mechanisms caused by ISR activation. We focused on analysis of stress granules (SGs) (membraneless cytoplasmic ribonucleoprotein aggregations), which have been identified as a key mediator of ISR activation and pathophysiology in adult chronic neurodegenerative diseases including ALS.

Methods: We used zebrafish and mouse EIF2B2 and EIF2B5 VWM models, and employed genetic and pharmacological manipulation tools. We analyzed SGs and other immunohistochemical, protein, and RNA markers in the CNS.

Results: We found an increase in SGs and in apoptosis in the brains of zebrafish and mice with VWM; more severe

mutants had larger increases in SGs and apoptosis. Genetic rescue of EIF2B2 expression normalized SG and apoptosis counts. Puromycin-induced SG formation worsened apoptosis, whereas nocodazole-prevention of SG formation reduced SGs and apoptosis. Knock-down of *staufen1*, a double-stranded RNA binding protein component of SGs, led to a reduction of SGs and apoptosis, and also reduced ISR activation measured by *chopII* qRT-PCR.
Conclusions: Our results indicate that SGs mediate VWM disease pathophysiology, and that *staufen1* acts as a feedback link between ISR activation and SG formation. Our findings suggest novel opportunities to disrupt CNS pathophysiology of VWM. Further, there may mechanisms of neurodegeneration shared from VWM with more common adult neurodegenerative conditions.
Keywords: Rare Diseases, Demyelinating Disorders

194. Long term benefit of EryDex treatment in patients with Ataxia Telangiectasia: delay of loss of autonomous walking

Perlman S (Los Angeles, CA), Whitehouse W, Zielen S, Leuzzi V, Fornasari L, Lederman H

Objective: To assess the long-term efficacy and safety of monthly infusions of intra-erythrocyte dexamethasone-sodium-phosphate (EryDex) in patients with A-T.
Methods: 175 patients were randomized to monthly EryDex high dose, low dose, or placebo. After the 12-month placebo controlled period, patients continued in an open label extension (OLE).
Results: In a Kaplan-Meier analysis of loss of autonomous walking during the ATTeST Study (n=97), a remarkable difference was observed between treated groups and placebo with a median number of months to loss of autonomous walking of 19.0 and 8.9, for low dose and placebo, respectively. For the high dose, >50% of patients retained autonomous walking capacity at last observation (23 months). As a result, the median number of months could not be calculated, indicating a stronger effect than seen in the low dose group.Analyses of the combined ATTeST and OLE trials suggest long term benefit with EryDex treatment. The analysis of high dose treatment for a mean of 31 months (n=43) after the initial 6-month period showed for the mICARS, an average 6-months slope of deterioration of 1.00 point which is still remarkably different from the 6-month slope of deterioration in the placebo group (2.45 points in initial treatment period). The pre-specified 6–9-year-old participants showed, for the long-term high dose group, a similar mean slope of 0.085. For those on placebo the mean deterioration slope was 0.418 RmICARS points/month.
Conclusions: The significant delay in loss of ambulation and preservation of function, translate into long-term clinical benefit for AT patients treated with EryDex.
Keywords: Rare Diseases

195. Development of Longitudinal Quantitative Performance Measures in a Leukodystrophy Featuring Progressive Ataxia

Fine A (Baltimore, MD), Goodman J, Amos D, Turk B, Bastian A, Fatemi S, Keller J

Objective: To identify quantitative sensorimotor performance measures that can detect disease severity and progression in leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL). LBSL is a leukodystrophy caused by biallelic mutations in DARS2, which encodes mitochondrial aspartyl tRNA synthetase. White matter changes in the cerebrum, cerebellum, and dorsal columns lead to worsening ataxia and spasticity with loss of independent ambulation. There are no targeted therapies for LBSL.
Methods: The study analyzes longitudinal data from wearable sensors and clinical scales used to assess walking and balance in LBSL and age-matched control participants' homes through video conferencing every 6 months over 3 years. Outcomes include parameters obtained from a wearable accelerometer system for gait and static postural sway in 4 standing conditions and the Scale for the Assessment and Rating of Ataxia (SARA).
Results: 11 LBSL participants and age-matched controls were included in the study. Cross-sectionally, LBSL participants had a slower gait speed, greater lateral step variability, and took higher steps compared with controls. During standing conditions with eyes closed and feet together, LBSL participants showed sway over a greater area than controls. Step variability and sway area correlated strongly with the SARA. Over 2.5 years, gait speed decreased, and double support time increased, indicating further gait instability.
Conclusions: Remote testing of gait and sway in the home using wearable sensors is a feasible and sensitive method for monitoring sensorimotor changes in LBSL. This work addresses the unmet need to establish quantitative outcome measures for clinical trials in LBSL.
Keywords: Rare Diseases, Genetics, Neurometabolic Disorders

196. Neuropsychology and Quality of Life (QOL) Profile in SSADH Deficiency (SSADHD)

DiBacco M (Boston, MA), Aygun D, Roullet J-B, Gibson KM, Pearl P

Objective: SSADHD, an autosomal recessive disorder of GABA degradation, leads to a complex neuropsychological phenotype assessed in the NICHD/NIH natural history study.
Methods: Subjects with confirmed SSADHD received comprehensive assessments including parent/subject interviews and age-appropriate cognitive and adaptive measures (Mullen Scales, DAS, Wechsler, VABS, REEL-3, Achenbach, CBCL, ADOS, MABC-II, PedsQL4.0). The PedsQL consists of 23 questions separated into Physical, Emotional, Social, and School Domains. QOL scores were compared to cutoff values applicable to other chronic conditions.
Results: The study cohort consisted of 33 subjects in the US, Spain, and Germany. Full neuropsychological evaluations were completed on 26 US patients: median FSIQ 50 (IQR 49-60, range 30 [floor value] to 87), verbal 49 (IQR 45-64, range 30 [floor] to 95), nonverbal 49 (IQR 47-59, range 30 [floor] to 84). Of 20 evaluated with ADOS/AOSI, 10 (50%) scored as ASD. The majority of subjects had low QOL scores across all domains: Physical 60.5, Psychosocial 64.8, Total 63.7. There was no statistically

significant difference in scores by age or gender. The majority, 28/33 (85%), tested below the cutoff for total health score, with 22/33(67%) inthe major impairment range.
Conclusions: Intellectual disability and autism spectrum disorder are common in SSADHD. Most patients show poor quality-of-life scores in all domains, regardless of age or gender, and score similarly to comparable chronic diseases, e.g. asthma 68.8, cancer 66.7, CP 51.3, IEMs 49.6 (59 with mild-moderate movement disorder and 33.7 with severe movement disorder). QOL in SSADHD shows major impairment, comparable to other chronic diseases.
Keywords: Rare Diseases, Neurometabolic Disorders

197. Burden of Disease Exploration in TUBB4A-related Leukodystrophy

Patel V (Philadelphia, PA), Gavazzi F, Cusack S, D'Aiello R, Vincent A, Vanderver A

Objective: *TUBB4A*-related leukodystrophy encompasses a spectrum of rare neurological disorders with varied clinical severity. Within the pediatric population, burden of disease from the caregiver's perspective is important to consider when assessing therapeutic efficacy. Currently, burden of disease has not previously been studied in *TUBB4A*-related leukodystrophy. We applied quality of life questionnaires and adaptive behavior assessments to identify critical functional domains and assess overall challenges in daily life.
Methods: Individuals with confirmed clinical and genetic diagnosis of *TUBB4A*-related leukodystrophy were consented under an IRB-approved protocol. Participants completed hybrid in-person or remote administration of the Vineland Adaptive Behavior Scale 3rd edition and remote administration of the Caregiver Priorities & Child Health Index of Life with Disabilities, Neuro Quality of Life, and Pediatric Quality of Life Inventory TM. Results were collected in REDCap and analyzed through Prism-Graphpad 9.0.
Results: Our cohort showed progressive decline in adaptive behavior abilities with increasing chronological age. Communication and social abilities are relatively spared when compared to motor abilities and daily living skills ($p<0.01$). Caregivers reported challenges associated with gross motor abilities limiting postural changes and independent mobility, challenges interpreting expressive communication, and overall moderate reduction of quality of life, with wide heterogeneity. Burden of disease assessment for caregivers showed social and emotional strain associated with caring for affected individuals.
Conclusions: *TUBB4A*-related leukodystrophy showed a dramatic impact on the quality of life of affected individuals and caregivers. These results will orient the selection of appropriate outcome measures to evaluate clinical trial efficacy, taking caregiver feedback into consideration.
Keywords: Rare Diseases

198. Clinical Improvements in the First Year Following Eladocagene Exuparvovec Gene Therapy in Patients With Aromatic L-Amino Acid Decarboxylase Deficiency

Hwu P (Taipei City, Taiwan), Wang A, Russell A, Turna J, Trifillis P, Tai C-H

Objective: The purpose of this post hoc analysis was to evaluate clinical outcomes in patients with the rare genetic disorder aromatic L-amino acid decarboxylase (AADC) deficiency during the first year after eladocagene exuparvovec gene therapy administration.
Methods: Eladocagene exuparvovec was administered bilaterally into the putamen of 28 patients with AADC deficiency in 3 open-label clinical trials. Patients received 1.8×1011 vg ($n=21$) or 2.4×1011 vg ($n=7$). Gross motor milestone development was evaluated using the Peabody Developmental Motor Scale–Second Edition. Physical and neurological exam data were used to evaluate swallowing function, body weight, autonomic symptoms, movement disorder symptoms, and rate of respiratory infections at baseline and ≤12-month follow-up.
Results: At baseline, 21% (6/28) of patients achieved partial head control. Within 12 months, 89% (25/28) achieved partial or full head control, 43% (12/28) could sit assisted or unassisted, and 4% (1/28) were able to stand with support. Among patients with available feeding data, 80% (8/10) showed improvements in swallowing function. This improvement was mirrored by increases in body weight and reduced rates of respiratory infection. The proportion of patients experiencing symptoms related to autonomic dysfunction and movement disorders also decreased from baseline to 12 months.
Conclusions: In this post hoc analysis of the ≤12 months following eladocagene exuparvovec delivery, patients demonstrated improvements in various symptoms of AADC deficiency. Specifically, swallowing function, body weight, rate of respiratory infection, autonomic dysfunction, and movement disorder–related symptoms improved. Patients also attained critical gross motor milestones that were not present at baseline.
Keywords: Rare Diseases, Genetics, Movement Disorders (including Cerebral Palsy)

199. Early and severe symptoms in children with de novo variants in ATL1 (SPG3A) – in silico predictions and a systematic cross-sectional analysis of the clinical spectrum

Alecu J (Boston, MA), Srivastava S, Blackstone C, Ebrahimi-Fakhari D

Objective: To describe the clinical and molecular features of children with *ATL1*-associated hereditary spastic paraplegia (*ATL1*-HSP, SPG3A) caused by *de novo* variants.
Methods: Five patients with *de novo* variants in *ATL1* were recruited. A systematic literature review identified 495 published cases of *ATL1*-associated HSP. *In silico* and cross-sectional natural history analyses were performed.
Results: Symptom onset was significantly earlier in patients with *de novo* variants (median: 12 months) compared to familial variants (median: 48 months, Mann-Whitney-*U* $p<0.0001$). While most patients with non-*de novo* variants presented with a pure form of HSP characterized by isolated lower limb spasticity (96.8%) and slow disease progression, the majority of patients with *de novo* variants were initially evaluated for global developmental delay (64.7%, OR = 9.7). Patients with *de novo* variants showed rapid

disease progression, with significant spasticity in early childhood and frequent upper extremity involvement (36.8%, OR = 45.5). Bulbar symptoms were frequent in patients carrying *de novo* variants (26.7% and 16.7%, respectively) but absent in familial cases. 80 distinct non-*de novo* and 24 *de novo* variants were found. *In silico* analyses revealed that most missense variants cluster in four regions along the linear protein structure. Analyses of the 3-dimensional atlastin-1 structure showed two hotspots for *de novo* variants in the middle domain.

Conclusions: We delineate the clinical and molecular spectrum of *de novo ATL1*-related HSP and demonstrate a distinct natural history. Our findings add *ATL1*-related HSP to the differential diagnosis of early-onset HSP with global developmental delay and rapid disease progression, which suggests a distinct molecular mechanism.

Keywords: Rare Diseases, Movement Disorders (including Cerebral Palsy), Genetics

200. Time to Clinical Event Measures in Individuals with Leukodystrophies

McCann J (Philadelphia, PA), D'Aiello R, Ramos M, Muirhead K, Pizzino A, Schmidt J, Gavazzi F, Shults J, Grundmeier R, Vanderver A

Objective: Leukodystrophies are heritable white matter disorders which profoundly affect motor function. Affected children present with loss of motor milestones, feeding difficulties, tone abnormalities, orthopedic complications, and respiratory failure.Large data sets in these rare leukodystrophies are lacking and an understanding of the frequency of medical complications is unknown. The EPIC Electronic Medical Record (EMR) was used to evaluate these events in a cohort of patients with confirmed leukodystrophies who received care at the Children's Hospital of Philadelphia (CHOP). Goal of this project was to calculate event frequency in this cohort.

Methods: Through an IRB-approved protocol, we identified a cohort of 403 individuals with leukodystrophies. Individual diagnoses were confirmed via genotype-phenotype correlation and medical complications were identified within the EMR. The verswlr command in Stata 17.0 was used to implement a versatile weighted log-rank test.

Results: Among individuals in our cohort, 150 (37.2%) had a feeding tube placed, 137 (34.0%) had a hip complication, 145 (36.0%) had a spine complication, and 66 (16.3%) required artificial ventilation outside of elective surgery. The median survival time was lowest in MLD (8.6 years, Table 1, Figure 1). The time to feeding tube placement differed significantly between diagnoses (p = 0.0001).

Table 1.

Diagnosis	N	Median_Years_to_Feeding_Tube_Placement
AGS	72	26.6
AxD	74	24.3
H-ABC	32	13.1
MLD	27	8.6
Other Dx	136	17.5
X-ALD	45	*

*The median time for X-ALD is missing because the survival curve did not cross 0.50 for this diagnosis.

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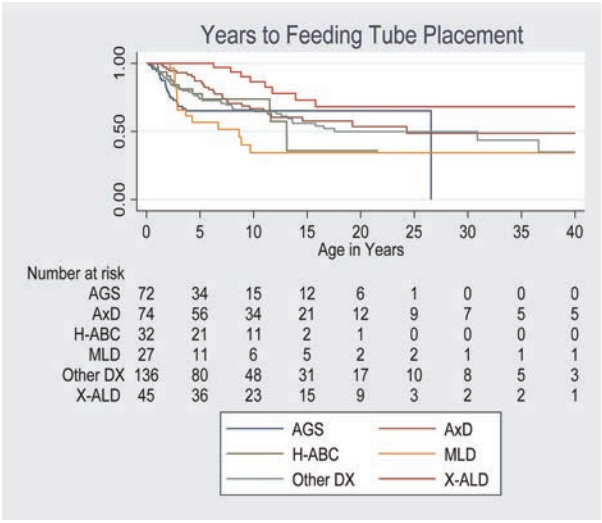

FIGURE 1. Abstract 200

Conclusions: Patients with leukodystrophies experience frequent medical complications with a significant rate of morbidity over time. These findings highlight the importance of early disease recognition and appropriate management as well as the need to explore possible curative treatments, given the current standard of care is most focused on the management of symptoms associated with these disorders.

Keywords: Rare Diseases, Genetics

201. Expanding the Phenotypic Spectrum of FLNA from Ventricle to Cortex

Shao D (Boston, MA), Doan R, Lai A, Chen MH, Walsh C

Objective: Confluent bilateral periventricular nodular heterotopias (PVNH) are a classic radiographic feature of individuals that harbor variants in *FLNA*. However, the full spectrum of brain developmental abnormalities that arise is unclear, in part to poor detection of disease-relevant non-coding or somatic variants in *FLNA*. This study characterizes the spectrum of brain malformations that arise due to *FLNA*.

Methods: Using deep sequencing probes spanning intronic and exonic regions of FLNA, and validation by ultra-deep MIPP-seq, 38 individuals with FLNA variants were identified for further review of brain MRI findings.

Results: 4/25 (16%) of females and 5/13 (38%) of males with FLNA candidate variants had cortical malformations in addition to PVNH. Malformations included cortical dysplasia, polymicrogyria, subcortical heterotopia, and corpus callosum abnormalities. Predicted splicing-altering intronic variants were significantly enriched in the subset of individuals with cortical malformations (4/9; 44%; Fisher Exact P-value < 0.01).

Conclusions: We describe an expansion of the *FLNA* spectrum of brain malformations, multiple of which are associated with novel non-coding variants in *FLNA*.

Keywords: Rare Diseases, Genetics, Neuroimaging

202. Clinical and imaging correlates of behavioral problems in children with Sturge-Weber Syndrome

Luat A (Detroit, MI), Gjolaj N, Jeong J, Behen M, Juhasz C

Objective: While research has demonstrated elevated levels of behavioral problems in children with Sturge Weber Syndrome (SWS), the nature/type of problems most commonly identified is unclear, and although seizure variables tend to predict the presence of problems, few studies have examined lesion location and/or extent as predictors of behavioral concerns.

Methods: 40 children (mean age=5.75 years; range= 2.2-12.8 years) with unilateral SWS underwent brain MRI and neuropsychological evaluations, including measurement of verbal intellect (VIQ), and caregiver-reported behavioral concerns. Side of lesion, number of lobes affected, whether the frontal lobe was involved, and seizure frequency were calculated. Incidence of elevated levels (T-score>65) of anxiety (ANX), depression (DEP), hyperactivity (HYP), aggressive behavior (AGG), attention problems (ATT), and atypicality (ATYP) were determined. Regressions (with age, seizure frequency, frontal involvement, # lobes affected, and VIQ entered simultaneously) were used to test for significant unique contributions from imaging/seizure variables to behavioral problems.

Results: ATT (25%) and ATYP (25%) were the most frequently elevated concerns, followed by HYP (18%), DEP (15%), AGG (12%), ANX (7%). Overall tests were significant for ATT, HYP, AGG, ANX, and ATYP - with *# lobes affected* (-), *frontal involvement* (+) and *VIQ* (-) making significant contributions to HYP; *# lobes* (-), *seizure frequency* (+), *VIQ* (-) to ATT; *seizure frequency* (+) to AGG; and *VIQ* (+) to ANX; right-sided lesions were associated with increased ATYP.

Conclusions: Seizures are known to be an important predictor of behavioral concerns in children with SWS; relationships between lesion location and extent and behavioral concerns are novel and warrant further investigation.

Keywords: Rare Diseases, Epilepsy/Sleep, Neuroimaging

203. Epileptic Encephalopathy Secondary to Homozygous TBC1 Domain-Containing Kinase (TBCK) Mutation in Four Patients of Puerto Rican Descent

De Luca-Ramirez J (Ponce, Puerto Rico), Rosado-Fernández S, Torres O

Objective: TBCK Syndrome is a rare autosomal recessive disorder characterized by congenital hypotonia, intellectual disability, motor impairment and intractable epilepsy. Mutations within TBCK lead to mTORC1 complex inactivation, causing subsequent accumulation of autophagic vesicles within fibroblasts. To date, there are 35 cases of TBCK reported worldwide. We present four TBCK cases with the p.R126X (p.ARG126*) mutation, a variant predominating amongst children of Puerto Rican-descent, recently denominated as TBCK-Encephaloneuropathy or Boricua Syndrome.

Methods: We describe four unrelated Puerto-Rican patients with no known consanguinity diagnosed with epilepsy during the year 2021 at our institution. Patient 1 is an 8-month-old female with global developmental delay, hypotonia, tongue fasciculations and epilepsy. Patient 2 is a 3-year-old male with global developmental delay, and hypotonia, who presented in status epilepticus. Patient 3 is a 3-year-old female with hypotonia, left hemiparesis, global developmental delay, presenting in status epilepticus. Patient 4 is a 2-year-old female with global developmental delay, hypotonia, facial diplegia, with a second episode of status epilepticus within 6 months.

Results: Genetic testing demonstrated the same homozygous pathogenic variants c.376C>T (p.ARG126*) within the TBCK gene in all four patients. All patients had congenital hypotonia, delayed motor milestones, profound intellectual disability, and expressive language delay prior to the diagnosis of epilepsy.

Conclusions: Pediatric patients of Puerto-Rican descent with a history of hypotonia, global developmental delays and new onset epilepsy should be evaluated for TBCK mutations, as prompt recognition can help providers facilitate appropriate medical management and prognosis counseling.

Keywords: Rare Diseases, Genetics

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Gonzalez, X. R., & Schneider, M. C. (2021). Boricua Founder Variant in FRRS1L Causes Epileptic Encephalopathy With Hyperkinetic Movements. Journal of Child Neurology, 36(2), 93–98. https://doi.org/10.1177/0883073820953001

204. Genetic Mutations in Patients with Atypical Sturge-Weber Syndrome

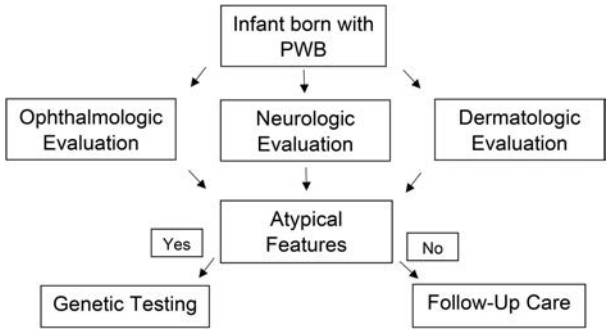
Yeom S (Baltimore, MD), Cohen B, Weiss C, Sobreira N, Hammill A, Comi A

Objective: This study aimed to assess genetic variation in patients presenting for evaluation of Sturge-Weber syndrome (SWS).

Methods: Five patients presented with facial capillary malformation but atypical features leading us to obtain genetic testing. Neuroimaging and clinical information were gathered, including demographics, neurologic and ophthalmologic symptoms, birthmarks characteristics, and family history. The study was done with patient/parent consent and IRB approval.

Results: Patients were referred for facial capillary malformations suggestive of SWS spectrum; three also had glaucoma. All presented with neurologic symptoms associated with SWS, but only 3 had epilepsy. Atypical features included extensive capillary malformation body involvement, significant limb hypertrophy, vascular family history, lack of seizures, or extensive dilated deep draining vessels on neuroimaging rather than leptomeningeal vascular malformation. Somatic genetic testing in three patients noted a *PIK3CA*-p.Met1043Ile pathogenic variant in the first, a *GNA11*-p.R183C pathogenic variant in the second, and a potentially pathogenic 9p23 deletion including *PTPRD* and *PTPRD-AS2* genes in the third patient. Germline testing in two patients demonstrated a *RASA1* frameshift pathogenic variant in one, and a germline ~580 kb deletion disruption the *COL3A1*, *COL5A2* and *SLC40A1* genes in the other.

	Gene Mutation	Neurologic Symptoms	Vascular Malformations
1	RASA1-c. 1414dupT	Flexor spasms at 4 months of age. Epilepsy, Left sided weakness	**Skin**: Right sided face capillary malformation **Brain**: left sided occipital-parietal involvement and right frontal venous angioma **Eye**: not involved to date *Strong family history* of capillary malformations and a brother who died or AVM
2	mosaic 2.5mb deletion of 9p23 including PTPRD and PTPRD-AS2 on the short arm of chromosome 9p23	Seizure onset at 1.5 yrs. Epilepsy and stroke-like episodes Receives speech therapy, OT, and special ED	**Skin***: Extensive PWB* on the left side of the face more than the right side and left lower torso extending down onto the left leg **Brain**: Left hemispheric SWS **Eye**: Left sided glaucoma; Had surgery for glaucoma after NICU
3	somatic PIK3CA variant c.3129G>T	Evidence of remote stroke, developmental delay, headaches, mild cognitive impairment	**Skin**: left facial and bodily capillary malformation, *hypertrophy*. **Brain**: bilateral enlarged deep draining vessels, hypertrophy left hemisphere, *no abnormal leptomeningeal enhancement* **Eye**: cataracts
4	GNA11-c.547C>T	Left-sided weakness, stroke-like episodes with slurring of speech and twirling sensation at 5 year of age, headache	**Skin**: right-sided facial capillary malformation, *hyperpigmentation on 70-90% of the body, significant limb hypertrophy* **Brain**: right occipital, parietal, and temporal lobe deep draining vessels, *no abnormal leptomeningeal enhancement* **Eye**: several glaucoma surgeries and implants
5	~580kb germline deletion including COL3A1, COL5A2, and SLC40A1	Seizure onset at 2 months of age	**Skin**: bilateral facial capillary malformation **Brain**: *microcephaly* with small bilateral cerebral hemispheres. *extensive bilateral contrast enhancing pial vascular malformation* **Brain**: bilateral congenital glaucoma



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Conclusions: While most patients with SWS have the *GNAQ*-p.R183 somatic variant, pathogenic variants in other genes may be identified in atypical patients which have implications for prognosis, drug trial eligibility, and medical care. Here we propose a workflow for genetic testing as indicated for patients presenting for a SWS evaluation and atypical features.

Keywords: Rare Diseases, Neurocutaneous Disorders, Genetics

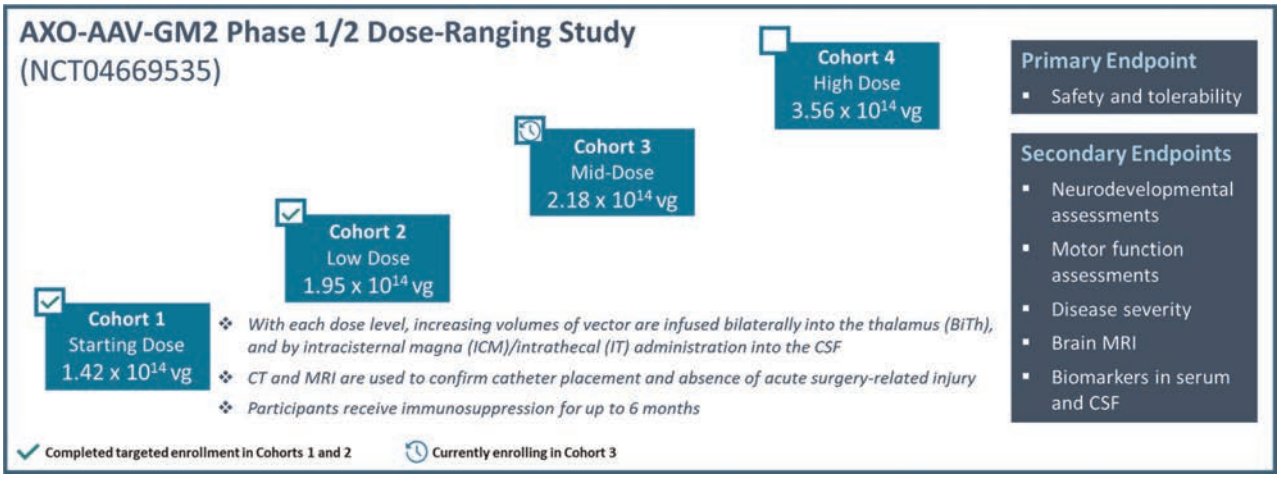
205. AXO-AAV-GM2 Gene Therapy for the Treatment of GM2 Gangliosidosis: Preliminary Results from a Phase 1/2 Trial

Eichler F (Boston, MA), Flotte T, Andonian H, Cataltepe O, Artinian R, Nagy A, Thorp B, Jameson J, Sheehan M, Vaughn T, Valencia D, De Boever E

Objective: To present interim study results of AXO-AAV-GM2 for treatment of GM2 gangliosidosis, known as Tay-Sachs (TSD) and Sandhoff (SD) disease.

Methods: Ongoing, open-label, dose-ranging, Phase 1/2 study including participants with infantile- (6-20 months old) and juvenile-onset (2-12 years old) GM2 gangliosidosis, enrolled in 4 cohorts.

Results: Five participants have been dosed to-date. Pre-treatment MRIs in the infants revealed extensive signal abnormalities in white matter, thalami, caudate and putamen. Baseline MRIs in the juvenile participants ranged from normal to extensive parenchymal volume loss and thalamic atrophy.The procedure was generally well-tolerated, with MRI evidence of accurate targeting and resolution of focal hyperintensities at thalamic injection sites. Most AEs have been mild or moderate, and none have led to interruption or



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Participants Dosed (as of April 2022)

Demographics	Disease Onset	Age at Diagnosis (months)	Dosing Cohort	Age at Gene Transfer (months)	Time Since Gene Transfer (months)
Pt1: Female, SD	Infantile	9	Starting Dose	14	14
Pt2: Male, TSD	Juvenile	41	Low Dose	56	10*
Pt3: Female, TSD	Infantile	15	Low Dose	17	6
Pt4: Female, TSD	Juvenile	40	Low Dose	75	4
Pt5: Female, SD	Juvenile	75	Mid-Dose	144	1

*Pt2 succumbed to *C. diff* infection 6 months post-dosing

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discontinuation of the procedure or study withdrawal. As of November 2021, 5 serious AEs (SAEs) were reported in a single participant who had extensive parenchymal volume loss and disease progression at baseline and succumbed to *C. diff* infection 6 months post-dosing. The investigators and independent data safety monitoring board (DSMB) determined 1 SAE of neurologic decompensation to be 'Possibly Related' to AXO-AAV-GM2 and underlying disease, and the fatal SAE of '*C. diff* infection' as 'Unrelated' to AXO-AAV-GM2. Following review, the DSMB recommended continued enrollment, and FDA agreed with enhanced participant monitoring.

Conclusions: AXO-AAV-GM2 gene therapy using combined BiTh/ICM/IT delivery was generally well-tolerated in all participants dosed to-date. The death of the participant with the most advanced disease points to a critical window for intervention, when disease stabilization may be possible.

Keywords: Rare Diseases, Translational/Experimental Therapeutics, Genetics

206. RGX-121 gene therapy for the treatment of severe mucopolysaccharidosis type II (MPS II): Interim analysis of data from a Phase 1/2 study

Insert (Rockville, MD), Harmatz P, Giugliani R, Escolar M, Ficicioglu C, Fiscella M, Yang L, Cho Y, Falabella P

Objective: MPS II is an x-linked lysosomal storage disease caused by deficiency of iduronate-2-sulfatase (I2S) leading to accumulation of glycosaminoglycans (GAGs). Severe MPS II results in irreversible neurodevelopmental decline not addressed by intravenously administered enzyme replacement therapy. RGX-121, a recombinant adeno-associated virus serotype 9 capsid containing a human I2S expression cassette (AAV9.CB7.hIDS), administered to the central nervous system (CNS) may provide a permanent source of secreted I2S, potentially improving neurologic and systemic disease manifestations.

Methods: MPS II is an x-linked lysosomal storage disease caused by deficiency of iduronate-2-sulfatase (I2S) leading to accumulation of glycosaminoglycans (GAGs). Severe MPS II results in irreversible neurodevelopmental decline not addressed by intravenously administered enzyme replacement therapy. RGX-121, a recombinant adeno-associated virus serotype 9 capsid containing a human I2S expression cassette (AAV9.CB7.hIDS), administered to the central nervous system (CNS) may provide a permanent source of secreted I2S, potentially improving neurologic and systemic disease manifestations.

Results: MPS II is an x-linked lysosomal storage disease caused by deficiency of iduronate-2-sulfatase (I2S) leading to accumulation of glycosaminoglycans (GAGs). Severe MPS II results in irreversible neurodevelopmental decline not addressed by intravenously administered enzyme replacement therapy. RGX-121, a recombinant adeno-associated virus serotype 9 capsid containing a human I2S expression cassette (AAV9.CB7.hIDS), administered to the central nervous system (CNS) may provide a permanent source of secreted I2S, potentially improving neurologic and systemic disease manifestations.

Conclusions: RGX-121 has the potential to provide sustained CNS clinical outcomes and additional systemic effects in severe MPS II patients.

Keywords: Rare Diseases, Neurometabolic Disorders

207. Meeting the care coordination needs of complex therapies for rare neuro-genetic disorders: the development of a complex drug program.

Haug K (Aurora, CO), Schwab T, Caneva C, Coffman J, Demarest S, Parsons J

Objective: Creation and utilization of a combined, dedicated operational and clinical team dedicated to ensuring patients with rare neuro-genetic conditions have timely access to novel high cost, complex therapies with minimal complications.

Methods: In 2016, the complex drug team of a lead physician, one registered nurse, and one administrative professional was assembled. The program has navigated the onboarding of new therapies and increasing patient counts by creating standardized clinical pathways, order templates, expectation agreements with families, consistent clinical-team training, financial team liaisons to assist with single case payor agreements, predictable outreach with manufacturers, and connections with necessary departments and subspecialties to ensure all care is delivered in a timely manner. Guidelines have been developed to determine if a medication is appropriate for the complex drugs program.

Results: This specialized program has successfully treated 50 patients with nusinersen, 12 patients with onasemnogene abeparvovec, 14 patients with risdiplam, 4 patients with cerliponase alfa for CLN2 Battens disease, and 8 patients with exon skipping therapies for DMD. SMA patients receive therapy, on average, 26 days after initial newborn screening identification. Of 540 nusinersen doses, only 6 (1.1%) experienced complications beyond a post-LP headache. Time to treatment with cerliponase alpha has reduced from 257 days to 8 days. Of 209 intraventricular accesses for cerliponase alpha, only 12 adverse events (.057% incidence).

Conclusions: A specialized clinical and administrative team is beneficial in ensuring timely treatment with complex, novel therapies with minimal complications.

Keywords: Rare Diseases, Neuroscience

208. Neurosarcoidosis in children: a systematic review and meta-analysis of cases, imaging and management

Young M (Chattanooga, TN), Goldman-Yassen A, Anderson M, Thakral A, Dutt M, Wolf D, Morris M, Gombolay G

Objective: Neurosarcoidosis is rare and has different presentations in children. We conducted a systematic review to highlight common presentations, symptoms, disease course, imaging, and management of pediatric neurosarcoidosis.

Methods: A systematic review was conducted of publications from January 1, 1990 until August 30, 2021. Databases searched include: PubMed, Google Scholar, Lincoln Memorial University and Emory University Library Databases. The terms "neurosarcoidosis," "pediatric," and "child" were used and the Boolean "AND" was used to combine

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Case #	Age	Sex (M/F)	Neuro as first symptom	Cranial nerve*	Seizure	Headache	Other neuro symptom	Abn MRI brain	CSF WBC	CSF lymph %	CSF pro	Immune tx	Other tx	Improved (Y/N)
1	7	M	Y	-	Y	N	Weakness	Y	10	60	Abn	CS, IG, CYC, AZA	PHT	Y
2	17	F	N	-	N	Y		Y	7	91.7	Nml	MTX, ADM, IVMP, CS		Y
3	15	M	Y	-	N	Y	Tandem gait ataxia	Y	17	91	Abn	MTX, CS		Y
4	9	F	Y	VI	Y	Y	Truncal ataxia	Y	350	52	Abn	CS	PHT	Y
5	12	F	N	-	N	N		Y	Nml	ND	Nml	IVMP, CS	FUR, BIP	Y
6	17	M	Y	-	N	N	Nystagmus, hyperreflexia, vertigo	Y	21	ND	Abn	CS, IVMP		Y
7	12	M	Y	I	N	N	Mass lesion in brain	Y	ND	ND	ND	CS		Y
8	12	M	Y	-	Y	Y	Aphasia, confusion	Y	50	93	Abn	None		Y
9	9	F	Y	-	N	N	Weakness, pain, urinary dysfunction, hyperreflexia and upgoing toes, sensory deficits below T6	Y	ND	ND	ND	CS, MTX		Y
10	15	M	Y	VIII	N	N	tinnitus, abnormal tandem gait	N	Abn	ND	ND	CS, IVMP		Y
11	18	M	Y	-	Y	N		Y	ND	ND	ND	IVMP, CS		Y
12	11	M	N	-	Y	N		Y	20	90	Nml	CS	CBZ, PHT	Y
13	13	M	Y	-	N	N	Paresthesias	N	Nml	ND	Abn	CS		Y
14	13	F	Y	-	N	N	Hemiplegia and hemineglect	Y	ND	ND	ND	CS, IVMP		Y
15	16	M	Y	-	N	N	Pyramidal neurological signs and symptoms	Y	ND	ND	ND	MMF, MTX, CS		Y
16	15	F	N	I	N	N	-	Y	ND	ND	ND	CS	DDAVP, OCP, LT4	Y
17	13	M	N	IV	N	N	Vision changes	Y	ND	ND	Nml	CS		Y
18	14	F	Y	I	N	Y	Vision changes	Y	ND	ND	ND	CS, IVMP		Y
19	10	F	N	-	N	N	-	Y	ND	ND	ND	none		N/A
20	15	M	Y	I	N	N	-	Y	ND	ND	ND	MTX + INX; ADM		Y
21	3	M	N	-	Y	N	aphasia	Y	ND	ND	ND	CS, other+		Y
22	2	F	N	-	Y	N	encephalitis	N	ND	ND	Abn	CS, other+		Y
23	0.17	M	Y	-	Y	Y	Somnolence	N	ND	ND	ND	CS, other+		Y
24	3	F	N	-	Y	N	spasticity	N	ND	ND	ND	CS, other+		Y
25	16	F	N	-	N	N	-	Y	ND	ND	ND	CS		N
26	17	F	Y	VII	Y	Y	Meningitis, hydrocephalus, temporal lobe mass	N	ND	ND	ND	CS	PHT	Y
27	17	F	Y	VII	N	N		N	ND	ND	ND	CS		Y
28	14	M	Y	-	N	N		Y	ND	ND	ND			Y

TABLE (Continued)

Case #	Age	Sex (M/F)	Neuro as first symptom	Cranial nerve*	Seizure	Headache	Other neuro symptom	Abn MRI brain	CSF WBC	CSF lymph %	CSF pro	Immune tx	Other tx	Improved (Y/N)
							right sided hemiplegia, right sided hemianopsia and disarticulated speech					IVMP, MTX, CYC, RTX, ADM		
29	16	F	N	I	N	N	Clonus and focal deficits	Y	ND	ND	ND	IVMP, CS, INX + MTX		Y
30	8	M	Y	VI, VII, IX, X, XI, XII	N	Y	Vision problem, afferent pupillary defect, right hemiparesis	Y	Abn	ND	ND	None		N/A
31	15	M	Y	III, VI	N	Y	diplopia, rapid vision loss, weakness, areflexia	Y	Nml	ND	ND	IVMP, CS	DDAVP	Y
32	11	F	N	II	N	Y	Vision loss, ocular pain, weakness/myelopathy	Y	Nml	ND	Nml	IVMP, CS, MTX, CYC, RTX		Y
Total			20 (63)	13 (41)	10 (31)	10 (31)		25 (78)	9/12 (75)	6/6 (100)	7/12 (59)			

*Cranial nerve includes papilledema + other cranial nerves

+ Other immunosuppressants included methotrexate and azathioprine, but was not detailed for each patient.

M = male, F = female, Y = yes, N = no; Nml = normal, abn = abnormal, ND = not done, MRI: magnetic resonance imaging, CS: corticosteroid, IG: immunoglobulin, CYC: cyclophosphamide, MTX: methotrexate, IVMP: methylprednisolone, RTX: rituximab, MMF: mycophenolate mofetil, AZA: azathioprine, ADM: adalimumab, INX: infliximab PHT: phenytoin, CBZ: carbamazepine, BIP: bisphosphonate, FUR: furosemide, DDAVP: desmopressin, OCP: oral contraceptive, LT4: levothyroxine

"neurosarcoidosis" with "pediatric" or "child." Cases were included if they met the criteria of patients 18 years old or younger, published before 1990 in English, had a diagnosis of neurosarcoidosis. All duplicate cases, as those found in previous systemic reviews, were excluded.

Results: Twenty-two (69%) had systemic sarcoidosis with neurological involvement and nine (31%) were primary neurosarcoidosis. The most common organ systems involved were eyes (34%) including uveitis (22%) and conjunctivitis (10%), lymph nodes (34%), and lungs (28%). Brain MRI was abnormal in 25 (78%). Hypothalamic involvement was reported in 2/32 (6%). The most common neurological symptoms were cranial neuropathy (41%), seizures (31%), and headaches (31%). Other neurological symptoms included weakness, areflexia or hyperreflexia, spinal cord involvement, encephalopathy, and speech changes.

Conclusions: Neurosarcoidosis presents in different ways, which makes it challenging to diagnose. With neurosarcoidosis in children being so rare, additional research is needed, including a multi-center international collaboration. The goal of future research and case reporting should be to identify additional, and less invasive, techniques for diagnosis so allow for early intervention and even prevention of this debilitating disease.

Keywords: Rare Diseases, Infections/Neuroimmunology, Neuroimaging

209. A Case Series of Pediatric Hemifacial Spasms

Chu C (Los Angeles, CA), Reynolds T

Objective: Hemifacial spasm (HFS) is defined as a non-voluntary unilateral (rarely bilateral) spasm of muscles innervated by the facial nerve. Such spasms occur anytime, even persisting into sleep. HFS is an exceedingly rare disease in pediatrics, with cases becoming increasingly rare as age decreases. Reported HFS incidences among those less than 25-30 years of age have an estimated prevalence rate from 0.9 to 6.5%.The most common etiologies of HFS include neurovascular compression of the facial nerve at the root exit zone (REZ), due to a variety of causes, such as a vascular loop or arteriovenous malformation. Treatments are varied, with surgical microvascular decompression and botulinum toxin injections as the most documented success among adult cases, with variable reported results in children.

Methods: Herein, we present a case series report of three (five months, four year old, three year old) pediatric hemifacial spasm cases, with varied presentations. HFS can have significant ramifications on pediatric patients' quality of life, exacerbated by social situations and stress, which have led to documented cases of secondary social anxiety. Even after treatment through surgical decompression, patients still reported social adaptability problems, possibly owing to their long-term disease course, and continued need for psychiatric

follow-up. Furthermore, given the exceedingly rare cases of pediatric hemifacial spasms, each report is crucial to shed light on this disease to further improve the long-term management and improvement of diagnosis, to differentiate HFS from other movement disorders such as tics or psychogenic facial spasms.

Results: (please see above)

Conclusions: (please see above)

Keywords: Rare Diseases, Movement Disorders (including Cerebral Palsy), Education

210. COASY-related disorder: a new clinical phenotype and a potential biochemical clue for diagnosis

Johnson J (Rochester, NY), Rosati J, Lee B

Objective: Bi-allelic pathogenic variants in *COASY* have been associated with COASY-protein associated neurodegeneration (CoPAN) and pontocerebellar hypoplasia type 12 (PCH 12). CoPAN is clinically characterized by progressive, childhood-onset dystonia, and cognitive impairment with MRI findings similar to those seen in other disorders of neurodegeneration with brain iron accumulation (NBIA)[1, 2]. A second distinct phenotype characterized by prenatal-onset PCH with microcephaly, congenital contractures and early death has also been described [3]. We report two siblings with neonatal-onset severe hypotonia, respiratory failure and striking brain MRI findings, expanding the range of phenotypes associated with *COASY*-related disorder.

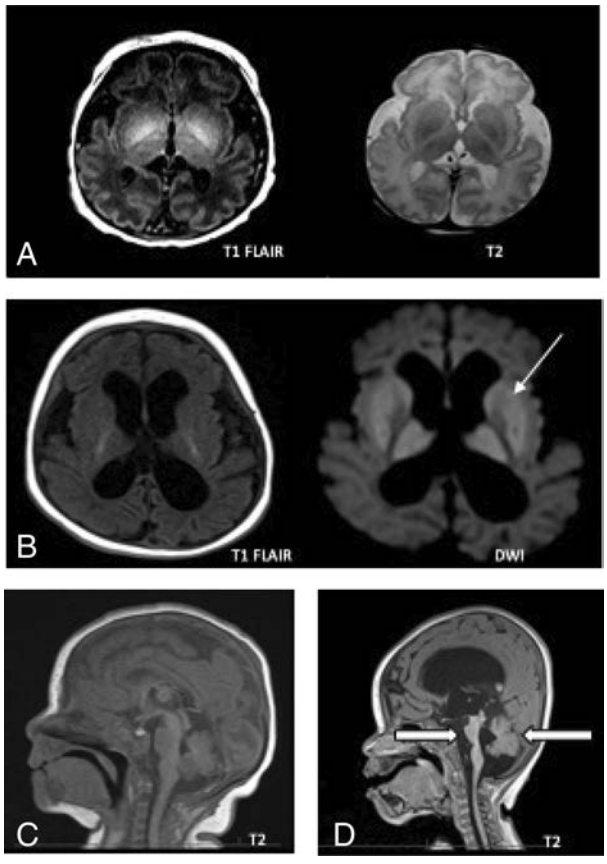

FIGURE 1: Serial brain MRI of sibling 1 demonstrating progressive cortical and brainstem atrophy at (a) birth and (b) 4 months of age. Persistent diffusion restriction in the bilateral basal ganglia is also seen (thin white arrows). Midline sagittal images comparatively at (c) birth and (d) 12 months of age demonstrates atrophy of the pons and cerebellum (thick white arrows), consistent with pontocerebellar hypoplasia. Abstract 210

Methods: Retrospective chart reviews were performed for two siblings with homozygous variants in *COASY* after written consent was obtained from parents. Studies performed as part of clinical care included newborn metabolic screening, serial brain MRI, metabolic and genetic testing, and in one patient, electromyography (EMG).

Results: Initial newborn screening results were suggestive of carnitine palmitoyltransferase (CPT1) deficiency but follow-up genetic testing (*CPT1A* del/dup analysis and sequencing) were negative. Serial brain MRIs show progressive diffuse parenchymal volume loss and persistent diffusion restriction in bilateral basal ganglia (Figure 1). EMG on one sibling showed profuse fibrillation potentials. Diagnosis was ultimately made by rapid genome sequencing in sibling 2 which identified homozygous variants (c.1664G>A) in the *COASY* gene.

Conclusions: *COASY*-related disorder should be considered in infants presenting with severe hypotonia, respiratory failure and suggestive brain MRI findings. Abnormal newborn screen acylcarnitine profiles with subsequently negative *CPT1A*testing may be a diagnostic clue.

Keywords: Rare Diseases, Genetics, Neurometabolic Disorders

References:

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211. Genome Sequencing Enables Precision Clinical Care in Genetic Leukoencephalopathies

Muirhead K (Philadelphia, PA), Hacker J, Gavazzi F, Woidill S, Sherbini O, Helman G, Kramer Golinkoff J, Velasquez G, Pizzino A, Schmidt J, Taft R, Vanderver A

Objective: Leukoencephalopathies are rare, heritable white matter disorders with variable presentations that encompass more than thirty distinct phenotypes. While recent studies have shown the efficacy of genome sequencing (GS) in this population, the impact of a GS diagnosis on clinical care has not yet been investigated.

Methods: The cohort consisted of 165 individuals with clinically ascertained leukoencephalopathies who were subsequently enrolled in the IRB-approved Myelin Disorders Biorepository Project and received clinical GS. Clinical data

from pre- and post-GS office notes was extracted and assessed for etiologic-specific screening, treatment and referrals to specialist providers after achieving a GS diagnosis to assess for outcomes of care.

Results: As a result of GS, 68 individuals (41%) achieved a positive test finding, 28 individuals (17%) had suspicious variants in a gene(s) of interest reported and 69 individuals (42%) had negative or non-diagnostic results. Of the 68 individuals who achieved a definitive diagnosis, 57 had sufficient clinical data available to investigate the impact of a GS diagnosis on clinical care. Within this group, 54 (95%) were referred to specialist providers for disease monitoring, 38 (67%) received additional targeted screening and 12 (21%) were eligible for disease-specific treatment.

Conclusions: Individuals with clinically ascertained leukoencephalopathies who achieved a diagnosis via GS received precision clinical care inclusive of specialist referral, screening and condition-specific treatment. These data suggest that GS should continue to be considered as a first-line test for this population. Future implementation studies may be necessary to understand barriers to adoption and widespread deployment.

Keywords: Rare Diseases, Demyelinating Disorders, Genetics

212. A phase 1, ascending dose study to assess the potential effects of trofinetide on QTc interval, safety and tolerability, and pharmacokinetics in healthy adults

Darwish M (San Diego, CA), Harlick J, Youakim J, DeKarske D, Stankovic S

Objective: Trofinetide is being developed as a treatment for Rett syndrome, a debilitating neurodevelopmental disorder. This study evaluated potential effects of trofinetide on QTc interval, ECG parameters, and safety and tolerability, in healthy adult subjects.

Methods: Healthy adult subjects (N=40) aged 18-45 years were randomized 1:1:1:1 to targeted single therapeutic (12 g) and supratherapeutic (18 g and 24 g) doses of trofinetide or placebo, and 400 mg of moxifloxacin (positive control for assay sensitivity) and placebo over 5 dosing periods (Figure 1). Concentration-QTc (C-QTc) modeling assessed QTc prolongation risk. Primary endpoints were to assess safety and evaluate the relationship between trofinetide blood concentrations and time-matched change in corrected QT interval using Fridericia's correction method (C-ΔQTcF; placebo-adjusted change [C-ΔΔQTcF]). Change from baseline in ECG parameters and trofinetide pharmacokinetics in blood were also assessed.

Results: Trofinetide underwent rapid systemic absorption (median T_{max} 2.5-3 hours), with initial rapid decline, then relatively slow elimination ($t_{1/2}$ ~11-12 hours). There was no clinically relevant effect on ECG parameters at trofinetide doses up to 24 g. C-QTc analysis showed the upper 90% 2-sided confidence bounds for C-ΔQTcF and C-ΔΔQTcF were <10 ms (threshold of concern for cardiac repolarization; Figure 2). Trofinetide was well tolerated. TEAEs were reported in 28/40 (70%) subjects, with diarrhea and nausea the most common (30% each) mostly at the supratherapeutic doses.

Conclusions: There was no evidence of cardiac repolarization or clinically meaningful effects on ECG parameters following therapeutic or supratherapeutic trofinetide doses. Trofinetide was well tolerated with no unexpected safety findings.

Keywords: Rare Diseases

213. High Quality Anatomical and Physiological MRIs in Young Children with Sickle Cell Disease

Lance E (Baltimore, MD), Lin Z, Gibbons B, Turney M, McIntyre T, McNeely S, Campbell A, Yang E, Lawrence C, Casella J, Tekes A, Lu H, Slifer K

Objective: Children with sickle cell disease (SCD), particularly children under 5 years of age, have a high risk of stroke and silent cerebral infarction (SCI). Sedation/anesthesia, necessary for diagnostic neuroimaging in this age group, may lead to complications. Our hypothesis is that obtaining high quality unsedated MRIs is feasible in young children with SCD using behavioral training.

Methods: Children with SCD under 5 years of age with no prior neurological history were enrolled in a prospective study recruited from local pediatric hematology clinics. MRIs were evaluated by a neuroradiologist and neurologist for diagnostic quality and by two physicists for quality metrics of

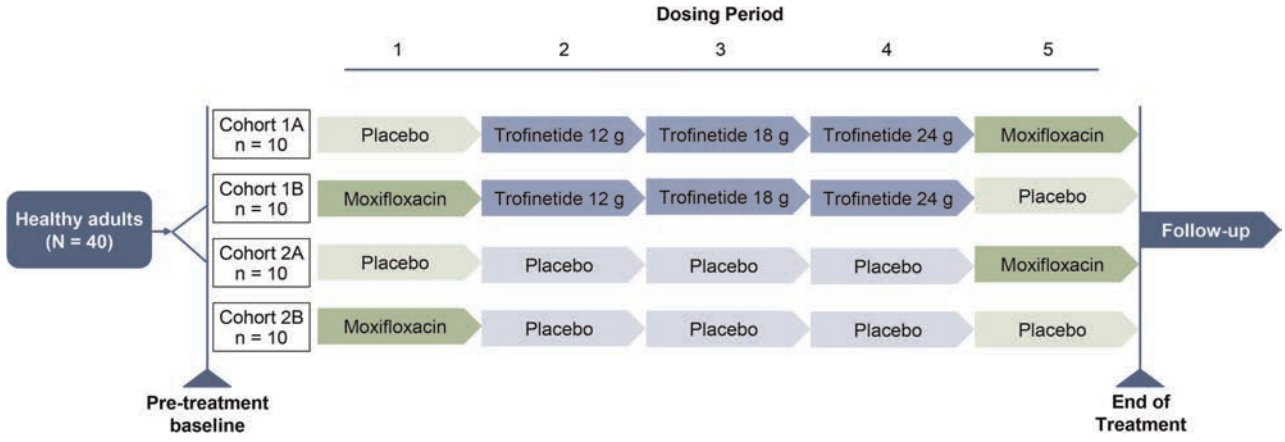

FIGURE 1. Schematic of study design. Abstract 212

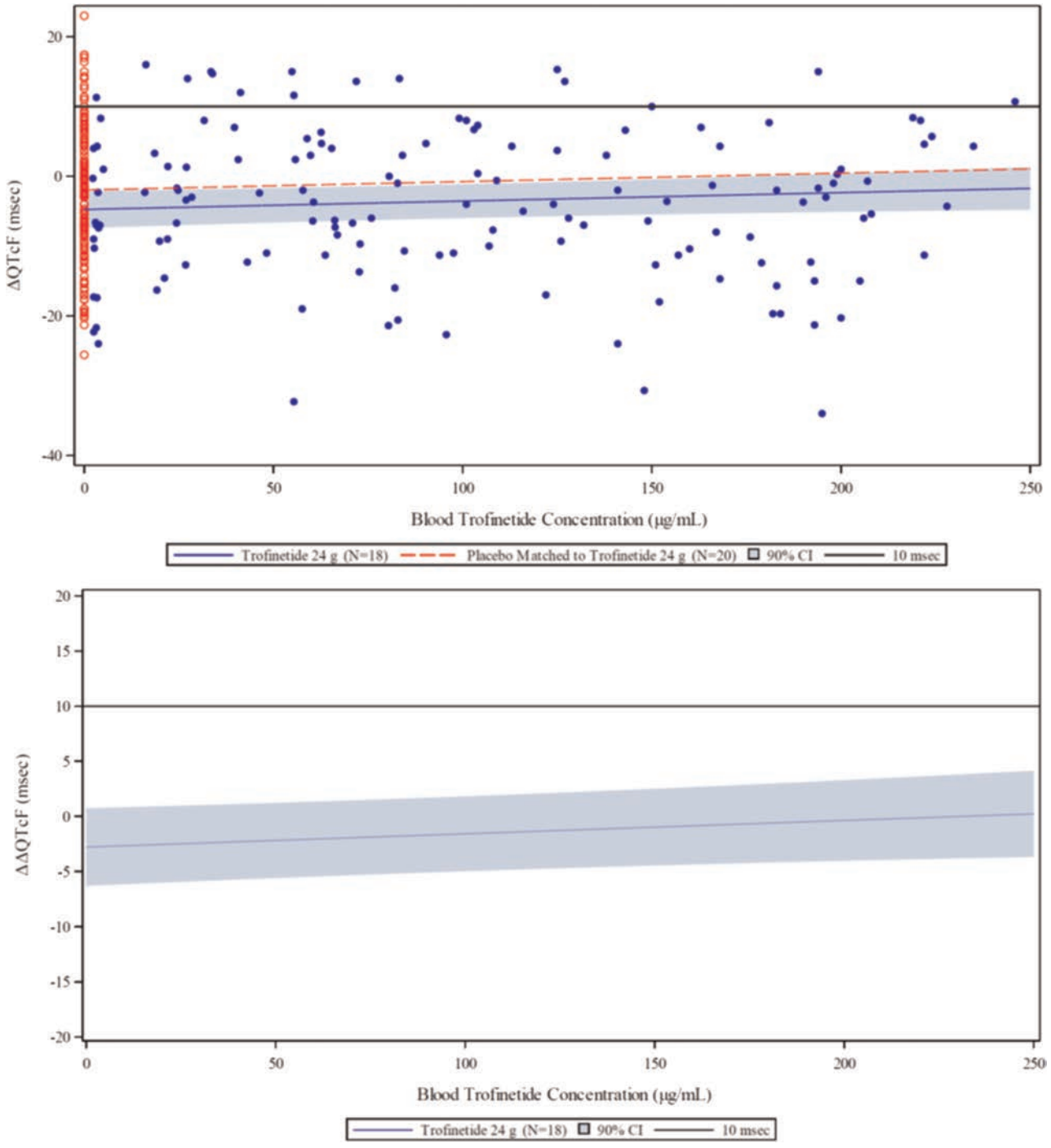

Figure 2. Change from time-matched baseline in QTcF (ΔQTcF; top) and placebo-adjusted ΔQTcF (ΔΔQTcF; bottom) blood concentration regressions with trofinetide 24 g. Abstract 212

T2-relaxation-under-spin-tagging (TRUST) and arterial spin labeling (ASL) MRI sequences.

Results: Twelve participants (mean age 4.93) completed initial MRIs before 7 years of age; three participants completed additional study exit MRIs (Table 1). Eight participants (67%) completed their initial MRIs before age 5 years. Two participants failed behavioral training. Six MRIs (50%) were abnormal.Fourteen out of 15 total MRIs (93%) met diagnostic quality criteria. One MRI was above the TRUST dR2 exclusion criteria, the 95% confidence interval of the T2 estimation. Three MRIs had elevated TRUST motion parameters, involving displacement across dynamics calculated from SPM realign. Thirteen MRIs (87%) received an excellent ASL quality rating by the ASL cloud pipeline. Mean ASL motion was 1.21 mm.

Conclusions: We obtained high quality neuroimaging in a majority of young children with SCD using behavioral training. Avoiding the risk of sedation has the potential to make

TABLE 1: MRI Training in Young Children with SCD. Abstract 213

Participant	Age at time of MRI Type of Sickle Cell Disease	Number of trainings	Notes
*1	4 years, 7 months HbSS	1	Participant had no difficulties with behavior at MRI training or during real MRI. Abnormal exit MRI.
2	4 years, 8 months HbSS	1	Participant had no difficulties with behavior at MRI training or during real MRI. Did not complete exit MRI due to lack of response to scheduling requests.
3	4 years, 9 months HbSS	2 (two weeks apart)	After first MRI training visit, the family was given instructions to practice at home and make it feel like a game. Normal initial and exit MRI.
4	4 years, 7 months HbSS	1	Participant completed MRI training the same day as real MRI and had no difficulties with behavior during either. Normal initial and exit MRI.
*5	4 years, 1 month HbSS	2 (one month apart)	Participant was apprehensive, but was able to complete the training at the 1st visit. A second training was done after discussion with parent. Parent sat in real MRI with participant due to excessive motion. Abnormal initial MRI.
6	3 years, 11 months HbSS	1	Study team member sat in real MRI with participant due to excessive motion after multiple verbal reminders and breaks. Normal initial and exit MRI.
7	4 years, 5 months HbSC	1	During first MRI training visit, participant was able to sit still for ~10 minutes. Participant was able to lie still during the real MRI for a majority of the time, however was restless at last 5 minutes of the scan and was unable to complete the last few images. Normal initial MRI.
8	5 years HbSS	7	Participant needed multiples trainings due to not liking the helmet cage over their head. They were motivated to complete the real MRI with a prize awaiting after the scan. COVID pandemic delayed scheduling. Normal initial MRI.
*9	6 years, 4 months HbSS	1	Technical difficulties occurred during the MRI training. Participant did not like the sounds but was able to remain still, especially when the movie and headphones were working properly. Real MRI went smoothly with movie playing. COVID pandemic delayed scheduling. Abnormal exit MRI.
*10	6 years, 11 months HbS-β^+ thalassemia	3	Patient had significant difficulties with behavior at initial MRI trainings. Further training planned with both trainers were delayed due to the pandemic. Patient passed first MRI training since the pandemic and completed real MRI within 3 months with no difficulties. Abnormal exit MRI.
*11	5 years, 5 months HbSS	1	Participant had no difficulties with behavior at MRI training or during real MRI. COVID pandemic delayed scheduling. Abnormal initial MRI.
*12	4 years, 6 months HbSS	2	Participant had no difficulties with behavior at MRI training or during real MRI. Abnormal initial MRI.

TABLE 1 (Continued)

Participant	Age at time of MRI Type of Sickle Cell Disease	Number of trainings	Notes
~13	5 years, 7 months HbSS	0	Participant was receiving behavioral therapy for clinical purposes and was not cleared to start study MRI training due to severe behavioral issues. Received clinical MRI under anesthesia. Has now aged out of study protocol (> 7 years of age).
~14	Not completed at this time HbS-β^+ thalassemia	2	Participant is still undergoing behavioral training but was unable to pass training prior to 5 years of age.

*abnormal initial or exit MRI ~did not complete study MRI

early diagnosis and intervention more practical in this population.

Keywords: Rare Diseases, Neuroimaging, Stroke (including other Vascular Disorders)

STROKE (INCLUDING OTHER VASCULAR DISORDERS)

214. Model development for automatic segmentation of chronic stroke lesions

Verma K (Austin, TX), Kumar S, Paydarfar D

Objective: Lesion studies are crucial in establishing brain-behavior relationships, and accurately segmenting the lesion represents the first step in achieving this. Manual lesion segmentation is the gold standard for chronic strokes. However, it is labor-intensive, subject to bias, and limits sample size. Therefore, our objective is to develop an automatic segmentation algorithm for chronic stroke lesions on T1-weighted MR images.

Methods: To train our model, we utilized an open-source dataset: ATLAS v2.0 (Anatomical Tracings of Lesions After Stroke). We partitioned the dataset of 655 T1 images with manual segmentation labels into five subsets and performed 5-fold cross-validation to avoid overfitting of the model. We used a deep neural network architecture (figure 1) for model training.

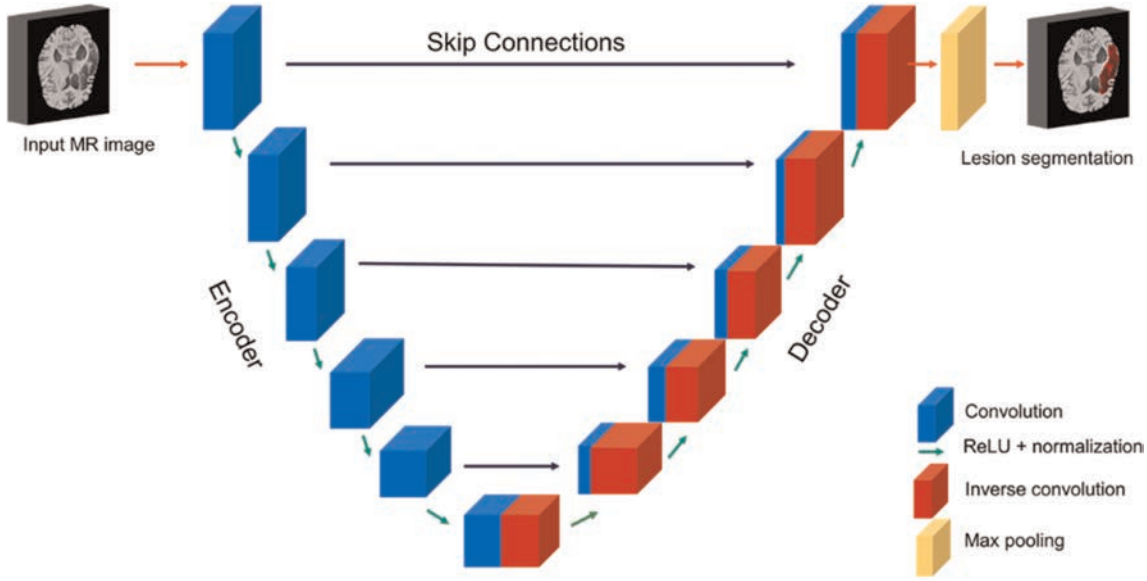

Figure 1: Schematic representation of 3D-UNet architecture

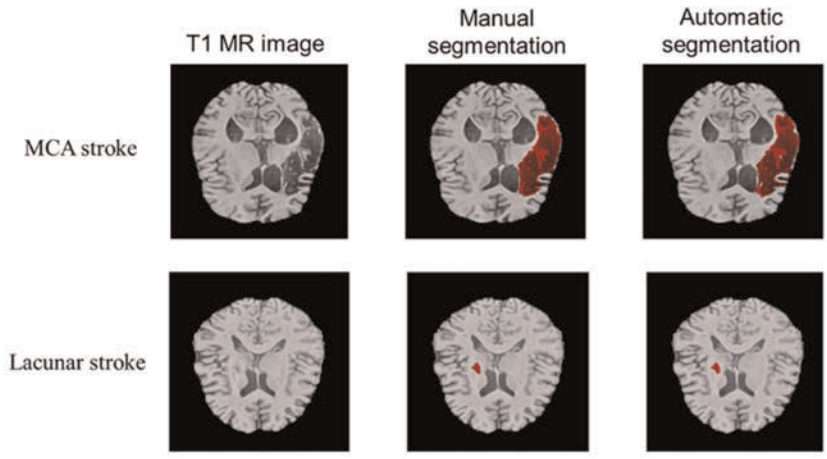

Figure 2a: Model performance examples

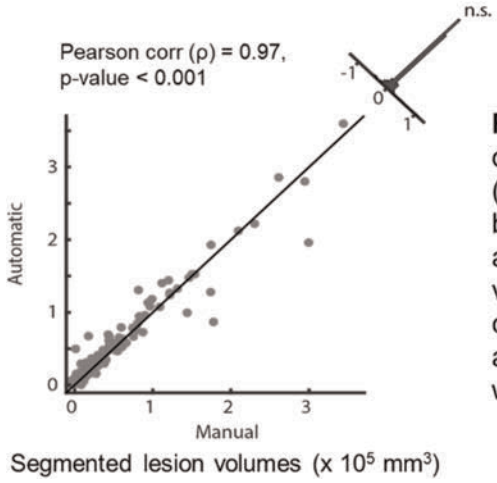

Figure 2b : A scatter plot with a histogram of differences shows no significant difference (Wilcoxon rank-sum test, p-value = 0.84) between the lesion volumes from manual and automated segmentation across cross-validation folds. Pearson correlation coefficient (ρ) between the manual and automatically segmented lesion volumes was 0.97(p-value < 0.001).

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Results: To evaluate the model performance, we used three metrics that pertain to diverse aspects of volumetric segmentation including shape, location, and size (figure 2a). Dice similarity coefficient (DSC) compares the spatial overlap between manual and machine segmentation. The average DSC was 0.65 (0.61- 0.67; 95% bootstrapped CI). Average symmetric surface distance (ASSD) measures contour distances between the two segmentations. ASSD between manual and automatic segmentation was 12mm. Finally, we compared the total lesion volumes. The Pearson correlation coefficient (ρ) between the manual and automatically segmented lesion volumes was 0.97(p-value < 0.001) (figure 2b).

Conclusions: We present the first automated segmentation model trained on a large multicentric dataset. Overall, our model enabled objective and automated assessment of chronic lesions secondary to stroke in vascular neurology at high throughput and will ultimately serve to improve clinical decision making.

Keywords: Stroke (including other Vascular Disorders), Neuroimaging, Neuroscience

215. Vascular Endothelial Dysfunction, Cognition and Stroke in Early Life Study (VECSELS)

Vu M (Toronto, ON, Canada), Walker K, Dlamini N

Objective: The first objective of the study is to demonstrate that children with congenital heart disease (CHD) and a history of arterial ischemic stroke (AIS) have abnormal perfusion in the contralesional hemisphere, and these observations are associated with specific cognitive impairments. The second objective is to demonstrate a spectrum of vascular endothelial dysfunction (VED) associated with cognitive function among children with CHD with and without a history of AIS.

Methods: This study has two arms. The cross-sectional arm addresses the first objective and compares magnetic resonance perfusion using the apparent diffusion coefficient (ADC) obtained for each subject and cognitive outcomes in a cohort of cardiac stroke patients. The prospective arm of the study addresses the second objective by assessing VED. VED and neuropsychological evaluation scores will be compared between patients with CHD with and without a history of AIS.

Results: Preliminary results from 3 patients in the cardiac stroke cohort and 3 age-matched controls in the cross-

sectional arm show that the patient cohort scored below average on most outcome sub-tests. Interestingly, processing speed (M=87.7, SD=26.4) and global executive composite (M=61, SD=13.5) scores display a spectrum of impairment that correspond to a spectrum of ADCs. The ADC values ($mm^2/s \times 10^{-3}$) in both the ipsilesional (M=0.83, SD=0.03) and contralesional (M=0.84, SD=0.05) hemisphere of cardiac stroke patients were elevated compared to controls.

Conclusions: This preliminary data suggests that specific cognitive outcomes may be moderated by global hypoperfusion and a gradient of VED in CHD patients with and without a history of AIS.

Keywords: Stroke (including other Vascular Disorders), Neuroimaging, Neuroscience

216. Vertebral artery configuration as a risk factor for dissection in Children

Laheji F (Dallas, TX), Dowling M, Braga B

Objective: The pathogenesis of pediatric vertebral artery dissection(VAD) is poorly understood.We previously described 2 configurations of the vertebral artery(VA) at the V3 segment:type A & type B depending on the angle of curvature of V3.All patients with V3 dissection who were diagnosed with bow hunter syndrome were found to have type B conformation.The aim of this study was to investigate these VA conformations.We hypothesized that type B was more prevalent in patients with VAD.

Methods: We conducted a retrospective chart review at Children's Medical Center(UTSW).We reviewed MRA or IR angiogram of 49 patients,19 with VAD(nontraumatic) & 30 controls. The V3 segment was classified into type A (presence of obtuse angle or no acute angulation) & type B (two consecutive acute angles, <110 degrees).Chi-square test was used for analysis.

Results: In 19 patients with VAD,15 were male,average age was 12.3 years.Type B was present in 79% of total dissected vessels(19/24) & type A in 20.83%(5/24).17 of these patients had a rotational angiogram with 12/17 showing vertebral artery compression or occlusion diagnostic of bow hunter syndrome and underwent a C1C2 fusion. In the control group,14 were male, average age was 13.9 years, & 51 vertebral arteries were available for review. Configuration type B was present in 25.5%(13/51) and type A in 74.5% (38/51). TypeB had a significantly higher prevalence in the V3 dissection group than controls (p= < 0.001).

Conclusions: The type B (acute angle) configuration of V3 seems to be a risk factor for VAD and warrants further investigation with a dynamic angiogram in the right setting.

Keywords: Stroke (including other Vascular Disorders), Neuroimaging

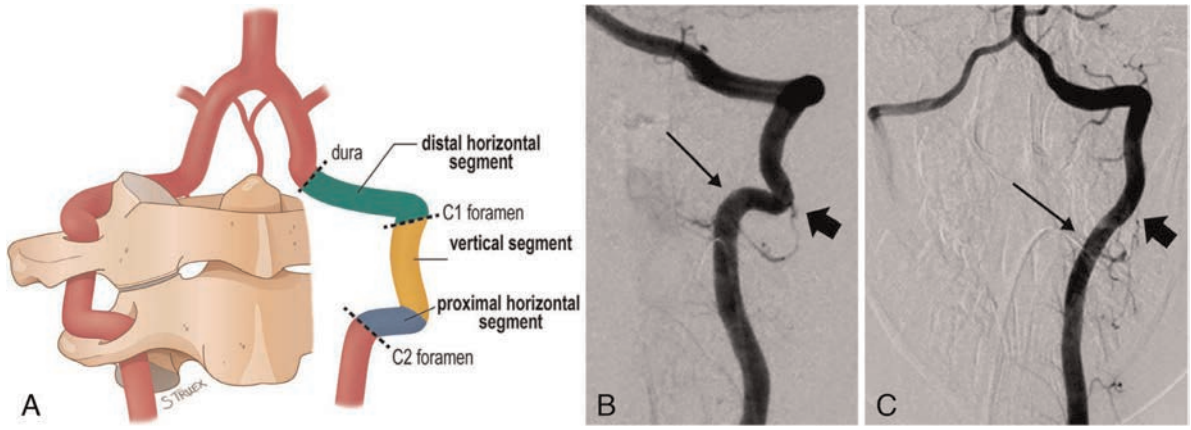
217. Role of Ethno-cultural Backgrounds in Childhood Stroke Outcomes

Pai A (Toronto, ON, Canada), Nichol D, MacGregor D, Bhathal I, Moharir M, To T, Ertl-Wagner B, Kassner A, deVeber G, Dlamini N

Objective: To characterize the role of ethnic and immigrant backgrounds in predicting outcomes following childhood arterial ischemic stroke in the most populated province of Canada, hypothesizing that ethnic and immigrant backgrounds influence outcome after stroke.

Methods: Measures of ethnic and immigrant backgrounds included neighbourhood-level data on the proportion of non-White and non-Indigenous residents and the proportion of immigrants who arrived in Canada within the past five years. Patients' postal codes were categorized as living in least, moderate, or most diverse neighbourhoods by using validated mapping techniques. Demographic, clinical, and radiological outcome predictors were examined along with measures of ethnic and immigrant backgrounds.

Results: Childhood arterial ischemic stroke patients (N = 234) with stroke onset between January 1, 2004 and December 31, 2019 at a Level 2 (comprehensive) stroke centre were included. Predictors of poor outcome at 5 years post-onset of stroke included residence in neighbourhoods with the lowest levels of diversity (OR 5.77, $p < 0.05$) and involvement of both the anterior and posterior circulation (OR 5.36,



a) Schematic drawing of the vertebral artery showing its V3 segments and subsegments and their relations to the C1 and C2 Foramina. b) Confirmation Type B c) Confirmation Typa A Braga BP, SilleroR, Pereira RM, UrgunK, Swift DM, Rollins NK, HoggeAJ, Dowling MM. Dynamic compression in vertebral artery dissection in children: apropos of a new protocol. Childs NervSyst. 2021 Apr;37(4):1285-1293. doi: 10.1007/s00381-020-04956-1. Epub2020 Nov 6. PMID: 33155060. Abstract 216

$p < 0.05$). Although, moderate-to-severe deficits at presentation were not associated with poor outcome at 5 years post-onset of stroke, however, a trend was observed (OR 4.44, $p = 0.05$).
Conclusions: The association between the level of diversity and poor outcome 5 years post-onset of stroke may be applicable to allocation of healthcare resources within the second-most diverse province in Canada. Thus, future studies exploring post-stroke outcomes should also consider ethnic and immigrant backgrounds within the broader social determinants of health.
Keywords: Stroke (including other Vascular Disorders), Equity, Diversity, Inclusion

218. Validation of the TelePSOM to Assess Recovery and Function After Neonatal and Childhood Stroke

Gatti J (Baltimore, MD), Malone L, Gottesman R, Sun L

Objective: To validate a modified version of the Pediatric Stroke Outcome Measure (PSOM) for telehealth administration.
Methods: Patients 2-18-years-old with imaging-confirmed perinatal or childhood stroke were recruited. PSOM scores were documented at in-person clinical encounters. Participants completed a modified neurologic exam within 90 days of in-person examination using a two-way audiovisual platform, and modified

Table 1: Inter-Rater Reliability for Total and Domain PSOM Scores. Abstract 218

	ICC Coefficient^	95% CI		p-value
Total PSOM Score				
TelePSOM Raters	0.96	0.84-0.99		**< 0.001**
PSOM vs. TelePSOM	0.93	0.83-0.98		**< 0.001**
	% Agreement	**Weighted Kappa†**	**Standard Error**	**p-value**
Left Sensorimotor				
TelePSOM Rater #1 vs Rater #2	100.0	1.00	0.24	**<0.001**
TelePSOM Rater #1 vs PSOM	97.0	0.93	0.24	**<0.001**
TelePSOM Rater #2 vs PSOM	97.0	0.93	0.24	**<0.001**
Right Sensorimotor				
TelePSOM Rater #1 vs Rater #2	97.0	0.85	0.25	**<0.001**
TelePSOM Rater #1 vs PSOM	91.0	0.60	0.20	**0.002**
TelePSOM Rater #2 vs PSOM	94.0	0.93	0.24	**<0.001**
Expressive Language‡				
TelePSOM Rater #1 vs Rater #2	100.0	--	--	--
TelePSOM Rater #1 vs PSOM	93.9	--	--	--
TelePSOM Rater #2 vs PSOM	93.9	--	--	--
Receptive Language‡				
TelePSOM Rater #1 vs Rater #2	100.0	--	--	--
TelePSOM Rater #1 vs PSOM	93.9	--	--	--
TelePSOM Rater #2 vs PSOM	93.9	--	--	--
Cognitive/Behavioral				
TelePSOM Rater #1 vs Rater #2	87.9	0.59	0.26	**0.011**
TelePSOM Rater #1 vs PSOM	94.0	0.81	0.27	**0.002**
TelePSOM Rater #2 vs PSOM	87.9	0.61	0.27	**0.012**

^Interpretation of ICC coefficient: <0.5, poor reliability; 0.5-0.75, moderate reliability; 0.75-0.9, good reliability; 0.9-1.0, excellent reliability
†Interpretation of kappa coefficient: 0.0-0.2, slight reliability; 0.2-0.4, fair reliability; 0.4-0.6, moderate reliability; 0.6-0.9, substantial reliability; 0.9-1.0, near perfect reliability
‡Unable to calculate weighted kappa coefficients for expressive and receptive language due to limited heterogeneity in these outcomes in the cohort. Percent agreement demonstrates high concordance among raters.

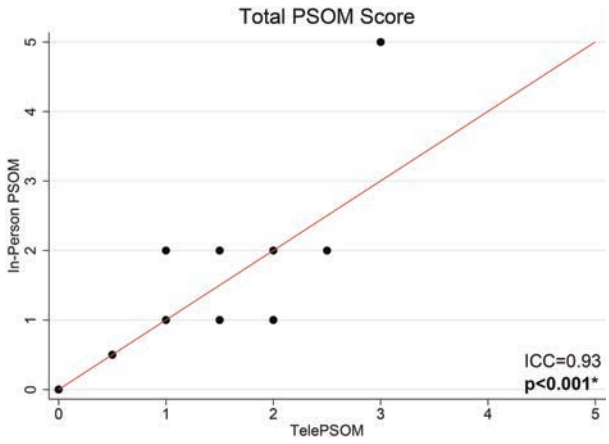


FIGURE 1: Scatterplot depicting TelePSOM ratings (x-axis) and in-person PSOM ratings (y-axis) for the total PSOM score. Red line depicts perfect agreement (y=x). PSOM, Pediatric Stroke Outcome Measure. Abstract 218

PSOM ("TelePSOM") scores were documented by two independent raters. Intraclass correlation (ICC) estimates based on absolute agreement and a two-way random-effects model were used to assess inter-rater reliability between total scores for 1) both TelePSOM raters and 2) PSOM and TelePSOM raters. Inter-rater reliability for individual domains was assessed using percent agreement and weighed kappa coefficients.

Results: To date, 11 participants have undergone a TelePSOM exam: 8 (73%) with childhood and 3 (27%) with perinatal stroke; 10 arterial (91%) and one venous (9%) ischemic stroke. The median age at TelePSOM exam is 6.4 years (IQR 4.4-10.1). Median time from in-person to TelePSOM exam is 7 days (IQR 6-18). Median in-person PSOM score is 1.0 (IQR 0.5-2.0; range 0-5.0). The TelePSOM exhibits excellent inter-rater reliability (total PSOM ICC 0.96, 95% CI: 0.84-0.99, p<0.001) and predicts the in-person PSOM score with excellent reliability (total PSOM ICC 0.93, 95% CI: 0.83-0.98, p<0.001).

Conclusions: The TelePSOM predicts in-person PSOM score with excellent reliability. Recruitment to more definitively validate the TelePSOM is ongoing. If validated, the TelePSOM will enable the PSOM to be used as a measurement across in-person and telehealth visits and facilitate outcomes assessment in pediatric stroke clinical research.

Keywords: Stroke (including other Vascular Disorders)

TRANSLATIONAL/ EXPERIMENTAL THERAPEUTICS

219. Germline and therapeutic suppression of Tubulin beta 4A rescues H-ABC leukodystrophy in mice

Hacker J (Philadelphia, PA), Sase S, Woidill S, Takanohashi A, Padiath Q, Marsh E, Vanderver A

Objective: Classical Hypomyelination and Atrophy of Basal ganglia and Cerebellum (H-ABC) is a rare leukodystrophy associated with p.Asp249Asn mutation in gene tubulin alpha 4A (*TUBB4A*). Assessment of whether Tubb4a mutations cause a toxic-gain-of function is important in understanding whether *Tubb4a* suppression is a potential therapy for H-ABC.

Methods: The study groups consisted of transgenic mouse models with variable amounts of wild type and mutant Tubb4a – (1) the H-ABC mouse model ($Tubb4a^{D249N/D249N}$); (2) germline Tubb4a deletion ($Tubb4a^{KO/KO}$), compound heterozygotes (3) $Tubb4a^{D249N/KO}$ and (4) $Tubb4a^{D249N/WT}$. Models were characterized to assess the dose associated pathology of Tubb4a mutations. We additionally screened antisense oligonucleotides (ASOs) that suppress overall Tubb4a and performed single intracerebroventricular (ICV) administration of ASOs in postnatal $Tubb4a^{D249N/D249N}$ mice and controls.

Results: We confirm that $Tubb4a^{KO/KO}$ mice exhibit normal motor function, with no myelination or neuronal deficits. $Tubb4a^{D249N/KO}$ mice have improved motor deficits, reduced myelination defects, decreased neuronal loss in the cerebellum and increased survival (~P108-110) relative to $Tubb4a^{D249N/D249N}$ mice (n=15-20, p<0.001). $Tubb4a^{D249N/WT}$mice have a further reduced phenotype with prolonged survival and limited myelination defects. A single ICV ASO administration postnatally improved motor deficits and survival in H-ABC ($Tubb4a^{D249N/D249N}$) micecompared to controls (n=5, p<0.01). Additionally, current Tubb4a ASO design demonstrate tolerability.

Conclusions: *Tubb4a* mutation causes toxic gain-of-function. Disease severity correlates with overall expression of mutant Tubb4a and relative preservation of wild-type tubulin. This report is first to provide feasibility of pre-clinical suppression of overall Tubb4a as a disease modifying treatment for H-ABC.

Keywords: Translational/Experimental Therapeutics, Neuroscience, Movement Disorders (including Cerebral Palsy)

220. Antisense oligonucleotide as possible therapeutic agent in DARS2-related leukodystrophy

Amanat M (Baltimore, MD), Guang S, Baek S, Ying M, Fine A, Nemeth C, Fatemi A

Objective: Most patients with leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) have compound heterozygous mutations in the mitochondrial Aspartyl-tRNA synthetase gene, *DARS2*, with one mutation within splicing site of intron 2 resulting in lacking exon 3 in mature mRNA. Antisense oligonucleotides (ASOs) alter gene expression using different mechanisms (Figure 1). This study aimed to assess the role of ASOs in modulating *DARS2* splicing to increase exon 3 inclusion.

Methods: Two ASOs were used to transfect induced pluripotent stem cells (iPSCs), derived from two LBSL patients and two healthy controls. The underlying mechanism included inhibition of intronic splicing silencer (ASO1) or inducing exonic splicing enhancer (ASO2). The combination of ASOs (Cocktail) was also used. Three doses of oligonucleotides

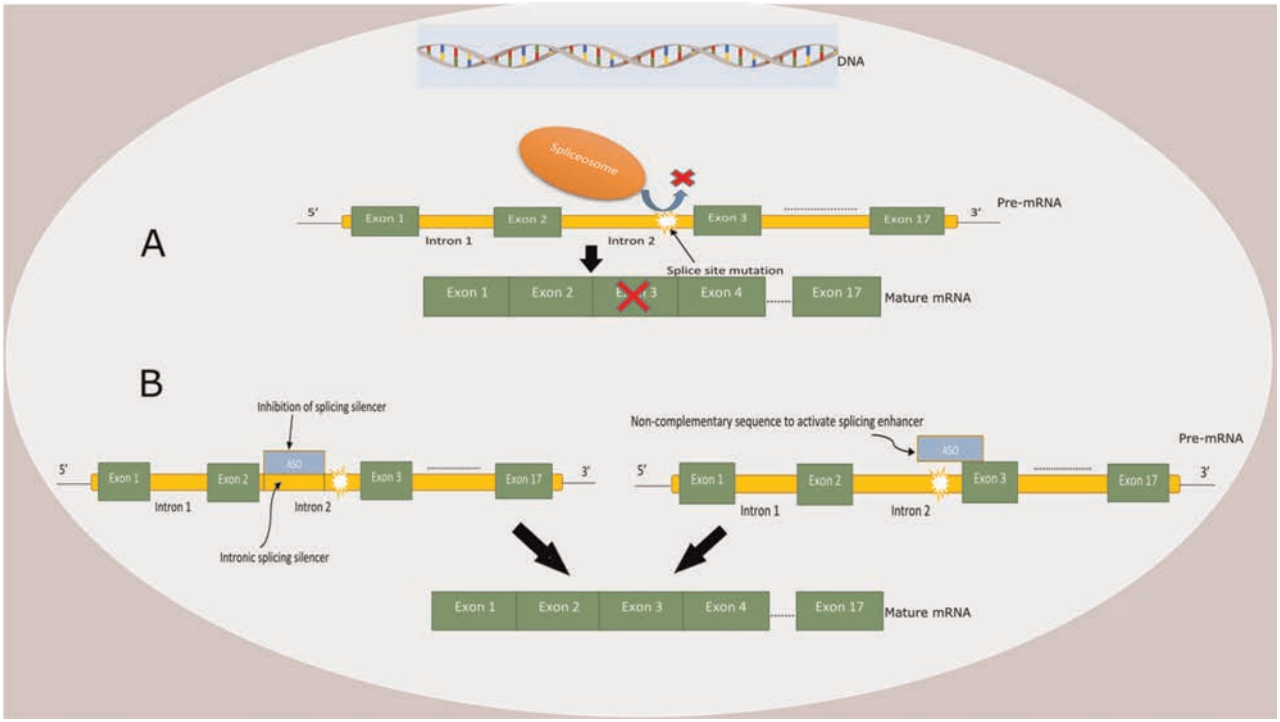


FIGURE 1. (A) Most patients with LBSL have one mutation in the splicing site placed in DARS2 intron 2 that inhibits the inclusion of exon 3 in mature mRNA. (B) Oligonucleotides can increase exon 3 inclusion with targeting splicing silencer or activating splicing enhancer. Abstract 220

(250ng, 500ng, and 1000ng) were administered. RNA extraction, rt-qPCR, and agarose gel were conducted to evaluate the level of *DARS2* with/without exon 3.

Results: Both ASOs and their combination increased the inclusion and reduced the exclusion of exon 3 in all cell lines. The expression of *DARS2* including exon 3 in LBSL1 iPSCs increased up to three-folds after adding intron- and exon-targeted ASOs, and over four-fold with Cocktail ASOs, compared to baseline control1 *DARS2* expression. Expression of *DARS2* including exon 3 in LBSL2 was similar to baseline

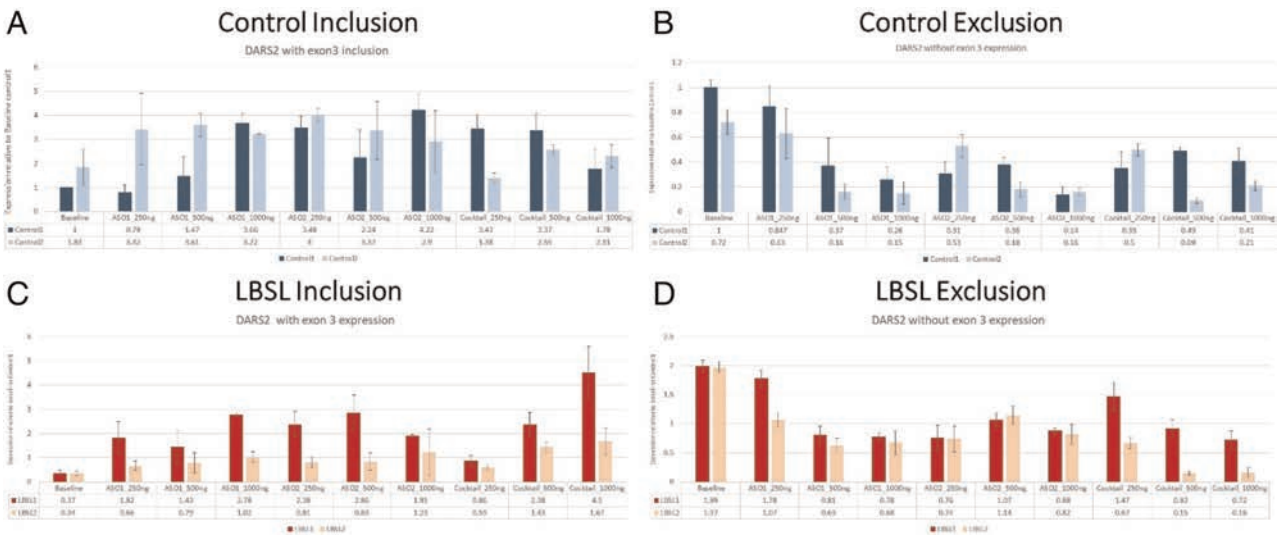


FIGURE 2. (A) Expression of *DARS2* including exon 3 in two iPSC control cell lines relative to baseline control1 *DARS2* expression (B) Expression of *DARS2* without exon 3 in two iPSC control cell lines relative to baseline control1 *DARS2* expression (C) Expression of *DARS2* including exon 3 in two iPSC LBSL cell lines relative to baseline control1 *DARS2* expression (D) Expression of *DARS2* without exon 3 in two iPSC LBSL cell lines relative to baseline control1 *DARS2* expression. Abstract 220

level of control1 after adding intron- and exon-targeted ASOs, and about 1.5-fold higher with Cocktail ASO (Figure 2).

Conclusions: Oligonucleotides are effective to modulate mRNA exon 3 in LBSL. Further assessments are needed to evaluate the safety and efficacy of ASOs in in-vitro and in-vivo studies.

Keywords: Translational/Experimental Therapeutics, Neuroscience, Demyelinating Disorders

221. A Prospective, Longitudinal, Observational Clinical Trial in Individuals with Angelman syndrome to Enable Endpoint Development for Interventional Trials (FREESIAS)

Berry-Kravis E (Chicago, IL), Bacino C, Bichell T, Bird L, Jeste S, Ochoa C, Rotenberg A, Sadhwani A, Shen M, Tan W-H, Wheeler A, Bustamante M, Crean B, Komorowski R, Krishnan M

Objective: Angelman syndrome (AS) is a neurodevelopmental disorder caused by absence of functional UBE3A, characterized by severe cognitive and motor impairment, lack of speech and other symptoms. Currently, there are no established feasible and suitable endpoints to holistically measure meaningful change in AS. FREESIAS aimed to identify such measures.

Methods: We followed 55 individuals with AS (<5 years: n=16; 5-12 years: n=27; >18 years: n=12; deletion: n=40, non-deletion: n=15)) and 20 typically developing children (1-12 years) in FREESIAS, for one year. The study tested a wide range of clinical outcome assessments (COAs), overnight electroencephalography (EEG), and digital health technologies (DHTs) across key AS characteristics, performed in-clinic and at-home.

Results: The completion-rate for the majority of COAs was high with >94% at the first and >80% at the second clinic visit. Adherence to and feasibility of the different DHTs varied by assessment. Only 85 (of 210) overnight-EEGs were performed, largely related to the Covid-pandemic. COA results were compatible with previously published natural history data, showing minimal developmental gain between the 5-12 and >18 year groups on the Vineland-3 and Bayley-III, and better overall performance on virtually all measures in the non-deletion group. The AS EEG phenotype of excess delta-band power was found in the home EEG and fell well within the range of previous reports.

Conclusions: FREESIAS data will support measure choice to holistically measure change in future interventional clinical trials in AS. The study identified suitable COAs, overnight EEG and DHTs, yet simultaneously illustrated the need for improved measures to assess change in AS.

Keywords: Translational/Experimental Therapeutics, Cognitive/Behavioral Disorders (including Autism), Genetics

222. Neurocognitive outcomes after elivaldogene autotemcel (eli-cel, Lenti-D) in the ALD-102 gene therapy study

Pierpont E (Minneapolis, MN), King K, Duncan C, Eichler F, Sevin C, Kühl J, Thrasher A, Williams D, Sieker J, Pan L, Dietz A, Orchard P

Objective: Eli-cel is an investigational gene therapy treatment for cerebral adrenoleukodystrophy (CALD). Previously reported efficacy outcomes from the ALD-102 study include 90.6% major functional disability-free survival at month 24, with median follow-up of 42.3 months. Safety results showed possibly related adverse events of viral cystitis (n=1) and vomiting (n=2). Three cases of myelodysplastic syndrome have been observed in ALD-102 and ALD-104. Herein are newly reported neurocognitive outcomes for ALD-102.

Methods: ALD-102 trial participants (followed long-term in LTF-304) completed neurocognitive assessment of

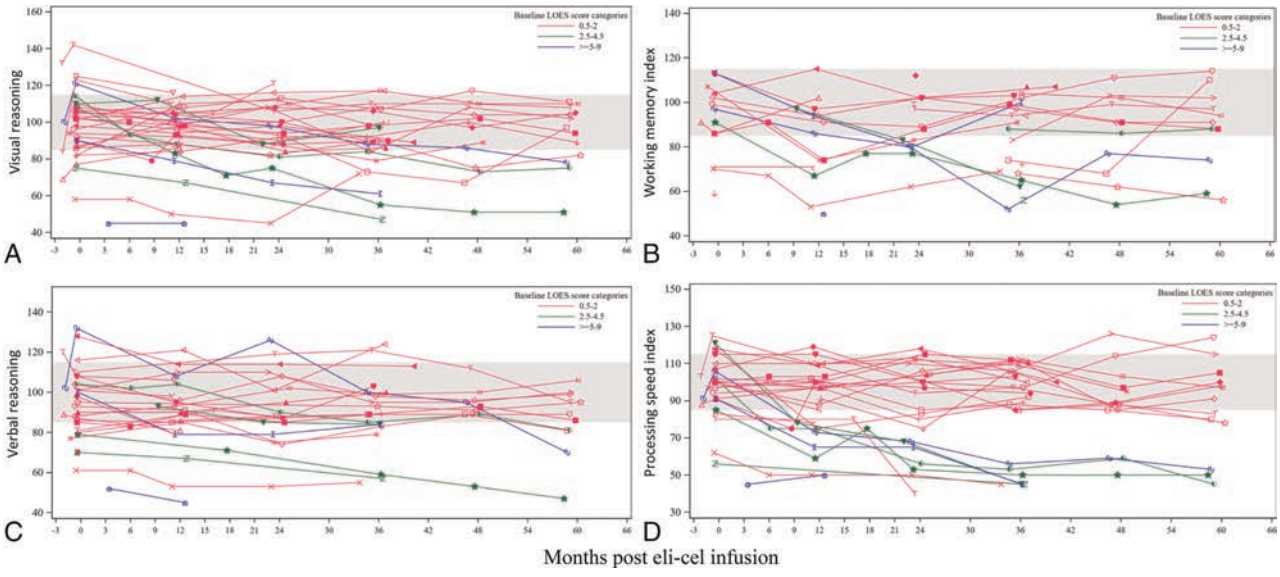


FIGURE 1: Longitudinal plots of Wechsler scales including (a) visual reasoning, (b) working memory, (c) verbal reasoning, and (d) processing speed, with participants identified by baseline Loes score (each line represents one participant, shaded gray area represents the normative mean plus or minus one standard deviation). Abstract 222

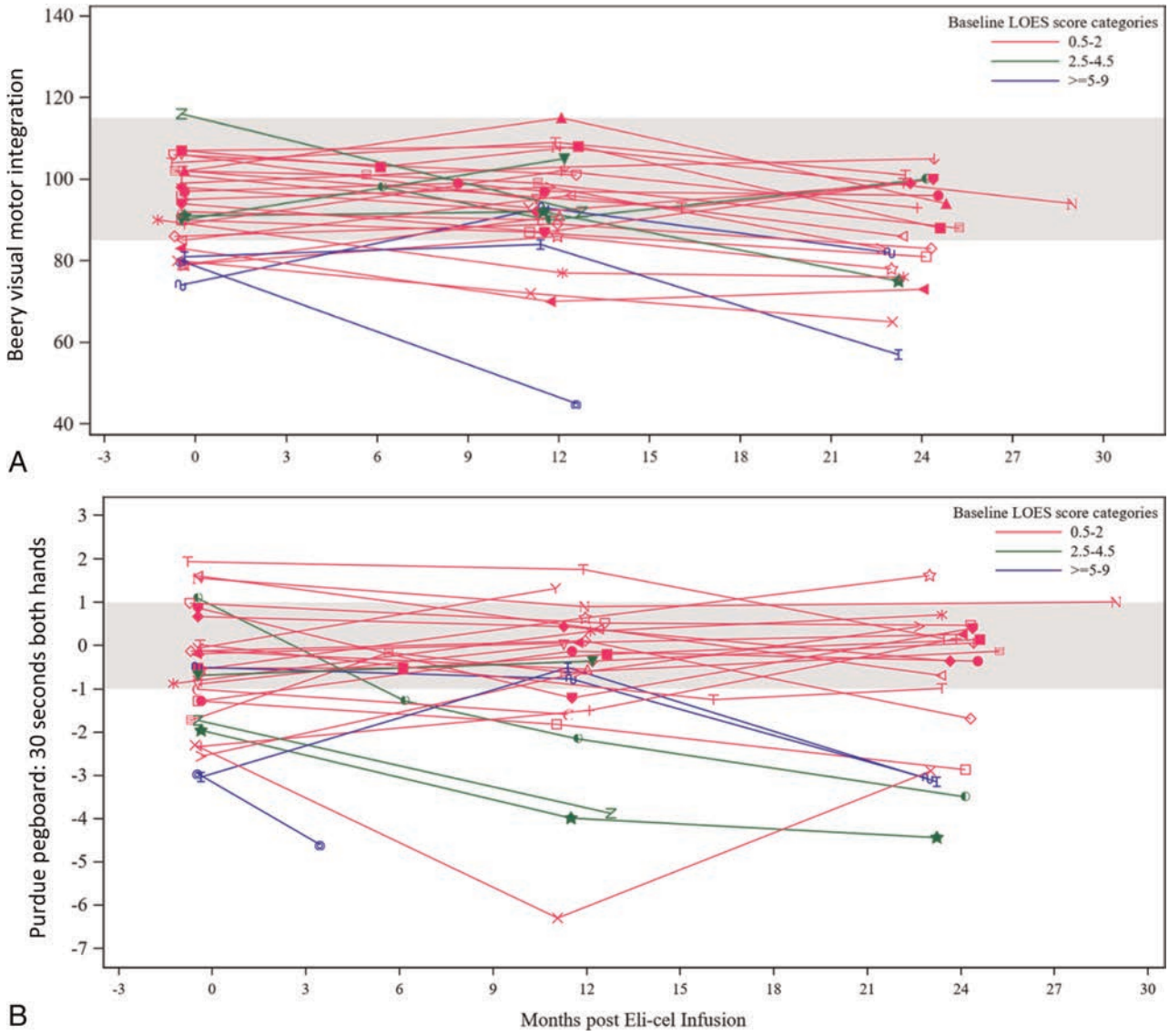


FIGURE 2: Longitudinal plots of (a) Beery VMI, and (b) Purdue pegboard, with participants identified by baseline Loes score (each line represents one participant, shaded gray area represents the normative mean plus or minus one standard deviation). Abstract 222

intellectual functioning (Wechsler scales), visual-motor integration (VMI), and fine motor dexterity (Purdue Pegboard) at baseline and in follow-up. Data presented as: median (range).

Results: Participants (n=32) were 6 (3-13) years old at screening with Loes MRI severity score of 2 (1-9) at baseline. Over 42.3 (13.4-83.7) months post-treatment, neurocognitive measures generally appeared stable. Most favorable neurocognitive outcomes occurred among boys with Loes ≤2 (25/32). In this subset, visual reasoning was within normal limits (i.e. score of ≥85) in 23/25 (92%) patients, with a normal processing speed in 19/25 (76%) patients at most recent evaluation. Similar to the experience in allotransplantation, patients with Loes >2 at baseline (7/32) were more likely to experience neurocognitive deficits. Two participants had early study discontinuation and received subsequent allogeneic stem cell transplantation.

Conclusions: Patients with very low MRI severity (Loes ≤2) and healthy neurocognitive function at baseline are likely to maintain neurocognitive stability after eli-cel gene therapy, reinforcing previous data showing that earlier treatment is associated with better outcomes.

Keywords: Translational/Experimental Therapeutics, Rare Diseases, Neurometabolic Disorders

223. CANaspire, a First-in-Human Phase 1/2 Controlled Open-Label Study of BBP-812, a Recombinant AAV9-hASPA Vector for the Treatment of Canavan Disease

Eichler F (Boston, MA), Laforet G, Andonian H, Kinane B, Kirby K, Nagy A, Shaywitz A, Balser J, Bley A

Objective: Canavan Disease (CD) is an ultra-rare leukodystrophy caused by mutations in the *ASPA* gene leading to

brain accumulation of N-acetylaspartic acid (NAA) and profound early-onset impairment of psychomotor development. The objective of the CAN*aspire* study is to evaluate the safety and pharmacodynamic and clinical activity of BBP-812, a systemically administered recombinant broad-tropism AAV9 h*ASPA* vector for the treatment of CD.

Methods: CAN*aspire* is a Phase 1/2 first-in-human dose escalation/dose expansion trial evaluating safety, pharmacodynamic activity (NAA levels) and developmental and quality of life assessments over a 1-year acute and 4-year long-term follow-up period. Clinical measures mirror those in the natural history study CAN*inform*, enabling use of CAN*inform* data as a control and for establishment of a primary clinical endpoint. Eligibility criteria include a confirmed diagnosis of CD, age ≤30 months, and absence of clinically meaningful medical co-morbidities or manifestations of advanced CD.

Results: Pre-treatment MRIs in the first 2 participants showed extensive abnormalities in white matter, globi pallidi, thalami and cerebellum as well as elevated NAA on MR spectroscopy and in CSF. Initial findings have provided evidence of tolerability as well as reduction of NAA levels in CNS and urine. Most AEs have been mild or moderate (none serious), and none have led to interruption or discontinuation of the infusion or study withdrawal.

Conclusions: CAN*aspire* is the first clinical trial of a systemically administered gene therapy candidate for CD. Preliminary data have supported overall tolerability of this approach and have demonstrated reduction of NAA levels in multiple compartments, including CNS, after treatment.

Keywords: Translational/Experimental Therapeutics, Neurometabolic Disorders, Rare Diseases

TRAUMA (INCLUDING CONCUSSION)

224. Oxygen reduces apoptosis in retinal cells following TBI in both adult and adolescent mice but only reverses visual deficits in adolescent mice.

Torrens J (Cincinnati, OH)

Objective: Vision impairment after head trauma can be mediated by traumatic injury to the optic nerve, termed traumatic optic neuropathy (TON), which has few effective treatment options. We previously noted post-injury apnea led to increased mortality in adolescents and brief 100% oxygen exposure significantly improved the mortality rate. We hypothesized that oxygen exposure may have an effect on the pathophysiology and functional deficits associated with TON and age at injury might influence oxygen's benefits.

Methods: We performed a blunt, closed-head injury on 6 or 8-week-old, male C57BL/6 mice and investigated visual impairment via the optokinetic response (OKR), an involuntary response to moving visual stimuli. Oxygen was administered for a total of five minutes immediately after injury. OKR was assessed over three days and retinal tissue or serum was collected for western blotting, RNA sequencing, rtPCR, and ELISA 7 days post injury (DPI).

Results: Although visual impairment after injury was similar between ages, oxygen more reliably improved OKR deficits in adolescent mice. Preliminary data show that oxygen does not prevent retinal cell loss but does reduce pro-apoptotic markers in the retina up to 7 DPI in both groups. We anticipate a greater increase in injury-associated mechanisms in adolescent mice compared to adults through analysis of inflammatory markers (ELISA) and transcription of markers associated with cell stress pathways (e.g., oxidative stress and endoplasmic reticulum stress).

Conclusions: Ultimately, even when pro-apoptotic markers in retinal cells were reduced, visual deficits persisted. Moreover, oxygen was more beneficial for adolescent mice.

Keywords: Trauma (Including Concussion), Neuroscience, Neuroopthalmology

225. Adolescent traumatic optic neuropathy induced retinal cell loss is associated with both endoplasmic reticulum and oxidative stress.

Hetzer S (Cincinnati, OH), Evanson N, Shah V

Objective: Traumatic brain injury (TBI) is a leading cause of death and disability and can lead to three-fold greater risk of visual impairment. TBI-induced optic nerve injury (traumatic optic neuropathy, TON) is a significant cause of *chronic* visual dysfunction and retinal thinning. Adolescents have a high incidence of TBIs (~1 million/year) with a higher mortality and proportion of visual pathway injury compared to adults. We seek to understand mechanisms of retinal cell loss using adolescent mice. Having implicated endoplasmic reticulum (ER) stress and oxygen toxicity in our TON model, we now hypothesize that TON-induced retinal cell loss is mediated by axonal oxidative stress, which triggers somal ER stress and cellular apoptosis.

Methods: We used a closed-head weight drop TBI model and *in vivo* retinal imaging to plot a time course of reactive oxygen species (ROS) generation and *ex vivo* immunohistochemistry and western blotting to determine whether ROS increase in the axon without ER stress and whether ER stress in the soma follows this axonal ROS increase.

Results: So far, we determined that axonal injury occurs 2.5 mm from the cell body, proximal to the optic chiasm. ROS also increase in the retina within seven days of injury but have yet to examine our earlier time points.

Conclusions: This long distance provides us with a unique opportunity to trace the proposed mechanisms along the axon, separate from the cell body. We anticipate that ROS will arise at the site of injury preceding somal ER stress, which will initiate apoptotic cascades.

Keywords: Trauma (Including Concussion), Neuroopthalmology, Neuroscience

226. Emergency Department visits for mild traumatic brain injury in early childhood

Rose S (Columbus, OH), Levine D, Shi J, Wheeler K, Stanley R, Beauchamp M

Objective: Most research regarding mild traumatic brain injury (mTBI) has focused on school-age children. TBI

during early childhood may disrupt key periods of neurodevelopment. We sought to characterize the incidence and healthcare utilization for mTBI in young children presenting to U.S. emergency departments (ED).

Methods: The Nationwide Emergency Department Sample was queried for children age 0-6 years with mTBI from 2016-2018. Patients were excluded for focal or diffuse TBI, drowning or abuse mechanism, death in the ED or hospital, Injury Severity Score >15, neurosurgical intervention, intubation, or blood product transfusion.

Results: National estimates included 1,066,565 patient visits: 63.6% were two years or younger, 57.6% were male, and 69.1% were injured in falls. Most were seen at low pediatric volume EDs (62.6%) and non-children's hospital EDs (85.8%), and 64.7% were seen at a teaching hospital. Over 98% were treated in the ED and discharged home. ED charges resulted in $540-599 million annually, and more than half of patients utilized Medicaid. The most common head injury diagnosis was "unspecified injury of head" (83.1%); this diagnosis decreased in frequency as age increased, in favor of a concussion diagnosis. Computed tomography of the head was performed in 19.2% of patients, more often at non-children's hospitals and hospitals that treat fewer children (P<0.001).

Conclusions: Early childhood mTBI is prevalent and results in high financial burden in the U.S. There is wide variation in diagnostic coding and CT scanning amongst EDs. More focused research is needed to identify optimal diagnostic tools and management strategies.

Keywords: Trauma (Including Concussion)

227. Macromolecular Dexamethasone Prodrug Ameliorates Neuroinflammation and Prevents Bone Loss Associated with Traumatic Brain Injury

Wie X (Omaha, NE), Zhao G, Jia Z, Zhao Z, Chen N, Sun Y, Kelso M, Rathore G, Wang D

Objective: Traumatic brain injury is (TBI) a leading cause of morbidity and mortality in children and adults. The pathology of TBI is heterogeneous, resulting from both primary and secondary injury mechanisms, the latter being attributed to the inflammation. Use of conventional glucocorticoid formulations (*e.g.*, dexamethasone or Dex) leads to limited distribution to the brain, pulsatile brain tissue concentration and systemic side effects, with controversial benefit in neuroprotection. We hypothesized that systemically administered *N*-(2-hydroxypropyl) methacrylamide (HPMA) copolymer-based Dex prodrug (P-Dex) will target the brain injury sites, substantially enhancing glucocorticoid therapy efficacy, and improve its systemic safety.

Methods: Mice (C57BL/6, 9 weeks old, female) were randomly assigned to P-Dex, Dex, saline and healthy control groups (15 mice/group). After establishment of the TBI (cortical impact), mice received the treatments vs Saline control intravenously. They then underwent neurological severity score, static weight bearing test. Their brain tissues were evaluated using optical imaging and immunohistochemistry. Bone quality was assessed using micro-CT.

Results: We found that P-Dex passively targeted the traumatic brain tissue and had sustained accumulation at the inflamed tissue for over 14 days. Histological evidence demonstrates the P-Dex's therapeutic effect on the amelioration

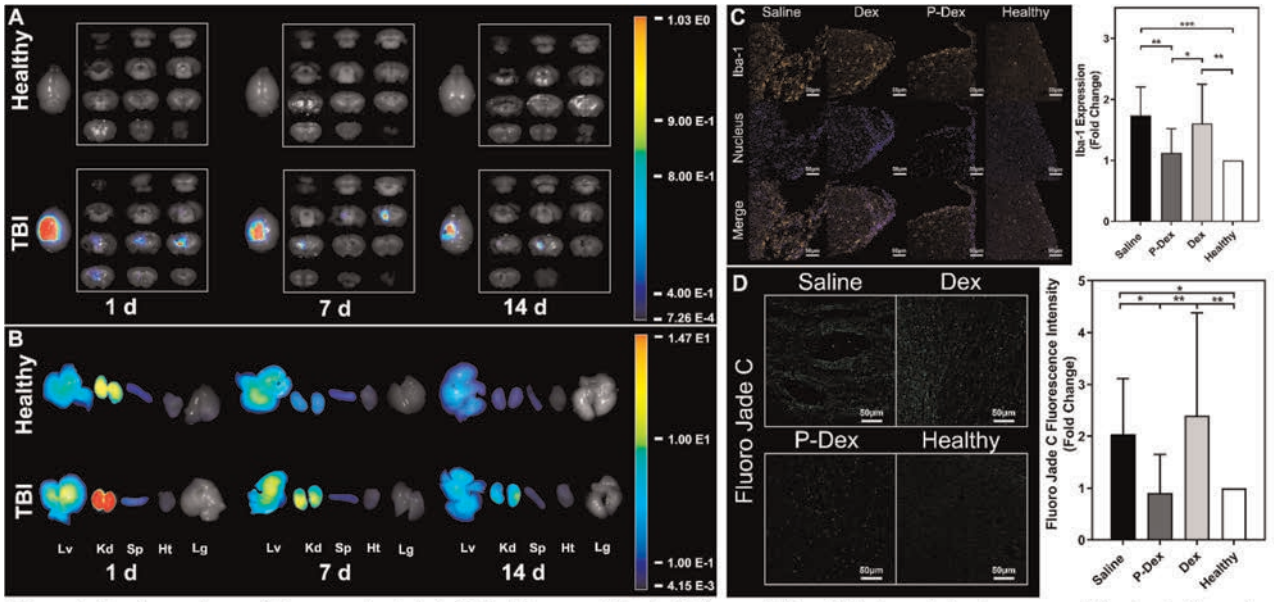


Figure 1. Ex vivo analyses of tissues collected. **A.** Optical images of the brain tissue. P-Dex-IRDye's sustained presence at the brain injury site for over 14 days after TBI while no accumulation in the healthy brain. **B.** Optical images of the brain tissue and major organs from mice received P-Dex IRDye. The P-Dex-IRDye distribution in major organs (liver, kidney, and spleen, heart, and lung) in the TBI and healthy mice at different time points post-injection. **C.** Iba1 expressions at the brain injury sites at 6 weeks post TBI. Saline group showed significantly higher expression of Iba1 when compared to the Healthy group. Dex treatment did not decrease the Iba1 expression when compared to Healthy and Saline group. P-Dex-treated TBI mice showed significant lower Iba1 expression when compared to the mice given saline and Dex. **D.** Fluoro-Jade C-staining degenerated neurons at 6 weeks after TBI. Saline group showed significantly higher neuronal degeneration when compared to the Healthy control and P-Dex-treated mice. Dex treatment did not provide any neuron protection when compared to Healthy and P-Dex-treated groups. One-way ANOVA with Tukey's test was used for comparison. (* P < 0.05, ** P < 0.01, *** P < 0.001)

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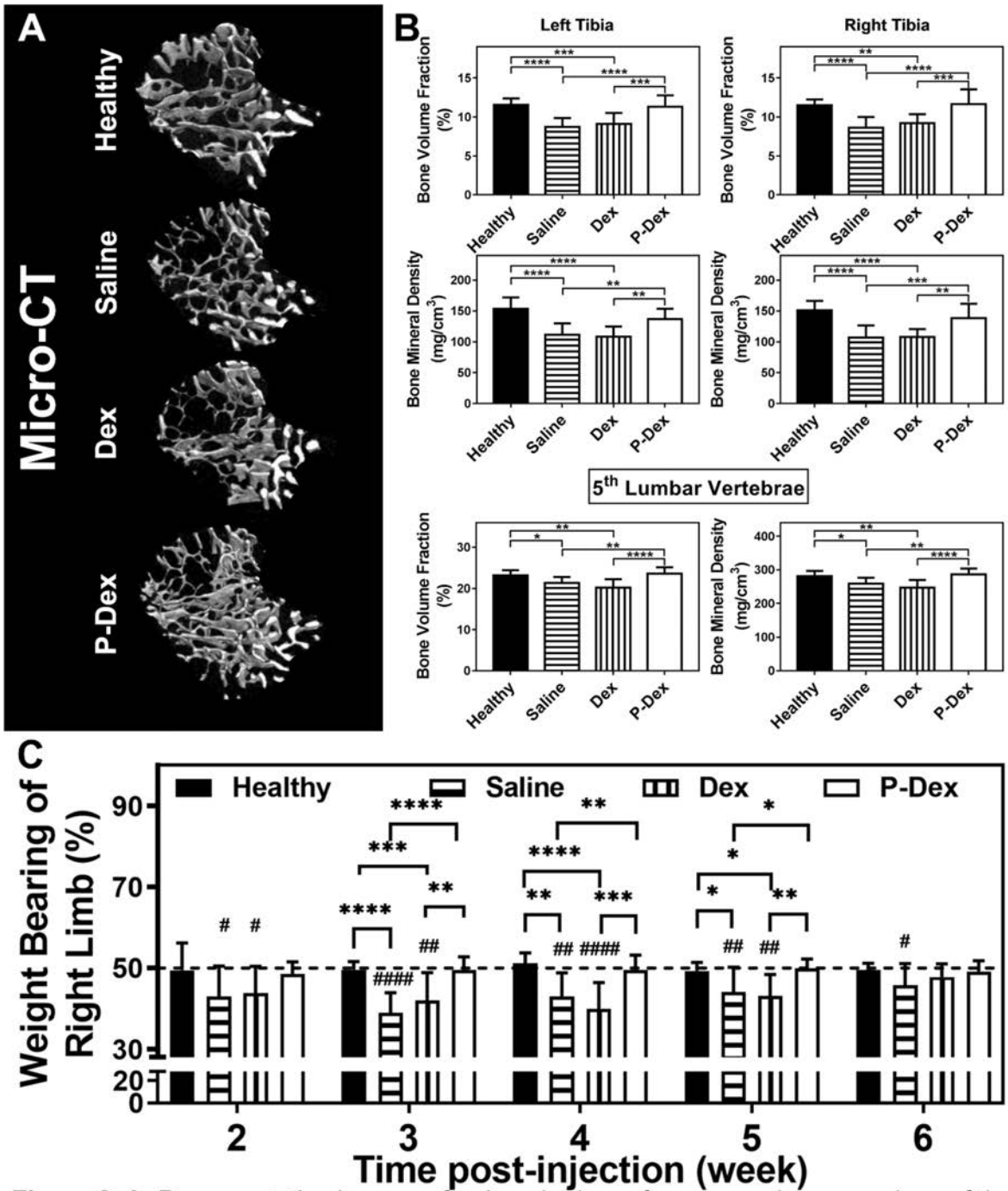

Figure 2. A. Representative images of trabecular bone from secondary spongiosa of the proximal tibia. **B.** Micro-CT analysis results of left and right tibias. Bone mineral density, bone volume fraction were evaluated presented. One -way ANOVA with Tukey's test was used for comparison. (* P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001). **C.** Static weight distribution of mice from week 2 post-TBI. The dotted line represents equal weight distribution between left and right limbs. (vs. ideal equal weight distribution, unpaired t-test, # P < 0.05, ## P < 0.01, ### P < 0.001, #### P < 0.0001) (comparing between treatment groups, one-way ANOVA with Tukey's test, * P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001)

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of neuroinflammation and prevention of neurodegeneration. Behaviorally, the P-Dex treated animals showed better recovery from imbalance. Higher bone mineral density and better bone microarchitecture were evident in the P-Dex treated animals, compared to the free Dex treated and Saline controls, confirming P-Dex's bone protection effect.

Conclusions: : P-Dex can be a potential therapy targeting neuro-inflammation and preserving the neurons from death, avoiding bone loss post-TBI.

Keywords: Trauma (Including Concussion), Neurorehabilitation

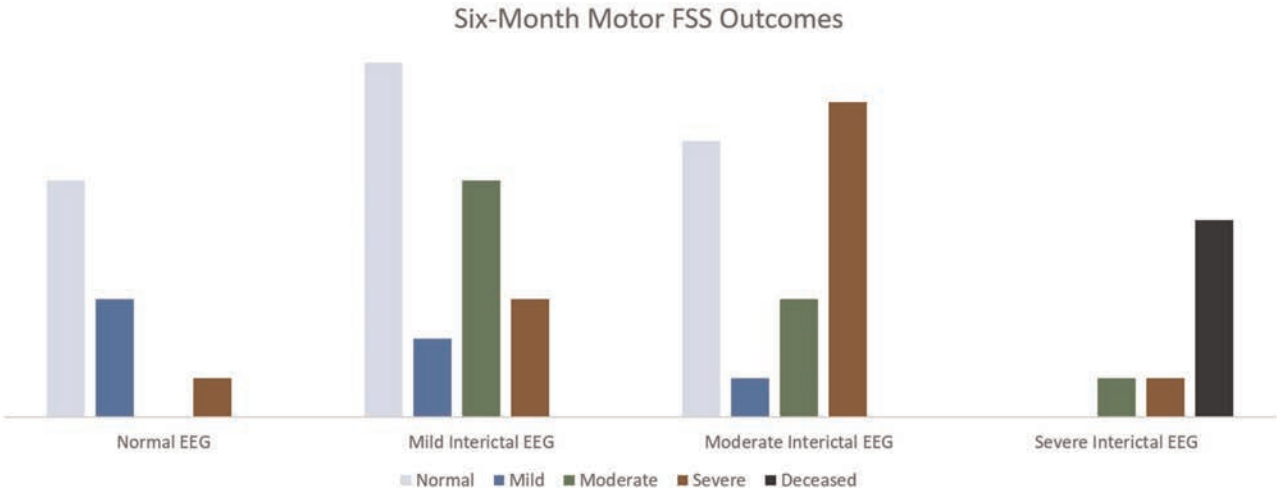
228. Early EEG to Predict Severity of Injury in Infants with Abusive Traumatic Brain Injury

Varughese N (Dallas, TX), Hasan A, Eaton D, Cohen N, Clarke R, Said R, Raman L, Sirsi D

Objective: To measure the utility of EEG during initial hospitalization to predict imaging and functional outcome in infants with abusive TBI

Methods: A retrospective chart review was conducted at a pediatric Level 1 trauma center. The cohort included children <1 year of age hospitalized with abusive TBI between 2015-2020 and followed outpatient by a child abuse specialist. Each of these patients was assigned a severity score for EEG background, MRI abnormalities, and motor and sensory neurologic outcome. Seizure burden was manually calculated (maximum seizure burden per hour). All scoring systems were previously published and validated for this age group. Spearman rank correlation was then used to assess the correlation coefficient.

Results: Out of 161 children with abusive head trauma, 64 had EEG during the initial hospitalization, including 28 with seizures. Clinic follow-up was obtained in 51 patients at 1-6 months and 46 at 7-12 months post-trauma. Ages ranged from 0.5 to 11 months, mean weight was 6 $\pm$ 2 kg, and 16 were born prematurely. Significant positive correlations were discovered between background EEG scores and MRI scores (0.338, $p = 0.011$) as well as motor outcome at 1-6 mo (0.332, $p = 0.017$) and 7-12 months (0.386,



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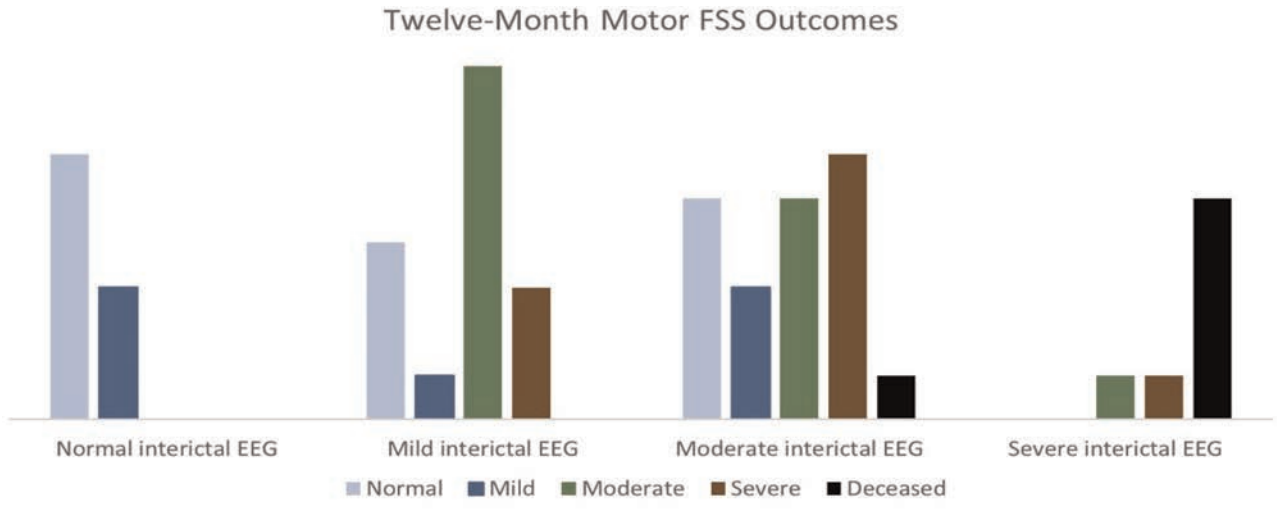

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p = 0.08). Seizure burden and sensory functional scores showed positive but insignificant correlations, possibly due to the small number of patients available.
Conclusions: In infants with abusive TBI, EEG may be useful as an early marker of prognosis. Higher background EEG scores correlated with worse MRI scores and neurologic outcomes during their first year post-trauma.
Keywords: Trauma (Including Concussion), Critical Care

229. Traumatic brain injury and chronic variable stress in adolescence

Urig M (Cincinnati, OH)

Objective: Adolescence represents not only a critical period for development but also a period of increased vulnerability to stress that further increases in situations of chronic illness. One of these chronic conditions can include experiencing a traumatic brain injury (TBI), of which adolescents are the second largest group (~1 million annually). Yet, there is no research examining the effects of stress on TBI outcomes. We hypothesize that chronic stress will prolong/exacerbate the neurodegenerative effects of TBI.
Methods: Using adolescent, male C57Bl/J mice, we induced a closed-head weight drop TBI followed by either return to home cage, or a chronic variable stress (CVS) paradigm (e.g., exposure to stressors like cage tilt, wet bedding, and hyperthermia) twice per day for two weeks. Brain tissue was collected 2-, 5-, 20-, and 28- weeks post injury and was stained with FlouroJade-B to asses axonal neurodegeneration, IBA1/CD68 to asses microglial phagocytosis/morphology, and GFAP/LAMP2 to asses astroglial reactivity. Because our TBI model induces traumatic optic neuropathy, we focused on optic regions and the stress-associated paraventricular nucleus (PVN) for signs of degeneration that might be exacerbated after excess stress.
Results: We show chronic degeneration in vision-associated regions but not in the PVN. However, at 20 weeks TBI + CVS mice showed a significant reduction in degeneration except in the optic tract where degeneration persisted through the time course. Preliminary glial data show that astrocytes are reactive but perhaps not functioning in a protective manner.
Conclusions: In contrast to our hypothesis, CVS may be neuroprotective despite persistent glial dysfunction.
Keywords: Trauma (Including Concussion), Neuro-opthalmology, Neuroscience

LATE BREAKING ABSTRACTS

230. Cation leak through ATP1A3 causes spastic paraparesis with or without episodic progression

Calame D (Houston, TX), Yano S, Vadillo C, Berger S, Lotze T, Shinawi M, Cohen J, Person R, Telegrafi A, Phitsanuwong C, Lupski J, Holmgren M, Regier D

Objective: Heterozygous pathogenic variants in *ATP1A3*, the gene encoding the α3 subunit of sodium-potassium ATPase, cause paroxysmal movement disorders including alternating hemiplegia of childhood (AHC), rapid-onset dystonia-parkinsonism (RDP), and cerebellar ataxia-areflexia-pes cavus-optic atrophy-sensorineural hearing loss (CAPOS). However, *ATP1A3* variants are increasingly identified in patients with atypical phenotypes without paroxysmal movement disorders. Here, we characterize the clinical and electrophysiologic properties of a recurrent *ATP1A3* variant, NM_152296.5:c.2324C>T; p.(P775L).
Methods: Five unrelated patients with *ATP1A3*: p.(P775L) were identified through diagnostic laboratory queries and personal communications. HEK293T cells were transfected with ouabain-resistant *ATP1A3* expression vectors, and rescue of cell survival was measured in ouabain-containing medium. Ion transport and binding kinetics were characterized in *Xenopus* oocytes using two-electrode and cut-open voltage clamp. Known pathogenic variants *ATP1A3:* p.(D801N) and *ATP1A1:*p.(L104R) were studied as controls.
Results: Key phenotypic features seen in all patients with *ATP1A3*: p.(P775L) include developmental delay (DD), intellectual disability (ID), and spasticity, occasionally progressing in a stepwise manner in the absence of neuroimaging abnormalities. No patients met diagnostic criteria for AHC, RDP, or CAPOS. p.(P775L) caused loss-of-function in the ouabain complementation assay, abrogated normal ion transport in oocytes, and disrupted sodium binding kinetics. Additionally, p.(P775L) caused inward sodium and proton leak in the presence of physiological ion concentrations.
Conclusions: We demonstrate a new *ATP1A3*-related phenotype associated with DD/ID, spastic paraplegia with or without episodic progression, resulting from cation leak due to *ATP1A3*: c.2324C>T; p.(P775L). This mechanism has not been reported among *ATP1A3* variants and supports a dominant-negative disease model in which cation leak opposes wildtype activity.
Keywords: Genetics, Movement Disorders (including Cerebral Palsy), Rare Diseases

231. A new self-regulating gene therapy improves multiple potentially translatable phenotypic domains in a mouse model of Rett Syndrome

Ross P (Edinburgh, Scotland), Ross P, Hector R, Gadalla K, Thomson S, Selfridge J, Jaggumantri S, Cobb S

Objective: Rett syndrome (RTT) is a neurodevelopmental disorder caused by mutations in the *MECP2* gene, characterized by a regression of previously acquired developmental milestones including loss of speech, gross and fine motor skills, purposeful hand function, and autonomic dysfunction. To harness the potential of gene replacement for RTT, we developed NGN-401, a new self-regulating MECP2 gene therapy designed to deliver desired levels of MECP2, while limiting its overexpression to avoid resulting toxicities. We will present NGN-401 safety and efficacy data in mouse models of RTT.
Methods: Equivalent NGN-401 or vehicle doses, route and timing of administration were employed in an acute efficacy model (*Mecp2*$^{-/y}$ mice) and tolerability study (*Mecp2*$^{+/-}$ mice mosaic for MECP2 expression). A conventional *MECP2* gene therapy product was similarly administered in the tolerability study as a control.
Results: NGN-401-treated *Mecp2*$^{-/y}$ mice demonstrated a dose dependent and significant extension of survival vs. vehicle treated mice (median 23, 37 weeks low and high dose respectively vs 9 weeks for vehicle). Importantly, NGN-401

treatment was also associated with significant amelioration of cardinal RTT-like phenotypes including mobility, gait, abnormal breathing, and limb clasping vs vehicle-treated animals. NGN-401 was well tolerated with no adverse findings in *Mecp2*$^{+/-}$ mice, while mice dosed with the conventional construct showed severe toxicity, requiring euthanasia.

Conclusions: NGN-401 demonstrated significant therapeutic benefit while avoiding toxicity associated with conventional gene therapy in Rett mouse model. These data suggest NGN-401 treatment has potential to improve clinically relevant domains, including motor and respiratory symptoms.

Keywords: Translational/Experimental Therapeutics, Cognitive/Behavioral Disorders (including Autism), Genetics

232. Fenfluramine increases survival and reduces markers of neurodegeneration in a mouse model of Dravet syndrome: neuroanatomical implications for disease modification

Reeder T (Emeryville, CA), Cha J, Filatov G, Smith S, Wong D, Gammaitoni A

Objective: To investigate the effect of fenfluramine on survival and neuroinflammation in a *Scn1a*$^{+/-}$ mouse model of Dravet syndrome (DS mice).

Methods: DS mice were treated subcutaneously once daily with fenfluramine (15mg/kg), diazepam (10mg/kg), or vehicle until postnatal day (PND) 35-37. Sagittal brain sections were evaluated semi-quantitatively by immunohistochemistry with fluorescence microscopy (scale, 0-5) using primary antibodies to degraded myelin basic protein (D-MBP; degenerated myelin) without antigen retrieval, or CD11b antibody (activated/inflammatory microglia). Apoptotic nuclei were quantified by TUNEL assay. Statistical significance was assessed by 2-sided t-test.

Results: In DS mice, there was a significant reduction in mortality in the fenfluramine-treated group (fenfluramine, 24%, $P<0.01$ vs control [55%]; diazepam-treated group, 62%). Degenerated myelin were enriched in DS mouse cortex and hippocampus relative to wild-type controls (Figure-1; 6.56 ± 1.24 vs 5.00 ± 0.71); D-MBP immunostaining was significantly reduced with fenfluramine (5.15 ± 0.80;

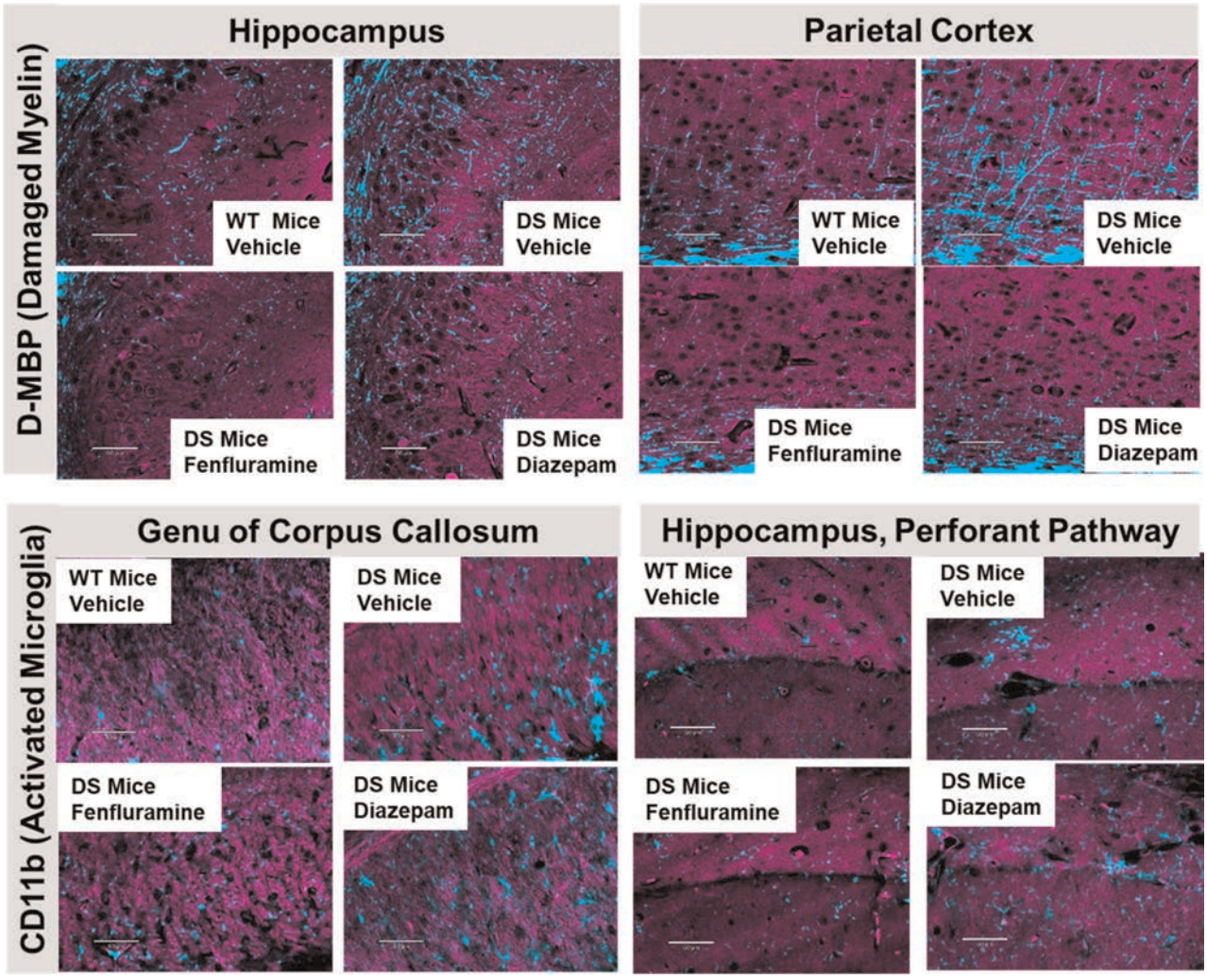

FIGURE 1: Reduction in neuroinflammatory markers in brains of Dravet syndrome (DS) mice after treatment with fenfluramine, but not diazepam (scale bars: 60 μm using a 20X objective). Abstract 232

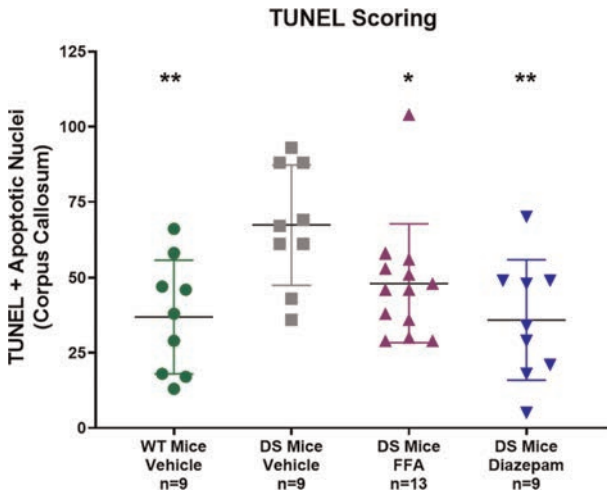

FIGURE 2: Reduction in apoptosis in the corpus callosum of Dravet syndrome (DS) mice after fenfluramine (FFA) or diazepam ($P<0.01$; * $P\leq0.05$ relative to DS mice).**
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$P<0.05$), but not with diazepam (5.67 ± 1.41; $P>0.05$). Activated CD11b+ microglia were enriched in DS mouse corpus callosum and hippocampus relative to wild-type controls (Figure-1; 6.67 ± 1.73 vs 4.56 ± 1.24; $P<0.01$). CD11b+ immunostaining was reduced with fenfluramine (5.31 ± 0.75; $P=0.05$), but not with diazepam (6.67 ± 0.87; $P>0.05$). TUNEL fluorescence was elevated in the corpus callosum of DS mice relative to wild-type controls (Figure-2; 67.3 ± 19.9 vs 36.9 ± 18.9; $P=0.004$); TUNEL staining was reduced with either fenfluramine (48.0 ± 19.6; $P=0.038$) or diazepam (35.9 ± 20.0;$P=0.004$).

Conclusions: This is the first report of increased survival with concurrent reduction in neuroinflammation in DS mice treated with fenfluramine. The results may provide neuroanatomical context for the disease-modifying potential of fenfluramine in seizure control, executive function (co-morbidities), and survival benefits.

Keywords: Epilepsy/Sleep, Translational/Experimental Therapeutics

233. Unraveling shared and cell-type specific transcriptomic and epigenomic responses to prenatal hypoxia in the developing brain

Cristancho A (Philadelphia, PA), Gadra E, Zarrinnegar D, Marsh E

Objective: Prenatal hypoxia is common cause of neurodevelopmental disabilities. However, there is a mechanistic gap in understanding why hypoxia causes lasting functional deficits even when there is no significant cell death at the time of injury. One hypothesis for lasting deficits is that prenatal hypoxia alters the epigenome during critical periods of development, disrupting cell maturation and function.

Methods: We performed single nucleus RNA and assay for transposase-accessible chromatin sequencing from the cortex of mice immediately after 8 hours of hypoxia at embryonic day 17.5. Over 140,000 nuclei were analyzed from 16 samples (8 normoxia/hypoxia). We used Golgi staining to quantify pyramidal neuron spine density in 1 month-old animals.

Results: Genes that were dysregulated in all cell types were enriched for regulators of mitochondrial function. By contrast, pathway analyses of cell type-specific differentially expressed genes demonstrated enrichment that may correspond to lasting deficits. For example, glutaminergic neurons demonstrated dysregulation of genes related to neuron structure and spine formation, which is correlated with decreased spine density 1 month after hypoxia. Compellingly, we are found that prenatal hypoxia leads to an uncoupling of chromatin accessibility and transcription in most cell types and disruptions of epigenetic maturation trajectories in differentiating cells.

Conclusions: Together these data demonstrate that the early cell type-specific shifts in the epigenome after prenatal hypoxia may provide novel insights into the effects of hypoxia that are independent of the direct, immediate effects on the transcriptome. Ongoing analyses will be used to suggest novel pathways that are amenable to pharmacologic intervention to improve neurodevelopmental outcomes.

Keywords: Neuroscience, Neonatal & Fetal Neurology

234. An open-label study of trofinetide for the treatment of Rett syndrome in girls 2 to 4 years of age

Percy A (Birmingham, AL), Ryther R, Marsh E, Feyma T, Lieberman D, Neul J, Benke T, Glaze D, Berry-Kravis E, Ananth A, Buhrfiend C, Stankovic S, Bishop K, Darwish M, Youakim J, Arkilo D

Objective: To evaluate safety/tolerability, pharmacokinetics (PK), and preliminary efficacy of trofinetide in girls aged 2–4 years with Rett syndrome (RTT).

Methods: This multicenter, open-label study (NCT04988867) is ongoing and consists of 12-week treatment period A and ~21-month, long-term treatment period B. Twice-daily trofinetide was given based on weight, orally or by gastrostomy tube. Interim results from treatment period A are presented for safety, PK, and exploratory efficacy endpoints (Clinical Global Impression–Improvement [CGI-I], Caregiver Global Impression–Improvement [CaGI-I], and the Overall Quality-of-Life Rating on the Impact of Childhood Neurologic Disability Scale [ICND-QoL]).

Results: As of the interim cut-off date of 14 March 2022, 14 participants were enrolled (aged 2 years [n=4], 3 years [n=5], 4 years [n=5]); 10 had completed period A. Twelve (85.7%) participants reported at least 1 treatment-emergent adverse event (TEAE). There were no SAEs or deaths. The most common TEAEs were diarrhea (64.3%) and vomiting (35.7%). Participants' scores improved on the CGI-I (mean [SE] 3.6 [0.19]) at Week 2 to 3.3 [0.24)] at Week 12), CaGI-I (Week 12, 2.2 [0.13]), and the ICND-QoL (increased from 3.9 [0.25] at baseline to 4.2 [0.44] at Week 12). Population PK analysis confirmed that exposure to trofinetide was similar to that observed in the phase 3, double-blind, pivotal study that demonstrated positive efficacy results.

Conclusions: In this ongoing study, treatment with trofinetide was safe and generally well tolerated over 12 weeks in girls aged 2–4 years with RTT and appeared to result in improvements in RTT-related efficacy measures.

Keywords: Rare Diseases, Cognitive/Behavioral Disorders (including Autism)

235. Mutation and phenotypic spectrum of mitochondrial leukodystrophies using whole exome sequencing in a cohort of 41 patients

Tavasoli AR (Philadelphia, PA), Hosseinpour S, Razmara E, Heidari M, Zare Dehnavi A, Rezaei Z, Azizimalamiri R, Saket S, Garshasbi M, Ashrafi MR

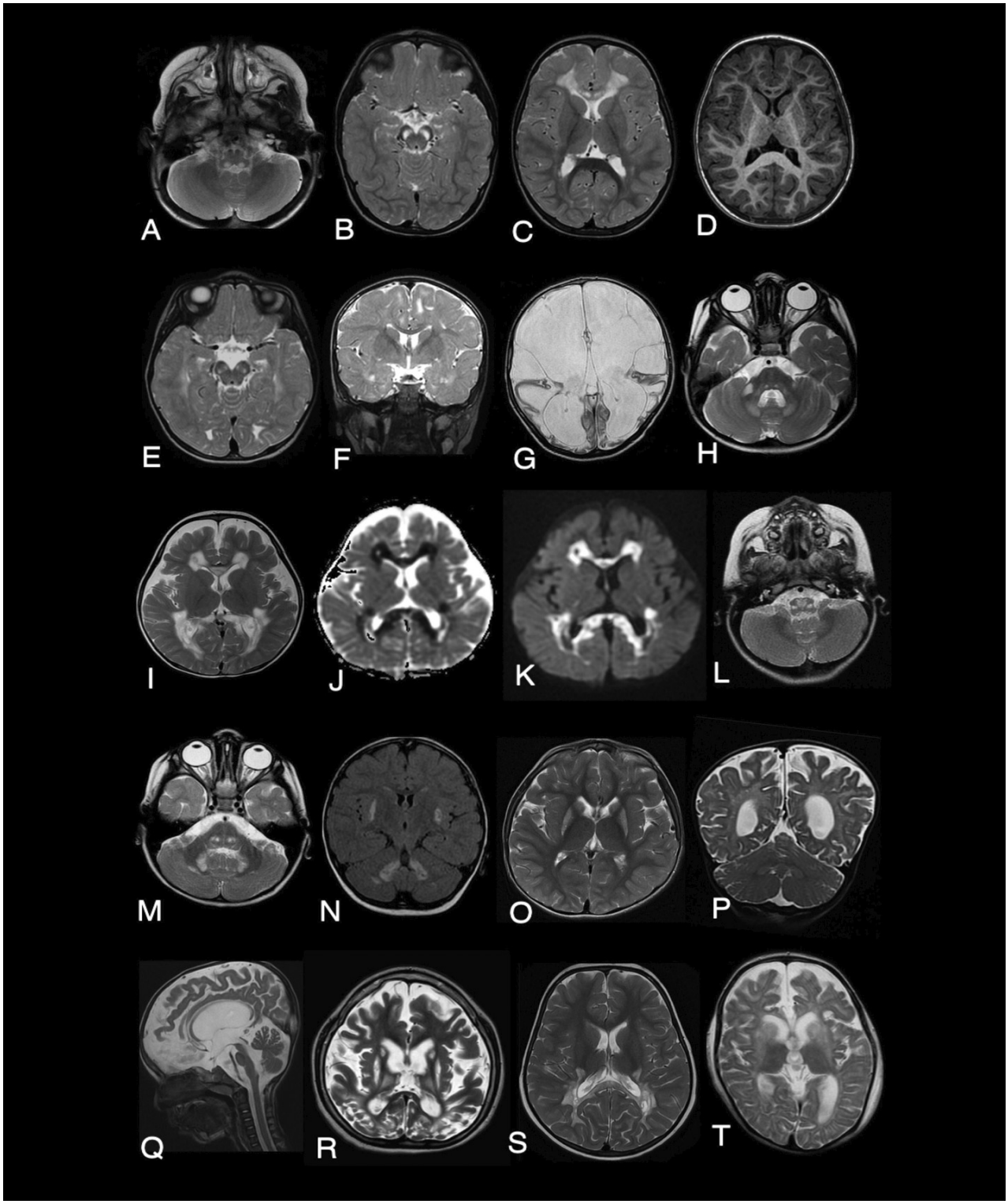

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FIGURE 1: **Brain MRI features of patients with Mitochondrial LDs.**
Figures "A-N" show MRI sequences in patients with variants in OXPHOS components pathway, and figures "O-Q" show MRI sequences in patients with variants in mtDNA maintenance and gene expression pathway. A) Patient with *NDUFS1* due to c.593G>C variant: an axial T2- weighted image (T2WI) with involvement of gracile nucleus. B-D) Patient with *NDUFS1* due to c. 551G>C variant, B: Axial T2WI indicates hyperintensity of substantia nigra. C & D: Axial T2 and T1 weighted images, respectively show involvement of genu of corpus callosum and periventricular white matter in frontal lobes. E-F) Patient with *NDUFV1* due to c.1156C>T variant, E: axial T2- weighted image with involvement of substantia nigra and central tegmental tract hyperintensity. F: A coronal T2- weighted image shows involvement of corpus callosum and subcortical white matter. G: Patient with *NDUFV1* due to c.1022C>T variant with white matter cystic degeneration on axial T2-weighted sequence. H-K) Patient with *LYRM7* due to c.244+6T>G variant, H: An axial T2-weighted image with involvement of middle cerebellar peduncle, central tegmental tracts and dentate nuclei. I: An axial T2-weighted image shows corpus callosum and periventricular white matter hyperintensity with cystic rarefaction. J & K: Apparent Diffusion Coefficient (ADC map) and Diffusion weighted image (DWI) sequences, respectively demonstrate restricted diffusion of involved regions on I. L) Patient with *SURF1* due to c.751C>T variant with involvement of pyramidal tract, medial longitudinal fasciculus, inferior olivary complex and internal arcuate fiber on axial T2-weighted image. M-N) Patient with *SURF1* due to c.532A>T variant, M: an axial T2-weighted image shows dentate, medial lemniscus and cerebellar white matter hyperintensities. N: Coronal Fluid Attenuated inversion recovery (FLAIR) sequence shows involvement of basal ganglia and dentate nuclei. O) Patient with *SUCLA2* due to c.997G>C variant shows involvement of putamen and caudate heads bilaterally. P-Q) Patient with *FBXL4* due to c.1538G>T variant. P: A coronal T2-weighted sequence with dentate nucleus diffuse cerebral white matter involvement. Q: A sagittal T2-weighted image shows pontine, corpus calosum and cerebral atrophy. , Figure "R" shows MRI sequence in a patient with a variant in metabolism of cofactors pathway. R) Patient with *SLC19A3* due to c.905T>C variant, significant cerebral atrophy and involvement of bilateral basal ganglia and thalami are visible on axial T2 - weighted image. Figure "S" shows MRI sequence in a patient with a variant in mitochondrial dynamics and homeostasis pathway. S) Patient with *APOPT1* due to c.360+2T>A variant, axial T2-weighted sequence shows corpus calosum involvement and periventricular white matter with cystic changes. Figure "T" shows MRI sequence in a patient with a variant in metabolism of toxic compounds pathway. T) Patient with *ECHS1* due to c. 476A>G variant, axial T2-weighted image shows ventriculomegaly, cerebral atrophy and basal ganglia hyperintensities. Abstract 235

Objective: Mitochondrial Leukodystrophies (MLs) are mainly caused by impairments of the mitochondrial respiratory chains. This study reports the mutation and phenotypic spectrum of a cohort of 41 pediatric patients from 39 distinct families with MLs among 320 patients with a molecular diagnosis of leukodystrophies.
Methods: This study summarizes the clinical, imaging, and molecular data of these patients for five years.
Results: The most three common symptoms were neurologic regression (58.5%), pyramidal signs (58.5%), and extrapyramidal signs. On analysis of 61 MRI series, cerebral white matter (55.7%), basal ganglia (62.2%), periaqueductal gray matter (54.1%), corticospinal tract (39.3%), brain stem other than PAG and corticospinal tract (42.6%), and corpus callosum (42.6%) were the most common affected areas. Because nuclear DNA mutations are responsible for a high percentage of pediatric MLs, whole exome sequencing was performed on all patients. In total, 39 homozygous mutations were detected. Additionally, two reported mtDNA mutations were identified with different levels of heteroplasmy in two patients. Among 41 mutant alleles, 33 (80.4%) were missense, 4 (9.8%) were frameshift (including 3 deletions and one duplication), and 4 (9.8%) were splicing mutations. Oxidative phosphorylation in 27 cases (65.8%) and mtDNA maintenance pathways in 8 patients (19.5%) were the most commonly affected mitochondrial pathways. In total, 5 novel variants in *PDSS1, NDUFB9, FXBL4, SURF1*, and *NDUSF1* were also detected. In silico analyses showed how each novel variant may contribute to ML pathogenesis.
Conclusions: The findings of this study suggest using whole-exome sequencing as a strong genetic approach to identify the causative variants in pediatric MLs.
Keywords: Neurometabolic Disorders, Rare Diseases, Genetics

236. Autoimmune Encephalitis Clinical Practice Guideline: Improving Time to Diagnosis and Treatment and Decreasing Hospital Length of Stay

Barter K (Nashville, TN), Vater M, Hanzlik E, Pagano L, Fuchs C, Graham B

Objective: Anti-N-methyl-D-aspartate receptor (NMDAR) antibody encephalitis is the most common type of autoimmune encephalitis (AE) in children. Early treatment leads to improved outcomes. A clinical practice guideline (CPG) was created to standardize initial workup and empiric treatment for patients suspected to have anti-NMDAR AE (Figures 1,2). This study evaluates the impact of the CPG on time to diagnosis, treatment, and hospital length of stay.
Methods: Patients with an inpatient consult to pediatric rheumatology for a three-year period after CPG publication were extracted from the medical record. Consults placed for AE were included. Data including final diagnosis, time to treatment, and length of hospital stay were collected manually. This was compared to previously published data at the same institution during a four-year period prior to publication of the CPG.
Results: Pre CPG, 34 patients received testing for AE. Diagnoses included 9 anti-NMDAR AE, 4 antibody negative AE, 21 other. Post CPG, 63 patients had pediatric rheumatology consults for AE. Diagnosis included 7 anti-NMDAR AE, 2 Hashimoto's thyroiditis, 4 antibody negative AE, 50 other. Average time from admission to treatment decreased from 10.4 to 3.8 days. Length of hospitalization decreased from 50 to 33 days.
Conclusions: Creation of a CPG for patients with suspected AE has led to improved time to diagnosis, treatment, and decreased hospital length of stay. Since publication of the CPG, more patients underwent workups for AE, though the

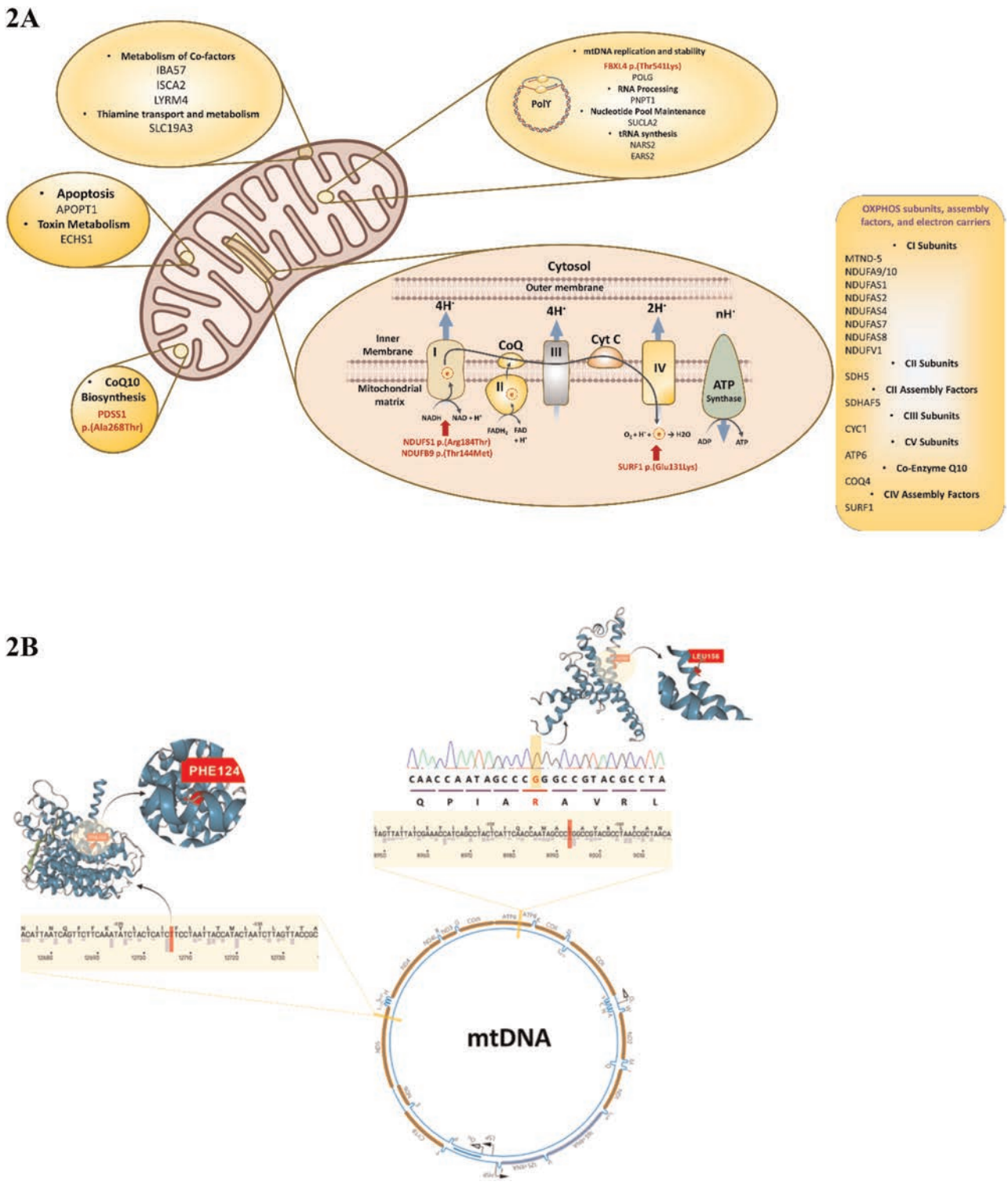


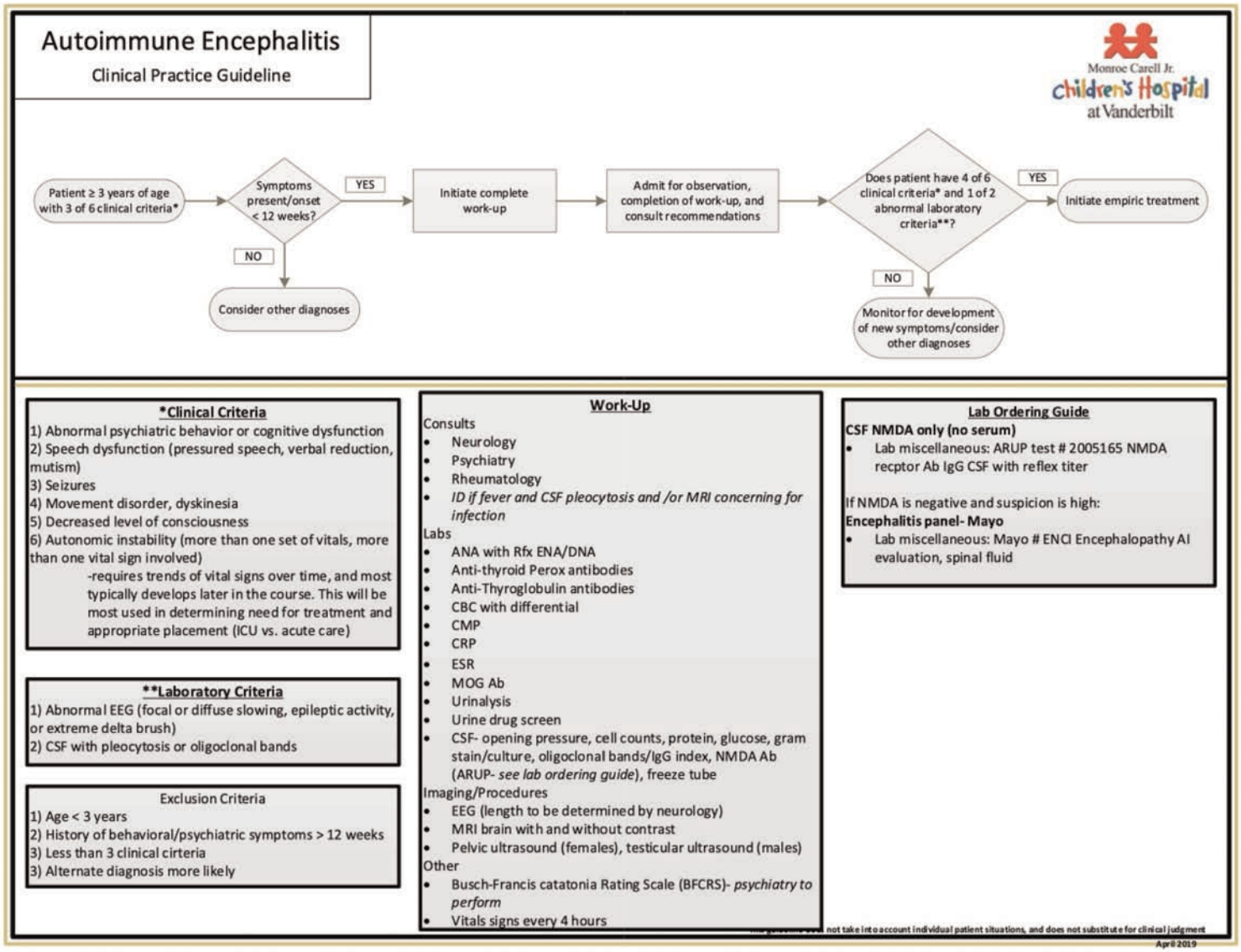
FIGURE 2: A. A summary of all identified genes in this study and showing how they may play roles in MLs pathophysiology. Novel variants have been shown in red color. B. Identified DNA alternations in patient showing maternal inheritance. *MT-ATP6*; m.8993T>G and *MTND5*; m.12706T>C were identified in two unrelated families. Abstract 235

number of AE diagnoses has remained the same. Next steps include reviewing patient clinical information and educating providers on clinical manifestations of the disease.

Keywords: Infections/Neuroimmunology

237. Potential Role of NOD-2 Receptor Signaling Pathway in Pediatric Autoimmune CNS Diseases

Jafarpour S (Los Angeles, CA), Banerjee A, Paulsen K, Ahsan N, Mitchell W, Jeste S, Santoro J


Autoimmune Encephalitis
Clinical Practice Guideline
Monroe Carell Jr. Children's Hospital at Vanderbilt
Patient ≥ 3 years of age with 3 of 6 clinical criteria*
Symptoms present/onset < 12 weeks?
YES
NO
Consider other diagnoses
Initiate complete work-up
Admit for observation, completion of work-up, and consult recommendations
Does patient have 4 of 6 clinical criteria* and 1 of 2 abnormal laboratory criteria**?
YES
Initiate empiric treatment
NO
Monitor for development of new symptoms/consider other diagnoses
*Clinical Criteria
1) Abnormal psychiatric behavior or cognitive dysfunction
2) Speech dysfunction (pressured speech, verbal reduction, mutism)
3) Seizures
4) Movement disorder, dyskinesia
5) Decreased level of consciousness
6) Autonomic instability (more than one set of vitals, more than one vital sign involved)
-requires trends of vital signs over time, and most typically develops later in the course. This will be most used in determining need for treatment and appropriate placement (ICU vs. acute care)
**Laboratory Criteria
1) Abnormal EEG (focal or diffuse slowing, epileptic activity, or extreme delta brush)
2) CSF with pleocytosis or oligoclonal bands
Exclusion Criteria
1) Age < 3 years
2) History of behavioral/psychiatric symptoms > 12 weeks
3) Less than 3 clinical cirteria
3) Alternate diagnosis more likely
Work-Up
Consults
Neurology
Psychiatry
Rheumatology
ID if fever and CSF pleocytosis and /or MRI concerning for infection
Labs
ANA with Rfx ENA/DNA
Anti-thyroid Perox antibodies
Anti-Thyroglobulin antibodies
CBC with differential
CMP
CRP
ESR
MOG Ab
Urinalysis
Urine drug screen
CSF- opening pressure, cell counts, protein, glucose, gram stain/culture, oligoclonal bands/IgG index, NMDA Ab (ARUP- see lab ordering guide), freeze tube
Imaging/Procedures
EEG (length to be determined by neurology)
MRI brain with and without contrast
Pelvic ultrasound (females), testicular ultrasound (males)
Other
Busch-Francis catatonia Rating Scale (BFCRS)- psychiatry to perform
Vitals signs every 4 hours
Lab Ordering Guide
CSF NMDA only (no serum)
Lab miscellaneous: ARUP test # 2005165 NMDA recptor Ab IgG CSF with reflex titer
If NMDA is negative and suspicion is high:
Encephalitis panel- Mayo
Lab miscellaneous: Mayo # ENCI Encephalopathy AI evaluation, spinal fluid
not take into account individual patient situations, and does not substitute for clinical judgment
April 2019

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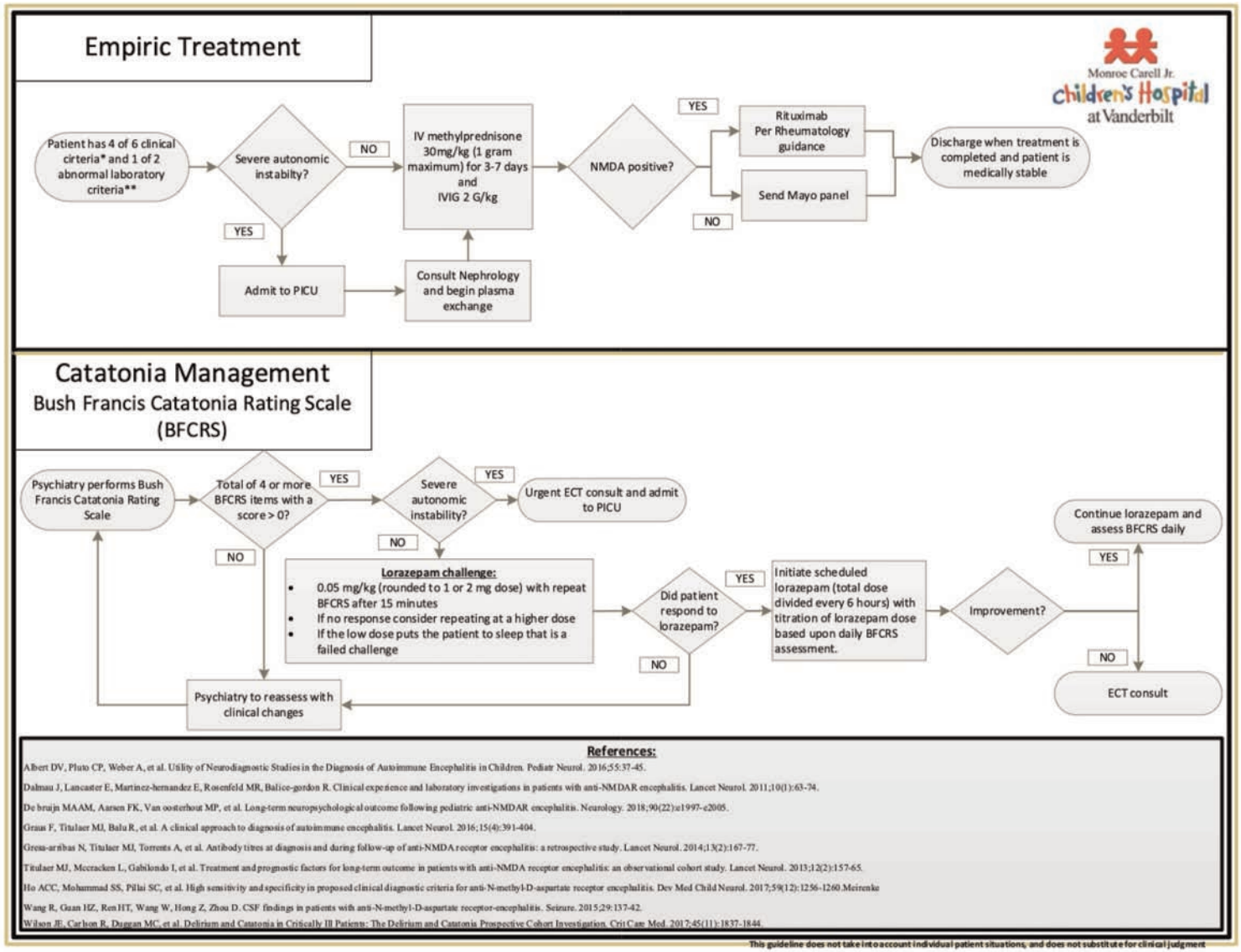

Objective: The genetic basis of autoimmune and neuroinflammatory central nervous system (CNS) disorders is not fully understood. We aimed to explore rare variants of genes implicated in immune dysregulation within pediatric autoimmune and inflammatory CNS disorders.

Methods: This was an observational study of patients presenting to Pediatric Neuroimmunology Disorders Program of a tertiary referral pediatric hospital between July 2019 and December 2021. We included patients <21 years with a diagnosis of autoimmune inflammatory CNS disorder who had genetic testing through next generation focused exome sequencing targeting 155 genes associated with primary disorders of innate or adaptive immunity. Lists of identified genes were analyzed using Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis.

Results: Of 54 patients identified, 42 (77.8%) carried variant(s) in immune dysregulation genes, among which 12 (22.2%) had 3 to 8 variants. Eighty-eight unique variants of 55 genes were identified. The highest number of variants were detected in *UNC13D, LRBA, LYST, NOD2, DOCK8, RNASEH2A, STAT5B, and AIRE*. KEGG pathway analysis revealed enrichment of primary immunodeficiency (Benjamini: 1.40E-06), NOD-like receptor signaling (Benjamini: 4.10E-04), Inflammatory Bowel Disease (Benjamini: 9.80E-03), and NF-kappa B signaling pathways (Benjamini: 1.90E-02).

Table 1: Demographics and clinical diagnosis. Abstract 237

Age	Mean (year)	13.4 ± 5.31
Sex (n, %)	Male	24 (44.4%)
	Female	30 (55.6%)
Ethnicity (n, %)	Hispanic/Latino	27 (50.0%)
	Not Hispanic/Latino	11 (20.4%)
	Not reported	16 (29.6%)
Diagnosis (n, %)	MS	15 (27.8%)
	MOGAD	13 (24.0%)
	Autoimmune Encephalitis	5 (9.25%)
	CNS vasculitis	3 (5.56%)
	ADEM	2 (3.70%)
	Idiopathic Transverse Myelitis	2 (3.70%)
	Meningoencephalitis of unknown etiology	2 (3.70%)
	Post-infectious meningoencephalitis	2 (3.70%)
	CIS	1 (1.85%)
	Down Syndrome Regression Disorder	1 (1.85%)
	Hemispheric inflammation	1 (1.85%)
	Inflammatory Stroke	1 (1.85%)
	MFS/Bickerstaff's Brainstem Encephalitis	1 (1.85%)
	Neuropychiatric SLE	1 (1.85%)
	Neurosarcoidosis	1 (1.85%)
	RIS	1 (1.85%)
	SLE cerebritis	1 (1.85%)
	Susac Syndrome	1 (1.85%)

ADEM: Acute disseminated encephalomyelitis, CIS: Clinically isolated syndrome, CNS: Central nervous system, MFS: Miller Fisher syndrome, MOGAD: Myelin oligodendrocyte glycoprotein antibody-associated disease, MS: Multiple Sclerosis, RIS: Radiographically isolated syndrome, SLE: Systemic Lupus Erythematous.

Table 2: List of rare variants, allele frequency, and results of *in silico* predictions categorized by diagnosis. Abstract 237

Dx	Gene	Variant	dbSNP	ExAC AF	PolyPhen	SIFT	Conserv	CADD
ADEM	***ADAR***	**c.577C>G (p.Pro193Ala)**	**rs145588689**	**0.003**	**NA**	**NA**	**Mod**	**23.5**
	AIRE	c.722G>T (p.Ser241Ile)	rs1260665653	NA	Probably damaging	Deleterious	Weak	5.897
	DEF6	**c.1745T>A (p.Leu582Gln)**	**rs751075162**	**0.0001**	**Possibly damaging**	**Deleterious**	**High**	**27.7**
	ITGB2	c.1358G>A (p.Ser453Asn)	rs138659490	0.0008	NA	NA	High	9.234
	NOD2	c.1151T>A (p.Phe384Tyr)	rs777343284	0.0003	Probably damaging	Tolerated	High	25.9
Autoimmune Encephalitis	*AIRE*	c.1256G>A (p.Cys419Tyr)	rs756933733	NA	Possibly damaging	Tolerated	Mod	19.08
	IL21R	c.585C>G (p.Ser195Arg)	rs773814550	NA	Possibly damaging	Tolerated	Mod	24.6
	RNASEH2A	**c.871C>T (p.Arg291Cys)**	**rs771858022**	**0.00006**	**Probably damaging**	**Deleterious**	**High**	**24.6**
	STAT1	c.1632+6G>A (Intronic)	rs185216067	0.0008	NA	NA	NA	5.658
	TNFRSF1A	c.271G>A (p.Ala91Thr)		NA	Possibly damaging	Tolerated	Mod	21.7
	XIAP	**c.844G>C (p.Glu282Gln)**		**NA**	**Probably damaging**	**Deleterious**	**High**	**37**
CIS	*CYBA*	c.553G>A (p.Val185Ile)	rs1158937022	NA	Tolerated	Tolerated	Weak	15.57
CNS vasculitis	*DOCK8*	c.4276A>G (p.Ser1426Gly)	rs755182322	0.00009	Tolerated	Tolerated	High	23.6
	IL21	c.470A>T (p.His157Leu)	rs1326239267	NA	Tolerated	Tolerated	Weak	12.68
	SLC7A7	**c.187C>T (p.Leu63Phe)**		**NA**	**Probably damaging**	**Deleterious**	**High**	**26**
	UNC13D	**c.652G>T (p.Gly218Trp)**	**rs775666284**	**0.00001**	**Possibly damaging**	**Deleterious**	**Mod**	**26.1**
Down Syndrome Regression Disorder	*CTLA4*	c.23G>A (p.Arg8Gln)	rs138279736	0.0005	Tolerated	Tolerated`	Mod	17.97
	IRF7	c.1405T>C (p.Trp469Arg)	rs746725871	0.00009	Benign	Tolerated	Mod	4.558
	LYST	c.1676G>A (p.Arg559His)	rs138011756	0.0008	Benign	Tolerated	Mod	16.15
	SMARCAL1	c.488C>A (p.Thr163Asn)	rs748188404	0.0003	Tolerated	Tolerated	Weak	6.197

TABLE 2 (Continued)

Dx	Gene	Variant	dbSNP	ExAC AF	PolyPhen	SIFT	Conserv	CADD
Hemispheric Inflammation	*RBCK1*	c.69T>G (p.Asp23Glu)	rs748386516	0.0007	Possibly damaging	Tolerated	High	13.08
	UNC13D	**c.419T>C (p.Ile140Thr)**	**rs1181554837**	**NA**	**Probably damaging**	**Deleterious**	**Mod**	**25.9**
Meningoencephalitis of Unknown Etiology	*CARD14*	c.652C>T (p.Arg218Cys)		NA	NA	NA	Weak	24.7
	CYBA	c.274G>A (p.Val92Ile)	rs202179890	0.0002	Benign	Tolerated	Weak	7.442
	DOCK8	c.1817G>A (p.Ser606Asn)	rs778451048	0.0003	Benign	Tolerated	High	21.3
	PLCG2	c.3092A>G (p.Asn1031Ser)	rs747605077	0.00001	Benign	Deleterious	High	2.114
	PSTPIP1	c.831G>T (p.Glu277Asp)	rs990986006	NA	Tolerated	Tolerated	Mod	6.831
	RMRP	n.189C>T (RNA change)		NA			NA	
	STAT5B	c.799C>T (p.Pro267Ser)		NA	Probably damaging	Tolerated	Mod	24.3
	TNFRSF13B	c.41G>A (p.Arg14His)	rs200309474	0.002	Tolerated	Tolerated	Weak	0.258
	TNFSF12	c.610G>A (p.Gly204Arg)	rs746979506	0.00009	Probably damaging	Tolerated	Weak	14.18
	TREX1	c.24G>A (Silent)	rs147463121	0.0001	NA	NA	NA	3.279
MOGAD	***ACP5***	**c.249C>G (p.Asp83Glu)**	**rs563929774**	**0.0001**	**Probably damaging**	**Deleterious**	**High**	**24.3**
	ADA2	c.1033G>A (p.Ala345Thr)	rs752798667	0.0002	Benign	Tolerated	Mod	26.6
	AIRE	c.1438A>G (p.Thr480Ala)		NA	Benign	Tolerated	Mod	21.6
	CTLA4	c.309C>T (Silent)		NA	NA	NA	NA	35
	IFIH1	c.1745C>T (p.Ala582Val)	rs889262310	NA	Benign	Tolerated	Weak	12.41
	LRBA	c.40A>G (p.Thr14Ala)	rs1200143430	NA	Probably damaging	Tolerated	Weak	21.4
	LRBA	c.8479A>G (p.Met2827Val)	rs1276578449	NA	Probably damaging	Tolerated	Mod	19.67
	LRBA	c.8476G>A (p.Ala2826Thr)	rs779604273	0.00009	Probably damaging	Tolerated	Weak	23.7
	MEFV	c.828A>C (p.Glu276Asp)	rs775020273	0.0005	NA	NA	Weak	0.1
	NOD2	c.2104C>T (p.Arg702Trp)	rs2066844	0.03	Probably damaging	Deleterious	Mod	8.082

TABLE 2 (Continued)

Dx	Gene	Variant	dbSNP	ExAC AF	PolyPhen	SIFT	Conserv	CADD
	RAG1	c.656G>A (p.Arg219Gln)	rs764179803	0.0001	Benign	Tolerated	Mod	10.03
	RBCK1	c.700G>C (p.Glu234Gln)	rs756811010	0.0001	Benign	NA	High	40
	STAT5B	c.2348C>T (p.Pro783Leu)		NA	Possibly damaging	Tolerated	Mod	23.6
	STIM1	c.1367T>C (p.Ile456Thr)		NA	Benign	Deleterious	Mod	5.025
	STXBP2	c.1453-9G>A (Intronic)	rs372742473	0.00002	NA	NA	NA	6.059
	TNFRSF13B	c.21C>G (p.Ser7Arg)	rs780461208	0.00002	NA	Tolerated	Weak	13.14
	UNC13D	c.3022A>C (p.Thr1008Pro)	rs753816739	0.0002	Probably damaging	Tolerated	Weak	24.5
	UNC13D	c.2783G>A (p.Arg928His)	rs113461073	0.002	Benign	Tolerated	Weak	0.44
	ZAP70	c.790+5C>T (Intronic)	rs56133341	0.0004	NA	NA	NA	0.239
MS	*ACP5*	c.131C>T (p.Thr44Met)	rs369804864	0.00003	Probably damaging	NA	High	7.842
	ADAM17	c.53C>T (p.Pro18Leu)	rs144458353	0.0006	Benign	Tolerated	Mod	21.4
	BACH2	c.2230A>G (p.Ile744Val)	rs1321699864	NA	Benign	Tolerated	Weak	13.41
	CARD14	c.2140G>A (p.Gly714Ser)	rs151150961	0.0007	NA	NA	Weak	6.068
	DOCK8	c.268_270del (p.Asp90del)	rs776468911	0.0003	NA	NA	NA	26.2
	DUOX2	c.1295G>A (p.Arg432His)	rs530736554	0.0007	NA	NA	High	24.3
	DUOX2	c.1825C>T (p.Pro609Ser)	rs201221237	0.0009	NA	NA	High	25.6
	G6PC3	c.1001T>C (p.Met334Thr)	rs746741551	0.0002	Benign	Tolerated	Weak	1.205
	G6PC3	c.413G>A (p.Arg138His)	rs763535974	0.0001	Benign	Tolerated	Mod	15.17
	IL10	c.434C>T (p.Ala145Val)	rs774072665	0.00001	Benign	Tolerated	Weak	14.84
	IL1RN	c.28G>C (p.Gly10Arg)	rs770976676	0.0002	Benign	Deleterious	Weak	33
	LRBA	c.5149G>A (p.Val1717Met)	rs143003767	0.0007	Benign	Tolerated	Weak	16
	LYST	**c.2465C>T (p.Thr822Ile)**	**rs199746236**	**0.0003**	**Probably damaging**	**Deleterious**	**Mod**	**26.4**

TABLE 2 (Continued)

Dx	Gene	Variant	dbSNP	ExAC AF	PolyPhen	SIFT	Conserv	CADD
	LYST	c.6454A>C (p.Ser2152Arg)	rs201317160	0.0003	Tolerated	Tolerated	Mod	14.68
	NLRC4	**c.443G>T (p.Arg148Leu)**	**rs377088692**	**NA**	**Possibly damaging**	**Deleterious**	**High**	**15.23**
	NOD2	**c.1295C>T (p.Ala432Val)**	**rs2076754**	**0.0002**	**Probably damaging**	**Deleterious**	**High**	**16.34**
	ORAI1	c.14C>T (p.Pro5Leu)	rs549883296	NA	Tolerated	Tolerated	Weak	24.7
	RAB27A	**c.543A>G (p.Ile181Met)**	**rs139025012**	**0.0001**	**Possibly damaging**	**Deleterious**	**High**	**22.4**
	RFXANK	**c.661G>A (p.Asp221Asn)**		**NA**	**Possibly damaging**	**Deleterious**	**Mod**	**NA**
	RMRP	n.*70G>A (Non-coding)		NA	NA	NA	NA	NA
	SH3BP2	c.1135C>T (p.Pro379Ser)	rs759054470	0.00003	Benign	Tolerated	High	23.4
	STAT5B	c.2358A>G (Silent)	rs568497349	0.0002	NA	NA	NA	23.6
	STIM1	c.1773C>G (p.Asp591Glu)	rs776241052	0.0002	Benign	Tolerated	Weak	13.73
	TBX1	c.1039C>A (p.Arg347Ser)		NA	Possibly damaging	Tolerated	Mod	NA
	TNFAIP3	c.2117G>A (p.Arg706Gln)	rs3734553	0.0001	Benign	Deleterious	High	22.4
	UNC13D	**c.2795T>C (p.Leu932Pro)**	**rs760552006**	**0.003**	**Probably damaging**	**Deleterious**	**High**	**26.4**
	UNC13D	c.681C>T (Silent)	rs779543680	0.0003	NA	NA	NA	11.53
Neuropychiatric SLE	*SLC29A3*	c.146G>C (p.Arg49Pro)	rs201610819	0.001	Probably damaging	Tolerated	Weak	24.3
Neurosarcoidosis	***RNASEH2A***	**c.101A>G (p.Asp34Gly)**	**rs762516714**	**0.001**	**Probably damaging**	**Deleterious**	**High**	**27.5**
Inflammatory Stroke	***NOD2***	**c.2722G>C (p.Gly908Arg)**	**rs2066845**	**0.014**	**Probably damaging**	**Deleterious**	**Mod**	**29.7**
	RTEL1	c.2306G>A (p.Arg769His)		0.0001	Tolerated	Tolerated	Weak	11.48
RIS	*NOD2*	c.2722G>C (p.Gly908Arg)	rs2066845	0.014	NA	NA	Mod	29.7
	TTC7A	**c.563G>A (p.Arg188His)**	**rs147471840**	**0.0002**	**Probably damaging**	**Deleterious**	**Mod**	**25.2**
SLE Cerebritis	*CARD8*	c.803A>G (p.Asn268Ser)		NA	Tolerated	Tolerated	Mod	NA
	LYST	c.7157A>G (p.His2386Arg)	rs758888571	0.0002	Probably damaging	Tolerated	High	23.2

TABLE 2 (Continued)

Dx	Gene	Variant	dbSNP	ExAC AF	PolyPhen	SIFT	Conserv	CADD
	NOD2	c.2104C>T (p.Arg702Trp)	rs2066844	0.03	NA	NA	Mod	8.082
Susac Syndrome	*DCLRE1C*	c.212C>T (p.Thr71Met)	rs147013097	0.0003	Tolerated	Tolerated	Mod	24.6
Transverse Myelitis	*IFIH1*	c.2973C>A (p.Phe991Leu)	rs763358277	NA	Possibly damaging	Tolerated	Mod	21.6
	RNASEH2A	c.821A>G (p.Asn274Ser)	rs373169862	0.0007	Benign	Tolerated	Weak	2.817

Variants for which available results of all platforms were in agreement predicting detrimental effect are bolded.
ADEM: Acute disseminated encephalomyelitis, CIS: Clinically isolated syndrome, CNS: Central nervous system, MOGAD: Myelin oligodendrocyte glycoprotein antibody-associated disease, MS: Multiple Sclerosis, RIS: Radiographically isolated syndrome, SLE: Systemic Lupus Erythematous.

Conclusions: We observed a high rate of identification of rare variants in immune regulatory genes in pediatric neuroinflammatory CNS disorders. We identified 88 unique single nucleotide variants of 55 genes. Pathway analysis revealed an enrichment of NOD2-receptor signaling within this patient cohort, consistent with involvement of the pathway within other autoinflammatory conditions and warranting further investigation.

Keywords: Infections/Neuroimmunology, Demyelinating Disorders, Genetics

238. Prevalence and characteristics of children with epilepsy in a pediatric primary care comprehensive clinic.

Clarke D (Austin, TX), Rosenbloom A, Alexander M-A, Das R, Koch K, Berhane R

Objective: Children with Medical Complexity (1-3% of the pediatric population) are responsible for an inordinate amount of pediatric cost. For children with intractable epilepsy, outcomes of care in medical homes has not been fully analyzed. We reviewed Children's Comprehensive Care (CCC) for epilepsy related care cost.

Methods: Data obtained from regional emergency rooms, EMRs, home health, patient reported and Durable Medical Equipment companies was reviewed over 2020, for epilepsy related variables. Claims data from a large Medicaid managed care organization (MCO) allowed for comparison of children with epilepsy versus those without.

Results: Of 825 children attending the CCC, 335 children were insured by a MCO, with annual net paid amount of $33,380,541 in 2020. Of these 106 had at least one primary diagnosis that included epilepsy. MCO patients with an Epilepsy diagnosis had a total net payment of $11,974,924 in 2020, with an average net payment of $11,297.00 per patient (13.4% higher than the net pay for all children). The top 3 highest MCO epilepsy patient costs accounted for 61.5% of epilepsy cost, and the top 10 MCO patients' costs accounted for 89.2% of the epilepsy cost (33% of the total net MCO payment). The highest net payment in MCO epilepsy cohort was $534,254.

Conclusions: Enhanced comprehensive medical homes manage a significant proportion of patients with complex epilepsy. These children carry more fiscal demand than other children with complex medical needs. Full integration of a comprehensive epilepsy program with rigorous implementation of a standardized protocol may have the highest impact on cost and utilization.

Keywords: Epilepsy/Sleep, Equity, Diversity, Inclusion, Education

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