

# PEDIATRIC NEUROLOGY BRIEFS

## A MONTHLY JOURNAL REVIEW

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# Editorial

**EDITORIAL**

# Pediatric Neurology Briefs: Year in Review

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**Keywords:** Neurology; Pediatrics; Child Development; Nervous System Diseases; Brain Diseases

In 2020, the mission of *Pediatric Neurology Briefs* (PNB) remains the same: "PNB is a continuing education service designed to expedite and facilitate the review of current scientific research and advances in child neurology and related subjects." PNB has been published since 1987 and consists of 33 volumes with greater than 3700 articles and includes over 10,000 citations referencing the works of approximately 28,000 scholarly authors. PNB was relaunched as an open access, peer-reviewed, journal with an expanded editorial board in January 2015. In 2018, the publishing model of PNB evolved even further. The canonical version of the article was published online as soon as it was accepted and typeset. The published articles are collected into online volumes and an annual collection for print will be available at the end of every year.

The Editors of PNB select source articles using criteria that include recent publication in a peer-reviewed journal and a topic of clinical value to practicing pediatric neurologists. Contributing Editors provide detailed summaries of published articles, followed by commentaries based on their experience and corroborated by appropriate supplementary citations. In 2015, PNB launched a new website and content management system capable of organizing peer-review and providing improved indexing, DOI assignment, and online full-text article view. Prior to the internet, the Editor periodically compiled and published the PNB articles in book form with index, according to subject heading and in chronological order [1-3].

In 2016, digitization of the 30 years of back issues was completed. There are now over 3700 full text open access articles available on the journal website. Also in 2016, PNB was selected for inclusion in PubMed Central® (PMC). PMC is a free archive of biomedical and life sciences journal literature at the U.S. National Institutes of Health's National Library of Medicine (NIH/NLM). The most highly accessed articles published in 2019 covered topics related to psychogenic seizures [4], spinal muscular atrophy [5], and the treatment of infantile spasms [6].

The Editors would like to take this opportunity to sincerely thank the 2019 Contributing Editors for their effort and expertise (listed below in alphabetical order):

S. Kathleen Bandt, MD  
Amber N. Buehner, APN-NP  
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In 2020, the Editor, Dr. John J. Millichap, is joined by two new Associate Editors, Dr. Andrea Pardo and Dr. Stephen Nelson. Topic experts interested in contributing to PNB as authors or reviewers are invited to contact the Editor at j-millichap@northwestern.edu.

## Disclosures

The author has declared that no competing interests exist.

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# Seizure Disorders

**SEIZURE DISORDERS****Stereo-EEG in Tuberous Sclerosis Complex**

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**Related Article:** Neal A, Ostrowsky-Coste K, Jung J, Lagarde S, Maillard L, Kahane P, et al. Epileptogenicity in tuberous sclerosis complex: A stereoelectroencephalographic study. *Epilepsia*. 2020 Jan;61(1):81–95

**Keywords:** Epileptogenic Zone; Stereo-EEG; Tuberous Sclerosis Complex; Pediatric Epilepsy Surgery

A collaborative research team lead by an investigator from the Lyon Neuroscience Research Center and Lyon University Hospital and Lyon 1 University studied epileptogenicity of tuber and its surrounding cortex using stereoelectroencephalography (SEEG) in patients diagnosed with tuberous sclerosis complex (TSC) (genetic or clinical). A study cohort of eighteen patients (11 children) who underwent presurgical SEEG evaluation between 2004 and 2018 was identified from four French tertiary epilepsy centers. The electrodes were implanted bilaterally in 14 patients, and the total number of electrodes ranged from 8 to 16 per patient. The total number of tubers in each patient ranged from 3 to 30 [1].

Epileptogenicity Index (EI) [2] was used to analyze seizures after defining five anatomical regions of interest (ROI): dominant tuber (tuber with highest median EI), perituber cortex, secondary tuber (tuber with second highest median EI), nearby cortex (normal-appearing cortex in the same lobe as the dominant tuber), and distant cortex (normal appearing cortex in other lobes). The value of EI ranged from 0 to 1 (peak epileptogenicity). The epileptogenic zone (EZ) organization was categorized as either focal tuber (EZ limited to dominant tuber with median EI>0.3) or complex (all other patients).

The dominant tuber was the most epileptogenic ( $P < .001$ ) of the five ROI. Seven patients with a focal tuber EZ organization had 80% Engel IA postsurgical outcome and the following 4 tuber characteristics: continuous interictal discharges (100%), fluid-attenuated inversion recovery (FLAIR) hypointense center (86%), stimulation – induced seizures (71%), and center-to-rim EI gradient. A combination of the first three characteristics showed a 98% specificity for a focal tuber EZ organization. Six patients with a complex EZ organization showed 40% Engel IA outcome with nearby cortex (4 patients) and distant cortex (1) as the most epileptogenic region. The authors concluded that tubers with focal EZ organization are much like type II focal cortical dysplasia, and that identification of these tubers relate to EZ hypothesis generation and invasive EEG/resection strategies. [1]

**COMMENTARY.** Talarirach and Bancaud developed “stereoecephalographie” in the 1960s as a tool to aid in

defining the EZ. Their definition of EZ was an ictal electro-clinical concept based on SEEG recordings. Over the past 50 years, the concept of EZ has evolved due to invention of sophisticated localizing tools. Hans Lüders et al. (2006) defined EZ as “the minimum amount of cortex that must be resected to produce seizure freedom [3].” Ultimately, identification of the EZ heavily influences seizure freedom after resective surgery. This article adds an important insight for identification of EZ in TSC, utilizing one of the advantages of SEEG that allows sampling of multiple cortical regions, unilateral and/or bilateral.

The authors reported the following results in consideration of EZ identification in TSC: 1. A combination of the three characteristics - continuous interictal discharges, FLAIR hypointense center, and stimulation-induced seizures, showed a 98% specificity in localizing the dominant tuber; 2. Nearby cortex (4 of 6 patients) was the most epileptogenic (with highest median EI) in the presence of a dominant tuber that lacked center-to-rim gradient in EI. Importantly, these results may contribute to development of an effective implantation strategy of intracerebral electrodes in further defining EZ in TSC, as one of the challenges of using SEEG is determining targets and trajectories based on presurgical data and EZ hypothesis. Experience and skill of a functional neurosurgeon who places intracerebral electrodes to confirm/modify/reject the hypothesis of EZ may also influence outcome. The current work is a welcome and laudable contribution to further our understanding of epileptogenicity in TSC.

**Disclosures**

The authors have declared that no competing interests exist.

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**SEIZURE DISORDERS**

# Wearable EEG Device for Continuous Spike–Wave in Sleep

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**Related Article:** Carvalho D, Mendes T, Dias AI, Leal A. Interictal spike quantification in continuous spike-wave of sleep (CSWS): clinical usefulness of a wearable EEG device. *Epilepsy Behav.* 2020 Jan;104 Pt A:106902.

**Keywords:** ESSES; CSWS; Spike Index; Wearable Ambulatory EEG

Investigators from the Hospital Dona Estefânia, Escola Superior de Tecnologias e Saúde de Lisboa and Centro Hospitalar Psiquiátrico de Lisboa investigated 38 patients with continuous spike-wave of sleep (CSWS) syndrome. A 10-20 montage long-term ambulatory electroencephalography (aEEG) and a wearable aEEG with two bipolar EEG channels simultaneously validate the latter's usefulness to quantify the spike index (SI) to analyze the EEG response to the treatments. The SI was digitally calculated every 10 minutes by semiautomatic template-match-spike search analysis compared to both aEEG. They also compared daily SI stability (three-consecutive night, N=4) and monthly SI stability (N=10) in individual patients and employed the SI obtained from averaging the maximum SI for each of the first four sleep cycles (avSI) for comparison to reduce variability. The wearable aEEG examinations were repeated up to 8 times per patient. The response to therapy using corticosteroids (n=10), sulthiame (n=7), and the ketogenic diet (n=3) was assessed by comparison of the avSI after therapy. As a result, corticosteroids most effectively reduced the SI among therapies, although sizeable individual variability in both the amount and time of onset of clinical responses. In conclusion, the wearable aEEG with two bipolar EEG channels, which are easily attached and tolerable for children, can provide accurate SI quantification repeatedly in clinical settings. [1]

**COMMENTARY.** CSWS syndrome, also known as encephalopathy related to status epilepticus during slow sleep (ESSES), is one of the most common epileptic encephalopathies of childhood [2]. In this syndrome, epileptic seizures themselves may be infrequent or even absent, but EEG demonstrates marked activation of spike-wave discharges during sleep. The latter EEG phenomenon is believed to cause cognitive/behavioral deterioration in this syndrome because it electrically affects cerebral function [2]. As CSWS has been observed before such deteriorations, it is essential to estimate the SI for early therapeutic intervention. In clinical practice, the SI has been evaluated by routine EEG examinations during naps or long-term EEG during hospitalization; however, both methods have limitations, i.e., difficult interpretation of the SI and expense of repeated examinations [3,4]. Thus, it is ideal to evaluate the SI using aEEG for 24 hours at home. However, the aEEG device

currently available is expensive, complicated to attach, and also intolerable to wear for a long time for children. In this study, the authors developed the wearable aEEG device capable of recording with bipolar two channels and digitally quantifying the SI, which was demonstrated to be accurate by comparing the SI with that of the full 10-20 long-term aEEG. The semiautomatic template-match-spike search analysis they employed can plot the SI every 10 minutes during overnight sleep accurately and without difficulty [5]. In CSWS syndrome, the methods to determine the SI and its boundary to limit the CSWS definition (initially SI >85%) have remained major concerns among specialists [2-4]. In terms of its simplicity, cost, and unification of the methods to quantify the SI, the wearable aEEG in this study should be useful not only in clinical practice but also in CSWS syndrome studies.

## Disclosures

The author has declared that no competing interests exist.

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# Neonatal Disorders

## NEONATAL DISORDERS

# Hypoglycemia in Infants and Effect on Neurodevelopment

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**Related Article:** van Kempen AA, Eskes PF, Nuytemans DH, van der Lee JH, Dijksman LM, van Veenendaal NR, et al.; HypoEXIT Study Group. Lower versus Traditional Treatment Threshold for Neonatal Hypoglycemia. *N Engl J Med.* 2020 Feb;382(6):534–44.

**Keywords:** Hypoglycemia; Child Development; Blood Glucose; Infant; Newborn

In a prospective, randomized treatment trial, investigators from multiple institutions in the HypoEXIT Study Group investigated the developmental outcomes after neonatal hypoglycemia, comparing the traditional glucose threshold 47 mg/dL vs. 36 mg/dL. Healthy infants without initial severe hypoglycemia (<35 mg/dL) but with asymptomatic moderate hypoglycemia between 3-24 hours of life were randomly assigned to the lower threshold group or, the higher threshold group. The study demonstrated non-inferiority in the lower threshold vs. traditional threshold group regarding Bayley III scores at 18 months. [1]

**COMMENTARY.** Management of hypoglycemia in the newborn period is highly variable among institutions and professional societies. 2011 AAP guidelines define neonatal hypoglycemia as blood glucose <47 mg/dL and recommend maintaining blood glucose >40 mg/dL in the first 4 hours and >45 between hours 4-24 [2]. The Pediatric Endocrine Society has an even stricter threshold of >50 mg/dL [3]. However, a higher cutoff necessitates additional interventions, as seen in this study. Both prolonged hyper and hypoglycemia have been associated with poor neurologic outcomes. However, less research has been done into the impact of more transient hypoglycemia episodes, which are generally thought to be insignificant [4]. As this paper demonstrates no difference in Bayley scoring at 18 months, perhaps added interventions to match a higher threshold are not needed. This study's strength is that it is prospective and randomized, rather than observational like many previous, similar studies. Also, as multiple centers enrolled and were instructed to tailor supplementation to their usual practices, this study focuses on the main effect and has greater applicability. The literature includes multiple contradictory studies suggesting that even moderate hypoglycemia impacts executive function [5] and cognitive functioning [6], evidenced at later ages by poor school performance [7]. A major limitation of this study is the single test and age used to evaluate cognitive function. Early assessment precludes testing of speech, comprehension, and motor planning previously seen to be impacted in other studies. Second, there have been varying definitions of "neurologic impairment" ranging from specific testing like the Bayley (as in this paper) to ICD diagnostic codes ranging from autism spectrum disorder to febrile

seizures [6], suggesting a lack of insight into the brain microcircuitry most at risk. Third, the authors recognize the potential for recurrent hypoglycemia, which may be more severe if starting at a lower threshold. Data are lacking from the biochemical literature on whether the brain is most susceptible to injury from repeated drops in glucose stores or total time spent in a hypoglycemic state.

Taken together, this paper reiterates the need for a critical reevaluation of treatment pathways based on lab values alone and the need to tailor treatment based on the clinical picture.

### Disclosures

The authors have declared that no competing interests exist.

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# Demyelinating Disorders

## DEMYELINATING DISORDERS

# Quality of Life in Multiple Sclerosis

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**Related Article:** McKay KA, Ernstsson O, Manouchehrinia A, Olsson T, Hillert J. Determinants of quality of life in pediatric- and adult-onset multiple sclerosis. *Neurology*. 2020 Mar;94(9):e932–41.

**Keywords:** Pediatric; Multiple Sclerosis; Quality of Life

Investigators from Karolinska Institute in Stockholm, Sweden report on their findings comparing quality of life (QoL) measures in both pediatric-onset multiple sclerosis (POMS) and adult-onset multiple sclerosis (AOM). Data was collected from the nationwide Swedish multiple sclerosis (MS) registry between 2010 & 2019 (354 POMS; 4,740 AOM). Analyses of their findings were interpreted as showing no significant difference between POMS and AOMS regarding QoL measures in adulthood. The most significant determinants that negatively influenced QoL were relapses, severe neurologic disability, and higher MSIS-29 psychological score. Those with higher information processing efficiency and exposure to first-line DMTs were associated with higher QoL scores. The authors suggest focusing on reducing neurological disability and psychological status as potential measures to improve QoL in both POMS and AOMS. [1]

**COMMENTARY.** The etiology of MS is not well understood; however, diagnostic criteria and therapeutic agents have continued to advance, and further refinement has progressed over the last several decades, especially in the field of POMS. Despite such advances, there remains a great deal of morbidity in both POMS and AOMS. The physical and cognitive effects of MS have been long recognized and studied in AOMS. However, until more recently, the factors affecting QoL in POMS had primarily been under-recognized. Pediatric patients typically have a comparatively quicker recovery from relapses and longer course until the progression to permanent neurological disability does so at a younger age [2]. The lasting cognitive effects in POMS have been found to occur early on in the course of the disease, with physical disability occurring later, which contrasts to adults where both physical and cognitive effects often parallel each other in the course of the disease. This clinical course difference may initially feel counter-intuitive, as it is generally known that the pediatric brain possesses more plasticity and cognitive reserve than its adult counterpart. More recent research indicates that the onset of MS in critical neurodevelopmental periods likely has a more significant impact on cognitive function than in the adult brain, significantly earlier in the disease course [3]. Although not fixed in its makeup, the adult nervous system has completed the myelination process and most of its synaptic formation

and other major critical structural pathways that may account for differences observed.

This study's impactful aspects are the large number of children they included in their cohort and the unique manner in which the QoL measures of the same disease were compared between children and adult-onset cases. Most studies involving QoL measures in children with neurological disorders compare the study cohort, which is often small, with children who do not have the disease process [4,5]. While this information is helpful, it is not as pertinent to a clinician as studying the same disease state across the life span or with onset at different ages. The authors' key finding that children with POMS experience significant impairments in several critical QoL measures is essential for practicing child neurologists. It should encourage them to adopt a multifaceted approach focusing on both psychological function and physical disability for better long-term outcomes.

### Disclosures

The authors have declared that no competing interests exist.

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## DEMYELINATING DISORDERS

# Plasma Exchange for Treatment of Refractory Demyelination

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**Related Article:** Savransky A, Rubstein A, Rios MH, Vergel SL, Velasquez MC, Sierra SP, et al. Prognostic indicators of improvement with therapeutic plasma exchange in pediatric demyelination. *Neurology*. 2019 Nov;93(22):e2065–73

**Keywords:** Plasma Exchange; Neuroinflammation; Demyelination

Researchers from the National Pediatric Hospital in Buenos Aires, Argentina, describe their experience with therapeutic plasma exchange (TPE) for refractory inflammatory central nervous system (CNS) attacks in children over the course of the last 15 years. The authors conclude that TPE is an effective treatment for severe CNS inflammatory demyelinating events that are not responsive to steroids and that the overall frequency of adverse events associated with therapy is low.

The authors analyzed a total of 78 children with confirmed acute CNS episodes who were treated with TPE. They assessed improvement after TPE using a series of standardized functional assessments across four domains. These assessments were conducted before, immediately following, and then 3 and 6 months after TPE. They found that 72% of patients (56 of 78) had moderate to marked improvement at the end of their first treatment with TPE and 82% of patients (56 of 68) after three months of treatment. The authors report four adverse events that they characterize as "serious" and 27 which they classify as "mild to moderate" out of 65 patients who underwent a total of 524 procedures. [1]

**COMMENTARY.** Treatment of refractory CNS inflammatory disorders in children is variable, and data supporting these practices is lacking. This study is an essential contribution to the pediatric literature on inflammatory CNS attacks, although there are some limitations as a retrospective analysis. First, there is no control group, and children who suffer acute demyelinating attacks can often recover independently of the treatment they receive, even those who present with profound impairment [2]. When describing the persistence of benefit at six months, the authors report that a higher percentage of patients experienced recovery (82%) in the TPE group. However, the absolute number of patients (56) remained the same because the patients who did not experience improvement did not continue to receive TPE therapy and were excluded from subsequent analysis. This raises the question of whether clinical improvement in the TPE group can be attributed to the TPE therapy itself.

TPE carries a risk for complications. Several of the events the authors classified as "mild" (hypotension, catheter-related infection, symptomatic hypocalcemia) are also

potentially life-threatening. Complications from the placement of central venous catheters in critically-ill children occur at rates that can be up to as high as 22% [3]. Younger children are also more likely to experience complications, including accidental removal of the catheter itself [3]. Younger children also require sedation to place a central venous catheter, further placing them at risk for additional complications. Finally, TPE's successful course requires expertise in many areas that may not be available at all centers [4].

Data from another large series suggest TPE should be used with caution in demyelinating disorders. In a retrospective study of 283 Canadian children with acute demyelinating attacks, most (< 90%) recovered, and only four received TPE [2]. In the series by Savransky et al., one patient died due to pulmonary embolism, thought to be attributable to central line placement [1]. The use of baseline and repeat assessments are strengths of this study and lend weight to the author's conclusion that TPE is an effective treatment for this disorder, even when delayed up to six months after symptom onset. The attention to the potential for TPE complications is a reminder that in seeking to help children with these debilitating illnesses, we must recognize potential risks in addition to the uncertain benefits.

### Disclosures

The authors have declared that no competing interests exist.

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# Vascular Disorders

## VASCULAR DISORDERS

# Stroke in the Adolescent Population

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**Related Article:** Rambaud T, Legris N, Bejot Y, Bellesme C, Lapergue B, Jouvent E, et al. Acute ischemic stroke in adolescents. *Neurology.* 2020 Jan;94(2):e158–69.

**Keywords:** Stroke; Ischemia; Adolescent; Revascularization; tPA

Investigators from 10 French academic centers studied a retrospective cohort of 60 patients aged 10-18 years (mean age 15.2 years) presenting with first-time stroke, as identified from discharge ICD-10 codes. These patients were treated in 10 adult and pediatric centers across 2 regions of France between 2007 and 2017. Subarachnoid hemorrhage or cerebral venous thrombosis were excluded from this study. Interestingly, the authors identified a significant proportion of their cohort with atheromatous risk factors more commonly associated with adult stroke, including cigarette smoking and obesity, although it is unclear how these rates compare to those of otherwise healthy adolescents. Among the underlying risk factors and conditions explored previously by the International Pediatric Stroke Study, chronic head and neck conditions, including migraine, were most common.

Although delayed diagnosis has been a significant problem in pediatric stroke, the majority of the patients in this study presented within 4.5 hours. 32% of patients were treated with hyperacute revascularization treatments, including IV tPA, intra-arterial thrombolysis, and mechanical thrombectomy. Patients presenting to adult hospitals were more likely to receive revascularization therapies. There were 3 instances of hemorrhagic transformation, one of which was symptomatic, and no symptomatic intracranial hemorrhages associated with revascularization treatments. There were no significant differences in 3-month outcomes with revascularization treatment, despite significantly higher initial NIHSS scores seen in these patients.

TOAST and CASCADE classifications were applied to each patient. 2 patients that were classified as undetermined in TOAST but were classified as unilateral arteriopathy according to CASCADE, possibly reflecting the focus on pediatric etiologies in this system. Recurrent cerebrovascular events occurred in 7 patients, all of whom had a vasculopathy based on CASCADE classification. [1]

**COMMENTARY.** Age-specific data to guide evaluation and management strategies is limited for adolescent stroke patients. In particular, the use of hyperacute revascularization therapies remain controversial [2]. Past efforts to study the safety and efficacy of tPA in children via a randomized controlled trial were unsuccessful, partially due to the

medical comorbidities and diagnostic difficulties associated with pediatric stroke. Although the sample size is relatively small, this trial adds to retrospective evidence suggesting that revascularizing therapies may be safe, in this case in older children. Nearly one-third of the adolescents in this study were treated with endovascular therapies, with no symptomatic hemorrhages reported among those treated. This is consistent with other recent pediatric data from another small retrospective series [3].

As demonstrated by the data presented here, adolescents with stroke may share characteristics of both pediatric and young adults. This retrospective series is a good start to explore how these older children may experience unique risk factors and responses to treatment. Further study will rely on being able to consistently describe and categorize the etiology of stroke among this group. The results of this study would suggest that, despite their mixed characteristics, a pediatric-specific categorization schema remains the best option for adolescents. CASCADE is notable for its distinction of anatomic vascular etiologies and seems to be a more appropriate classification system in the adolescent population [4].

## Disclosures

The authors have declared that no competing interests exist.

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# Sleep Disorders

## SLEEP DISORDERS

# Iron and Insomnia in Autism Spectrum Disorder

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**Related Article:** Reynolds AM, Connolly HV, Katz T, Goldman SE, Weiss SK, Halbower AC, et al. Randomized, Placebo-Controlled Trial of Ferrous Sulfate to Treat Insomnia in Children With Autism Spectrum Disorders. *Pediatr Neurol.* 2020 Mar;104:30–9.

**Keywords:** Autism; Insomnia; Restless Legs Syndrome; Iron; Ferrous Sulfate

Investigators from four major Universities studied the impact of iron supplementation on insomnia symptoms in children with Autism Spectrum Disorder (ASD) and ferritin levels not indicative of iron deficiency anemia. The study assessed twenty children who had confirmed ASD, difficulties with sleep onset or maintenance, and ferritin levels 17-50 ng/mL. [1]

**COMMENTARY.** Sleep disorders are prevalent in children with ASD and have tremendous implications on their physical and social-emotional health [2]. In addition to strengthening positive behavioral patterns surrounding sleep, pediatric neurologists must also consider organic sleep disorders that contribute to sleep challenges. This study focused on children with insomnia and ferritin levels <50 ng/mL, a value at which treatment with iron repletion is indicated for Restless Legs Syndrome (RLS) or Periodic Limb Movement Disorder (PLMD) in children [3]. The aim was to assess if difficulties with sleep onset or maintenance would improve with empiric treatment of a ferritin <50 ng/mL without a formal sleep disorder. While empiric therapy was not shown to be effective in managing insomnia in the setting of ASD, it highlights the importance of evaluating for at least two independent sleep disorders that may also present with difficulties falling or staying asleep: RLS and PLMD [1].

A reported history of uncomfortable sensations, often in the legs, diagnoses RLS, which are associated with the urge to move and are 1) worse at night, 2) worse at rest, and 3) relieved by movement [3]. Ferritin levels are often empirically treated when <50 ng/mL. The lack of an improvement in sleep onset after empiric treatment in this study suggests that the sample may primarily represent children with ASD who do not have RLS. Hopefully, our ability to diagnose RLS in children with ASD will improve in the future to allow for more targeted treatment.

PLMD is diagnosed in children with polysomnography demonstrating >5 limb movements/hour with impairment in daytime functioning [4]; a “wild sleeper” to a parent. Parental observations may also represent Restless Sleep Disorder (RSD), who has subjective reports of sleep movements but no polysomnographic evidence of PLMD [5]. Early findings suggest that these children have decreased iron stores, as well [5]. Arousal with limb movements may also

lead to prolonged awakenings if re-initiating sleep is a challenge [6]. Iron testing/treatment follows the RLS pathway. However, as used in this study, actigraphy is not validated to diagnose or assess the response to treatment in PLMD [7]. As with RLS, children with PLMD (or RSD), who could be responders to iron, must be appropriately identified before making therapeutic decisions.

Sleep-focused history taking and formal sleep testing, when indicated, will help identify patients with ASD who could benefit from iron testing and supplementation for the treatment of specific sleep disorders. Selecting these patients out of future studies will help clarify what role, if any, iron can play in managing sleep in this complex population.

### Disclosures

The authors have declared that no competing interests exist.

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# Movement Disorders

## **MOVEMENT DISORDERS**

# **Hand Stereotypies in Rett Syndrome**

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**Related Article:** Stallworth JL, Dy ME, Buchanan CB, Chen CF, Scott AE, Glaze DG, et al. Hand stereotypies: Lessons from the Rett Syndrome Natural History Study. *Neurology*. 2019 May;92(22):e2594–603.

**Keywords:** Motor Stereotypies; Rett Syndrome; Movement Disorders

Researchers from the Rett Syndrome Natural History Study (RNHS) present longitudinal data across the United States of America aimed to characterize hand stereotypies (HS) in this large cohort of patients with Rett syndrome. They reported 922 patients with classic Rett syndrome, 75 with atypical severe and 77 with atypical mild Rett syndrome. All patients were female and were assessed every 6 to 12 months between 2006 to 2015. The comparison group consisted of 49 patients who did not meet the clinical criteria for Rett syndrome but had documented MECP2 mutations. MECP2 mutations were classified according to severity in mild, moderate or severe. Hand stereotypies were pre-classified in 8 groups. The authors detected HS in 99.5% of Rett syndrome patients at enrollment against only 35% among the non-Rett group, confirming the specificity of thus clinical finding.

The authors detected HS in 99.5% of Rett syndrome patients at enrollment against only 35% among the non-Rett group, confirming the specificity of this clinical finding. Hand mouthing and clapping/tapping were more frequently found than wringing/washing. No difference was observed when comparing hand stereotypies prevalence and specific mutations in MECP2; there was, however, an association between severity of MECP2 mutation and a higher frequency and number of stereotypies. Prevalence and frequency of hand stereotypies did not differ when comparing patients younger than 21 years to participants 21 years and older. The number stereotypies and severity of mouthing was higher among the pediatric population. Age of onset was remarkably different between study categories, with atypical severe patients having an earlier onset ( $1.52 \pm 1.1$  years) compared to typical Rett syndrome ( $1.87 \pm 1.1$  years) and atypical mild patients ( $3.06 \pm 2.5$  years;  $p < 0.001$ ). Additionally, the majority of Rett syndrome patients showed developmental regression first and later developed hand stereotypies (62.7%).

Finally, the presence of hand stereotypies was not related to disease severity or other characteristics. The longitudinal analysis of this study showed that while the level of hand function seems to relate to the age at onset and frequency of hand stereotypies, the progressive decline in manual abilities does not follow the same path. In fact, the loss of function should be analyzed in a broader context considering other features of the disease, such as rigidity and bradykinesia. [1]

**COMMENTARY.** Motor stereotypies are common childhood onset movement disorders with complex aetiologies [2]. By the beginning of this decade Edwards et al proposed it to be defined as “*a non-goal-directed movement pattern that is repeated continuously for a period of time in the same form and on multiple occasions, and which is typically distractable*” [3]. Hand stereotypies are a defining characteristic of Rett syndrome, confirmed by this paper. The present study however has two very interesting aspects, especially for a rare disease: its longitudinal design and a large number of patients. Here the authors explore from different angles hand stereotypies, probably the most remarkable clinical sign of the disease. The identification of the multiple causative MECP2 mutations [4] has aided in understanding the phenotypical variety observed in clinical practice. Interestingly, they found that severe mutations correlated with a greater number of stereotypies and not with their severity. These findings may help identify a genotype-phenotype correlation related to each specific mutation, however more data is necessary.

It should be observed, that in this article, adults represented only 12% of the population studied and male patients were excluded. Although these are infrequent clinical findings, it is reasonable to expect such cases as clinical care and diagnostic tools become more available throughout the world. Hence, a focused analysis including these groups is necessary in future studies.

### **Disclosures**

The authors have declared that no competing interests exist.

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# Neuromuscular Disorders

## **NEUROMUSCULAR DISORDERS**

# **Utility of Repetitive Nerve Stimulation in Myopathies**

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**Related Article:** Elahi B, Laughlin RS, Litchy WJ, Milone M, Liewluck T. Neuromuscular transmission defects in myopathies: rare but worth searching for. Muscle Nerve. 2019 Apr;59(4):475–8.

**Keywords:** Neuromuscular Junction; Myopathy; Repetitive Nerve Stimulation

Investigators from the Mayo Clinic, Rochester, MN, evaluated 157 patients with confirmed myopathy who had electrodiagnostic studies done between January 2007 and May 2017. Diagnosis of myopathy was confirmed by muscle pathology or genetic studies in those 157 patients. The study examined the frequency and electrophysiologic characteristics of decrement in these patients.

Of the 157 patients with confirmed myopathy on muscle pathology, 4 patients (2.55%) showed a significant decrement (greater than 10% decrement at 2Hz RNS with a train of 4 stimuli). These 4 patients, with age of onset of symptoms between 18 and 75 years of age, were ultimately diagnosed with the following: centronuclear myopathy (Patient 1), distal myopathy with nonspecific pathological findings (Patient 2), anti-synthetase (Jo-1) antibody-associated inflammatory myopathy as well as hydroxychloroquine associated myopathy (Patient 3), and hydroxychloroquine associated myopathy with minimal perimysial inflammatory reaction (Patient 4).

Patient 1 had improvement in muscle strength with a trial of pyridostigmine and no improvement with immunotherapy. Patient 2 and Patient 3 showed no response to pyridostigmine and were not treated with immunomodulatory therapy. Patient 3 showed no improvement with pyridostigmine. Patient 4 was not treated with any medications. [1]

**COMMENTARY.** In the evaluation of a suspected disease of the neuromuscular junction, repetitive nerve stimulation (RNS) is a time-honored technique to help confirm a defect in neuromuscular junction (NMJ) transmission. Decremental response can occur in a subset of patients with either hereditary or acquired myopathies. Additionally, multiple studies in adults and children have shown neuromuscular transmission defects and abnormal RNS in both animal models and human subjects that did not have a primary NMJ pathology. Aside from primary disorders of the NMJ, decrement can sometimes be seen in pediatric patients with motor neuron disease, muscular dystrophies, and myotonic disorders [2]. The mechanism of neuromuscular transmission defect is thought to be multifactorial and hypotheses include increased refractoriness associated with repetitive discharges, as seen in myotonic disorders, and a co-occurring primary

defect at the junction, as seen in some hereditary muscle diseases.

Clinically differentiating congenital myasthenic syndromes, congenital myopathies and other disorders of the neuromuscular axis can be a diagnostic challenge for even an experienced pediatric neuromuscular clinician. Infants with myasthenic syndrome do not always present with fatigable weakness. Furthermore, those presenting with a defect in neuromuscular transmission can have a broader differential beyond a primary defect of the NMJ.

Repetitive nerve stimulation was not a technique commonly used in the work-up and evaluation of congenital myopathy but would be beneficial in children for identifying a defect in neuromuscular transmission. Low Frequency stimulation (2-5Hz) can aid in identifying post synaptic disorders whereas high frequency settings (20-50 Hz) can help with presynaptic disorders. An alternative technique to consider would be single-fiber EMG. Children found to have a decrement on RNS might also benefit from further analysis, such as presence of myasthenia gravis antibodies and genetic testing for congenital myasthenic syndromes. Even in the neonatal period, RNS can be extremely useful to help guide the initial work-up and reach a diagnosis in a timely manner. Furthermore, therapeutic strategies could be employed such as a trial of an AChEI along with cautious use of immunotherapy. Other therapies that could be considered include 3,4-DAP (amifampridine) and albuterol, as these have shown to be effective in some myasthenic syndromes and help enhance NMJ transmission.

Further studies in children with congenital myopathies will aid clinicians to better understand the benefits of RNS in myopathies.

### **Disclosures**

The authors have declared that no competing interests exist.

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## **NEUROMUSCULAR DISORDERS**

# **Treatment with Ataluren for Duchene Muscular Dystrophy**

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**Related Article:** Mercuri E, Muntoni F, Osorio AN, Tulinius M, Buccella F, Morgenroth LP, et al.; STRIDE; CINRG Duchenne Natural History Investigators. Safety and effectiveness of ataluren: comparison of results from the STRIDE Registry and CINRG DMD Natural History Study. *J Comp Eff Res.* 2020 Apr;9(5):341–60.

**Keywords:** Pediatric; Neuromuscular; Duchenne Muscular Dystrophy; STRIDE Registry

Investigators from Europe and the USA, representing the STRIDE Registry and Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS), examined the effectiveness of ataluren and standard of care in the Registry versus stand of care alone in the CINRG DNHS. The CINRG DNHS was a prospective, longitudinal worldwide study of more than 400 patients with Duchene Muscular Dystrophy (DMD) followed between 2006 and 2016. This analysis indicated that ataluren and standard of care delays DMD progression of functional milestones in patients with nmDMD and that ataluren was well tolerated. [1]

**COMMENTARY.** The clinical potential of ataluren in the treatment of DMD was described by Namgoong et al. [2]. Ataluren is a first-in-class, oral treatment for patients with nmDMD, designed to enable full-length dystrophin protein production. Ataluren has been evaluated previously in patients with nmDMD in two randomized controlled trials. Both trials showed that ataluren (40 mg/kg/day) had favorable functional efficacy. Ataluren is indicated for the treatment of nmDMD in ambulatory patients aged five years or older in Brazil, Chile, Israel, the Republic of Korea, Ukraine, and two years or older in Iceland, Liechtenstein, and Norway. Efficacy has not been demonstrated in non-ambulatory patients.

The STRIDE Registry constitutes the first drug registry for patients with DMD. Mean & Standard deviation (SD) ages of patients at muscle biopsy and genetic diagnosis were 4.5 (2.5) years and 5.2 (2.9) years, respectively; the time from first symptoms to genetic diagnosis was 2.4 (2.4) years. Results from a separate international multicenter registry study showed that the mean (SD) patient age at DMD diagnosis by muscle biopsy or genetic testing was 4.3 (2.5) years, and the mean (SD) time from first symptoms to this diagnosis was 1.3 (1.8) years across countries. These figures suggest that patients in the STRIDE Registry are diagnosed later than those in the total DMD population. This phenomenon is probably related to the sequential genetic testing process for DMD introducing delays in diagnosis. However, compared with five years ago, next-generation sequencing is now more accessible and less expensive; thus,

performing the second step in the genetic testing process is more feasible now, closing this diagnostic delay [3].

The STRIDE Registry provided the opportunity to follow-up patients over a more extended period than clinical studies. The study's limitation is that the STRIDE and CINRG DNHS populations were not matched according to nmDMD mutation type or location. However, this would not be considered a real source of bias because patients were matched based on other factors that predict disease progression, such as age at onset of first symptoms. (4). Overall, the results corroborate previous evidence that ataluren treatment can slow disease progression in nmDMD. The STRIDE Registry contains patients with a broader range of ages and ambulatory ability than those in clinical trials, and thus, the data represents a broader range of real-world experiences [3].

These analyses are based on interim data, but the STRIDE Registry study's final results are expected 2025. Large clinical trials are required to assess ataluren's role and its long-term impact on disease progression in non-ambulant nmDMD patients, but the introduction of ataluren in the field is an achievement [2].

### **Disclosures**

The author has declared that no competing interests exist.

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## NEUROMUSCULAR DISORDERS

# Outcome Measures for *COL6* and *LAMA2*-Related Dystrophies

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**Related Article:** Jain MS, Meilleur K, Kim E, Norato G, Waite M, Nelson L, et al. Longitudinal changes in clinical outcome measures in *COL6*-related dystrophies and *LAMA2*-related dystrophies. *Neurology*. 2019 Nov;93(21):e1932–43.

**Keywords:** *LAMA2*-Related Dystrophies; *COL6*-Related Dystrophies; Muscular Dystrophy

Investigators from the NIH performed a longitudinal, prospective, natural history study looking at patients with *COL6*-related dystrophies (*COL6*-RDs) and *LAMA2*-related dystrophies (*LAMA2*-RDs), the two most common congenital muscular dystrophies (CMDs). Over four years, 47 individuals were assessed using the Motor Function Measure 32 (MFM32) scale, myometry, goniometry, pulmonary function tests, and quality-of-life measures. The study aimed to identify the rate of change in clinical outcome measures with these subtypes of CMD. [1]

**COMMENTARY.** CMDs are a heterogeneous group of disorders with early-onset weakness and dystrophic changes on muscle biopsy. The major categories of CMDs are characterized by the defective protein's location and function [2]. *COL6*-RDs and *LAMA2*-RDs both involve defects in proteins integral to maintaining the integrity of the extracellular matrix.

Children with pathogenic variants in genes encoding *COL6* can present in infancy, referred to as Ullrich CMD, or present later in childhood with the benign form called Bethlem myopathy. *COL6A1*, *COL6A2*, and *COL6A3* are the three genes with known pathogenic variants. Ullrich CMD is associated with congenital muscle weakness, hypotonia, joint contractures and hyperextensibility, and average intellect. Bethlem myopathy has similar features but a later presentation with some individuals maintaining ambulation into adulthood [3].

*LAMA2*-RD is associated with pathogenic variants in *LAMA2*, encoding a merosin subchain, and children usually present at birth with weakness and hypotonia. Merosin binds to alpha-dystroglycan, and defects lead to an unstable dystrophin-glycoprotein complex. Other features include joint contractures, scoliosis, breathing difficulties, and seizures. White matter changes are seen on brain MRI, but intelligence is usually average. Children with *LAMA2*-RD achieve independent ambulation less frequently (about 1/3 in this cohort). The phenotype severity correlates with a complete or partial loss of laminin-a2 on immunohistochemical staining [4].

This study evaluated the annual rate of change in outcome measures to better understand the natural history and progression over time. Overall, non-ambulatory

individuals with *COL6*-RD had a more significant decline rate than ambulatory *COL6*-RD individuals and ambulatory/non-ambulatory *LAMA2*-RD individuals. The most sensitive outcome measure was the MFM32 score, which showed a measurable decline in both ambulatory and non-ambulatory individuals with both subtypes. Five individuals lost the ability to ambulate, and those children showed a decline in all domains of the MFM32. As seen in previous studies, the mean age of loss of ambulation in *COL6*-RD was ten years, while individuals with *LAMA2*-RD lost ambulation at a later age. The other outcome measures also showed a decline but not in all subgroups. Quality of Life (PedsQL) did not demonstrate statistically significant changes. The MFM32 scale was the only outcome measure showing a consistent decline over four years.

This study demonstrates the importance of understanding the natural history and establishing validated outcome measures in rare diseases. Understanding natural history and tools to monitor disease progression over time allows one to design and adequately power clinical trials of rare diseases with the hopes of future therapeutic interventions.

### Disclosures

The authors have declared that no competing interests exist.

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## NEUROMUSCULAR DISORDERS

# Prognosis in Pediatric Myasthenia Gravis

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**Related Article:** Vecchio D, Ramdas S, Munot P, Pitt M, Beeson D, Knight R, et al. Paediatric myasthenia gravis: prognostic factors for drug free remission. *Neuromuscul Disord.* 2020 Feb;30(2):120–7.

**Keywords:** Pediatric Myasthenia Gravis; Myasthenia Antibody; Myasthenia Gravis Prognosis

Investigators from Oxford John Radcliff Hospital and Great Ormond Street Hospital for Children performed a retrospective study of myasthenia patients diagnosed before the age of 16 years. Investigators looked at demographics, clinical features, neurophysiologic testing, and antibody testing to evaluate prognostic features. The cohort included 74 patients, 69% female. Thirty-five had symptom onset by or before five years of age, and 54 had symptom onset before ten years of age. The population had a higher percentage of Afro-Caribbean, Asian, Arabic, or mixed-race backgrounds than was expected from the surrounding population. Antibodies were detected in a majority of patients (89%, 66/74). Of these patients, 52 (70%) were diagnosed via Radioimmunoprecipitation assay (RIA), and 10 (14%) were diagnosed by clustered Acetylcholine Receptors (AChR) in a cell-based assay (CBA). Three patients were found to have MuSK antibodies, and one patient had LRP4 antibodies. Eight patients (11%) were seronegative. Seronegative patients were classified by clinical symptoms and standard electrophysiologic testing, repetitive nerve stimulation, single-fiber EMG, or both. Seronegative patients also completed genetic testing to rule out common congenital myasthenic syndromes. A slight majority of the cohort presented with purely ocular symptoms. Twenty-three patients (31%) had a thymectomy performed. Seventeen (23%) of these patients reached remission.

Regarding outcome, only antibody status and repetitive nerve stimulation showed a statistically significant effect on the chance of remission. Remission was more likely in patients who were seronegative or only had antibodies identified by clustered AChR CBA than not. Remission was also more likely in patients with normal repetitive nerve stimulation at diagnosis than not. Age at onset (<10 years) and race (Asian and Caucasian) approached significance for a greater chance of remission but was not statistically significant. [1]

**COMMENTARY.** Juvenile myasthenia gravis is a rare disorder, and this paper represents a large cohort of pediatric patients. Overall, pediatric patients have a better prognosis than adult patients, but treatment tends to be less standardized. Seronegative patients represent a particularly challenging dilemma.

Traditional testing for acetylcholine receptor antibodies utilizes RIA, which works by radiolabeling acetylcholine receptors. The CBA increases the sensitivity of antibody testing by clustering receptors on a cell membrane, which is similar to the structure of the neuromuscular junction. The CBA can improve sensitivity for antibodies present in lower quantities or with lower binding affinity [2,3]. In one study, CBA was found to identify additional acetylcholine antibodies in 5-10% of “seronegative” patients. RIA is still recommended initially and is the only test able to quantify antibody levels [4].

The increased sensitivity of CBA could prove beneficial in younger patients. The 2016 international consensus guidelines for the management of myasthenia gravis currently recommends thymectomy be considered in children with antibody-positive myasthenia gravis [5]. CBA could prove helpful to establish the diagnosis of myasthenia gravis, distinguish between congenital and antibody-mediated syndromes and help prognosticate, even in cases presumed to be seronegative.

## Disclosures

The author has declared that no competing interests exist.

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# Febrile Seizures

## FEBRILE SEIZURES

# Long-term Risks of Recurrent Febrile Seizures

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**Related Article:** Dreier JW, Li J, Sun Y, Christensen J. Evaluation of Long-term Risk of Epilepsy, Psychiatric Disorders, and Mortality Among Children With Recurrent Febrile Seizures: A National Cohort Study in Denmark. *JAMA Pediatr.* 2019 Oct;173(12):1164–70.

**Keywords:** Prognosis; Febrile Seizures; Epilepsy; Psychiatric Diagnosis; Seizure Disorders

Investigators from Denmark at Aarhus University studied the long-term risk of epilepsy, psychiatric disorders, and mortality among children with recurrent febrile seizures. This was a population-based cohort study that used data from the Danish civil registration system. Children born in Denmark between 1977 and 2011 were included. From a cohort of 2,103,232 children, 75,593 children (3.6%) diagnosed with febrile seizures were identified. The risk of febrile seizures peaked at age 16 months, and 90.9% had their first febrile seizure before age three years. History of recurrent febrile seizures appeared to be associated with a risk of epilepsy and psychiatric disorders, but only individuals who later developed epilepsy had an increased risk of mortality. The cumulative risk of recurrent febrile seizures was 22.7% after the first febrile seizure, 35.6% after the second, and 43.5% following the third. The 30-year cumulative incidence of epilepsy increased with the number of hospital admissions for febrile seizures, and it was 2.2% at birth, 6.4% after the first febrile seizure, 10.8% after the second, and 15.8% following the third. The 30-year risk of a psychiatric disorder was 17.2%. After the first febrile seizure, the risk increased to 21.4%, 25% after two or more admissions with febrile seizures, and 29.1% after three or more. Mortality increased with the number of hospital admissions associated with febrile seizures, which was likely explained by a subsequent diagnosis of epilepsy. [1]

**COMMENTARY.** Febrile seizures are common, affecting 2–5% of children six months to 5 years of age. Several retrospective and prospective studies suggest that 2–7% of children with febrile seizures will later develop epilepsy [2]. Recognized risk factors for epilepsy after febrile seizures are complex features (focality, status epilepticus), abnormal developmental history, and a family history of epilepsy [3]. A prospective study of 560 children with febrile seizures showed that recurrent febrile seizures increased the risk of epilepsy 10-fold, though focality was the highest risk factor [2]. Dreier et al.'s results indicate that recurrent febrile seizures increase the risk for subsequent epilepsy, with the authors showing a cumulative effect based on the number of seizures [1].

Another interesting finding is the association with recurrent febrile seizures and psychiatric disorders; reported previously by the same authors. While the initial analysis in

this paper did not detail the types of psychiatric disorders, a subsequent letter to the editor showed the most common psychiatric diagnoses were anxiety, mood, attention-deficit/hyperactivity, and personality disorders [4].

The increased risk of epilepsy in this study is supported by a recent, large retrospective study that found an 18-fold increased incidence of epilepsy in children with recurrent febrile seizure admissions in Taiwan [5]. However, both studies have similar limitations by relying on hospital admissions and lacking classification between simple and complex febrile seizures. Many patients with simple febrile seizures could have been missed in this study, as these children are not likely to require admission.

Nevertheless, the current study adds important prognostic information regarding recurrent febrile seizures and the long-term risk of epilepsy, neuropsychiatric outcomes, and mortality.

## Disclosures

The authors have declared that no competing interests exist.

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# Neurocutaneous Syndromes

## NEUROCUTANEOUS SYNDROMES

# Epilepsy and TSC-Associated Neuropsychiatric Disorders

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**Related Article:** Gupta A, de Bruyn G, Tousseyn S, Krishnan B, Lagae L, Agarwal N; TSC Natural History Database Consortium. Epilepsy and Neurodevelopmental Comorbidities in Tuberous Sclerosis Complex: A Natural History Study. *Pediatr Neurol.* 2020 Feb 4:S0887-8994(20)30050-3.

**Keywords:** Tuberous Sclerosis Complex; TSC-Associated Neuropsychiatric Disorder; Autism Spectrum Disorder; Epilepsy

Investigators from multiple institutions (Cleveland Clinic, University Hospital Leuven, ZOL Genk, Kempenhaeghe and Maastricht UMC+, and Children's Hospitals and Clinics of Minnesota) used the Tuberous Sclerosis Complex Natural History Database (TSCNHD) to evaluate the relationship between epilepsy and neuropsychiatric disorders in individuals with TSC, along with any potential influence of genotype. Epilepsy was seen in 88% of patients and was more frequent in individuals with a TSC2 mutation. Individuals with TSC2 mutation were also more likely to have epilepsy onset at less than two years of age, as well as infantile spasms. Epilepsy was associated with intellectual disability (ID), particularly those with more severe ID. Also, age of seizure onset before age two years was associated with more severe ID but not epilepsy duration. Autism spectrum disorder (ASD) was diagnosed more frequently in patients with co-existing epilepsy, particularly among those with an age of seizure onset before two years. There was a trend toward a higher frequency of ID and ASD in individuals with a TSC2 mutation. There was no association with genotype. ADHD was diagnosed more frequently in patients with co-morbid epilepsy. Neither anxiety nor depression was associated with epilepsy or genotype. The study concludes that Epilepsy is associated with an increased risk for intellectual disability, autism spectrum disorder, and ADHD in individuals with TSC. Earlier age of seizure onset appears to increase the risk for several neuropsychiatric disorders in TSC. [1]

**COMMENTARY.** Tuberous Sclerosis Complex (TSC) is a genetic disorder with a high incidence of epilepsy and TAND (TSC-Associated Neuropsychiatric Disorders). The study showed a strong association between early onset of epilepsy and intellectual disability, and risk for development of ASD. This finding is consistent with several prospective studies, including a prospective study by Bolton and colleagues, who found that a higher tuber load, history of status epilepticus, and genetic mutation for TSC contributed to overall cognition [2]. A large, multi-center, prospective natural history study of young children with TSC found that early onset of seizures was associated with worse developmental outcomes and a higher risk of developing ASD [3,4]. A significant strength of the current study was utilizing the TSC Natural History

Database, which was established to characterize and study many individuals with TSC throughout the lifespan. The relationship between early seizures and subsequent TAND highlights the need for more early preventative treatment.

### Disclosures

The author has declared that no competing interests exist.

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# Neurodevelopmental Disorders

## NEURODEVELOPMENTAL DISORDERS

# Autism Genetics: Over 100 Risk Genes and Counting

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**Related Article:** Satterstrom FK, Kosmicki JA, Wang J, Breen MS, De Rubeis S, An JY, et al.; Autism Sequencing Consortium; iPSYCH-Broad Consortium. Large-Scale Exome Sequencing Study Implicates Both Developmental and Functional Changes in the Neurobiology of Autism. *Cell.* 2020 Feb;180(3):568–584.e23.

**Keywords:** Autism Spectrum Disorder; Genetics; Exome Sequencing

Researchers from the Autism Sequencing Consortium (ASC) led by Joseph Buxbaum at the Icahn School of Medicine at Mount Sinai report the largest exome sequencing study in autism spectrum disorder (ASD) to date. Combining sequencing data from 35,584 individuals, including 11,986 with ASD, they implicate a total of 102 genes in disease risk. By analyzing de novo variants in ASD probands, the authors identify a 3.5-fold enrichment of protein-truncating variants in loss-of-function intolerant genes and a 2.1-fold enrichment of damaging missense variants in ASD cases. Four risk genes (*SLC6A1*, *DEAF1*, *KCNQ3*, *SCN1A*) were associated with a disproportionate enrichment in missense variants compared to protein-truncating variants, suggesting that gain-of-function mechanisms may increase liability for ASD in this subset. Of the 102 risk genes, 12 genes were located in regions impacted by copy number variation (CNV), potentially nominating driver genes in CNVs associated with ASD.

To isolate genes with a bias for ASD without severe neurodevelopmental co-morbidities, the authors compared the rate of disruptive de novo variants identified in ASD to rates of de novo variants identified in severe neurodevelopmental disorders (NDDs). This analysis yielded 53 risk genes with a bias for ASD and 49 genes with a bias for NDDs. Individuals with variants in NDD-predominant risk genes were associated with later age of walking and a lower full-scale IQ than individuals with variants in ASD-predominant risk genes. Functionally, the 102 risk genes clustered into three main categories, including gene expression regulation (58), neuronal communication (24), and cytoskeletal organization (9). The authors conclude that the ASD phenotype arises from diverse neurobiological mechanisms, and dissecting the convergence points of these pathways will be central to understanding the disorder. [1]

**COMMENTARY.** This article is a landmark study providing a comprehensive analysis of autism genetics and revealing essential genes, cell-types, and time points most associated with the disease. Although most of the genetic risk in ASD is due to common variation, only a few risk polymorphisms have been identified [2]. However, exome sequencing studies of rare variants such as this study have provided critical

insight into ASD etiology. Despite rare variants cumulatively representing ~5% of individuals, these variants often significantly affect disease risk and represent a fundamental entry point for disease modeling and mechanistic understanding of disease [3,4].

Interestingly this study implicates both excitatory and inhibitory neurons in ASD pathogenesis. In concert with data from animal and cellular models, these data support the notion that dysfunctional excitation or inhibition may lead to ASD via an imbalance of brain circuitry [5]. Given the functions of the 102 risk genes, these neurobiological deficits may be most commonly caused by directly impacting neuronal communication (e.g., synapses) or by dysregulating gene expression during brain development.

### Disclosures

The authors have declared that no competing interests exist.

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**NEURODEVELOPMENTAL DISORDERS**

# Safety and Efficacy of Cannabis in Autism Spectrum Disorder

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**Related Article:** Bar-Lev Schleider L, Mechoulam R, Saban N, Meiri G, Novack V. Real life Experience of Medical Cannabis Treatment in Autism: Analysis of Safety and Efficacy. *Sci Rep.* 2019 Jan;9(1):200.

**Keywords:** Autism; Cannabis; Cannabidiol; Neurodevelopment; CBD; THC; ASD; Neurology; Pediatrics

Investigators from the Soroka University Medical Centre, The Hebrew University of Jerusalem, and Tikun Olam Ltd. in Israel studied the safety and efficacy of medical cannabis treatment on 188 patients with autism spectrum disorder (ASD) for six months. The study examined the efficacy of cannabidiol (CBD) through a quality-of-life assessment, global assessment rating, and an ASD symptom severity assessment looking at restlessness, rage attacks, agitation, speech impairment, cognitive impairment, anxiety, incontinence, depression, and more. The safety of CBD was examined by assessing physiological and cognitive side effects. The largest national provider of medical cannabis in Israel employed several of the authors and sponsored this study. [1]

**COMMENTARY.** ASD is a developmental disorder with two clusters of symptoms: 1. persistent deficits in social communication and social interaction, and 2. restricted, repetitive patterns of behavior, interests, or activities [2]. Pharmacological treatment in ASD focuses on attenuating comorbid symptoms. Recent studies and anecdotal evidence have contributed to the increasing popularity of cannabidiol as a possible addition to current treatment regimens. Although the exact mechanism is unknown, cannabidiol is hypothesized to target a dysfunctional endocannabinoid system [3] and effect oxytocin release during social interaction [4]. Prior studies have looked at CBD's utility in treating hyperactivity, sleep, self-injury, anxiety, and other behavioral issues [5]. This study arrives at similar conclusions supporting the potential therapeutic utility of CBD.

Safety was assessed by analyzing the frequency of side effects, while efficacy was analyzed using the ASD symptom severity assessment. Many of the same symptoms were reported as both side effects of the treatment and comorbid symptoms of prior diagnoses, making it difficult to interpret the results. The safety of medical cannabis was assessed within a one-month, and six-month follow up. Progress of patients who received extra THC doses was not differentiated from the remainder of patients.

Long-term safety from prolonged usage could not be determined from this study. Patient outcomes and side effects were only recorded at months one and six; the selection of

this specific follow-up period is not clearly explained. Observational studies, such as this one, are essential in identifying the short-term safety and efficacy of medications; CBD's long-term safety for ASD spectrum patients is unclear.

Subjective self-reporting by parents of patients was used as the basis of this study. Parents' expectations likely influenced their reporting. Assessment of parental perceptions and expectations of safety and efficacy at baseline could have elucidated these potentially confounding factors. Furthermore, this study was sponsored by a large local CBD manufacturer and the study population was using the product, which could have added an extra layer of parental reporting bias. Prospective, independent, placebo-controlled clinical trials are required to determine more accurate long-term efficacy and dosing guidelines for CBD in ASD.

## Disclosures

The authors have declared that no competing interests exist.

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# Neuroimaging

## NEUROIMAGING

# Rapid Brain MRI Use in a Pediatric Emergency Department

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**Related Article:** Ramgopal S, Karim SA, Subramanian S, Furtado AD, Marin JR. Rapid brain MRI protocols reduce head computerized tomography use in the pediatric emergency department. *BMC Pediatr.* 2020 Jan;20(1):14.

**Keywords:** Rapid MRI; Emergency Medicine; Neuroimaging; Pediatrics

Investigators from the University of Pittsburgh (Department of Emergency Medicine and Division of Pediatric Radiology) and Feinberg School of Medicine (Division of Emergency Medicine) studied the rates of neuroimaging (rapid brain MRI [rMRI], head CT [HCT], and full MRI) before and after implementation of four rapid MRI protocols in their ED. Their rationale for this study is that rMRI is a safe, efficient alternative to head CTs. They evaluated differences in time to index neuroimaging, the total length of stay in the ED, rates of unsuccessful index imaging, follow-up imaging, and undetected pathology on the index imaging (for those who had rMRI or HCT as the initial study that was followed by a full MRI within 14 days). The data were retrospectively collected from a high-volume freestanding children's hospital ED. Comparing the control and rMRI periods, rates of rMRI for index imaging were 10.8% and 38.5%, respectively. When looking at HCT use, the rates were 70.0% and 48.5%, respectively. Both differences reached statistical significance. Notably, time to neuroimaging and length of stay in the ED was longer for rMRI versus HCT (182 [IQR 138-255] vs. 86 [IQR 52-137] minutes and 396 [IQR 304-484] vs. 257 [IQR 196-344] minutes respectively). Of note, 3.6% of rMRI studies were unsuccessful versus no HCT studies. No other undetected pathologies were demonstrated in follow-up studies after rMRI, whereas the false-negative rate for HCT was as high as 25%. The authors suggested that rMRI could be seen as a viable alternative to HCT for nontraumatic presentations to the ED. The authors suggested that a longer time to neuroimaging for rMRI may be worthwhile to receive a definitive test if the patient's stability allows. [1]

**COMMENTARY.** Traditionally, the HCT has been the imaging modality of choice in EDs due to their speed of attainment and thus a minimal need for sedation – the main drawback being, however, that the child is exposed to ionizing radiation. HCTs remain the study of choice, and appropriately so, for traumatic brain injury and intracranial hemorrhage – where emergent interventions, without the need for detailed delineation of injury, are life-saving [2]. In these situations, an rMRI would delay care due to the potential contraindications to being in the MRI suite (e.g., penetrating injury) and the need for readying tubing and machinery to be MRI compatible. Alternatively, MRI brain

is superior to HCT for identification of acute stroke, posterior fossa lesions, and in patients with undifferentiated encephalopathy.

Interestingly, there is an emerging evidence-base suggesting that rMRI is at least non-inferior for many other novel modalities. As such, rMRI is emerging as the imaging modality of choice for several different indications – most commonly evaluating cerebral ventricles, as noted by a recent North American survey of pediatric neurosurgeons [3]. It is important to emphasize that a significant reason why rMRI protocols have become so popular is that the sequences have been selected to offer the highest yield for the shortest amount of time in the scanner – such as in rMRI for ventriculomegaly, but also, as the authors utilized, abusive head trauma, stroke, and "neurologic." Consequently, MRI use in pediatric EDs is increasing for several different indications [4]. The authors contributed to this body of research by showing that implementation of rMRI protocols – precisely more than one protocol – leads to reductions in HCT use (and thus exposure to ionizing radiation) without missed diagnoses or increases in the need for follow-up imaging. Rapid MRI protocols should be considered the initial choice for index imaging as access and appropriate protocols.

## Disclosures

The authors have declared that no competing interests exist.

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# Autoimmune Disorders

## AUTOIMMUNE DISORDERS

# Double Pathology in Rasmussen Encephalitis

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**Related Article:** Gilani A, Kleinschmidt-DeMasters BK. How frequent is double pathology in Rasmussen encephalitis? [published online ahead of print, 2019 Dec 19]. Clin Neuropathol. 2019 Dec.

**Keywords:** Rasmussen Encephalitis; Double Pathology; Epilepsy

Investigators from Children's Hospital Colorado and University of Colorado conducted a retrospective review of electronic medical records to identify all Rasmussen Encephalitis (RE) cases that had undergone surgery with subsequent pathologic evaluation at Children's Hospital Colorado during 2005-2019 to determine the frequency of double pathology. Eleven patients (with a total of 13 resections) were included in the study, 7 of which presented with double pathology.

The most common secondary microscopic abnormality found was focal cortical dysplasia with a predominance of type Ia and type IIa morphology. The investigators documented one case that contained leptomeningeal neuronal heterotopia and another case that contained leptomeningeal melanocytic nevus, both of which have not been previously reported in association with RE. They also noted that areas with dysmorphic neurons or abnormal cortical lamination have more prominent inflammation. The investigators concluded that double pathology may be prevalent in RE, but due to the subjective nature of several of the secondary histologic findings, there may be substantial interobserver variability that imposes limitations on evaluating the frequency of double pathology in RE. [1]

**COMMENTARY.** The estimated incidence of RE is 2.4 cases per 10 million people under the age of 18. [2] The reported frequency of double pathology in RE is highly variable, as some investigators observed it in less than 10% of their cases [3], while others observed it in 100% of their cases [4]. The literature predominantly consists of isolated case reports and case series from single institutions, and to date, a standardized, large sample, multi-institution study has not been performed to generate a reliable frequency of double pathology. Therefore, it is difficult to draw conclusions about the relationship between cases with and without double pathology in RE.

In non-RE cases, focal cortical dysplasia is diagnosed upon resecting and evaluating a discrete lesion that contains a presumed epileptogenic zone, and it typically does not contain inflammation. In contrast, RE

resections tend to be larger (often hemispheric) with diffuse cortical atrophy and inflammation. There is no standardized approach for evaluating secondary pathology occurring in RE since the entire hemisphere is epileptogenic and does not necessarily contain a single, discrete lesion. Some institutions may describe the presence of these secondary microscopic abnormalities, rather than assigning an ILEA classification. When cortical dysplasia is well-defined, one may be more willing to include it as a concomitant diagnosis.

As molecular diagnostics become more accessible and widely utilized, there will be more clarity and congruence in annotating the previously variable reporting of pathology in RE. It may be beneficial to create a registry, biorepository, or a centralized database to provide open access resources to aid in determining the true prevalence of double pathology and pathogenesis of RE. This would be an invaluable asset for researchers as it would provide an opportunity to study a greater number of these rare cases that would otherwise not be available at a single, tertiary institution.

### Disclosures

The authors have declared that no competing interests exist.

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# Epileptic Encephalopathies

## EPILEPTIC ENCEPHALOPATHIES

# Fenfluramine: New Treatment for Seizures in Dravet Syndrome

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**Related Article:** Lagae L, Sullivan J, Knupp K, Laux L, Polster T, Nikanorova M, et al.; FAiRE DS Study Group. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet. 2020 Dec;394(10216):2243–54.

**Keywords:** Dravet Syndrome; Seizures; Fenfluramine

Investigators for the FAiRE DS Study Group assessed the efficacy and safety of Fenfluramine for treating seizures in patients less than 18 y.o. with Dravet Syndrome in an international double-blind, placebo-controlled clinical trial. A total of 119 patients (mean age 9.0 y, 54% male) were enrolled in the study. Patients were on stable anti-epileptic drugs with poorly controlled convulsive seizures, with an average monthly convulsive seizure frequency (MCSF) of 40.3 in the prior 28 days. For a total of 14 weeks, caregivers provided participants with either placebo, Fenfluramine 0.2mg/kg/day or Fenfluramine 0.7mg/kg/day. Exclusion criteria included recent use of Stiripentol, Cannabidiol or Serotonergic medications. Importantly, patients were monitored with echocardiograms and electrocardiograms.

The study met the primary endpoint as patients saw a significant estimated decline in the MCSF relative to placebo for both Fenfluramine 0.7mg/kg/day (62.3% reduction, p<0.0001) and 0.2mg/kg/day (32.4% reduction, p=0.0209). For the higher dose of Fenfluramine, a number of secondary endpoints were met, including reduction in rescue medication use, improvements in both caregiver and investigator assessments and improvement of some behavioral measures. The high dose of Fenfluramine resulted in weight loss for patients aged 13-18 years. Adverse side-effects were reported more in both Fenfluramine groups (95%) compared to the placebo group (65%). The most common side effects were decreased appetite, diarrhea, nasopharyngitis, lethargy, and pyrexia. Fenfluramine was not associated with any cardiovascular complications. [1]

**COMMENTARY.** Fenfluramine is an amphetamine derivative that was found to have anti-epileptic effects since 1980s [2]. The medication became popular in the 1990s as an appetite suppressant but was removed from the market due to cardiovascular complications at high doses. The mechanism by which Fenfluramine treats seizures is believed to be through regulation of serotonin signaling. Invertebrate animal models with SCN1A mutations demonstrate activity at 5-HT1D and 5-HT2C receptors [3].

Dravet Syndrome is an epileptic encephalopathy with a significant seizure burden, often refractory to anticonvulsant treatment. In recent years, Stiripentol and Cannabidiol have been approved for the treatment of seizures

in Dravet Syndrome, both having encouraging clinical trial and post-approval data [4]. In this study 49% of patients were previously on Stiripentol and 26% were previously on Cannabidiol, indicating an ongoing need for additional treatment options.

The paper demonstrates that low dose Fenfluramine is a safe and effective add-on medication for providers to consider to significantly reduce seizure frequency in patients with Dravet Syndrome. Importantly, despite extensive monitoring, no cardiovascular risk was associated with either dose of Fenfluramine. Weight loss was a mild side effect that should be well-tolerated if a patient experiences seizure reduction. Furthermore, a separate retrospective analysis of 10 patients with Dravet Syndrome on long-term Fenfluramine (6-27 years) demonstrated better seizure control without any significant medication side effects [5]. The promising results in this study of Fenfluramine in Dravet Syndrome raise the possibility of future studies using the medication to treat additional forms of epilepsy.

### Disclosures

The authors have declared that no competing interests exist.

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# Genetic Disorders

## **GENETIC DISORDERS**

# **Genetic Diagnosis of Cockayne Syndrome**

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**Related Article:** Epanchintsev A, Rauschendorf MA, Costanzo F, Calmels N, Obringer C, Sarasin A, et al. Defective transcription of ATF3 responsive genes, a marker for Cockayne Syndrome. *Sci Rep.* 2020 Jan;10(1):1105.

**Keywords:** Cockayne Syndrome; DNA repair deficiency; Activating Transcription Factor 3

Researchers from the University of Strasbourg investigated whether defective transcription of ATF3 responsive genes is a marker for Cockayne Syndrome (CS). CS is a rare genetic disorder caused by pathogenic variants (dysfunction) in the *CSA* and *CSB* genes. CS patients exhibit mild photosensitivity and severe neurological problems. *ATF3* is over-expressed following cellular stress and closely linked to motor and sensory neuron degradation and sometimes used as a neuronal damage marker. When activated during stress, *ATF3* will repress up to 5000 genes for a short period. In CS cells, *CSA* and *CSB* dysfunction impairs the degradation of the chromatin-bound *ATF3*, leading to a permanent transcriptional arrest as observed by immunofluorescence and ChIP followed by RT-PCR. Currently, CS diagnosis is based on CS cells' inefficiency to recover RNA synthesis upon genotoxic (e.g., UV) stress. This study has demonstrated results of ChIP-seq of Pol II and *ATF3* promoter occupation analysis and RNA sequencing-based gene expression profiling in CS cells, immunofluorescence study of *ATF3* protein stability, and quantitative RT-PCR screening in 64 patient cell lines. The results confirm that the analysis of a few *ATF3* dependent genes, for example, *CDK5RAP2*, *NIPBL*, and *NRG1*, could serve as prominent molecular markers to discriminate between CS and non-CS patient's cells. Utilizing this assay can significantly simplify the CS diagnostic procedure's timing and complexity compared to the currently available methods. [1]

**COMMENTARY.** The phenotype and diagnosis of CS are complex. Clinical features of CS include cachectic dwarfism, severe neurological manifestations including microcephaly, cognitive deficits, pigmentary retinopathy, cataracts, sensorineural deafness, which overlaps with progeria and xeroderma pigmentosum (XP) with average life expectancy up to the second decade [2]. CS is inherited as an autosomal recessive genetic trait. The genes are responsible for CS -type I mapped to chromosome 5, known as ERCC8, and for CS-type II on chromosomal locus 10q11, known as ERCC6. Mutations in ERCC6 account for about 75% of cases, while mutations in ERCC8 cause about 25% of cases [2]. So far, the molecular bases of a defect in transcription and related coupled nucleotide excision repair have been evaluated for diagnostic purposes, in addition to clinical features. The

traditional prenatal diagnosis of CS is performed with the reduced recovery of DNA-synthesis in UV-irradiated cultured chorionic villus cells or amniocytes, which is time-consuming [3]. The new ATF3 Promote analysis technique includes a multistep approach with treating cell lines with UVC treatment followed by immunostaining of DNA testing with ChIP seq, RNA seq, and NG Sequencing of CS genes. ATFE3 Promote assay is sensitive to test most involved genes in CS, including *CSA*, *CSB*, *XPB*, *XPD*, *XPG*, in a time-sensitive manner, especially in prenatal diagnosis or in early stages of disease in the absence of any identified molecular defect. In response to cellular stress, *ATF3* immediate early gene activated and rapidly transiently targets genes harboring a CRE/ATF binding site to repress their expression. This test detects mutations in *CDK5RAP2*, *NRG1*, and *NIPBL* genes involved in neurodevelopmental or neurodegenerative processes and confirms the same pattern in all proven CS / XP patients neurological symptoms or but not observed in mutations in XP genes associated with dermatological symptoms. As of now, the limitation of the test is a small number of patients. For the neurologist community, using *ATF3* Promote analysis can improve diagnostic yield when conventional testing with the reduced recovery of DNA synthesis analysis is nonconclusive, especially in the early stages of CS and highly suspected CS cases with neurological and non-neurological phenotypes [1].

### **Disclosures**

The author has declared that no competing interests exist.

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**GENETIC DISORDERS****Neurologic Features with Pathogenic Copy Number Variants**Jason Coryell, MD, MS<sup>1\*</sup><sup>1</sup>Departments of Pediatrics and Neurology, Oregon Health & Sciences University, Portland, OR

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**Related Article:** Misra S, Peters G, Barnes E, Ardern-Holmes S, Webster R, Troedson C, et al. Yield of comparative genomic hybridization microarray in pediatric neurology practice. *Neurol Genet.* 2019 Oct;5(6):e367.

**Keywords:** Comparative Genomic Hybridization; Genetic; Pediatric Neurology

Investigators from Children's Hospital at Westmead, University of Sydney, performed a retrospective review (2006-2012) of the diagnostic yield of array comparative genomic hybridization (aCGH) among 555 children with diverse neurologic phenotypes in whom a genetic etiology was suspected [1]. Pathogenicity of copy number variants (CNV) was classified according to previously published guidelines [2]. Forty-seven patients (8.6%) had pathogenic variants. The neurologic phenotype was divided into 17 broad categories. Those with significantly increased odds ratios of a pathogenic CNV included: global developmental delay (DD) [OR 3.69], dysmorphism [OR 2.75], cortical visual impairment [2.73], and microcephaly [OR 2.16]. Logistic regression analysis showed an additive effect of multiple phenotypic categories being more likely associated with a pathogenic CNV (OR 1.18). The combination of developmental delay/intellectual disability with dysmorphism and abnormal head circumference showed the greatest effect among combined categories (OR 2.86). Epilepsy, cerebral palsy, tone abnormality, ataxia, movement disorder, psychiatric comorbidity, and abnormal neuro-diagnoses (MRI brain or spine, EEG) were not independently predictive for pathogenic CNV. [1]

**COMMENTARY.** This study is in line with multiple prior studies showing increased frequency (~15%) of pathogenic CNVs in individuals with developmental delay (DD)/intellectual disability (ID) [3]. Pathogenic CNVs have also been shown at higher rates in those with multiple congenital anomalies (17%) [4]. Additionally, >50% of individuals with pathogenic CNVs may have dysmorphic features when refined phenotyping is applied [5].

The authors suggest that the diagnostic yield of aCGH warrants this as a first-tier test in pediatric neurology patients; however, aCGH is perhaps best suited for a targeted population: including those with DD/ID, dysmorphic features, multiple congenital anomalies, or microcephaly. Other studies addressing specific neuro-phenotypes, such as epilepsy or weakness, show a higher diagnostic yield with whole-exome sequencing (WES) or targeted panels. For example, in pediatric epilepsy patients, a meta-analysis revealed a diagnostic yield of 45% for WES, 23% for a targeted panel (TP), and 8% for CGH. A cost-effectiveness

analysis indicated that a tiered testing system was cheaper when the initial test was WES or TP, rather than aCGH [6]. Similarly, the diagnostic yield of WES within a pediatric neuromuscular clinic was 39% [7].

This chart review predates the increased use of next-generation sequencing panels or WES. As the authors indicate, the increasing use of WES as a first test will identify many CNVs previously detected on aCGH. If there is a high a priori suspicion that the phenotype is more consistent with a CNV than a single gene disorder, aCGH could be a more rapid and cost-effective approach for that subset of neurology patients.

This article contributes to pediatric neurogenetics literature by helping to narrow the spectrum of neuro-phenotypes for whom CGH may be the best initial test.

**Disclosures**

The author has declared that no competing interests exist.

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# Pseudotumor Cerebri

## PSEUDOTUMOR CEREBRI

# Diagnosing Pseudotumor Cerebri: An Age-based Approach

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**Related Article:** Mahajnah M, Genizi J, Zahalka H, Andreus R, Zelnik N. Pseudotumor Cerebri Syndrome: From Childhood to Adulthood Risk Factors and Clinical Presentation. *J Child Neurol.* 2020 Apr;35(5):311–6.

**Keywords:** Idiopathic Intracranial Hypertension; Pseudotumor Cerebri; Pediatrics; Headache; Papilledema

Investigators from Hillel-Yaffe, Carmel, and Bnai Zion Medical Centers in Israel studied the comparative clinical presentations and predisposing factors for idiopathic intracranial hypertension (IIH) across age groups. They retrospectively evaluated 72 patients and compared their data using pooled analyses with 1499 patients from previously published literature. Modified Dandy criteria were used for the diagnosis of IIH. They found that female predominance and association of obesity with IIH increases with age. As expected, headache was the most common symptom across age groups. Vomiting was seen in 10% of children, 45% of adolescents, and 8% of adults ( $P<0.01$ ), while dizziness was reported only in adolescents (9%) and adults (10%). The incidence of papilledema and CSF opening pressure was not significantly different across age groups. Comparison of this data set with the pooled literature analysis showed only minor differences in numbers. [1]

**COMMENTARY.** The diagnostic criteria for IIH have evolved. The modified Dandy criteria put forth in 1985 used symptoms, signs, elevated opening pressure, and CT findings for diagnosis. The Pseudotumor Cerebri Syndrome (PTCS) criteria, developed in 2013, removed the components emphasizing subjectivity (symptoms) and gave specific CSF opening pressure parameters for children with IIH [2]. Although a common undercurrent amongst the pediatric population is an inability to clearly state their symptoms, the complete exclusion of symptoms and reliance on clinical signs and testing alone may lead to underdiagnosis, problematic for a disorder that may lead to irreversible vision loss [3]. From a practical standpoint, symptoms form one of the data points for follow-up care of children and determine response to treatment. The absence of headache in the diagnostic criteria presents a practical conundrum because how else would the clinician's attention be drawn towards eliciting signs of IIH? Further, as noted by Aylward et al., even papilledema -long considered an essential component for the diagnosis -may not be present in a subset of children with IIH [4].

Since the 1990s and until as recently as 2014, most of the published literature on IIH focused on and explicitly stated that IIH was a disease of young, obese women and was almost exclusively seen in this patient population [5,6]. Although some studies specifically geared towards IIH in

children, they primarily dealt with risk factors and did not differentiate clinical presentations or compare different age groups [7].

In summary, this study provides practicing pediatric neurologists a categorization of various clinical presentations of IIH in different age groups, so the diagnosis is hopefully not missed in children not belonging to the "typical" patient population. It also provides a framework for further prospective studies, identifies data points for creating more inclusive diagnostic testing with high sensitivity (though it may be at the cost of specificity) for early diagnosis of IIH, and hopefully lays the groundwork for creating data-driven treatment pathways. The former remains a striking void in the field of pediatric IIH – one that such large-scale analyses can potentially fill in the not-too-distant future.

## Disclosures

The authors have declared that no competing interests exist.

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# Nutrition, Diet and The Nervous System

**NUTRITION, DIET AND THE NERVOUS SYSTEM**

# Ketogenic Diet: A Role in Immunity?

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**Related Article:** Goldberg EL, Molony RD, Kudo E, Sidorov S, Kong Y, Dixit VD, et al. Ketogenic diet activates protective  $\gamma\delta$  T cell responses against influenza virus infection. *Sci Immunol.* 2019 Nov;4(41):eaav2026.

**Keywords:** Ketogenic Diet; Immunity; Epilepsy

Investigators from The Department of Comparative Medicine, from Yale School of Medicine report the effect of the ketogenic diet on the T cell immune function in mice exposed to influenza virus. The investigators examined transgenic immunocompetent mice exposed to an intranasal challenge of influenza virus. The mice were fed ketogenic diet prior to the infection. The team studied survival and weight loss on the mice. This study noted that mice that were fed ketogenic diet had better survival and decreased loss when compared to mice that were not exposed to the ketogenic diet. The investigators sought to analyze the molecular underpinnings of this finding. They performed transcriptome analysis of the mice's lungs noting that several genes were upregulated in ketogenic diet fed mice; particularly genes associated to  $\gamma\delta$  T cell responses were increased; including number of cells in lung tissue, and release of cytokines related to this specific cell type. The mice consistently showed lower virus titers than controls. The investigators then tested whether the ketogenic diet was actually exerting an effect on these T cell populations by comparing the function in mice fed a non-ketogenic high caloric density diet. They noted that these effects were specific for the ketogenic diet fed animals only. Additionally, the investigators noted that the ketogenic diet increased  $\gamma\delta$  T cell proliferation, noting that this was not directly related to increases in  $\beta$ -hydroxybutyrate, the primary energy substrate during glucose deprivation associated to ketogenic diet, but rather finding that the effect on  $\gamma\delta$  T-cell population is mediated by favoring fatty acid oxidation. This paper concludes that the effect of ketogenic diet exerts a potentially previously unrecognized immune effect. [1]

**COMMENTARY.** The ketogenic diet has been used since the early twentieth century for the treatment of epilepsy. There are multiple mechanisms by which the ketogenic diet exerts its anticonvulsive effect. The increased levels of ketone bodies such as  $\beta$ -hydroxybutyrate have shown to be protective of injury by oxygen reactive species. The modulation and metabolism of GABA systems may also be implicated in the antiseizure mechanism of the ketogenic diet. Additionally, enhanced excitatory neurotransmitter metabolism, effects on synaptic transmission and energy metabolism may be associated to its antiepileptic effect [2].

The role of the ketogenic diet in the treatment of super-refractory status epilepticus has been reported in recent literature, particularly its efficacy in immune mediated encephalitis as well as febrile infection-related epilepsy syndrome (FIREs), and new onset refractory status epilepticus (NORSE) [3]. The efficacy of the ketogenic diet on the treatment of this immune mediated status epilepticus may be mediated by the systemic and metabolic effects of the ketogenic diet on the immune system [4]. Further studies are required to determine the direct mechanisms by which the ketogenic diet affects inflammation and immunity. The current study highlights molecular pathways of modulation of the immune system that may potentially be harnessed for the treatment of epilepsy. Additionally, it highlights the systemic effects of ketogenic diet identifying a novel immune modulating mechanism

## Disclosures

The author has declared that no competing interests exist.

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# Neurocritical Care

## NEUROCRITICAL CARE

# Prediction of EEG Seizures in Critically Ill Children

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**Related Article:** Fung FW, Jacobowitz M, Parikh DS, Vala L, Donnelly M, Fan J, et al. Development of a model to predict electroencephalographic seizures in critically ill children. *Epilepsia*. 2020 Mar;61(3):498–508.

**Keywords:** Seizures; Encephalopathy; Critical Care; EEG monitoring; Pediatric; Neurology

In a prospective observational study, investigators from the Children's Hospital of Philadelphia devised a predictive model for capturing electrographic seizures in critically ill pediatric patients. The study included a total of 719 children admitted to the intensive care unit of a quaternary care institution. Neonates below 30 days and patients who presented with status epilepticus were excluded. Continuous electroencephalographic (EEG) monitoring (CEEG) was performed for abnormal movements, encephalopathy, or seizures. Electrographic seizures were captured in 26% (184 children) of the cohort, and 6% (44 children) diagnosed with electrographic status epilepticus. Variables included age, etiological category of acute encephalopathy (structural, non-structural, or epilepsy-related), clinical seizures before initiation of CEEG, EEG background, and epileptiform abnormalities. The following factors were associated with a statistically significant difference in the odds of capturing electrographic seizures: Patients < 1 year of age, seizures before CEEG, epileptiform discharges during the initial 30 minutes of the recording, and EEG showing a slow disorganized, discontinuous, or burst suppression background. The optimal, most inclusive model had a sensitivity of 92% with a negative predictive value of 93%. [1]

**COMMENTARY.** Multiple previously published studies indicated the high risk of electrographic seizures in encephalopathic children admitted to the critical care units [2,3]. Seizures, if untreated, could be detrimental to the neurological outcome of those patients. Unfortunately, the availability of CEEG is variable from one institution to another based on resources, including staffing and available equipment. The authors took a welcomed initiative to provide a risk assessment tool to determine critically ill patients at risk for electrographic seizures, which would benefit from CEEG.

Based on the reviewed study results, if the devised predictive model was utilized to be most sensitive, Fung et al. concluded that CEEG would be done in all patients with epileptiform discharges in the first 30 minutes (for example, on a routine EEG). Stratifying patients further can be done based on their age, being younger or older than one year. To elaborate, CEEG would be done in those younger than one year except if all the factors as mentioned earlier associated

with higher statistically significant odds ratios were absent; no clinical seizures, no epileptiform discharges during the initial 30 minutes of the recording, and normal or attenuated EEG background. On the other hand, CEEG would not be done in patients older than one year with non-structural etiologies to their encephalopathy and normal EEG background regardless of a clinical seizure before monitoring. Additionally, CEEG would not be done in patients older than one year who carry a diagnosis of epilepsy with no clinical seizures on presentation and normal or attenuated EEG background. Finally, CEEG would not be done in patients older than one year with clinical seizure and normal/attenuated EEG background or without a clinical seizure and slow disorganized EEG background.

Adult seizure prediction models, for example, 2HELP2B score by Struck et al., gave more weight to electrographic elements on the initial EEG with a focus on hospitalized rather than critically ill patients [4]). Children with critical illness and encephalopathy have different EEG patterns as opposed to their adult counterparts. With the addition of clinical acumen and variables not accounted for in the study (e.g., type of epilepsy and intractability), the ability to prioritize critically ill children to CEEG rather than a briefer EEG or clinical monitoring could be a powerful addition to a neurologist's toolbox and especially significant in institutions with more limited resources.

### Disclosures

The authors have declared that no competing interests exist.

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## NEUROCRITICAL CARE

# Ancillary Tests for Death by Neurologic Criteria in Children

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**Related Article:** Kirschen MP, Puccetti DF, Morrison W. Incidence, and Indications for Ancillary Testing in the Determination of Death by Neurological Criteria in Children. *Pediatr Neurol.* 2020 May;106:68–9.

**Keywords:** Brain Death; Death by Neurologic Criteria; Ancillary Test; EEG; Pediatrics; Neurology

Investigators from Children's Hospital of Pennsylvania reported on the usage of ancillary studies in the declaration of brain death in children in a single-center retrospective descriptive study. In their cohort of 73 patients, 47% underwent ancillary testing. Nearly all of those patients (88%) had a technetium brain scan; the remaining 12% (4/34) had an electroencephalogram (EEG). Nearly half of the ancillary tests (16/34) were performed because of the inability to complete the clinical exam, primarily due to cervical spine injuries (10/16). Other common indications included the inability to perform the apnea test (15% of ancillary tests) and uncertainty about the neurologic exam (12%). Only one of the 34 ancillary tests was not consistent with brain death; this result occurred in a child with a devastating neurologic injury who subsequently had two complete clinical exams and apnea tests that were consistent with death by neurologic criteria (DNC). [1]

**COMMENTARY.** The 2011 AAP guidelines for declaration of DNC include two separate clinical exams and apnea tests consistent with brain death, separated by 12-24 hours, depending on the patient's age [2]. Ancillary studies, which can include EEG and technetium cerebral blood flow study, are not required unless: an element of the clinical exam or apnea testing cannot be completed, there is uncertainty about the results of the neurologic exam, a medication effect may confound the exam, or reduction of the inter-examination period is desired. Despite guidance regarding ancillary testing in these specific scenarios, there is wide variability in institutional protocols and individual practice regarding the use of ancillary tests in DNC declaration and which ancillary studies are available [3]. In a recent survey of US pediatric intensivists and neurologists, 20% perform ancillary tests for reasons beyond those outlined in the national guidelines, with some respondents routinely incorporating an ancillary study [4]. In this study, most tests (79%) were performed according to the current DNC guidelines. Other indications were performed by parental request, three were performed based on institutional protocol more stringent than national guidelines, and three were performed with indications unknown. No other patients in this cohort had ancillary testing indications that did not subsequently have ancillary testing performed.

The high rate of ancillary testing in this cohort reflects the challenges and uncertainties of DNC clinical evaluation in pediatric populations. However, ancillary studies have low sensitivity and specificity. They require providers with expertise in performing these tests and interpreting the results in the context of a DNC declaration in a pediatric patient. The high rate of congruence between the clinical exam and the ancillary studies results in this study highlight the importance of the clinical exam in determining an appropriate patient population in whom the pre-test probability of a positive test is high [1]. Ancillary studies are best used when necessary and as confirmatory, rather than diagnostic, tests. DNC is a clinical diagnosis; however, the high prevalence of indications for ancillary testing in this study also highlights a pressing need to ensure that institutions performing DNC evaluations in children are competent in the indications, techniques, and interpretations of ancillary testing for brain death.

### Disclosures

The authors have declared that no competing interests exist.

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