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NEONATAL DISORDERS

Impact of Seizure Burden in Hypoxic Ischemic Encephalopathy

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Related Article: Srinivasakumar P, Zempel J, Trivedi S, Wallendorf M, Rao R, Smith B et al. Treating EEG Seizures in Hypoxic Ischemic Encephalopathy: A Randomized Controlled Trial. Pediatrics 2015 Nov;136(5):e1302–e1309.
Keywords: Seizure Burden; Hypoxic Ischemic Encephalopathy; Neurodevelopmental Outcome

Investigators from Washington University St. Louis studied the impact of electroencephalographic monitoring of neonates with Hypoxic Ischemic Encephalopathy (HIE) and their degree of MRI injury and neurodevelopmental outcomes when increasing seizure burden was present. Investigators performed a randomized controlled trial to investigate the effect of seizure burden on neurodevelopmental outcomes in infants with recognized electrographic seizures versus infants with clinically recognized seizures. Researchers found 15/35 neonates in the electrographic seizure group (ESG) and 20/34 neonates in the clinical seizure group (CSG) to have seizures. The researchers found that the ESG presented with a lower cumulative seizure burden (SB) than the CSG (p=0.02) likely due to faster identification and subsequent treatment of seizures. The investigators found no difference between ESG and CSG groups regarding developmental outcome due to the power of the study. However, analysis of the cohort as a whole indicated that an increasing SB correlated with worsened outcomes on the Bayley Scales of Infant Development III (p=0.03). The investigators also showed that greater SB in the cohort was associated with a worse MRI injury severity. [1]

COMMENTARY. Neonatal seizures are prevalent in infants with HIE [2]. However, they are difficult to diagnose clinically since most seizures in neonates are subclinical [3]. This study highlights the need for electrographic monitoring of infants in accordance to the American Clinical Neurophysiology Society guidelines [4]. Although this study does not show a difference among groups monitored clinically or electroencephalographically due to the power of the study, it shows that greater cumulative seizure burden may correlate with poor neurodevelopmental outcomes and worse MRI injury scoring. Further prospective studies are necessary to establish whether treatment of seizures and interventions to reduce seizure burden have an impact on neurodevelopmental outcome in infants with HIE.

Disclosures

The author(s) have declared that no competing interests exist.

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NEONATAL DISORDERS

Autoregulation in Infants with Neonatal Encephalopathy

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Related Article: Burton VJ, Gerner G, Cristofalo E, Chung SE, Jennings JM, Parkinson C et al. A pilot cohort study of cerebral autoregulation and 2-year neurodevelopmental outcomes in neonates with hypoxic-ischemic encephalopathy who received therapeutic hypothermia. BMC Neurol 2015;15(1):209.
Keywords: Hypoxic Ischemic Encephalopathy; Therapeutic Hypothermia; Autoregulation

Researchers from Johns Hopkins School of Medicine report a pilot observational study investigating the influence of hemodynamic management in 28 neonates with hypoxic ischemic injury (HIE). This cohort of neonates, all of whom underwent therapeutic hypothermia, were evaluated with Near Infrared Spectroscopy (NIRS) to obtain the hemoglobin volume index (HVx) as a marker of cerebral autoregulation that identifies the optimal mean arterial blood pressure (MAPOPT) at which optimal autoregulation is achieved. The investigators identified the MAPOPT for 3 time periods: hypothermia, rewarming and first 6 hours of normothermia. They compared the effect of MAPOPT on neurodevelopmental outcomes at 2 years. A total of 19 patients remained in the study after follow up. Within the cohort of 19 patients, only 15 patients underwent the full research battery of standardized cognitive and motor scales. Neurodevelopmental outcomes were classified as impaired or unimpaired. In this cohort, 42% of the children were identified as having impaired cognitive or motor function. The investigators only found differences in outcome when they compared the MAPOPT during the rewarming period. The investigators found that children with an impaired outcome had higher MAPOPT (p=0.023), and spent a greater percentage of time during rewarming with blood pressures under their identified MAPOTP (p=0.048). The authors suggest that monitoring and management of HVx as a marker of autoregulation may have an impact on neurodevelopmental outcomes of neonates affected by HIE. [1]

COMMENTARY. HIE in the neonate remains a public health concern. Therapeutic hypothermia is currently the standard of care for neonates with moderate to severe HIE, and although it has decreased death and disability, adverse neurodevelopmental outcomes are still prevalent [2]. The mechanisms of cerebral perfusion patterns in neonates are not well understood [3]. Understanding patterns of cerebral blood flow and autoregulation is paramount to establish therapies directed at maintaining adequate cerebral perfusion and avoid reperfusion injury. Although NIRS monitoring does not provide a direct prognostic utility in the management of infants with HIE undergoing hypothermia [4], it may provide a putative value for autoregulation and optimal blood pressures goals, and guide management to achieve adequate cerebral perfusion in the neonate.

This study highlights the need for closer hemodynamic monitoring aimed at maintaining optimal cerebral autoregulation in neonates undergoing therapeutic hypothermia as this may impact neurodevelopmental outcomes.

Disclosures

The author(s) have declared that no competing interests exist.

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VASCULAR DISORDERS

Preventable Pediatric Stroke via Vaccination?

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Related Article: Fullerton HJ, Hills NK, Elkind MS, Dowling MM, Wintermark M, Glaser CA et al.; VIPS Investigators. Infection, vaccination, and childhood arterial ischemic stroke: results of the VIPS study. Neurology 2015 Oct;85(17):1459–1466.
Keywords: Pediatric Stoke; Infection; Vaccination

Investigators from the Vascular Effects of Infection in Pediatric Stroke (VIPS) group studied the risk of arterial ischemic stroke (AIS) associated with minor infection and routine childhood vaccinations. Children from 1 month to 18 years of age presenting with AIS (n=355) were compared to age-matched controls presenting for a routine health visit or due to trauma (n=354). Etiology of the strokes comprised arteriopathy (46%), cardioembolic stroke (21%), a prothrombotic condition (9%), another risk factor (5%) or were idiopathic (5%). Patients with AIS were more likely to have reported infection in the week prior with an odds ratio (OR) of 6.3 (95% [CI] 3.3–12). This effect diminished by one month. The most common infections and symptoms were upper respiratory (URI) (50%) with cough and fever. Preceding infection was common across all subtypes of AIS. Patients with a recent infection were more likely to be younger with a median age of 4.0 compared to 9.1. Notably, children who were reported to have some, few, or no vaccinations had an increased rate of AIS 7.9% vs 1.2% (OR of 7.3 (95% [CI] 2.5–21)). Both the effect of recent infection and vaccination remained significant in a multivariable logistic regression model adjusting for age, sex and season of enrollment. [1]

COMMENTARY. This paper builds on previous retrospective cohort studies supporting a relationship between infection and AIS [2,3] in particular for arteriopathy [4]. There are many proposed mechanisms by which recent infection could increase the risk of AIS: by inflammation causing a prothrombotic state, direct arterial wall infection and inflammation, or dehydration. However, the finding that AIS was less likely for patients who received a vaccination the week prior suggests that systemic inflammation is not the entire story. Further, URIs were the most common infection as opposed to gastroenteritis (making dehydration as a trigger less compelling), and suggesting local head and neck infection as the more specific risk factor.

The juxtaposition of recent infection increasing the risk of AIS while more comprehensive vaccination reducing this risk, is striking. If the vaccinations were against known causes of common minor infections a causative association would be more plausible. Several possibilities could explain this discrepancy: 1) vaccine-preventable diseases are responsible for the increased AIS risk, 2) vaccination changes the immune milieu altering the inflammatory response which leads to AIS or 3) vaccinations indirectly prevent additional infections (i.e. URI) thus decreasing AIS risk. Further research using Next Generation Sequencing, proteomic and RNA expression analysis may identify interactions between the immune system and the infectious microbiome increasing childhood AIS risk. The association of infection with increased risk for all AIS types may indicate a common mechanism or is a marker of an underlying vulnerability to infection and AIS.

While further study is needed, these results suggest that obtaining a detailed infectious and vaccination history for children with AIS is important, and may help identify the causes of otherwise unexplained AIS. This unclear causal relationship between infection and stroke will require further study as is already proposed by the VIPS investigators [5] and we look forward to these results.

Disclosures

The author(s) have declared that no competing interests exist.

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TRAUMATIC DISORDERS

Cerebrovascular Pressure Reactivity in Children with TBI

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Related Article: Lewis PM, Czosnyka M, Carter BG, Rosenfeld JV, Paul E, Singhal N et al. Cerebrovascular Pressure Reactivity in Children With Traumatic Brain Injury. Pediatr Crit Care Med 2015 Oct;16(8):739–749.
Keywords: Pediatric; Traumatic Brain Injury; Cerebral Autoregulation

Investigators from University of Melbourne, Australia, studied Pressure-Reactivity Index (PRx) and optimal Cerebral Perfusion Pressure (CPP) in 36 children aged between 6 months and 16 years treated for traumatic brain injury (TBI) at the Royal Children's Hospital, Melbourne, from 2007 to 2013. All patients received care according to the local TBI protocol. Patients were monitored for a median of 3.8 days. The authors described PRx in this cohort of children with TBI and examined its association with other patient variables. They also compared patients in the favorable and unfavorable outcome groups. PRx quantifies the correlation between intracranial pressure (ICP) and arterial blood pressure to assess the integrity of cerebral blood flow autoregulation. CPP refers to the difference between mean arterial pressure and ICP. Optimal CPP is the ideal pressure gradient driving cerebral perfusion in light of the evolution of PRx over time for each patient.

PRx was significantly higher in children with unfavorable outcome ($p<0.01$). Therefore, loss of cerebral autoregulation was associated with worse outcome. The ideal PRx threshold to discriminate between favorable and unfavorable outcome is still unknown, but a threshold PRx value of both 0 and 0.25 seem to delineate between a favorable and an unfavorable outcome (both thresholds, $p<0.01$). Nonetheless, PRx is a useful prognostic marker.
In line with previous adult studies, the relationship between the PRx and CPP respected a U-shape curve, allowing detection of an optimal CPP for each patient. The optimal CPP varied significantly with age. In this cohort of patients the optimal CPP ranged from 53 to 78 mm Hg. Furthermore, the patients with unfavorable outcome spent a greater percentage of their monitoring time with a CPP at least 5 mm Hg inferior to their optimal CPP. [1]

COMMENTARY. The prognostic role of PRx has been established in adult studies, but the concept is relatively new in the pediatric population [2]. An impaired cerebral autoregulation increases the risk of poor outcome. This study confirms the utility of PRx in children with TBI to discriminate outcome.

Secondary brain injuries are the result of events following the initial TBI. Avoidance of further secondary insult to the injured brain is the basis of TBI management. The Guidelines for the acute medical management of severe pediatric TBI suggest a CPP threshold of 40 to 50 mm Hg to avoid secondary ischemic injury, with the understanding that age-specific threshold probably exists, with infants at the lower end and adolescents at the higher end of this range [3]. This current study underlines the increase of optimal CPP with age. Age-specific and individualized CPP targeting may be the future of TBI management as patients of similar age demonstrate different optimal CPP. This may partly explain why targeting a specific CPP number for all patients have not been proven successful [4].

In summary this article emphasizes the potential value of PRx monitoring as both a prognostic marker and a determinant of individualized optimal CPP. The potential therapeutic role of individualized care for patient and optimal CPP targeting based on PRx evaluation need further clinical evaluation to assess the clinical impact on patient outcome [5].

Disclosures

The author(s) have declared that no competing interests exist.

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NEURODEVELOPMENTAL DISORDERS

Relationship between Age at Diagnosis of ADHD and ASD

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Related Article: Miodovnik A, Harstad E, Sideridis G, Huntington N. Timing of the diagnosis of attention-deficit/ hyperactivity disorder and autism spectrum disorder. Pediatrics 2015 Oct;136(4):e830–e837.
Keywords: ADHD; Autism; DSM-IV-TR; DSM-5

Investigators from the Division of Developmental Medicine and Clinical Research Center, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts, studied the relationship between the timing of Attention Deficit Hyperactivity Disorder (ADHD) diagnosis in children with Autism Spectrum Disorder (ASD) and the age at ASD diagnosis. Prior studies have suggested that symptoms of ADHD may overshadow or mask the symptoms of ASD but none has examined the relationship between the age at ADHD diagnosis and the age at ASD diagnosis. Data were drawn from the 2011-2012 National Survey of Children's Health, which asked parents to provide the age at which their child received a diagnosis of ADHD and/or ASD. There were 1496 children with a current diagnosis of ASD reported by parents of children between ages 2 to 17 years; approximately 20% of these children had been initially diagnosed with ADHD. Children diagnosed with ADHD before ASD were diagnosed with ASD ~3 years (95% confidence interval 2.3-3.5) after children in whom ADHD was diagnosed at the same time or after ASD. The children with ADHD diagnosed first were 30 times more likely to receive their ASD diagnosis after age 6 (95% confidence interval 11.2-77.8). The disparity in delay of age for ASD diagnosis for the ADHD before ASD group was maintained across all severity levels. The findings support implications that children with ADHD before ASD may exhibit unique dimensional traits that could bias clinicians toward an ADHD diagnosis. Diagnostic criteria and screening measures for ASD may need to reflect the overlapping symptomatology between ASD and ADHD. [1]

COMMENTARY. The new DSM-5 restructuring of the ASD and ADHD diagnostic categories has caused concern about how these changes may impact prevalence rates, and rates of comorbid psychopathology. Under the DSM-5, symptoms of ADHD should be present before age 12, not 7 years, and the number of symptoms required is 5, not 6. To investigate the prevalence of inattention and impulsive symptoms, 1722 infants and toddlers were separated into three diagnostic groups for analyses: DSM-5 ASD group, an atypically developing group, and a DSM-IV-TR ASD group. Significantly elevated rates of inattention/impulsive symptoms were identified in toddlers meeting DSM-5 criteria for ASD. ASD symptom severity was positively correlated with inattention/impulsive symptoms regardless of the primary diagnosis. The expression of impulsive and inattentive symptoms did not differ significantly within diagnostic groups [2]. The similarity of symptoms is supportive of the theory that ASD and ADHD represent a continuum, a deviance from an acceptable norm, and having a common origin [3]. ASD prevalence estimates may be lower under DSM-5 criteria [4], but the need for treatment is dependent on multiple factors, and not restricted to an arbitrary number of DSM criteria.

Disclosures

The author(s) have declared that no competing interests exist.

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SEIZURE DISORDERS

CSF Amino Acids, Pterins and Mechanism of the Ketogenic Diet

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Related Article: Sariego-Jamardo A, García-Cazorla A, Artuch R, Castejón E, García-Arenas D, Molero-Luis M et al. Efficacy of the ketogenic diet for the treatment of refractory childhood epilepsy: cerebrospinal fluid neurotransmitters and amino acid levels. Pediatr Neurol 2015 Nov;53(5):422–426.
Keywords: Ketogenic Diet; Neurotransmitters; Pterins; Amino Acids; Refractory Epilepsy

Investigators from Hospital Sant Joan de Deu, Barcelona, Spain, studied the relationship between the etiology of refractory childhood epilepsy, CSF neurotransmitters, pterins, and amino acids, and response to a ketogenic diet in 60 patients with refractory epilepsy, 83% focal and 52% idiopathic. Patients with GLUT-1 deficiency, pyruvate dehydrogenase deficiency, or other inborn error of metabolism were excluded. Mean age at epilepsy onset was 24 months. A 4:1 ratio ketogenic diet was followed in 40 patients, 3:1 ratio in 12, and 1 or 2:1 ratio in the remainder. The ketogenic diet was effective (> 50% reduction in seizure frequency) in 31.6% of patients, at 6 months after initiating the diet. Lysine and arginine CSF values analyzed in ketogenic diet responders were significantly lower than for nonresponders ($P<0.05$), but the remainder of a battery of amino acids and the glucose and lactic acid levels analyzed showed no differences for responders and nonresponders.. The rate of efficacy of the diet was not related to the etiologies of epilepsy nor to CSF pterins or biogenic amine concentrations. The authors consider that changes in biogenic amines and amino acids in CSF should be considered as potential mechanisms for the ketogenic diet efficacy in treatment of refractory epilepsy. [1]

COMMENTARY. The ketogenic diet was first introduced in the treatment of epilepsy in 1921, by Wilder [2] at the Mayo Clinic. He attributed the effect of the diet to ketosis and specifically to acetoacetic acid. Several theories for the anticonvulsant effect followed, many supported by effects in laboratory animals with experimental seizures and by clinical studies, and summarized in an editorial commentary in Epilepsia by Nordli and De Vivo in 1997 [3]. In earlier studies, the emphasis was on the effect of the diet on water and electrolyte balance, the anticonvulsant action correlated with an increased urinary excretion and negative balance of sodium and potassium, independent of acidosis and ketosis, and similar to the effect of acetazolamide [4]. De Vivo and associates (1978) reported changes in cerebral metabolites in chronically ketotic rats, but in contrast to clinical systemic studies, no alterations in brain water content, electrolytes, or pH [3]. Millichap and associates in balance studies (1964) in children with absence epilepsy found decreases in blood pH, PCO2, and standard bicarbonate [4]. Urinary excretion of electrolytes was increased, and the balance of sodium, potassium and other electrolytes was negative. The excretion of free amino acids was variable. Increase in level of leucine in the serum was the only change noted in amino acids. Fluid intake and urine output were reduced, and fall in body weight was initially rapid. Further studies comparing metabolic changes in ketogenic diet responders and nonresponders and significance of amino acid and pterin variations are indicated. Recent articles regarding the mechanism of action of the diet (previously reviewed in *Pediatric Neurology Briefs*) reemphasize the importance of ketone bodies as a factor [5], and introduce a novel mechanism and potential treatment with LDH inhibitors [6].

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HEREDO-DEGENERATIVE DISORDERS

Visual Evoked Potentials in Rett Syndrome

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Related Article: LeBlanc JJ, DeGregorio G, Centofante E, Vogel-Farley VK, Barnes K, Kaufmann WE et al. Visual evoked potentials detect cortical processing deficits in Rett syndrome. Ann Neurol 2015 Nov;78(5):775–786.
Keywords: Rett Syndrome; MECP2 Gene; VEP; Cortical Processing Deficits

Investigators from the Boston Children's Hospital recorded pattern-reversal visual evoked potentials (VEPs) in Mecp2 heterozygous female mice and in 34 girls with Rett syndrome (RTT). The amplitudes and latencies of VEP waveform components were quantified, and were related to disease stage, clinical severity, and MECP2 mutation type in RTT patients. Visual acuity was also assessed in mice and patients by modulating the spatial frequency of the stimuli.

Mecp2 heterozygous female mice and RTT patients exhibited a similar decrease in VEP amplitude, most striking in the later stages of the disorder. RTT patients showed a slower recovery from the principal peak of the VEP response that was impacted by MECP2 mutation type. Both patients and mice displayed a deficit in discriminating small patterns when the spatial frequency of the stimulus was increased, indicating a lower visual spatial acuity in RTT.

In conclusion, VEP may be used to assess brain function across species and in children with severe disabilities like RTT. The findings support the introduction of standardized VEP analysis in clinical and research settings to probe the mechanism underlying functional impairment and to monitor progression of the disorder and response to treatment. [1]

COMMENTARY. VEP analysis using a checkerboard pattern stimulus appears to provide a promising method of evaluation of cortical functioning in patients with Rett syndrome. Factors that may weaken the significance of VEP analysis as a biomarker of cortical functioning in RTT include the occurrence of seizures and rarely, pattern-sensitive epilepsy. About 60% of RTT have epilepsy, usually with onset between 3 and 20 years of age [2], and 5% of children with epilepsy in general may have pattern sensitive seizures [3,4]. Epilepsy, diagnosed in 45% of patients in the above study, was treated with antiepileptic drugs that may have modified VEP responses, but this risk was considered to be small [1]. Studies of auditory brainstem responses in Rett syndrome at the Kennedy Krieger Institute, Baltimore, conclude that sedation can cause prolongation of the I-V interpeak latency intervals, and cautious interpretation of evoked potentials is warranted if sedated control groups are not used for comparison [5]. Reports of altered auditory and somatosensory processing suggest that the present VEP impairments represent a global cortical deficit in RTT [1].

Finally, the authors cannot explain a contribution of any ophthalmic abnormalities to the cortical deficits reported. A study of visual function in RTT at Glasgow Caledonian University, UK, found substantial refractive errors were common and all 11 subjects with RTT had pattern-onset VEPs. Latencies and amplitudes did not differ from those in 18 normal controls [6]. In future studies, a complete eye exam will be incorporated in the study design at the time of the VEP recording [1].

Disclosures

The author(s) have declared that no competing interests exist.

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