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EDITORIAL

The 30-Year Anniversary of *Pediatric Neurology Briefs*

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Over the past 30 years, *Pediatric Neurology Briefs* (PNB) has been published monthly as a continuing education service designed to expedite and facilitate review of current medical literature concerning pediatric neurology. The journal was founded in 1987 by J. Gordon Millichap in London, England, while the founding editor was on sabbatical as honorary consultant at Great Ormond Street Hospital. PNB has reviewed and referenced articles from over 200 journals since inception. So far, PNB consists of 29 volumes with greater than 3300 articles, and includes over 10,000 citations referencing the works of approximately 28,000 scholarly authors. Prior to the advent of 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].

The past year has been very successful. Recall that PNB was relaunched as an open access, peer-reviewed, journal with an expanded editorial board in January 2015. PNB had a new website and content management system capable of organizing peer-review and providing improved indexing, DOI assignment, and online full-text article view. Digitization is ongoing with over ten years of back issues including over 1100 full text open access articles available on the journal website so far. In 2016, we are proud to announce that 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). In addition, articles published in PNB are searchable on PubMed (http://www.ncbi.nlm.nih.gov/pubmed/).

Also in 2015, John J. Millichap became the journal Editor and continues to be supported by J. Gordon Millichap, as Founding Editor, the Editorial Advisory Board, and invited expert Contributing Editors. 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. PNB covers a comprehensive group of subject areas related to progress in pediatric neurology with notable additions in 2015 including Complementary/Integrative Therapies [4]. Contributing Editors provide detailed summaries of published articles, followed by commentaries based on their experience and corroborated by appropriate supplementary citations. The two most highly accessed articles published in 2015 covered topics related to epilepsy including the mechanisms of the ketogenic diet [5] and the history of the specific EEG term, "hypsarhythmia" [6].

The mission of PNB remains the same: "Pediatric Neurology Briefs is a continuing education service designed to expedite and facilitate the review of current scientific research and advances in child neurology and related subjects." The Editors of PNB endeavor to deliver a 'clinical pearl' with each commentary that will be of interest and use in clinical practice. New in 2016, topic experts interested in contributing to PNB as authors or reviewers are invited to contact the Editor at j-millichap@northwestern.edu.

Disclosures

The authors have declared that no competing interests exist.

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TRAUMATIC DISORDERS

Concussions in Collision Youth Sports

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Related Article: Kontos AP, Elbin RJ, Sufrinko A, Dakan S, Bookwalter K, Price A et al. Incidence of concussions in youth ice hockey players. Pediatrics 2016 Feb;137(2):1–6.
Keywords: Concussion; Traumatic Brain Injury; Sports Medicine

Investigators from the University of Pittsburg, University of Arkansas, Lake Erie College of Osteopathic Medicine, and Boston Children's Hospital/Harvard Medical College researched the incidence of concussions in youth hockey in relation to age and activity setting. They prospectively followed 397 ice hockey players, aged 12-18 years, from 31 teams, during 2 competitive seasons. Team representatives were trained to record athletic exposures (AEs) and identify suspected concussions. A concussion was defined as any mild closed head injury involving altered cognitive functioning, signs/symptoms, or loss of consciousness of no longer than 1 minute, after direct or indirect blow to the head. Thirty-seven concussions were diagnosed during 23,3069 AEs, 12,784 in practices, 10,585 in games. The combined concussion incidence rate (IR) for games and practices was 1.58 per 1000 AEs. The majority of concussions (N=26, 70.3%) occurred during games. All identified mechanisms of injury involved player-to-player contact. More than half involved secondary contact with the boards. Forty-three percent of mechanisms were attributed to illegal contact leading to a penalty. The authors conclude that concussion incidence rates in youth ice hockey are similar to those in other collision sports, and that younger players have higher rates than older players. [1]

COMMENTARY. Concussions are mild traumatic brain injuries (TBIs) that are a growing public health concern. Heightened awareness of concussions has led to a 29.1% increase in emergency department visits for TBI between 2006 and 2010, with over 2.5 million total visits in 2010 [2]. Particular concern has been raised about the safety of youths participating in collision sports such as football, rugby, and wrestling in which intentional physical collisions (e.g. tackling, takedowns) are a required component. Hockey is also considered a collision sport; however, the collisions are either incidental or strategic (body checking) and not required for participation. Concussion rate in boy's ice hockey (5.4 per 10 000 AEs) is the second highest in collision sports, and only slightly lower than the rate in youth football (6.4 per 10 000 AEs). Previous research has demonstrated 30% of the concussions in boy's ice hockey result from body checking [3]. While this study did not specify body checking as a mechanism, it is important to note that all concussions resulted from player-to-player contact and more than half involved secondary contact with the boards, both of which occur with body checking. Forty-three percent of the mechanisms of concussion in this study were additionally attributed to illegal contact, highlighting the need for improved enforcement of current rules. A recent study demonstrated that implementing a "no checking" rule in a Pee Wee hockey league decreased the rate of concussions and all injuries by nearly threefold (IRR 2.83 for concussions, IRR 2.97 for all injuries) [4]. Such rules targeting collision reduction are essential to injury prevention. The American Academy of Pediatrics Council on Sports Medicine recommends delaying introduction of body checking until age 15 with strict reinforcement of rules promoting player safety [5]. Adoption of additional rules, policies and educational interventions to decrease unsafe tactics may further reduce the incidence of collisions that have been shown to lead to concussions, especially for youth participating in competitive hockey.

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The authors have declared that no competing interests exist.

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VASCULAR DISORDERS

Cavernous Sinus Thrombosis in Children

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Related Article: Smith DM, Vossough A, Vorona GA, Beslow LA, Ichord RN, Licht DJ. Pediatric cavernous sinus thrombosis: A case series and review of the literature. Neurology 2015 Sep;85(9):763–9.
Keywords: Carotid Arteries; Cavernous Sinus; Cerebrovascular Disorders; Infection; Magnetic Resonance Imaging

Investigators from the Children's Hospital of Philadelphia analyzed the clinical and radiographic findings in 12 cases of cavernous sinus thrombosis (CST) seen between 2000 and 2013, and conducted a literature search and review of the pooled data. Three of 12 (25%) cases experienced morbidity. Contrast enhanced MRI and contrast enhanced CT were 100% sensitive in detecting CST, while noncontrast MR venography and noncontrast CT were not sensitive (0% sensitive). The aggregate mortality rate in a total of 52 cases (12 plus an additional 40 cases from literature review) was 4 (8%) and morbidity rate was 10 of 40 (25%). Morbidity and mortality were low with early aggressive surgical, antimicrobial, and anticoagulation therapies, but outcome was not significantly changed. [1]

COMMENTARY. Pediatric cavernous sinus thrombosis (CST) is a rare and life-threatening complication of septic or aseptic etiologies, and is associated with low morbidity and mortality if aggressive therapies including antimicrobials, anticoagulation, and/or surgical treatment are implemented early on [1]. CST is associated with neurologic disability if not detected in a timely manner. Septic origin is often due to septic emboli or extension of a thrombophlebitis. The most common organism is Staphylococcus aureus (69%), followed by the Streptococccal species (17%), Pneumococcus (5%), gram negative species (5%), Bacteroides (2%), and Fusobacterium (2%). Valveless communications between the facial and ophthalmic veins and the cavernous sinus are responsible for infectious spread between the paranasal sinus and orbit to the cavernous sinus [2]. CST can also be a complication of otitis media and less often, pharyngitis or dental infection. The most common cause is acute sinusitis. Infections of the middle third of the face were responsible for most septic CST in the pre-antibiotic era though incidence has significantly decreased with the advent of antibiotic [3]. Aseptic CST is due to trauma or a pro-thrombotic etiology [3].

The most common presenting symptoms are due to the specific structures affected within the cavernous sinus. Compression of cranial nerves III, IV, and VI result in impaired extraocular movement with sixth nerve paresis being the most common.3 Compression of the ophthalmic and maxillary branches of cranial nerve V result in facial sensory deficits, periorbital sensory loss, and/or an impaired corneal reflex [3]. Unilateral periorbital edema, headaches, photophobia, chemosis, and proptosis are classic signs due to impaired venous drainage of the orbit [3,4]. Papilledema, retinal hemorrhages, worsening visual acuity or blindness may also occur due to impaired venous drainage with resulting retinal congestion. Progression to bilateral orbital involvement due to an intercavernous communication, meningitis, subdural empyemas, and sepsis are common in CST [3]. Presence of Horner syndrome and sixth nerve paresis classically localize to the cavernous sinus. Systemic clinical features include pyrexia, tachycardia, hypotension, emesis, confusion, and even coma. Transient central hypopituitarism due to contiguous infectious spread leading to necrosis has also been reported with bilateral CST. Other complications of CST include infectious arteritis of the internal carotid artery, vasospasm, and infarcts, either embolic in origin or secondary to hypoperfusion [4]. Differentials include orbital cellulitis, intracranial infections, and superior ophthalmic vein thrombosis [5].

Disclosures

The authors have declared that no competing interests exist.

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HEADACHE DISORDERS

Review of Prevention for Pediatric and Adolescent Migraine

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Related Article: Hickman C, Lewis KS, Little R, Rastogi RG, Yonker M. Prevention for Pediatric and Adolescent Migraine. Headache 2015 Nov;55(10):1371–81.
Keywords: Migraine; Preventive; Pediatric Migraine; Prophylaxis

Authors from the Barrow Neurological Institute at Phoenix Children's Hospital present a narrative overview of preventive treatment for pediatric and adolescent migraine. Tricyclic antidepressants (TCAs) were thought to have the most evidence for pediatric migraine prevention, particularly amitriptyline and to a lesser extent nortriptyline. Serotonin selective reuptake inhibitors (SSRIs) have conflicting evidence for use in pediatric migraine. Selective serotonin and norepinephrine reuptake inhibitors (SSNRIs) including venlafaxine and duloxetine were thought to have more evidence for pediatric use. Antihypertensives including beta blockers, calcium channel blockers and angiotensin receptor blockers were discussed. The one with the most evidence in pediatric migraine was thought to be flunarizine, although it is not easily available in the U.S.. Propranolol, metoprolol, and candesartan may also be effective, however it is noted that the evidence is greater in adult studies. The anticonvulsant medications with the most support for use include topiramate and valproic acid. The antihistamine cyproheptadine was also recommended for preventive use. Finally, the authors review the evidence for botulinum toxin A injections. The authors admit the difficulty in drawing firm conclusions on its use in pediatrics based on the small, limited studies performed. They emphasize the need for effective migraine preventive measures in reducing headache-related disability and improving patients' quality of life. [1]

COMMENTARY. Pediatric migraine is a common and potentially debilitating disorder. Migraine preventive treatment is commonly prescribed for young people affected by migraine at least 4 days per month or those who have experienced a significant impact on quality of life. This review proposes that preventive treatment can be considered successful when the patient has fewer than 4 migraine attacks per month which also subside with abortive therapy. In practical use, this definition of treatment success may be a bit stringent. A migraineur with 24 days of headache per month may be very satisfied if they are able to reduce this to 8 headache days per month. Alternatively, patients may also be satisfied with treatment if they are able to perform more routine daily activities even without a reduction in headache days. Data on what pediatric migraineurs, and their families, desire from preventive migraine treatment is a current gap in the literature.

This review has nicely summarized many of the typical migraine preventives used, common side effects, pertinent studies, and provides a concise list with starting dosage and dose range. To date there is no clinically available medication that was developed for the purpose of migraine prevention. However, there are promising recently completed phase IIb trials involving calcitonin gene related peptide (CGRP) antibodies for migraine prevention in adults [2] and hopefully these agents will ultimately be found to benefit children and adolescents as well.

Nutraceuticals including riboflavin, coenzyme Q10 and magnesium were not reviewed. Although the current evidence is limited, neutraceuticals may be an appropriate option for some patients. There is also increasing evidence in the adult literature for use of memantine, an NMDA antagonist [3]. Memantine is typically very well tolerated in our experience and has no monitoring requirements. Lastly, melatonin has been shown to be useful in adult migraine [4], and there is some evidence for its use in pediatrics [5]. Melatonin is typically well tolerated in children and adolescents and has minimal drug interactions [4].

Disclosures

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PAROXYSMAL DISORDERS

Prognosis of Cyclic Vomiting Syndrome

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Related Article: Hikita T, Kodama H, Ogita K, Kaneko S, Nakamoto N, Mimaki M. Cyclic vomiting syndrome in infants and children: A clinical follow-up study. Pediatr Neurol 2016 Jan [Epub ahead of print].
Keywords: Vomiting; Migraine; Valproic Acid; Adrenocorticotrophic Hormone; Antidiuretic Hormone

Investigators from Teikyo University School of Medicine, Tokyo, Japan, evaluated the clinical features, prognosis, and prophylaxis of cyclic vomiting syndrome and the relationship between the syndrome and levels of adrenocorticotropic/antidiuretic hormones (ACTH/ADH). In 31 patients with the syndrome admitted between 1996 and 2008 the diagnosis was based on criteria of the 2nd edition of the International Headache Classification, and 25 were followed until 2013. Abdominal pain, diarrhea, and headache were associated in 23, 10, and 18 patients, respectively. A family history of migraine was identified in 13 (42%) patients. The median duration of the disorder was 66 (3-179) months, and 44% (n=11) developed migraine. Prophylactic therapy was started for 18 patients with severe symptoms; valproic acid (VA), VA with phenobarbital, phenobarbital, and amitriptyline were effective in 9, 4, 3, and 1 patient, respectively. The median frequencies of attacks were 0.75 and 0.33 per month with and without prophylaxis, respectively. Abnormally high levels of ACTH (n=17) and ADH (n=18) were found among the 25 patients with data available. Attack duration was correlated with levels of ACTH (p=0.0084) and ADH (p=0.0031). ADH levels in patients with bilious vomiting were higher than in those without (p=0.048). Most patients with cyclic vomiting syndrome recovered completely and responded to prophylactic therapy, but half of the patients developed migraine. [1]

COMMENTARY. The cause of cyclic vomiting syndrome is usually undetermined and is made by exclusion following extensive testing. In a study of 106 patients aged <21 years at the Cleveland Clinic, neuroimaging revealed intracranial abnormalities in <10% of patients, none of which explained the vomiting. Abdominal ultrasound revealed abnormalities in 15% of patients during an acute episode and 7% when well. An upper gastrointestinal series was normal in all of 61 patients tested. Laboratory testing in 92% of patients revealed abnormalities suggesting mitochondrial dysfunction in 38% [2]. A relationship between mitochondrial dysfunction and migraine is supported by biochemical, muscle biopsy, genetics, and therapy with riboflavin, coenzyme Q10, niacin, carnitine, and topiramate [3]. That cyclic vomiting may represent a form of epilepsy in children was proposed in a report of 33 patients, 7 (21%) having a history of generalized tonic-clonic or complex partial seizures in addition, and 25 (76%) with seizure discharges in the EEG, some focal and predominantly temporal in localization [4]. Most of the EEGs were not recorded at the time of the vomiting, and in retrospect, some of these cases may be classified as a form of migraine. A response to antiepileptic medication was compatible with a diagnosis of epilepsy or migraine [5]. In a 1970s study of recurrent headaches and EEG abnormalities in 100 children, phenytoin controlled migraine in 77% and the response was unrelated to the degree of EEG abnormality. In the present report of cyclic vomiting syndrome, the cause appears to favor a migraine, but the EEG and family history of epilepsy are not recorded, despite a positive response to treatment with the antiepileptic medication, valproate. Future search for the cause or causes of cyclic vomiting should consider the inclusion of the EEG.

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BEHAVIOR DISORDERS

Dystonia with MPH/Risperidone Combined Therapy for ADHD

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Keywords: Risperidone; Methylphenidate; ADHD; Dystonia; Dyskinesia

Investigators from Child Neurology and Pediatrics, University of Texas Health Science Center, Houston, report extrapyramidal symptoms in a 13-year-old boy with a psychiatric history of schizophrenia, bipolar disorder, ADHD, and autism, responsive to combination risperidone, oxcarbazepine, and MPH. Risperidone was started at age 4 for aggressive behavior and titrated to 1.5 mg. twice daily. Because of significant weight gain, risperidone was tapered and, at a dose of 0.5 mg twice daily, he developed severe painful cervical dystonia and dyskinesia consisting of involuntary movements of the upper extremities, and uncontrollable sense of restlessness and agitation. Treatment with quetiapine, diphenhydramine, benztropine, clonidine, or lorazepam was ineffective and symptoms worsened. Risperidone was reinstated at 0.5 mg twice daily and increased to his previous dose of 1.5 mg twice daily within 3 days, after which the dystonia, akathisia, and tardive dyskinesia resolved. The authors consider this the first case of acute onset of extrapyramidal symptoms as a result of discontinuation of risperidone during combination therapy with MPH in a child. [1]

COMMENTARY. Although pediatric neurologists do not generally prescribe the antipsychotic risperidone as primary treatment for ADHD, patients taking risperidone are sometimes referred to neurology from psychiatry for a second opinion regarding refractory symptoms or untoward side-effects. The addition of a psychostimulant, methylphenidate (MPH) is a frequent recommendation and, in our experience, using conservative dosages, extrapyramidal side effects have not occurred. The present report of extrapyramidal symptoms during discontinuation of risperidone in a child taking combination RIS/MPH therapy we consider unusual and worthy of further study.

A Pubmed search in the past two years uncovered five reports of dyskinesia associated with combination RIS/MPH therapy prescribed for ADHD and comorbid disorders. An analysis of 44 cases treated in psychiatry where children received either MPH (n=28) or risperidone (n=16) as primary treatment and the majority combination treatment, symptoms of ADHD and conduct disorder were benefited, and only one case of dyskinesia occurred that resolved with the discontinuation of treatment [2]. MPH/risperidone therapy was considered particularly effective in ADHD with conduct disorder. An acute dystonic reaction in an adolescent followed the abrupt discontinuation of MPH from a combination drug regimen risperidone/MPH; the patient experienced acute dystonia on 3 occasions when he forgot to take his MPH [3]. An acute and transient dyskinesia occurred on starting long-acting MPH in a 7-year-old boy who had recently stopped taking risperidone [4]. A further report concerns three children with ADHD who developed severe hyperactivity and agitation on starting MPH after discontinuing risperidone [5]. The adverse reaction resolved after withdrawal of MPH, and following a drug-free interval, MPH was re-administered without adverse effect. In treating ADHD with the drug combination risperidone/MPH, particular care is advised when switching, starting, or discontinuing either treatment, and particularly when changing MPH. Conservative dosages are often better than mega, and to festina-lente is advised in dosage increments.

Disclosures

The author has declared that no competing interests exist.

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INFECTIOUS/AUTOIMMUNE DISORDERS

Zika Virus Infection and Microcephaly

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Related Article: Schuler-Faccini L, Ribeiro EM, Feitosa IM, Horovitz DD, Cavalcanti DP, Pessoa A et al.; Brazilian Medical Genetics Society–Zika Embryopathy Task Force. Possible Association Between Zika Virus Infection and Microcephaly - Brazil, 2015. MMWR Morb Mortal Wkly Rep 2016 Jan;65(3):59–62.
Keywords: Zika virus; Microcephaly; Brazil; Aedes mosquitoes

A Task Force established by the Brazil Ministry of Health investigated the possible association of microcephaly with Zika virus infection during pregnancy and a registry for microcephaly cases among women suspected to have had Zika virus infection during pregnancy. In early 2015, an outbreak of Zika virus, a flavivirus transmitted by Aedes mosquitoes, was identified in northeastern Brazil. By September 2015 an increase in the number of infants born with microcephaly began to emerge, and Zika virus RNA was identified in the amniotic fluid of 2 women with fetuses having microcephaly on ultrasound. Among a cohort of 35 infants with microcephaly born during August-October 2015 in eight of Brazil's 26 states and reported to the registry, the mothers of all 35 had lived in or visited Zika virus-affected areas during pregnancy, 25 (71%) infants had severe microcephaly (head circumference >3 SD below the mean for sex and gestational age), 17 (49%) had at least one neurologic abnormality (hypertonia/spasticity [37%], seizures [9%]), and among 27 infants who had neuroimaging studies, all had abnormalities (brain calcifications [74%], ventricular enlargement [44%], neuronal migration disorders [33%]). Tests for other congenital infections were negative. CSF tests for Zika virus infection are not yet available, and further studies are needed to confirm the association of microcephaly with Zika virus infection during pregnancy. [1]

COMMENTARY. Microcephaly is defined as a head circumference -/= SD below the mean for sex and gestational age at birth [2]. Except in cases of craniosynostosis, a small skull reflects a small brain. Microcephaly is either primary (anomaly of development during the first 7 months of gestation) or secondary to an insult incurred during the last 2 months of gestation or during the perinatal period. CDC has developed interim guidelines for health care providers in the US caring for pregnant women during a Zika virus outbreak. Pregnant women with a history of travel to an area with Zika virus transmission (as of Jan 2016, 19 countries in the Americas outside Brazil) and who report two or more symptoms of Zika virus disease (acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis) during or within 2 weeks of travel, or who have ultrasound findings of fetal microcephaly or intracranial calcifications, should be tested for Zika virus infection. In pregnant women with laboratory evidence of Zika virus infection, serial ultrasound should be considered to monitor fetal growth [3]. No specific antiviral treatment for Zika virus is available.

Disclosures

The author has declared that no competing interests exist.

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