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TRAUMATIC DISORDERS

Levetiracetam for Pediatric Posttraumatic Seizure Prophylaxis

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Related Article: Chung MG, O'Brien NF. Prevalence of Early Posttraumatic Seizures in Children With Moderate to Severe Traumatic Brain Injury Despite Levetiracetam Prophylaxis. Pediatr Crit Care Med 2016 Feb;17(2):150–6.
Keywords: PICU; Antiepileptics; Epilepsy

Investigators from Nationwide Children's Hospital performed an observational cohort study of early post-traumatic seizures (EPTS) among 34 children with moderate to severe traumatic brain injury (TBI) who received levetiracetam (LEV) prophylaxis following admission to their pediatric intensive care unit. EPTS were defined as clinical seizures occurring within seven days from the brain injury. The authors found that 6/34 (17%) children developed EPTS despite LEV prophylaxis. The authors conclude that EPTS remain common despite LEV prophylaxis, and that young children and those suffering abusive head trauma are at particularly high risk. [1]

COMMENTARY. EPTS are common following moderate to severe TBI, and are associated with worse outcome [2]. These seizures may contribute to secondary brain injury through a variety of mechanisms, including regional hypoxia-ischemia due to the increased metabolic demands of seizures, glutamate-mediated excitotoxicity, and increased intracranial pressure. Current guidelines for the management of severe TBI published by the American Academy of Neurology [3] and the Brain Trauma Foundation [4] recommend acute seizure prophylaxis during the first seven days after TBI. Prophylactic phenytoin has been shown to reduce the prevalence of EPTS in both adults and children [5,6]. Phenobarbital, carbamazepine and valproic acid have not been as extensively investigated, but given their side-effect profiles and pharmacodynamic properties, there is no clear advantage to using these agents over phenytoin [7]. On the other hand, LEV has become a popular choice for EPTS prophylaxis in many centers, prompted by its favorable side-effect profile compared to phenytoin [8].

Despite the growing popularity of LEV for EPTS prophylaxis in children with TBI [8], evidence for its efficacy remains scant. Hence, this study is an important contribution. The authors conclude that LEV may be less effective than phenytoin in preventing EPTS because the observed prevalence of EPTS (17%) was higher than previously reported with phenytoin prophylaxis (2-15%). However, this was not a comparative study, therefore other clinical factors may have accounted for the higher prevalence of EPTS observed in this cohort. Nevertheless, these findings highlight the need for a prospective randomized controlled trial to compare the safety and efficacy of LEV vs. phenytoin for the prevention of EPTS. Ideally, this study should apply continuous EEG monitoring to identify children with seizures because of the high prevalence of subclinical seizures known to occur in this population [9].

Disclosures

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

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TRAUMATIC DISORDERS

Predicting Post-Concussion Symptom Risk in the ED

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Related Article: Zemek R, Barrowman N, Freedman SB, Gravel J, Gagnon I, McGahern C et al.; Pediatric Emergency Research Canada (PERC) Concussion Team. Clinical risk score for persistent postconcussion symptoms among children with acute concussion in the ED. JAMA 2016 Mar;315(10):1014–25.
Keywords: Concussion; Postconcussion Syndrome; Mild Traumatic Brain Injury; Children; Pediatrics

Investigators from The Pediatric Emergency Research Canada (PERC) Concussion Team developed a clinical risk score for predicting persistent post-concussion symptoms (PPCS) at 28 days post injury in a large cohort of children initially evaluated at the emergency department (ED) within 48 hours of injury. This prospective multicenter study first recruited a derivation cohort of 2006 patients followed by a validation cohort of 1057 patients across 9 Canadian Hospitals. Persistent post-concussion symptoms were present in 31.0% of the derivation cohort and 33.0% of the validation cohort. The initial 12 predictor PPCS risk score from the derivation sample was refined to a final risk score that incorporated 9 predictors including: age, sex, prior concussion with symptom duration of longer than 1 week, physician-diagnosed migraine history, headache, sensitivity to noise, fatigue, answering questions slowly, and abnormal tandem stance balance performance. The researchers also compared the ability of the new PPCS clinical risk score to accurately predict PPCS with physician prognosis. Treating physicians completed a standardized survey, which included the question, "How likely is this patient to develop persistent symptoms beyond 1 month?" with response options starting with 0-10% and increasing in 10% increments up to 100%. The PPCS clinical risk score was significantly better than physician prognosis for predicting PPCS at 28 days post-injury. However, the discrimination of the PPCS risk score model was moderate (AUC=0.71) and requires further refinement and validation. The authors suggest further research is needed for assessment of accuracy in an office setting and determination of clinical utility before the score is adopted in clinical practice. [1]

COMMENTARY. Given the increasing number of concussions seen in pediatric EDs over the last decade [2], concussion has become a serious public health concern [3]. Although most patients recover within 2 weeks, approximately one-third of patients will continue to experience symptoms (i.e., PPCS) and impairment for a prolonged period following a concussion. Determining which factors at the time of presentation to the ED predict PPCS is important to inform better prognosis and potential early interventions for patients. Researchers have demonstrated that certain factors (e.g., age, sex, post-traumatic migraine) may place patients at greater risk for prolonged recovery [4,5]. Currently, there is no validated clinical algorithm for predicting PPCS in patients. Developing such an algorithm for use in the pediatric ED could substantially reduce morbidity associated with concussion and inform better follow-on care for this at-risk population.

The current study was the first to attempt to quantify risk for PPCS in a large sample of pediatric patients based on factors routinely assessed during patient evaluations in the ED. The authors utilized brief clinical assessments commonly used in the ED, and assigned risk points for each variable to assess the overall risk for PPCS in two independent samples. The resulting risk score stratifies patients into low, medium, or high risk for PPCS. Unfortunately, the current model only provided modest discrimination of risk for PPCS. Additional data on the sensitivity and specificity of the risk score with additional independent samples from other clinical settings that include concussed patients and controls are needed before the PPCS risk score can be applied clinically.

Disclosures

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

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NEUROMUSCULAR DISORDERS

Utility of Pediatric Nerve Biopsy in Tertiary Care Referral

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Related Article: Ida CM, Dyck PJ, Dyck PJ, Engelstad JK, Wang W, Selcen D et al. Pediatric Nerve Biopsy Diagnostic and Treatment Utility in Tertiary Care Referral. Pediatr Neurol 2016 May;58:3–11.
Keywords: Biopsy; Diagnosis; Neuropathy; Pediatric; Peripheral Nerve

Investigators from Mayo Clinic in Rochester, MN, report the utility of nerve biopsy as a diagnostic tool in their institution. The authors identified 316 nerve biopsies performed on patients <18 years of age between 1950 and 2009. Two thirds of these biopsies were performed within their institution, while the other third were performed externally, though all patients were evaluated at the Mayo Clinic and had clinically relevant details, electromyography (93%) and genetic testing results (14%). The utility of biopsies was determined by their effect on diagnosis (confirmation, change or refinement), treatment (with or clinical improvement) or additional testing. The authors found a distinct histopathologic diagnosis was present in 33% (106) of cases, with 33% (106) showing nonspecific histological abnormalities while the remaining biopsies were normal 29% (91) or could not be interpreted 5% (13). Clinical impact was credited to biopsy in 86% of cases (273). Two thirds of clinically impactful biopsies were attributable to refinement or change of the pre-biopsy diagnosis. Biopsy results altered treatment in 25% (80) of cases with clinical improvement seen in 18.6% (59). Additional testing was ordered based upon biopsy results in 20% (62%) of patients yielding significant diagnostic information in 8.8% (28) of patients. The reported nerve biopsy complication rate was 1% (3). [1]

COMMENTARY. This is a well conducted and important study looking at the role of nerve biopsy in a large series of pediatric patients. One limitation of the study is that it retrospectively evaluated the role of nerve biopsy from 1950 to 2009, a time when genetic testing was difficult. Today, some of these nerve biopsies may have been avoided. Another issue is that the study had a number of CIDP patients which in general do not require a nerve biopsy for diagnosis, since symptoms and signs as well as specific findings on nerve conduction studies and electromyography would establish the diagnosis. Despite these minor issues, there are 3 important messages to take from this study: 1) nerve biopsies in pediatric patients with normal nerve conduction studies are unnecessary 2) the role of nerve biopsy is still very important in specific situations and 3) the complications from the nerve biopsies are extremely low.

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NEUROMUSCULAR DISORDERS

Guidelines for Corticosteroid use in Treatment of DMD

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Related Article: Gloss D, Moxley RT 3rd, Ashwal S, Oskoui M. Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2016 Feb;86(5):465–72.
Keywords: Corticosteroids; Guidelines; Duchenne muscular dystrophy

The guideline development subcommittee of the American Academy of Neurology has provided an update to the 2005 treatment guidelines for use of corticosteroids (CS) in Duchenne muscular dystrophy (DMD). These addressed questions of (i) Efficacy of CS related to survival, quality of life (QoL), motor function, scoliosis, pulmonary and cardiac function (ii) side effects of CS treatment (iii) comparison of prednisone (PS) and deflazacort (DF) wrt efficacy and adverse effects (AE) profile (iv) optimal dosing regimens of CS and (v) useful interventions for maximizing bone health health. Guidelines were developed based on medline and Cochrane database searches of relevant articles addressing the issue. Class I-III trials from the original guideline were included and fewer than 10 patient trials were excluded. 63 articles met the inclusion criteria of which 24 were graded class I-III.

Following are the recommendations based on the analysis: Prednisone (a) should be used for improving strength and may be useful for improved timed motor function (eg time to stand) (b) should be used to improve pulmonary function (c) may reduce need for scoliosis surgery and (d) may delay onset of cardiomyopathy by 18yrs of age. Deflazacort (a) improves strength and timed motor function and delayed loss of ambulation by 1.4-2.5 yrs (b) improves pulmonary function (c) reduces the need for scoliosis surgery (d) delays cardiomyopathy by 18yrs of age and (d) increased survival at 5 and 15 years.

When compared both PS and DF are equivalent in improving motor function but there is insufficient evidence to establish a difference in effect on cardiac function. PS is associated with increased weight gain in first years of treatment compared to increased risk of cataracts with DF.

PS 0.75/mg/kg/d is the preferred dosing regimen. PS 10mg/kg on the weekend is equally effective over 12 months but long term effect is not established. AE profile is similar with both regimens over 12 months of treatment. PS 0.3mg/kg/d has lesser in efficacy and fewer AE profile. PS 1.5mg/kg/d is equivalent to 0.75mg/kg/d but with more AE.

There is insufficient evidence to support or refute the following: (a) addition of calcifediol or alendronate for improving bone health on PS (b) benefit of bisphosphonates on survival in patients on CS (c) benefit of prednisone for survival (d) differences in efficacy of AE between daily, alternate day or intermittent regimens for prednisone or prednisolone (e) preferred dose of deflazacort or (f) effect of corticosteroids on QoL. [1]

COMMENTARY. It has often been the experience of many in the field treating DMD, of time spent highlighting the paucity of evidence regarding the choice of CS, dosing regimens and AE thereof when patients are newly diagnosed. This paper has tried to address such issues and provided updates to previous guidelines that make such decisions somewhat easier in the short term. It should be noted that choice of PS vs DF in the US is also influenced by availability, as DF needs to be shipped from overseas.

Further questions that need to be answered include the time of initiation of CS treatment, length of CS therapy, change in dosing over time as motor functions decline. Some of these questions are being dealt in an ongoing large multicenter trial titled "finding the optimum regimen for DMD (FOR-DMD)", which is actively recruiting and the results of which are much awaited.

In the interim, I strongly support treating DMD with CS while counseling parents on the current evidence available regarding efficacy, dosing regimens and AE. Gaps in knowledge need to be presented during initiation of treatment. While there are clinical trials underway trying to ameliorate the genetic mutations in DMD, CS still remain the best available medication and the above mentioned gaps should not the deter initiation of such.

Disclosures

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

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INFECTIOUS/AUTOIMMUNE DISORDERS

Evidence for Resident Memory T cells in Rasmussen Encephalitis

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Related Article: Owens GC, Chang JW, Huynh MN, Chirwa T, Vinters HV, Mathern GW. Evidence for Resident Memory T Cells in Rasmussen Encephalitis. Front Immunol 2016 Feb;7:64.
Keywords: Rasmussen Encephalitis; Resident Memory T Cells; CD103 Antigen; Natalizumab; Focal Cortical Dysplasia

Investigators from University of California Los Angeles studied the presence of different T cell subset population in the brain tissue of 7 patients with Rasmussen encephalitis, a rare neuroinflammatory disorder characterized by intractable seizures and usually associated with progressive hemi cerebral atrophy, who underwent brain surgery and compared them to patients with focal cortical dysplasia. Clusters of T cell (mostly CD8) were found at the gray and white matter junction in patients with Rasmussen encephalitis. The majority of these CD8 T cell express CD103 and CD 69, markers of tissue resident memory T cells, irrespective of the time between surgery and the onset of seizure. This finding suggests that the immune response occurs very early in the course of the disease as early as 3 months. In contrast, T cells in patients with focal cortical dysplasia were found near the blood vessels and less than 10% of these cells expressed CD103. However, the percentage of CD103 + CD 8 T cell correlated with the duration of illness suggesting that inflammation occurs later in the disease course and it is accumulative over time. [1]

COMMENTARY. Naive T cells undergo rapid proliferation phase (clonal expansion) after interacting with antigen on antigen presenting cell. The majority of these activated T cells differentiate into different effectors cells based on the cytokine milieu and travel to the affected organ by expressing different tissue homing molecules. After successful elimination of the pathogens, these cells die by apoptosis (contraction phase). Small percentage of naive T cells differentiate to memory T cells, which live for long period of time and protect the body from future infections. There are 3 distinct types of memory T cell: 1) Central memory T cells (TCM) which express CCR7 and home to secondary Lymphoid organs. 2) Effectors memory T cells (TEM) which are shorter-lived but more active cells. These cells are able to go to blood stream and different tissues. 3) Resident memory T cells (TRM), a newly recognized type of memory T cells that express CD103 and/or CD69. These cells reside in the affected tissue even after the pathogen is cleared and do not circulate in the blood stream [2]. Beside the role of these cells in clearing pathogens, there is growing body of evidence of their role in organ-specific autoimmunity like psoriasis and Crohn's disease [2]. TRM cell has been found in the junction between gray and white matter in a mouse model of relapsing - remitting CNS disease (multiple sclerosis) suggesting that these cells can present in the tissue even in the absence of previous infection [3]. Natalizumab, a monoclonal antibody that blocks the T cell's ability to cross the blood brain barrier by targeting alpha-4 integrin and an FDA approved treatment of multiple sclerosis, has been used with good success in a patient with Rasmussen encephalitis [4]. Unfortunately, the use of Natalizumab is associated with increased risk of PML (progressive multifocal leukoencephalopathy) from reactivation of JC virus infection. For patients with inflammatory bowel disease, this risk can be minimized by using Vedolizumab, alpha-4 beta-7 integrin antibody which is gut homing molecule and does not interfere with CNS lymphocytes trafficking [5]. The investigators in this study showed the presence of memory resident T (TRM) cell in the brain tissue of Rasmussen encephalitis patients at early stages of the disease. This finding expands our knowledge about Rasmussen encephalitis, a poorly understood inflammatory disease and gives insight about new therapeutic approaches, such as using Natalizumab to slow the disease progression and hopefully eliminate the need for surgery in patients with Rasmussen encephalitis.

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INFECTIOUS/AUTOIMMUNE DISORDERS

Autoimmune Post-Herpes Simplex Encephalitis

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Related Article: Armangue T, Moris G, Cantarín-Extremera V, Conde CE, Rostasy K, Erro ME et al.; Spanish Prospective Multicentric Study of Autoimmunity in Herpes Simplex Encephalitis. Autoimmune post-herpes simplex encephalitis of adults and teenagers. Neurology 2015 Nov;85(20):1736–43.
Keywords: Herpes Simplex Virus; Encephalitis; Autoimmunity

Investigators at August Pi Sunyer Biomedical Research Institute and University of Barcelona performed a prospective surveillance study in 14 patients with immune-mediating relapsing symptoms of post-herpes simplex encephalitis (HSE). The study aimed to compare the clinical and immunologic features of HSE in teenage and adult patients with those of young children. Groups were divided into 6 young children aged 6 to 20 months (median, 13 months) and 8 teenager and adult patients aged 13-69 years (median, 40 years). All patients underwent repeat serum and CSF HSV PCR and MRI of the brain. CSF was also sent for antibodies to cell surface and synaptic proteins, including NMDA and GABA. Repeat CSF was negative for HSV in all patients with symptoms suggestive of disease recurrence. Symptoms concerning for recurrence differed between groups. Adults and teenagers had longer delays in diagnosis (85 days, range 17-296) when compared to children (4 days, range 0-33, p= 0.037). All Children <20months of age developed choreoathetosis (6/6 vs 0/8, $p < 0.01$) and decreased level of consciousness (6/6 vs 2/8, $p < 0.01$) in association with IgG antibodies against NMDA receptor subunits (6/6). In contrast, the teenage and adult patients did not develop choreoathetosis. 3/8 older patients presented with symptoms resembling acute viral relapse; 5/8 developed symptoms while in rehabilitation initially attributed to disease recrudescence. 7/8 patients developed severed neuro-psychiatric and behavioral symptoms. 1/8 developed blepharospasm. 5/8 had CSF antibodies against NMDA receptor and 3/8 against unknown neuronal cell surface proteins. In 5/6 patients the MRI showed new areas of contrast enhancement during relapse that decreased after immunotherapy. 1/8 patients showed spontaneous recovery and other 7/8 were treated with immunotherapy. Therapies included steroids alone, steroids with IVIG, or steroids with IVIG, and plasma exchange. Immunotherapy was beneficial in 100% of patients treated. [1]

COMMENTARY. The current literature supports the hypothesis that HSE triggers auto-antibodies against synaptic proteins, like N-methyl-D-aspartate receptor (NMDAR) and other brain autoimmunity [2,3,4]. The current study adds important information to the theory of auto-immunity after HSE. It also shows that symptoms of HSE relapse and subsequent brain autoimmunity differs between children and older patients. Specifically, teenage and adult patients should be monitored closely as they tend to present with milder symptoms early in their relapse that may be difficult to distinguish from exacerbation of baseline deficits. Physicians should assess these patients for both recurrent HSV infections as well as antibodies against synaptic proteins. The authors report an excellent response to immunotherapy; larger placebo-controlled trials are necessary to study the benefit of immunotherapy in prevention and treatment of immune-mediated relapse. Additionally, given the varying symptoms that were present during relapse between age groups, multicenter placebo-controlled studies would help to better characterize the clinical, immunological and neuro-radiographic findings in immune-mediated post-HSE relapse.

Disclosures

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VASCULAR DISORDERS

Cerebral Sinovenous Thrombosis in Neonates and Children

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Related Article: Lolli V, Molinari F, Pruvo J, Soto Ares G. SoroAres, G. Radiological and clinical features of cerebral sinovenous thrombosis in neonates and older children. J Neuroradiol 2016;43(4):280–9.
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Investigators from Erasmus University Hospital in Belgium and Gustave-Dron Hospital and Roger-Salengro Hospital in France studied the clinical and neuroradiologic characteristics of cerebral sinovenous thrombosis (CSVT) in neonates and children. The authors retrospectively reviewed charts for 11 neonates and 16 older children under the age of 18 that were diagnosed with CSVT between 2011 to 2014. Seizures occurred in 26.9% of patients. Systemic illness as a risk factor was more common in the neonates and 36.4% patients did not have a pre-disposing risk factor. Imaging characteristics also differed between the neonatal versus non-neonatal populations. Thrombosis affected the deep venous structures in most of the neonates (51.8%). All neonates had evidence of intraventricular hemorrhage and many also had parenchymal infarcts (38.5%). Extra-parenchymal lesions were more common in neonates than non-neonates and parenchymal lesions tended to be larger in neonates. Cortical vein thrombosis and superficial vein involvement were seen more frequently in the older children (66.7%, p=0.01). This retrospective study provides further information about the clinical presentation and imaging in pediatric CSVT and differences between neonatal and non-neonatal populations. [1]

COMMENTARY. Cerebral sinovenous thrombosis occurs in approximately 0.67 per 100,000 children with a neonatal predominance [2,3]. The results of this study suggest that the radiological presentation and venous structures involved in CSVT differ between neonates and older children.

The pediatric stroke literature historically has focused upon the superficial cerebral venous system; the superior sagittal sinus (SSS) is reported to be the most frequently involved sinus in pediatric CSVT, especially in neonates [2]. A recent study found that neck positioning and occipital bone compression of the SSS in supine neonates may contribute significantly to the development of neonatal CSVT [3]. In contrast, neonates in this study were more likely to have thrombosis of the deep venous system than of the superficial venous system. The involvement of the deep venous system may explain the high incidence of hemorrhage in neonatal CSVT. The deep venous system drains the germinal matrix so vascular congestion may lead to injury of the germinal matrix (especially if it is immature) and subsequent intraventricular and extra-parenchymal hemorrhage. However, the high prevalence of deep venous thrombosis in this study may have been affected by the small number of neonates (11), all of whom presented with intraventricular hemorrhage.

This study also found a significant portion of older children had cortical vein thrombosis which provides further evidence that cortical vein thrombosis may be underreported. Traditionally, cortical vein thrombosis has been thought to be rare. However, a recent study of cortical vein thrombosis in children reported that almost a quarter of the patients with CSVT actually had cortical vein thrombosis; the children with cortical vein thrombosis also were more likely to have significant neurological complications, such as infarction and seizures [5].

Overall, the results of this study indicate that that thrombosis of the deep venous system and cortical veins may play significant roles in the pediatric CSVT and warrant further investigation. Given the differences in involvement of the venous structures and associated brain injury, this study also provides additional evidence that CSVT in neonates and older children are not a single entity and that studies evaluating etiology, treatment and outcome should differentiate between neonatal and non-neonatal populations.

Disclosures

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

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