PEDIATRIC NEUROLOGY BRIEFS
A MONTHLY JOURNAL REVIEW

J. GORDON MILLICHAP, MD. EDITOR
JOHN J. MILLICHAP, MD. ASSOCIATE EDITOR

Vol. 28, No. 10 October 2014

INFECTIOUS DISORDERS

FOCAL ENCEPHALITIS FOLLOWING VARICELLA-ZOSTER VIRUS REACTIVATION WITHOUT RASH

Staff members at the Mayo Clinic, Rochester, MN, and University of Iowa Children's Hospital, Iowa City, report a healthy 22-year-old man with a focal encephalitis following varicella-zoster virus (VZV) reactivation without rash, triggered by varicella vaccination required for employment in a hospital. Between 2 to 3 weeks following vaccination he developed intermittent left temporal headaches and 2 days later, he had a seizure. MRI demonstrated a T2/FLAIR hyperintense and T1 hypointense lesion involving the left inferior temporal sulcus. A routine EEG recorded 2 subclinical left temporal lobe seizures. The differential diagnosis favored a low-grade astrocytoma or oligodendroglioma. The pathology report on the resected lesion excluded a tumor, and perivascular inflammation of leptomeningeal vessels indicated a viral etiology for the gliosis. VZV immunostaining of brain tissue and VZV serology were positive for VZV antigens, and wild-type VZV sequences were detected. He was treated with valacyclovir. At follow-up examination 1 year later he was free of CNS symptoms. Further examination of childhood records revealed that at 6 months of age he was exposed to varicella in his older sister, but he had no exanthem at that time. At 27 months of age he had developed a left-sided T6/T7 dermatomal rash and a diagnosis of herpes zoster. It was concluded that this case represents VZV reactivation, most likely in the trigeminal ganglion, in the absence of clinical herpes zoster. (Halling G, Giannini C, Britton JW, et al. Focal encephalitis following varicella-zoster virus reactivation without rash in a healthy immunized young adult. **Jrnl Infect Dis** 2014 Sep 1;210(5):713-6).

PEDIATRIC NEUROLOGY BRIEFS © 1987-2014, ISSN 1043-3155 (print) 2166-6482 (online), is published monthly and covers selected articles from the world literature. The Editor is Pediatric Neurologist and the Associate Editor, Pediatric Epileptologist and Neurologist at the Ann & Robert H. Lurie Children's Hospital of Chicago; Northwestern University Feinberg School of Medicine, Chicago, IL. PNB is a continuing education service designed to expedite and facilitate the review of current scientific information for physicians and other health professionals. Apply to PediatricNeurologyBriefs.com for Subscriptions (12 issues, January-December). Digital Edition PDF: $72; Print + Free Digital: $96 within US/UK, $128 outside US/UK. Institutions: Digital Edition IP Access $188, Print + Free Digital $228. Mailing address for subscription: Pediatric Neurology Briefs Publishers, PO Box 11391, Chicago, IL 60611

COMMENTARY. The close temporal proximity of the VZV reactivation with 2 varicella vaccinations during the previous 2 to 3 weeks is strong suggestive evidence for a causal association. However, the authors argue in favor of a coincidental association since virology sequencing showed that the VZV infection in the brain was caused by wild-type VZV. Wild-type VZV has been isolated from vesicles in patients with herpes zoster after immunization, indicating that herpes zoster in immunized people also may result from natural varicella infection that occurred before or after immunization [1]. They suggest that the varicella vaccination, rather than having a detrimental effect, may have prevented further inflammation by stimulating a rapid anti-VZV immune response. Furthermore, the surgical excision of the area of inflammation in the temporal lobe may have prevented further extension of viral infection.

Link between VZV reactivation and CNS disease. Neurological complications of VZV reactivation include zoster induced postherpetic neuralgia, myelitis, meningoencephalitis, VZV vasculopathy, and stroke [2]. Stroke as a complication of VZV reactivation is reported in the elderly but is rare in childhood [3]. When these complications occur without rash (zoster sine herpete), VZV-induced disease is diagnosed by detection of VZV DNA or anti-VZV antibody in CSF. Awareness of the expanding spectrum of neurological complications of VZV reactivation leads to earlier diagnosis and antiviral treatment. A case of congenital varicella syndrome (CVS) in a male infant presented with generalized clonic cerebral seizures at age 4 months [4]. An intracerebral viral reactivation following intrauterine VZV infection was suspected and confirmed. Antiviral treatment was aimed at preventing progression of the disease. CVS presents with skin lesions, neurological defects, eye diseases, and limb hypoplasia.

References.

1. American Academy of Pediatrics. Varicella zoster infections. In: Pickering LK, ed. Red Book: 2012 Report of the Committee on Infectious Diseases. 29th ed. Elk Grove Village, IL: AAP; 2012:784.
2. Nagel MA, Gilden D. Curr Opin Neurol. 2014 Jun;27(3):356-60.
3. Grose C, et al. Expert Rev Anti Infect Ther. 2014 May;12(5):527-30.
4. Sauerbrei A, et al. Dev Med Child Neurol. 2003 Dec;45(12):837-40.

INTRACRANIAL HYPERTENSION

SYMPTOMS AND ETIOLOGIES OF PSEUDOTUMOR CEREBRI

Investigators from Ankara Pediatrics, Turkey, evaluate the clinical symptoms and etiology in records of 53 patients (32 female) diagnosed with pseudotumor cerebri (PTC) in a child neurology department between 2005 and 2012. Mean age at presentation was 10.9 years (range 3-17) and one half were age 11 years or younger. Prepubertal patients (under 12 years old) were male in >50%, while 74% patients at puberty were girls. Etiology was undetermined or idiopathic in 30 and symptomatic in 23. Obesity rate was 41% for pubertal patients and 31% for prepubertal patients. Obesity was not related to etiology or puberty. In idiopathic cases, headache was the most common symptom (in 88%), nausea and/or vomiting in 30%, diplopia in 28%, and dizziness in 9%. Papilledema was found in 100%, and VI or VII nerve palsy in 11.3%. An etiologic factor for symptomatic PTC was identified in 43% of patients and included cerebral venous sinus

thrombosis in 6 patients, upper respiratory tract infections in 4, iron deficiency anemia in 3, steroid withdrawal in 3 epilepsy patients, risperidone or cyclosporine usage in 3, Brucella infection, post-traumatic and slit ventricle syndrome in one each of the secondary PTC group. Comorbid disorders in the idiopathic group were related to obesity (hypertension, diabetes), and in the symptomatic group, epilepsy, and vitamin D deficiency. Papilledema was lessened by acetazolamide in 72%. (Degerliyurt A, Teber S, Karakaya G, et al. Pseudotumor cerebri/idiopathic intracranial hypertension in children: An experience of a tertiary care hospital. **Brain Dev** 2014 Sep;36(8):690-9).

COMMENTARY. Idiopathic intracranial hypertension (IIH) is defined as intracranial pressure increase with no intracranial pathology and a normal CSF content [1]. The term, "pseudotumor cerebri," is used where an etiology for intracranial hypertension is identified or suspected [2]. Olfactory impairment, an under-recognized complication of idiopathic intracranial hypertension, is studied in relation to astronauts in head-down tilt positions [3]. Many long-duration astronauts develop signs of elevated intracranial pressure and have olfactory threshold dysfunction.

Controversy regarding efficacy of acetazolamide in IIH. The efficacy of acetazolamide in IIH is questioned since a randomized controlled trial failed to show a significant difference in lumbar puncture pressure, headache disability and visual acuity in the acetazolamide vs placebo groups [4]. A prospective cohort study found that weight loss is an effective therapy in IIH [5][6], leading to the proposition that weight loss may be the reason for the small improvement in the acetazolamide cohort in a most recent IIH Treatment Trial [6]. Proponents of a positive effect of acetazolamide in IIH argue that the effect of acetazolamide on visual field function is independent of its effect on weight loss and does not relate to the anorexigenic effect of acetazolamide [7].

References.
1. Skau M, et al. Cephalalgia. 2006 Apr;26(4):384-99.
2. Spennato P, et al. Childs Nerv Syst. 2011 Feb;27(2):215-35.
3. Bershad EM, et al. J Neurol Neurosurg Psychiatry. 2014 Sep;85(9):959-64.
4. Ball AK, et al. J Neurol. 2011 May;258(5):874-81.
5. Sinclair AJ, et al. BMJ. 2010 Jul 7;341:c2701.
6. Sinclair AJ, et al. JAMA. 2014 Sep 10;312(10):1059-60.
7. Wall M, et al. JAMA. 2014 Apr 23-30;311(16):1641-51.

HEADACHE DISORDERS

SYMPTOMS AND ETIOLOGIES OF ALICE IN WONDERLAND SYNDROME

Investigators from Children's Hospital of Philadelphia, PA, conducted a retrospective chart review of 48 children (average age at presentation 8.1 yrs, range 5-14 yrs; 73% male) diagnosed with "Alice in Wonderland" syndrome (AWS) or "Alice in Wonderland"-like syndrome between 1993 and 2013. Micropsia occurred in 69%, teleopsia in 50%, macropsia 25%, metamorphopsia 15%, and pelopsia (objects appear nearer) in 10%. MRI and EEG were normal. Etiology was infection (viral or

streptococcal sore-throat) in 33% of patients, migraine in 6%, and head trauma in 6%. A family history of migraine was elicited in 46%; 5 parents (33%) of affected patients had experienced AWS symptoms. Of 15 patients with follow-up by telephone interview, 20% had occasional recurrences, 40% had no further attacks, 40% were still having symptoms, 4 (27%) developed migraine, and 1 patient (7%) had seizures. The interval between initial diagnosis and telephone contact was an average of 6.5 yrs (range, 2.1-13.53 yrs). (Liu AM, Liu JG, Liu Alm GW, Liu GT. "Alice in Wonderland" syndrome: Presenting and follow-up characteristics. **Pediatr Neurol** 2014 Sep;51(3):317-20).

COMMENTARY. AWS is a disorder of childhood that affects boys more often than girls, and may subsequently 'metamorphose' and develop into migraine in one quarter of patients.

Headache metamorphosing into AWS. Patients with a diagnosis of childhood headache in 1983 were interviewed by telephone in 1993, 2003, and 2013. Of 28 patients monitored, headaches were ongoing in 71%, and distortions of time and space were experienced by >25% and ~20%, respectively. There was no clear correlation with migraine, and patients with tension-type headaches also reported the AWS symptoms. Distortions of space and time persist into the fifth decade for many patients initially observed with headaches in childhood [1].

References.

1. Dooley JM, et al. Pediatr Neurol. 2014 Sep;51(3):321-3.

NUTRITIONAL DISORDERS

THIAMINE DEFICIENCY IN INFANCY

Investigators at Tel Aviv University, Loewenstein Rehabilitation Hospital, Schneider Children's Medical Center, and other centers in Israel report the clinical presentation of acute encephalopathy in 11 children and the long-term sequelae of 8 who initially survived an episode of thiamine deficiency. In 2003, 20 Israeli infants were seriously affected after being fed an international brand of soy-based formula later found to contain no thiamine. In the acute phase, 6 had bulbar signs, 5 had ophthalmologic signs and 2 had phrenic neuropathy. MRI, the best test for diagnosis of thiamine deficiency in the acute phase, showed symmetric involvement of frontal, temporal and parietal lobes, lesions in the periaqueductal region, thalami, and the mammillary bodies, findings similar to sequelae of hypoxic-ischemic injury. Of 5 patients with cardiac involvement, 3 had cardiomyopathy and died in the acute phase, and one presented with a complete atrioventricular block. Lactic acidosis was present in 10 patients. In long-term follow-up, one patient in a chronic vegetative state died after 6 years, 7 children were mentally retarded and had motor abnormalities, 6 developed severe epilepsy, 3 with West syndrome, 2 had kyphoscoliosis, and one remained in complete A-V block. (Mimouni-Bloch A, Goldberg-Stern H, Strausberg R, et al. Thiamine deficiency in infancy: Long-term follow-up. **Pediatr Neurol** 2014 Sep;51(3):311-6).

COMMENTARY. The majority of infants exposed to the thiamine deficient formula in infancy were asymptomatic but a small minority developed encephalopathy and/or cardiomyopathy that were sometimes fatal. Infants who survive thiamine-deficient encephalopathy have a poor prognosis, with motor and cognitive impairment and epilepsy. Thiamine deficiency in a developed country is unusual, but as many as 12.5% of a population of critically ill Canadian children were found to have significant thiamine deficiency [1]. Wernicke encephalopathy and beriberi during total parenteral nutrition was attributed to multivitamin infusion shortage in a patient with Crohn's disease in California [2]. Almost immediately following intravenous thiamine, the hypotension resolved and the following day she no longer had diplopia, and the ophthalmoplegia had improved. Thiamine deficiency should be considered in patients with malabsorption, malnutrition, and malignancies.

References.
1. Seear, et al. J Pediatr. 1992 Oct;121(4):533-8.
2. Hahn JS, et al. Pediatrics. 1998 Jan;101(1):E10.

NEUROMUSCULAR DISORDERS

CONGENITAL MYASTHENIC SYNDROME WITH AGRIN MUTATIONS

Investigators at Newcastle University, UK, and Hopitaux de Paris, France, report 5 patients from 3 unrelated families with a strikingly homogeneous clinical entity combining congenital myasthenia with distal muscle weakness and atrophy resembling a distal myopathy. MRI and neurophysiological studies were indicative of a mild distal myopathy, but decrement in response to 3 Hz repetitive nerve stimulation suggested a neuromuscular transmission defect. Post-exercise increment up to 285% in distal limb muscles was compatible with presynaptic congenital myasthenic syndrome. Immunofluorescence and ultrastructural analyses of muscle end-plate regions showed synaptic remodelling with denervation-reinnervation. Whole-exome sequencing identified five new recessive mutations in the gene encoding agrin. These findings expand the spectrum of congenital myasthenic syndromes due to agrin mutations. (Nicole S, Chaouch A, Torbergsen T, et al. Agrin mutations lead to a congenital myasthenic syndrome with distal muscle weakness and atrophy. **Brain** 2014 Sep;137(Pt 9):2429-43).

COMMENTARY. The authors recommend examination of patients with apparent distal myopathy for a neuromuscular transmission disorder and for agrin mutations.

Prevalence of congenital myasthenia. The UK prevalence of genetically confirmed congenital myasthenic syndrome (CMS) is 9.2 per million children under 18 years of age. CMS is equally prevalent in girls and boys. CHRNE, RAPSN and DOK7 are the most commonly identified mutations. Prevalence varies across geographical regions in England (2.8 to 14.8 per million). The mean incidence of antibody-positive autoimmune myasthenia was 1.5 per million children per year. Girls were affected more frequently than boys [1].

Investigators at the John Radcliffe Hospital, University of Oxford, UK, provide a review with updates of new mutations of known CMS causative genes and treatment strategies. The use of salbutamol and ephedrine alone or combined with physostigmine or 3,4-DAP is reported to benefit various CMS subtypes [2].

Of 51 patients attending the myasthenia clinic at the Massachusetts General Hospital, Boston, in 1958–1960, 35 were the juvenile type, 10 the transient neonatal type, and 6 a congenital myasthenia syndrome, under-recognized as a separate phenotype at that time [3].

References.
1. Parr JR, et al. Arch Dis Child. 2014 Jun;99(6):539-42.
2. Cruz PM, et al. Curr Opin Neurol. 2014 Oct;27(5):566-75.
3. Millichap JG, Dodge PR. Neurology. 1960 Nov;10:1007-14.

SEIZURE DISORDERS

MOTOR CO-ACTIVATION OF JUVENILE MYOCLONIC EPILEPSY IN SIBLINGS

Investigators at UCL Institute of Neurology, Queen Square, London, UK, used functional magnetic resonance imaging to study the effect of cognitive effort during a working memory task as a trigger of myoclonic jerks in 15 unaffected siblings (10 female; age range 18-65 years, median 40 yrs) of 11 patients with juvenile myoclonic epilepsy (6 female; age range 22-54 yrs, median 35). fMRI activations were compared with 20 age- and gender-matched healthy control subjects.

Unaffected siblings showed abnormal primary motor cortex and supplementary motor area co-activation with increasing cognitive load, as well as increased task-related functional connectivity between motor and prefrontal cognitive networks, with a similar pattern to that in patients with JME ($P<0.001$). This finding in unaffected siblings suggests a mechanism for impairment of frontal lobe functions in both patients and siblings, independent of effects of medication or seizure, an endophenotype of JME. (Wandschneider B, Centeno M, Vollmar C, et al. Motor co-activation in siblings of patients with juvenile myoclonic epilepsy: an imaging endophenotype? **Brain** 2014 Sep;137(Pt 9):2469-79).

COMMENTARY. The abnormal frontal lobe function demonstrated by fMRI in adults with JME and their siblings is also demonstrated in children.

Neurodevelopment in new-onset juvenile myoclonic epilepsy. Investigators at Irvine University, CA, studied the maturation of cognitive and brain development in 19 children with new-onset JME in the first 2 years after diagnosis and 57 healthy controls. Abnormal patterns of brain development affecting frontoparietotemporal regions, as assessed by MRI, were evident in children with JME and included attenuation of age-related decline in cortical volume, thickness, and surface area. Children with JME have abnormal structural brain development and impaired cognitive development early in the course of the epilepsy [1].

References.

1. Lin JJ, et al. Ann Neurol. 2014 Aug 1. [Epub ahead of print].

NEUROMETABOLIC CAUSES OF INFANTILE SPASMS

Investigators at King Abdulaziz Medical City, Riyadh, Saudi Arabia, studied the prevalence of hereditary neurometabolic causes of infantile spasms in 80 cases presenting over a 15-year period. Of 10 patients (12.5%) diagnosed with metabolic causes, 2 had a Leigh-like disorder, and 1 patient had each of the following diagnoses: ethylmalonic aciduria, nonketotic hyperglycinemia, hyperinsulinemic hypoglycemia, leukodystrophy, short-chain acyl-coenzyme A dehydrogenase deficiency, molybdenum cofactor deficiency, primary carnitine deficiency, and neonatal hypoglycemia due to panhypopituitarism. Most of the patients were born of consanguineous parents, and the hereditary group had a strong history of other family members affected. The typical hypsarrhythmia pattern in the EEG was more common in the hereditary metabolic group (P=0.003), and this group had a poor response to therapy (P=0.04). Metabolic disorders are a relatively common cause of infantile spasms in this subpopulation of Saudi patients. Early diagnosis with metabolic and genetic testing is important in selection of specific treatments and facilitating family counseling. (Alrifai MT, AlShaya MA, Abdulaban A, Alfadhel M. Hereditary neurometabolic causes of infantile spasms in 80 children presenting to a tertiary care center. **Pediatr Neurol** 2014 Sep;51(3):390-7).

COMMENTARY. In patients suspected of having a hereditary metabolic cause for infantile spasms, the authors recommend a more liberal application of advanced diagnostic techniques, such as whole exome sequencing, muscle biopsy for mitochondria biochemical and genetic studies, and newer neuroimaging techniques such as 3 Tesla MRI and PET scanning [1]. More extensive genetic testing is justified in higher risk populations where high consanguinity rates are prevalent. A review of etiology of infantile spasms in the United Kingdom where consanguinity is rare finds the common causes are hypoxic-ischemic encephalopathy (10%), chromosomal anomalies (8%), malformation (8%), perinatal stroke (8%), and tuberous sclerosis complex (7%) [2][3].

References.

1. Alrifai MT, et al. Pediatr Neurol. 2014 Sep;51(3):390-7.
2. Pavone P, et al. Brain Dev. 2014 Oct;36(9):739-751.
3. Osborne JP, et al. Epilepsia. 2010 Oct;51(10):2168-74.

DEVELOPMENTAL DISORDERS

AAP GENETICS DIAGNOSTIC APPROACH TO INTELLECTUAL DISABILITY OR GLOBAL DEVELOPMENTAL DELAY

The American Academy of Pediatrics Committee on Genetics present a recommended clinical genetics diagnostic approach to the evaluation of intellectual disability or global developmental delays. The report addresses the advances in diagnosis and treatment of children with intellectual disabilities since the original AAP report in

2006 [1]. *Intellectual disability* (ID) is characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social and practical adaptive skills. The disability originates before age 18 years, and the prevalence is estimated at 1% to 3%. *Global development delay* (GDD) is defined as a significant delay in 2 or more developmental domains, including gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living, and is thought to predict a future diagnosis of ID. GDD is applied to younger children < 5 years, and the prevalence is 1% to 3%, similar to that of ID. The term ID is applied to older children for whom IQ testing is valid and reliable.

In patients with GDD or ID, chromosome microarray and fragile X are first line diagnostic tests. MRI remains important in some patients. The use of whole-exome sequencing as a diagnostic test is gaining popularity. (Moeschler JB, Shevell M. Committee on Genetics. Comprehensive evaluation of the child with intellectual disability or global development delays. **Pediatrics** 2014 Sep;134(3):e903-18).

COMMENTARY. The benefits of a comprehensive evaluation were studied in 20 families of children with ID, with and without an etiologic diagnosis [2]. A diagnosis was thought to help guide expectations and management and provide hope for treatment. Diagnosis assisted families in obtaining desired services, especially in schools. Families differed in their "need to know" a specific diagnosis, ranging from strong to indifferent. Families varied in their emotions and actions regarding prenatal genetic diagnosis. The importance of the pediatrician and clinical geneticist discussion is stressed before deciding on the best approach to the diagnostic evaluation. The pediatric neurologist has an equally important role in the arrival at the correct etiological diagnosis and management of a child with GDD or ID.

References.

1. Moeschler JB, Shdevell M. Pediatrics. 2006 Jun;117(6):2304-16.
2. Makela M, et al. Am J Med Genet A. 2009 Nov;149A(11):2393-402.

SUBDURAL HEMORRHAGE AND ANTITHROMBOTIC THERAPY

Investigators at the Mott Children's Hospital, Ann Arbor, MI, report 4 infants with diffuse brain injury and cerebral atrophy who developed cerebral venous sinus thrombosis and were treated with the low-molecular-weight heparin, enoxaparin. The infants subsequently developed subdural hemorrhages, diagnosed on routine MRI, and one had focal seizures. The use of enoxaparin in infants with diffuse brain injury has a risk of intracranial subdural hemorrhage. (Dang LT, Shavit JA, Singh RK, et al. Subdural hemorrhages associated with antithrombotic therapy in infants with cerebral atrophy. **Pediatrics** 2014 Sep;134(3):e889-93).

COMMENTARY. Asymptomatic subdural hematomas are common in infants with congenital heart disease and they resolve within 3 months of birth [1].

References.

1. Kelly P, et al. Pediatrics. 2014 Sep;134(3):e773-81.