PEDIATRIC NEUROLOGY BRIEFS
A MONTHLY JOURNAL REVIEW

J. GORDON MILLICHAP, M.D., F.R.C.P., EDITOR

Vol. 27, No. 3 March 2013

HEADACHE DISORDERS

RELATION OF TRIGGER FACTORS TO MIGRAINE WITH AURA

Researchers from the University of Copenhagen, Denmark studied the relation between natural trigger factors and migraine with aura (MA) in 27 patients who reported that bright or flickering light or strenuous exercise would trigger their attacks. Patients were provoked by photic stimulation, strenuous exercise, or a combination of these two factors. Three patients (11%) reported attacks of MA following provocation. An additional 3 patients reported migraine without aura (MO) attacks. Following exercise, 17% developed an aura, 4 out of 12 patients reported migraine (1 MA, 3 MO) headaches, while no patients developed attacks following photic stimulation alone. Patients were exhausted after the exercise and 5 developed nausea, 2 vomited, and 6 complained of dizziness. Light stimulation, especially low frequency of 1-5 Hz, was considered unpleasant but was well tolerated. (Houguard A, Amin F, Hauge AW, Ashina M, Oleson J. Provocation of migraine with aura using natural trigger factors. **Neurology** 2013 Jan 29;80(5):428-31). (Respond: Dr Olesen. jeol@regionh.dk).

COMMENT. In an editorial (Goadsby PJ, Silberstein SD. **Neurology** 2013 Jan 29;80(5):424-5), the trigger effect of exercise demonstrated in the present study is considered small (10%) compared to that of nitroglycerin infusion that induces migraine and premonitory symptoms in 75% of patients. (Iversen H. Human migraine models. **Cephalalgia** 2001 Sep;21(7):781-5). Food triggers or sensitivities, frequently discussed in the migraine literature (Egger J, Carter CM, Wilson J, et al. **Lancet** 1983 Oct 15;2(8355):865-9) **(**Millichap JG, Yee MM. **Pediatr Neurol** 2003 Jan;28(1):9-15), have variable effects or mechanisms. As an example, ingredients in chocolate implicated in the mechanism of dietary-triggered migraine include phenylethylamine, theobromine, caffeine, and catechin. These chemicals may initiate a headache by alteration of cerebral

PEDIATRIC NEUROLOGY BRIEFS © 1987-2013, ISSN 1043-3155 (print) 2166-6482 (online), is published monthly and covers selected articles from the world literature. The editor is Pediatric Neurologist at the Ann & Robert H. Lurie Children's Hospital of Chicago; Professor Emeritus, Northwestern University Feinberg School of Medicine. 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 2012): Digital PDF, $72 (Residents/Fellows $36); Print + Digital, $96 within US & UK; $128 outside US & UK. Institutional rates also available. To order by mail: Pediatric Neurology Briefs Publishers, PO Box 11391, Chicago, IL 60611

blood flow and release of norepinephrine from sympathetic nerve cells. (Martin VT, et al. **Med Clin North Am** 2001 Jul;85(4):911-41). Alternatively, a chocolate trigger may be explained by a premonitory food craving; and chocolate is consumed because of a response to a migraine attack and not a cause. Also, an urge to exercise may represent a premonitory symptom of migraine. The classic advice to avoid suspect triggers may be incorrect, and the migraineur should instead, be advised to become habituated to the provocative factor. (Martin PR. Managing headache triggers: think 'coping' not 'avoidance.' **Cephalalgia** 2010 May;30(5):634-7). Indeed, some adult patients advised to avoid chocolate and red wine would rather suffer an occasional migraine.

DEMYELINATING DISORDERS

LONG-TERM OUTCOME OF PEDIATRIC-ONSET MS

Researchers at University Hospital of Wales, Cardiff; and University of Bristol, UK studied the clinical features and disability in pediatric-onset multiple sclerosis (POMS) in a population-based cohort with long-term follow-up, and compared to a cohort of patients with adult-onset (AOMS) disease. Of 2068 patients identified with MS since 1985, 111 (5.4%) had POMS and in 110, disease onset was relapsing. Age of onset ranged from 4 to 17 years (mean, 15 years). Initial most frequent manifestations were motor in 52.8% and optic neuritis in 26.4%. No significant differences in sex ratio, familial recurrence, relapse rate, ethnicity or clinical symptoms at presentation were identified between POMS and AOMS. Compared to AOMS, POMS cases had a longer interval to second relapse (5 vs 2.6 years, $p=0.04$), less common primary progressive disease (0.9% vs 8.5%, $p=0.003$), longer time to develop secondary progressive disease (32 vs 18 years, $p=0.0001$), and longer to reach disability milestones ($p<0.0001$). Incomplete recovery from initial event was significantly associated with a shorter time to reach disability milestones ($p=0.01$). Patients with POMS become disabled at a younger age and have a poorer age-related prognosis than AOMS cases. (Harding KE, Liang K, Cossburn MD, et al. Long-term outcome of paediatric-onset multiple sclerosis: a population-based study. **J Neurol Neurosurg Psychiatry** 2013 Feb;84(2):141-7). (Respond: Professor Neil C Robertson, Institute of Psychological Medicine and Clinical Neuroscience, Cardiff University, University Hospital of Wales, Heath Park, Cardiff, CF14 4XN, UK. E-mail: robertsonnp@cardiff.ac.uk).

COMMENT. While prognosis of POMS appears more benign than that of AOMS in early disease, later stages of the disease are similar to AOMS and lead to an earlier disability.

FIBRONECTIN AGGREGATION AND REMYELINATION IN MS

Researchers at Universities of Groningen and Amsterdam, The Netherlands, and Universities of Cambridge and Edinburgh, UK examined the expression of the extracellular matrix molecule fibronectin on demyelinating injury and how this affects remyelination by oligodendrocytes progenitors. In lesions undergoing remyelination, fibronectin expression was transiently increased in demyelinated areas and declined as remyelination proceeded. In chronically demyelinated MS lesions, fibronectin expression

persisted as aggregates, resistant to degradation. Fibronectin aggregates within MS lesions contribute to failure of remyelination and are potential therapeutic targets for promoting remyelination. (Stoffels JMJ, de Jonge JC, Stancic M, et al. Fibronectin aggregation in multiple sclerosis lesions impairs remyelination. **Brain** 2013 Jan;136(Pt 1):116-31) (Response: Dr Wia Baron. E-mail: w.baron@umcg.nl).

CHILDHOOD OBESITY AND RISK OF PEDIATRIC MS

Researchers at Kaiser Permanente of Southern California studied a possible relation between childhood obesity and pediatric-onset multiple sclerosis (MS) or its potential precursor, clinically isolated syndrome (CIS), which encompasses optic neuritis (ON) and transverse myelitis (TM). Seventy-five newly diagnosed pediatric cases of MS or CIS were identified between 2004 and 2010; 41 (55%) were girls, and 54 (72%) were age 11-18. Onset of MS/CIS was uncommon at ages 2-11 years. Thirty-eight (50.7%) children or adolescents with MS/CIS were overweight or obese. Obesity was associated with a significantly increased risk of MS/CIS in girls but not in boys. Moderately and extremely obese patients were more likely to present with TM compared with normal/overweight children (p=0.003). (Langer-Gould A, Brara SM, Beaber BE, Loebnick C. Childhood obesity and risk of pediatric multiple sclerosis and clinically isolated syndrome. **Neurology** 2013 Feb 5;80(6):548-52). (Response: Dr Langer-Gould. E-mail: Annette.M.Langer-Gould@kp.org).

COMMENT. Childhood obesity is independently associated with an increased risk of pediatric-onset MS/CIS in girls but not in boys. The authors speculate that the rapid rise and high estrogenic exposure of obese, peripubescent girls coupled with inflammatory mediators released by adipose tissue accelerate MS/CIS onset in adolescence. Pregnancy in females and tobacco smoke among males (Palacios N, et al. **Ann Epidemiol** 2011 Jul;21(7):536-42), additional potential risk factors for MS, were not addressed in this study. The need to further address the progress of the childhood obesity epidemic is stressed, especially in girls.

PERINATAL DISORDERS

MELATONIN AND EXPERIMENTAL PERINATAL ASPHYXIA

Researchers from University College London, Hopital Robert Debre, and Universite Paris Diderot, Paris assessed the neuroprotective effects of melatonin combined with therapeutic hypothermia after transient hypoxia-ischemia in a piglet model of perinatal asphyxia. Melatonin administered intravenously 10 min after transient hypoxia-ischemia and repeated at 24 hr augments hypothermic neuroprotection based on improved cerebral energy metabolism, using magnetic resonance spectroscopy biomarkers and continuous EEG monitoring. The piglet model of H-I resembles the clinical setting in a neonatal intensive care unit. The observed benefits and safety profile of melatonin support consideration of phase I and II clinical studies of melatonin-augmented therapeutic hypothermia for neonatal encephalopathy. (Robertson NJ,

Faulkner S, Fleiss B, et al. Melatonin augments hypothermic neuroprotection in a perinatal asphyxia model. **Brain** 2013 Jan;136(Pt 1):90-105). (Response: Dr Nicola J Robertson. E-mail: n.robertson@ucl.ac.uk).

COMMENT. Melatonin (N-acetyl-5-methoxytryptamine), a naturally occurring hormone secreted by the pineal gland, when administered alone has neuroprotective actions against H-I brain injury in animal models. The present study demonstrates that melatonin augments the neuroprotective effect of hypothermia.

Potential synergistic neuroprotective therapies with hypothermia include inhaled xenon, N-acetylcysteine, erythropoietin, anticonvulsants and cannabinoids, in addition to melatonin. (Cilio MR, Ferriero DM. **Semin Fetal Neonatal Med** 2010 Oct;15(5):293-8) (Kelen D, Robertson NJ. **Early Hum Dev** 2010 Jun;86(6):369-77).

SEIZURE DISORDERS

PROGNOSTIC FACTORS FOR REFRACTORY STATUS EPILEPTICUS

Researchers at the Mayo Clinic, Rochester, MN studied the outcome and identified prognostic factors for refractory status epilepticus (RSE) in 54 adult patients, median age 52 years [range 18-93]. RSE was defined as generalized convulsive or nonconvulsive status epilepticus that continued despite initial first and second-line therapies. Patients younger than 18 years, anoxic/myoclonic, psychogenic, simple partial, and absence SE were excluded. Of 63 consecutive episodes of RSE, anesthetic agents were used in 55 (87.3%). Duration of drug-induced coma was a mean of 11 days (SD 17.9 days). Cardiac arrhythmias occurred in 21 of 60 episodes (35%) and required intervention in 14 of 21 cases (66.67%). In hospital mortality was 31.75%, in 20 of 63 episodes. Functional outcome at discharge was poor in 48 (76.19%) episodes. Hospital length of stay was a mean of 27.7 days (SD 37.3 days). Poor functional outcome was associated with drug-induced coma ($p=0.03$), cardiac arrhythmias requiring intervention ($p=0.01$), and pneumonia ($p=0.01$). Prolonged mechanical ventilation was associated with mortality ($p=0.04$). Good functional recovery ($p=0.01$) followed seizure control without suppression-burst or isoelectric EEG. Functional outcome was not related to age, history of epilepsy, previous SE, type of SE, and anesthetic drug used. (Hocker SF, Britton JW, Mandrekar JN, Wijdicks EFM, Rabinstein AA. Predictors of outcome in refractory status epilepticus. **JAMA Neurol** 2013 Jan 1;70(1):72-7). (Response: Sara E Hocker MD, Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail: Hocker.sara@mayo.edu).

COMMENT. In adults with refractory status epilepticus, risk factors for a poor prognosis include the severity of the SE, the need for drug-induced coma, cardiopulmonary complications requiring prolonged mechanical ventilation, and pneumonia. Aggressive EEG suppression does not improve outcome of RSE. Three-quarters of adult RSE patients have a poor outcome.

A review of studies of status epilepticus published from 1990-2009 shows that children have a better prognosis than adults, and age and depth of coma are the strongest

predictors of outcome of SE. (Neligan A, Shorvon SD. Prognostic factors, morbidity and mortality in tonic-clonic status epilepticus: a review. **Epilepsy Res** 2011 Jan;93(1):1-10). In otherwise normal children with focal epilepsy, SE has no significant effect on long-term intellectual and seizure outcome. (Camfield P, Camfield C. **Pediatrics** 2012 Sep;130(3):e501-6).

CLINICAL, BIOCHEMICAL, AND MOLECULAR STUDIES AND TREATMENT OF PYRIDOXINE-DEPENDENT EPILEPSY

Researchers at Autonomous University of Madrid, and other centers in Spain studied the clinical, biochemical, and genetic spectrum of pyridoxine-dependent epilepsy (PDE) in 12 patients with the clinically proven diagnosis. Onset of seizures varied from neonatal to first months of life. Seizures were focal or multifocal, clonic or myoclonic, and generalized tonic; 50% had status epilepticus. Seizures were controlled transiently with conventional AEDs for 15 or more days in 8 of 12 patients, leading to a delay in diagnosis. The effective dose of pyridoxine to suppress seizures ranged from 10 to 30 mg/kg/day. Neurologic symptoms in addition to seizures included hypotonia, irritability, and psychomotor retardation. EEG abnormalities were variable and included focal or multifocal discharges, burst-suppression pattern, and generalized slowing. A normal EEG in one patient does not rule out the diagnosis. All EEGs became normal after pyridoxine therapy. MRI abnormalities, mainly posterior fossa, included mega cisterna magna, Dandy Walker syndrome, ventriculomegaly, and corpus callosum dysgenesis. Six patients followed for more than 5 years show cognitive dysfunction and borderline or mildly retarded IQs. Delay in treatment and dysgenesis of the corpus callosum are risk factors for neurodevelopmental delay. Treatment with pyridoxine does not normalize the IQ. Urine levels of a-aminoadipic semialdehyde (a-AASA) and plasma/CSF levels of pipecolic acid (PA) are diagnostic biomarkers. Genetic analysis of these Spanish patients showed 12 mutations, 7 novel, and different from other populations. (Perez B, Gutierrez-Solana LG, Verdu A, et al. Clinical, Biochemical, and molecular studies in pyridoxine-dependent epilepsy: Antisense therapy as possible new therapeutic option. **Epilepsia** 2013 Feb;54(2):239-48). (Response: Dr Belen Perez. E-mail: bperez@cbm.uam.es).

COMMENT. PDE should be considered in any infant with intractable seizures, including patients with MRI abnormalities such as corpus callosum dysgenesis or Dandy Walker syndrome. The long-term outcome of PDE was poor in a Dutch PDE cohort of 14 patients. (Bok LA, Halbertsma FJ, Houterman S, et al. **Dev Med Child Neurol** 2012 Sep;54(9):849-54). EEG background and epileptiform activity were not correlated with outcome. Delayed initiation of pyridoxine and the association of corpus callosum abnormalities were significantly associated with unfavorable neurodevelopmental outcome, findings similar to the Spanish experience.

PDE WITH MOLYBDENUM COFACTOR DEFICIENCY

PDE with molybdenum cofactor deficiency is reported in 2 siblings. Molecular investigations revealed a homozygous mutation in the MOCS2 gene. Pyridoxine supplementation is recommended in patients diagnosed with molybdenum cofactor or

sulfite oxidase deficiencies. (Struys EA, Nota B, Bakkali A, et al. **Pediatrics** 2012 Dec;130(6):e1716-9).

ATTENTION DEFICIT AND AUTISTIC DISORDERS

FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDIES OF INHIBITION AND ATTENTION IN ADHD

Researchers at King's College, London; Kyushu University, Japan; and Barcelona, Spain conducted a meta-analysis of functional magnetic resonance imaging (fMRI) in ADHD during inhibition and attention tasks, with reference to age and effects of long-term use of stimulant medication. Twenty-one data sets were included in the inhibition meta-analysis (7 adult and 14 pediatric samples), and 13 data sets in the attention meta-analysis (2 adult and 11 pediatric samples). Combined, the inhibition studies included 287 patients with ADHD and 320 healthy controls. Compared to controls, patients with ADHD showed reduced activation for inhibition in the right inferior frontal cortex, supplementary motor area, anterior cingulate cortex, and striato-thalamic areas, and reduced activation for attention in the right dorsolateral prefrontal cortex, posterior basal ganglia, thalamic and parietal regions. Long-term stimulant medication use was associated with more normal right caudate activation during the attention domain. For the inhibition meta-analysis only, the supplementary motor area and basal ganglia were under-activated in children with ADHD, while the inferior frontal cortex and thalamus were under-activated solely in adults with ADHD relative to controls. (Hart H, Radua J, Nakao T, Matai-Cols D, Rubia K. Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder. **JAMA Psychiatry** 2013 Feb;70(2):185-198). (Response: Dr Katya Rubia. E-mail: katya.rubia@kcl.ac.uk).

COMMENT. In conclusion, patients with ADHD have cognitive dysfunctions in right fronto-basal ganglia-thalamic networks, and long-term stimulant medication is associated with normalization of right caudate deficits during attention. In addition to inhibition and attention studies, future meta-analyses should include other compromised functions such as timing and motivation. In the present study, for the inhibition domain, go/no-go, stop tasks and Stroop tasks were used, and for the attention domain, tasks that measured visuospatial selective attention, sustained attention, and flexible attention.

SELECTIVE DOPAMINE REUPTAKE INHIBITOR AND ADHD

ADHD treatments act as dual norepinephrine (NE) and dopamine (DA) reuptake inhibitors (psychostimulants) or selective NE reuptake inhibitors (SNRIs). Benztropine analogs (AHN2-005) act as highly selective DA reuptake inhibitors while lacking the abuse potential of psychostimulants. A cognition-enhancing dose of AHN 2-005 increased levels of DA and NE in the prefrontal cortex (PFC) and may be effective in the treatment of ADHD associated with PFC dysfunction. (Schmeichel BE et al. **Neuropharmacology** 2013 Jan;64:321-8). Neuropharmacology and fMRI studies should expand the development of new, more effective agents in the treatment of ADHD.

MATERNAL FOLIC ACID AND RISK OF CHILDHOOD AUTISM

Researchers from the Norwegian Institute of Public Health, Oslo; Institute of Child Health, London, UK; and other centers in Norway, UK, and the US examined the association between maternal use of prenatal folic acid supplements (4 weeks before to 8 weeks after start of pregnancy) and risk of autistic spectrum disorders in children derived from the population-based, prospective Norwegian Mother and Child Cohort Study (MoBa). The age-range at end of follow-up was 3.3 – 10.2 years (mean, 6.4 years). The total daily maternal folate intake varied widely from 62-5673 ug (mean, 497 ug/day).

At end of follow-up, a total of 270 children (0.32%) were diagnosed with ASDs: 114 autistic disorder, 56 Asperger syndrome, 100 PDD-NOS. Autistic disorder was diagnosed in 0.1% of children exposed to folic acid compared with 0.21% in those unexposed. The adjusted odds ratio for autistic disorder in children of folic acid users was 0.61. In contrast, children of mothers who supplemented their diet with fish oil showed no association with autistic disorder. The findings do not establish causality but they do add support to prenatal folic acid diet supplementation. (Suren P, Roth C, Bresnahan M, et al. Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children. **JAMA** 2013 Feb 13;309(6):570-7). (Response: Pal Suren MD, MPH, Norwegian Institute of Public Health, PO Box 4404, Nydalen, N-0403 Oslo, Norway. E-mail: pal.suren@fhi.no).

COMMENT. Maternal folic acid supplementation during pregnancy, widely known to reduce the risk of neural tube defects in children, is now shown to be associated with a lower risk of childhood autism. It has also been linked to a lower risk of severe language delay at age 3 years, a study also conducted in Norway (Roth C, et al. **JAMA** 2011 Oct 12;306(14):1566-73).

GESTATIONAL AGE AT BIRTH AND RISK OF AUTISM

The association between gestational age (GA) at birth and the risk of autistic spectrum disorder (ASD) in 218,110 singleton live births between 1998 and 2004 in Alberta, Canada was studied at each completed week of gestation (GA<23 weeks vs >23 weeks to <43 weeks vs >43 weeks, in 1-week increments). A gradual increased risk of developing ASD was noted with shorter gestation. Cutoffs between 29 and 40 weeks clearly denoted an elevated risk of ASD compared with longer gestation, and the risk increased with earlier GA cutoff. The association was independent of sex and fetal growth measures. (Leavey A, Zwaigenbaum L, Heavner K, Burstyn I. Gestational age at birth and risk of autism spectrum disorders in Alberta, Canada. **J Pediatr** 2013 Feb;162(2):361-8). (Reprints: Igor Burstyn PhD, Drexel University, Philadelphia, PA. E-mail: igor.burstyn@drexel.edu). This study confirms the findings in an earlier smaller sample size population (Gillberg C, Gillberg IC. Infantile autism: a total population study of reduced optimality in the pre-, peri- and neonatal period. **J Autism Dev Disord** 1983 Jun;13(2):153-66).

DEVELOPMENTAL MALFORMATIONS

FOCAL CORTICAL DYSPLASIA TYPE IIB AND HUMAN PAPILLOMAVIRUS

Researchers at Temple University School of Medicine, Philadelphia, PA tested the hypothesis that human papillomavirus type 16 oncoprotein E6 (HPV16 E6) is present in human focal cortical dysplasia type IIB (FCDIIB) specimens. HPV was assayed by immunohistochemistry in FCDIIB specimens (n=50) and control brain specimens (n=36). HPV DNA was assayed by PCR and in situ hybridization. HPV16 E6 protein was expressed in all FCDIIB specimens in balloon cells (BC), but not in regions without BCs or control tissue including normal brain and cortical tubers. Transfection of E6 into fetal mouse brains caused a focal cortical malformation in association with enhanced mTORC 1 signaling. (Chen J, Tsai V, Parker WE, et al. Detection of human papillomavirus in human focal cortical dysplasia type IIB. **Ann Neurol** 2012 Dec;72(6):881-92). (Response: Dr Crino. E-mail: peter.crino@temple.edu).

COMMENT. HPV16 E6 expression during fetal brain development is a novel etiology for FCDIIB, but the mechanism and relation of the HPV16 to the cause of epilepsy associated with focal cortical dysplasia is unexplained.

TORC1 ACTIVATION AND INFLAMMATION IN FETAL TSC LESIONS

A current neuropathological publication from the University of Amsterdam; University of Calgary, Canada; and other centers reports that abnormal cells scattered through the cortex and white matter of fetal brain lesions in tuberous sclerosis complex (TSC) show activation of TORC1, similar to that observed in FCD/HPV. This finding supports the concept of increased TORC1 activity during embryonic brain development as a precursor and precipitant of brain malformations in tuberous sclerosis complex. (Prabowo AS, Anink JJ, Lammens M, et al. **Brain Pathology** 2013 Jan;23(1):45-59). This study also provides evidence for the immunogenicity of giant cells and the prenatal activation of inflammatory pathways in developing TSC brain lesions, a probable explanation for the epileptogenicity of TSC lesions and focal cortical dysplasias.

ICTAL LATERALIZING SIGN IN REFRACTORY EPILEPSY

Researchers in Cuba and Columbia studied the frequency of ictal dorsiflexion of the great toe and its lateralizing value for the epileptogenic focus in seizures of patients consecutively evaluated at two tertiary centers for epilepsy surgery. Ictal dorsiflexion of the great toe occurred in 15 (9.1%) of 165 patients and in 25 (9.2%) of 272 seizures. The seizure localized to the temporal lobe in 22 (88%) of 25 seizures, > 50% associated with hippocampal sclerosis. Ictal toe dorsiflexion was contralateral to the epileptogenic zone in 72% of the patients with refractory partial epilepsy. (Machado RA, Mila RA, Astencio AG, Santos AS. Lateralizing value of ictal dorsiflexion of the great toe in refractory partial epilepsy. **Epilepsy Behav** 2013 Feb 7;27(1):102-106). (Response: Dr Machado. E-mail: renemachado@infomed.sld.cu).