PEDIATRIC NEUROLOGY BRIEFS
A MONTHLY JOURNAL REVIEW

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

Vol. 22, No. 5 May 2008

ATTENTION DEFICIT DISORDERS

CONGENITAL HEART DISEASE AND ADHD

Risk factors for inattention, hyperactivity and impaired school performance were examined in 109 children, 5 to 10 years of age, who had undergone newborn cardiac surgery for complex congenital heart disease (CHD) at Children's Hospital of Philadelphia, PA. Data obtained by questionnaires completed by parents and teachers showed that 53 (49%) were enrolled in remedial educational programs, 15% in special education. On an ADHD Rating Scale-IV, 30% received high-risk scores. On a Behavior Assessment System for Children, the number of children with significant scores for inattention and hyperactivity was 3 to 4 times higher than that in the general population. Adverse effects on behavior and learning were not related to pre-,peri-, or post-operative factors, including hypoxemia and CHD. (Shillingford AJ, Glanzman MM, Ittenbach RF, Clancy RR, Gaynor JW, Wernovsky G. Inattention, hyperactivity, and school performance in a population of school-age children with complex congenital heart disease. **Pediatrics** April 2008;121:e759-e767). (Respond: Amanda J Shillingford MD, Division of Cardiology, Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104).

COMMENT. School-age children with a history of neonatal cardiac surgery for complex CHD are at increased risk for ADHD and poor performance in math and reading skills. In view of the PDR precautions and contraindications regarding medications for ADHD in children with cardiac disorders, the management of these patients presents a unique challenge for parents, teachers, and physicians. A recent statement released by the American Heart Association advocates screening children routinely for cardiac conditions before and during treatment with stimulant drugs for ADHD.

PEDIATRIC NEUROLOGY BRIEFS (ISSN 1043-3155) © 2008 covers selected articles from the world literature and is published monthly. Send subscription requests ($68 US; $72 Canada; $75 airmail outside N America) to **Pediatric Neurology Briefs - J. Gordon Millichap, M.D., F.R.C.P.- Editor,** P.O. Box 11391, Chicago, Illinois, 60611, USA. The editor is Pediatric Neurologist at Children's Memorial Hospital and Professor Emeritus, Northwestern University Medical School, Chicago, Illinois.
PNB is a continuing education service designed to expedite and facilitate review of current scientific information for physicians and other health professionals. Fax: 312-943-0123.

SLEEP PROBLEMS AND ADHD

The prevalence of sleep problems and their associations with quality of life (QOL), school attendance, and family impacts in children with ADHD were determined in a study at Royal Children's Hospital, University of Melbourne, Australia. Caregivers' (primarily mothers) in 239 eligible families reported sleep problems during the previous 4 weeks that were mild in 28.5%, and moderate or severe in 44.8% of ADHD children. Moderate or severe sleep problems were associated with impaired child QOL, child daily functioning, caregiver mental health, and family functioning. Children with sleep problems were more likely to miss or be late for school, and their caregivers were more likely to be late for work. Caregivers for sleep deprived ADHD children were 2.7 times more likely to be clinically depressed or anxious. Pediatricians had enquired about child sleep problems in 45% cases, and caregivers had received treatment advice in 60% of those affected. (Sung V, Hiscock H, Sciberras E, Efron D. Sleep problems in children with attention-deficit/hyperactivity disorder. **Arch Pediatr Adolesc Med** April 2008;162:336-342). (Respond: Valerie Sung MBBS, Centre for Community Child Health, Royal Children's Hospital, Flemington Road, Parkville, Victoria, Australia 3052. E-mail: valeriesung@rch.org.au).

COMMENT. Sleep problems in schoolchildren with ADHD are common and are associated with impairment of QOL, daily functioning, and school attendance. Caregivers' mental health and work attendance are also adversely affected. Treatment of sleep disorders might improve daytime attention and behavior and lessen the need for stimulant medication.

Two further articles and an editorial on sleep disorders and behavior appear in the same issue of this journal. Hvolby A and associates in Denmark (**Arch Pediatr Adolesc Med** 2008;162:323-329) found that children with ADHD have significantly longer sleep onset latency and a more irregular sleep pattern than controls. Comorbid ODD is not related to sleep disorders. Parents over-report irregular sleep patterns as compared to objective measurements using actigraphy.

In a study at Brown University, Rhode Island Hospital, Providence, Owens JA and associates (**Arch Pediatr Adolesc Med** 2008;162:313-321) report risk factors, including overweight, short sleep duration, and comorbid sleep disorders, affecting behavioral outcome in children with sleep-disordered breathing (SDB). More than half (56%) of the sample was overweight, and more than one-third (36%) were short sleepers. Almost half (49%) had an additional sleep diagnosis, particularly insomnia. SDB severity has a weaker influence on behavioral outcome. Behavior problems were reported in 47%; ADHD in 23%.

In the editorial, Cao M and Guilleminault C, Sleep Disorders Clinic, Stanford University, emphasize cultural differences in sleeping behaviors including cosleeping, limitations of polysomnography as a diagnostic tool, orthodontic problems as a cause of parasomnias, sleep-related disorders as cause or complication of ADHD, and the relation of early childhood sleep disorders to adolescent and adult emotional and behavioral problems. The relation between sleep duration and childhood obesity requires more investigation, and the importance of stricter sleep schedules in young children needs more emphasis in parental education. (**Arch Pediatr Adolesc Med** 2008;162:385-389).

VASCULAR DISORDERS

EARLY ARTERIAL ISCHEMIC STROKE IN PREMATURE INFANTS

Presentation, clinical course, and outcomes for 23 premature children with arterial ischemic stroke before 44 weeks gestational age are reported from Riley Hospital for Children, Indianapolis, IN. Infants were born between 23 and 35 weeks gestational age; 10 (43%) were male, and 5 (22%) were part of twin pregnancies. Presentation at 1-4 days (median 1 day) was a respiratory difficulty or apnea in 83%. Seizures occurred at onset in 7 (30%), poor feeding in 6 (26%), and abnormal tone in 5 children (22%). All had imaging studies suggestive of stroke within the first 44 weeks gestational age, and confirmed by MRI in 18 children. The middle cerebral artery was most commonly affected; 10 had small branch middle cerebral infarcts, and the remainder had infarcts affecting various arteries and territories. Intraventricular hemorrhage occurred in 12, and white matter injury (periventricular leukomalacia and/or hypoxic-ischemic encephalopathy) in 12. Prothrombotic disorder was diagnosed in 7 of 9 tested. NICU stay ranged from 14-365 days (median, 63 days). One child died at 123 days, and all 22 survivors had disabilities, including cerebral palsy in 17 (77%), epilepsy in 10 (45%), and cognitive impairment in 17 (77%). (Golomb MR, Garg BP, Edwards-Brown M, Williams LS. Very early arterial ischemic stroke in premature infants. **Pediatr Neurol** May 2008;38:329-334). (Respond: Dr Meredith R Golomb, Pediatric Neurology, Indiana University School of Medicine, 575 West Dr, Building XE 040, Indianapolis, IN 46202).

COMMENT. The authors refer to the paucity of reports of very early arterial ischemic stroke in premature infants, the additional neurologic disorders complicating prematurity, and the limitations of cerebral imaging in fragile prematures. Presenting symptoms of ischemic stroke (respiratory difficulties, apnea and seizures) are common presenting signs of respiratory distress syndrome, intraventricular hemorrhage, and periventricular leukomalacia in the neonate. The incidence of cerebral palsy, epilepsy, and cognitive impairment in this cohort of premature infants was higher but not significantly different from that in a previously reported study of term infants with perinatal stroke. (Golomb MR et al. **Pediatr Neurol** 2007;37:245-249).

In a review of recent developments in childhood arterial ischemic stroke, Amlie-Lefond C and associates (**Lancet Neurol** May 2008;7:425-435) from Medical College of Wisconsin; University of Sherbrooke, QC, Canada; and University of California, San Francisco, estimate incidence rates in neonates at 1 per 5000 livebirths. Arteriopathies (dissection, moyamoya, vasculitis, focal stenosis) account for 80%, more than half have long-term sequelae, and 6-19% have recurrences. Inflammatory reactions triggered by infections play an important role in the pathophysiology of arteriopathies. Varicella zoster virus infection and stroke has been reported frequently, secondary reactivation of the virus is also associated, and stroke following varicella vaccination is reported in 2 children. Varicella zoster virus replication in the CNS is confirmed by PCR or antibodies in the CSF. Treatment is not well defined and includes antipyretics for fever and aspirin antithrombotic.

HEADACHE DISORDERS

TREATMENT OF MENSTRUAL-RELATED MIGRAINE

A review and meta-analysis of therapy trials for menstrual-related migraine headache (MRM) and evidence-based recommendations for acute and short-term preventive treatment are reported from Toronto Western Hospital, ON, Canada. Nineteen prospective, double-blind, randomized controlled trials of medications for relief or prevention of MRM were included in the guideline. For 9 acute treatment trials that met inclusion criteria, outcome considered was pain response and pain-free response at 2 hours. For 10 short-term prevention trials, the response criteria were the incidence of MRM or number of headache days. Trials involved women aged 18 to 65 with a history of MRM in at least two or 3 previous regular menstrual cycles. Trial quality was based on US Task Force criteria. Grade B recommendations (good evidence to treat - benefits outweigh harms) for use of sumatriptan, mefenamic acid, and rizatriptan in acute management of MRM in adult patients. Grade B recommendations for premenstrual use of transcutaneous estrogen, frovatriptan, and naratriptan in preventive treatment of adults with MRM. Choice of evidence-based regimens for MRM is based on clinical considerations. (Prinsheim T, Davenport WJ, Dodick D. Acute treatment and prevention of menstrually related migraine headache. Evidence-based review. **Neurology** April 22, 2008;70:1555-1563). (Reprints: Dr Tamara Pringsheim, Movement Disorders Centre, Toronto Western Hospital, 399 Bathurst Street, Toronto ON M5T 258 Canada).

COMMENT. The above report concerns adults, and sumatriptan is much less effective against migraine in children and adolescents. Sumatriptan is not licensed for use in patients <18 years of age in the US. In 23 children, aged 8 to 16 years, a randomized placebo-controlled, crossover trial of oral sumatriptan in Finland showed no significant differences in pain relief, although 13 preferred sumatriptan. (Hamalainen ML et al. **Neurology** 1997;48:1100-1103). A failure of response to oral sumatriptan is reported by others. In contrast, a placebo-controlled, crossover trial in Germany found *nasal* sumatriptan to be effective and well tolerated in children over 8 years of age. (Ahonen K, Hamalainen ML et al. **Neurology** 2004;62:883-887) (Ueberall MA, Wenzel D. **Neurology** 1999;52:1507-1510). A search of the literature found no study of effects of triptans in children with menstrual-related migraine.

PAROXYSMAL HEMICRANIA

The clinical characteristics of paroxysmal hemicrania (PH) are reported in a series of 31 patients, ages 5-68 years (mean age 37), identified and followed prospectively at the National Hospital and the Hospital for Sick Children, Great Ormond Street, London, UK from May 1995 to January 2007. Pain was exclusively right-sided in 15 (48%) and exclusively left-sided in 15 (48%). The location of pain in the majority was the same as that recognized by the International Headache Society (IHS), 2004: temporal and orbital in 24 (77%), and retro-orbital in 19 (61%). Pain was also frontal in 55%, occipital in 42%, at the vertex in 36%, and located in other areas of the head, neck, and shoulders in some. Pain was

rated as severe in the majority, and the mean duration of an attack was 17 min. Cranial autonomic features, at least one required by IHS classification, involved lacrimation in 87%, conjunctival injection in 68%, rhinorrhea in 58%, and ptosis in 54%. Agitation or restlessness occurred in 80%. All patients responded to indomethacin, a sine qua non for paroxysmal hemicrania. MRI or CT scan obtained in 25 (80%) patients was normal in 16 (64%) and showed abnormalities in 9 (36%). Abnormal scans included vascular loop compressing the trigeminal nerve, ophthalmic A-V malformation, sphenoid wing meningioma, and ischemic lesions in basal ganglia and pons. The authors suggest that the IHS revise the diagnostic criteria for paroxysmal hemicrania to include a wider location for pain, and a more inclusive range of autonomic features. An indomethacin test should be given to any patient with lateralized discrete attacks of head pain with associated cranial autonomic symptoms. **Brain** April 2008;131:1142-1155). (Respond: Professor Peter J Goadsby, Headache Group, Department of Neurology, University of California, San Francisco, Box 0114, 505 Parnassus Avenue, San Francisco, CA 94143-0114, USA).

COMMENT. Paroxysmal hemicrania is classified as a trigeminal autonomic cephalgia and is defined by the IHS (2004) as a severe unilateral orbital, supraorbital or temporal pain, lasting 2-30 min, accompanied by ptosis, eyelid edema, conjunctival injection, lacrimation, nasal blockage or rhinorrhea. Attacks usually occur >5 times a day and respond to indomethacin. Both chronic and episodic variants are described. The disorder is rare, with estimated prevalence of 1 in 50,000. In one third of cases, a cranial structural cause may be defined, some responding to surgery. The cohort reported above comprised 4% of trigeminal autonomic cephalalgia cases seen in the same time period. The female preponderance usually reported was not seen in this series. In differential diagnosis, cluster headache differs from PH in affecting 3 males to 1 female, attacks last longer (30-180 min), and no response to indomethacin. PH is reported in association with migraine, cluster headache, trigeminal neuralgia and cough headaches. The authors link pathogenesis to posterior hypothalamic activation, similar to cluster headache. A correct diagnosis of PH and its differentiation from other autonomic cephalalgias are important because of the dramatic and rewarding response of PH to indomethacin.

SEIZURE DISORDERS

EFFECT OF SEIZURE CLUSTERING ON EPILEPSY OUTCOME

A prospective, long-term population-based study was performed to determine whether seizure clustering (3 or more afebrile seizures during a 24 hour period) is associated with drug resistance and increased mortality in childhood-onset epilepsy, in a study at University of Turku, Finland, and the Epilepsy Research Group, Berlin, Germany. At an average 37 years follow-up, 26 (22%) of 120 childhood-onset epilepsy patients had recorded clusters of seizures. Patients with clusters had at least one seizure per week at the initial stage in 63% vs 32% of those without clusters (P=0.0178) and during follow-up. During drug therapy, patients with clusters were (1) more likely to have drug resistant epilepsy compared to those without (42% vs 13%, P=0.01); (2) less likely to enter 5-year remission (P=0.0230); and (3) had a higher risk of death (42% vs 14%, P=0.0299). In contrast, patients with seizure clustering before but not during treatment showed no difference in seizure outcome or

mortality risk. The causes of death included dissection of the aorta and pneumonia (non-epilepsy related), and accidental drowning, and SUDEP. Five of the patients with clusters during treatment died, whereas none with pre-treatment clusters died. (Sillanpaa M, Schmidt D. Seizure clustering during drug treatment affects seizure outcome and mortality of childhood-onset epilepsy. **Brain** April 2008;131:938-944). (Respond: Prof Dr Dieter Schmidt, Epilepsy Research Group, Goethestr 5, D-14163 Berlin, Germany, E-mail: dbschmidt@t-online.de).

COMMENT. Clustering of seizures during treatment is associated with a less favorable long-term outcome compared to clustering prior to treatment. Patients with seizure clustering during treatment compared to those without are four times more likely to have drug resistant epilepsy and an increased risk of mortality. Patients with clustering before beginning treatment is not associated with a poor prognosis. Clustering was not associated with status epilepticus in this study. The authors favor trials of aggressive treatment of seizure clustering.

SCREENING TEST FOR DRAVET SYNDROME BEFORE ONE YEAR

Risk factors for Dravet syndrome were determined in 96 children who experienced febrile seizures before age one year, in a retrospective study at Okayama University and other centers in Japan. Clinical characteristics were compared in 46 patients who had developed Dravet syndrome and 50 without the syndrome. Significant risk factors included an age of onset of febrile seizure <7 months, a total of >5 seizures, and prolonged seizures >10 min. Other highly predictive factors were hemiconvulsions, partial seizures, myoclonic seizures, and hot water-induced seizures. A total clinical score of 6 or above was the cut-off value for a high risk of Dravet syndrome. (Each risk factor was assigned a score of 0-3, based on the p-value; >5 seizures [3], hemiconvulsion [3], prolonged seizure [3], onset <7 mos [2], hot water-induced seizure [2], focal or myoclonic seizure [1]). SCN1A mutations were detected significantly more often in the Dravet group (41-43%) than in the non-Dravet syndrome group (0-12%) of patients. (Hattori J, Ouchida M, Ono J et al. A screening test for the prediction of Dravet syndrome before one year of age. **Epilepsia** 2008;49(4):626-633). (Respond: Dr Iori Ohmori, Department of Cellular Physiology, Graduate School of Medicine, Okayama University, 5-1 Shikata-cho, 2-chome, Okayama 700-8558, Japan. E-mail: iori@md.okayama-u.ac.jp).

COMMENT. In this practical screening test for the differentiation of Dravet syndrome from febrile seizures, if the patient has a clinical risk score of 6 or more, there is a high risk of Dravet syndrome. SCN1A mutation analysis is recommended if available in infants with a risk score of -/>6. Dravet syndrome or SMEI (severe myoclonic epilepsy of infancy), an intractable form of epilepsy, is difficult to differentiate from a febrile seizure disorder before the first birthday. Seizures are febrile hemiclonic or generalized tonic-clonic, frequently recurrent and prolonged, and are complicated by status epilepticus during infancy. Myoclonic, focal, absence and atonic seizures evolve between 1 and 4 years, and are accompanied by slow development and regression. Neurologic abnormalities include spasticity, ataxia and cognitive impairment. SMEI is one of a spectrum of infantile epileptic encephalopathies with SCN1A mutations. (see **Ped Neur Briefs** April 2007;21:25-26). Early

diagnosis should allow more accurate parental counseling and more effective long-term treatment.

ABORTED AND REFRACTORY STATUS EPILEPTICUS COMPARED

Clinical and EEG characteristics, etiologies, treatment response, and predictors of long-term outcome were determined in 154 children with status epilepticus (SE) hospitalized at the Mayo Clinic, Rochester, MN, 1994-2004. Patients with status aborted with medication (ASE) in 69% were compared to 39% with refractory SE (RSE). SE was defined as continuous tonic-clonic or electrographic seizure activity for at least 10 min or intermittent seizure activity without recovery of consciousness for at least 30 min. (Mayer SA et al. Arch Neurol 2002;59:205-210). Etiology of SE was acute symptomatic in 26%, remote symptomatic 35%, idiopathic 20%, and febrile in 10%. RSE compared to ASE was significantly associated with a higher family history of seizures, higher number of seizures and AEDs, nonconvulsive SE, and focal or electrographic seizures on initial EEG. In-hospital mortality was significantly higher with RSE (13.3%) than ASE (2.1%). RSE patients developed more neurological deficits and more epilepsy at long-term follow-up than ASE children. More aggressive treatment resulted in better responses and outcomes. Poor outcome risk factors included long seizure duration, acute symptomatic etiology, nonconvulsive SE, and young age (<5 years) at admission. Prospective, randomized trials of different treatment protocols are advocated. (Lambrechtsen FACP, Buchhalter JR. Aborted and refractory status epilepticus in children: a comparative analysis. **Epilepsia** 2008;49(4):615-625). (Respond: Jeffrey R Buchhalter MD, Phoenix Children's Hospital, 1919 E Thomas Road, Phoenix, AZ 85016).

COMMENT. Status epilepticus in children is refractory in 40%, and RSE is related to family history, number of seizures and AEDs, nonconvulsive status, and initial EEG abnormalities. Etiology is an important determinant of outcome, especially acute symptomatic causes. Identification of these risk factors should lead to more aggressive therapy and better outcome.

INFECTIOUS DISORDERS

HERPES SIMPLEX VIRUS-1 AND BELL'S PALSY

The association between herpes simplex virus-1 (HSV-1) infection and Bell palsy was determined in 47 children studied at Children's Hospital at Montefiore, Bronx, NY. Swabs of saliva and conjunctiva were taken for PCR testing. To validate PCR testing, swabs were obtained from patients with oral lesions of herpes gingivostomatitis. An HSV-1 enzyme-linked immunosorbent assay was positive in 33 of 42 affected patients compared to 16 of 41 controls (P=0.0003). HSV-1 polymerase chain reaction was positive in 10 of 47 affected patients compared to 4 of 45 controls (P=0.08). The findings support an association between HSV-1 infection and Bell palsy in children. (Khine H, Mayers M, Avner JR, Fox A, Herold B, Goldman DL. Association between herpes simplex virus-1 infection and idiopathic unilateral facial paralysis in children and adolescents. **Pediatr Infect Dis J** May

2008;27:468-469). (Respond: David L Goldman MD, Division of Pediatric Infectious Diseases, Children's Hospital at Montefiore, Albert Einstein College of Medicine, 1300 Morris Park Ave, Bronx, NY 10461).

COMMENT. These findings in children confirm previous reports of a probable role for HSV-1 infection in adults with Bell's palsy. Acyclovir in treatment of Bell's palsy deserves further study. Other infectious causes reported include Epstein-Barr virus, mumps, enteroviruses, and rarely, varicella zoster virus (geniculate herpes, Ramsay Hunt syndrome).

INFLUENZA-ASSOCIATED ENCEPHALITIS/ENCEPHALOPATHY

The role of influenza A and influenza B in acute childhood encephalitis and encephalopathy (ACE) was evaluated prospectively in all children admitted to the Hospital for Sick Children, Toronto, Canada, during an 11-year period from Jan 1994- Dec 2004. Influenza infection was defined by detection in the nasopharynx by immunofluorescence microscopy or viral culture and/or by a 4-fold or greater rise in complement fixation titer. In 311 children with ACE, influenza infection was detected in 22 (7%); 11 were <5 years of age. Fourteen fulfilled criteria for ACE. Influenza A was detected in 13 of 14 cases, and influenza B in 1 case. Neurologic manifestations developed within 5 days of onset of respiratory symptoms in 64%. These included seizures, cranial nerve abnormalities, focal motor deficits, gait abnormalities, meningismus, torticollis, hyperreflexia and opisthotonus. Two presented with status epilepticus, and 2 had hemiparesis. CSF pleocytosis occurred in 3 patients, and elevated protein in 4. Neuroimaging abnormalities noted in 8 of 14 tested were more common in children <2 years of age. Neurologic sequelae occurred in 8 patients (in 5 <2 years of age), and included seizures, hemiparesis, ataxia, and speech disorder. EEGs were abnormal in all 8 of those with neurologic sequelae and in 4 of 6 without sequelae. An acute rather than a postinfectious process was suggested by the briefness of the respiratory prodrome. (Amin R, Ford-Jones E, Richardson SE, et al. Acute childhood encephalitis and encephalopathy associated with influenza. A prospective 11-year review. **Pediatr Infect Dis J** May 2008;27:380-395). (Respond: Ari Bitnun MD, FRCPC, University of Toronto, Division of Infectious Diseases, Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada M5G 1X8. E-mail:ari.bitnun@sickkids.ca).

COMMENT. Influenza virus infection is associated with 5% of cases of acute childhood encephalitis/encephalopathy in Canada. The younger children <5 years of age are most susceptible, and children <2 years of age are most likely to have neurologic sequelae.

A Japanese study of prognostic factors in influenza-associated encephalopathy evaluated 442 cases retrospectively. (Nagao T, Morishima T, Kimura H et al. **Pediatr Infect Dis J** 2008;27:384-389). Type A influenza was detected in 84% and type B in 9.5%. Fifty-four cases (22%) had a history of febrile convulsions. Significant factors for a poor prognosis and death in 35(19%) of 184 cases were an elevated transaminase, hyperglycemia, hematuria or proteinuria, and use of diclofenac sodium for fever during the infection. Factors showing a trend toward poor prognosis were elevated body temperature (>41C), low platelets, and low blood sugar. The occurrence of these signs should prompt admission to intensive care.