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

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ATTENTION DEFICIT AND BEHAVIOR DISORDERS

ENTEROVIRUS 71 CNS INFECTION AND ADHD

ADHD symptoms as long-term sequelae of virus-confirmed enterovirus 71 infection were evaluated in 86 children, aged 4 to 16 years, followed at National Taiwan University Hospital, Taipei, and Chang Gung Children's Hospital, Taoyuan, Taiwan. CNS involvement diagnosed at the time of infection, 3 to 7 years before the study, was a viral meningitis in 42 (49%) of the children, and encephalitis, poliomyelitis-like syndrome, or encephalomyelitis in 35 (41%). CNS symptoms were complicated by cardiopulmonary failure in 9 (10%) patients. Scores on teacher- and mother-rated scales of ADHD and ODD were higher in the children previously infected with enterovirus 71 compared to matched controls. The rate of elevated ADHD symptoms among children with prior history of enterovirus 71 CNS infection was 20% compared to 3% among controls. Internalizing problems, also, were more frequent. WISC-III scores were significantly inversely correlated with severity of ADHD but not with ODD. Clinical severity of enterovirus 71 CNS infection during hospitalization was not predictive of ADHD sequelae. Age at time of infection showed no association with later occurrence of ADHD. (Gau S S-F, Chang L-Y, Huang L-M, Fan T-Y, Wu Y-Y, Lin T-Y. Attention-deficit/hyperactivity-related symptoms among children with enterovirus 71 infection of the central nervous system. **Pediatrics** August 2008;122:e452-e458). (Respond: Luan-Yin Chang MD, PhD, National Taiwan University Hospital, Department of Pediatrics, College of Medicine, National Taiwan University, 7 Chung-Shan South Rd, Taipei 100, Taiwan. E-mail:ly7077@tpts6.seed.net.tw).

COMMENT. Enterovirus 71 CNS infection in young children is associated with an increased rate of symptoms of ADHD, ODD, and internalizing problems. IQ scores are correlated with the severity of ADHD symptoms but not with ODD. The authors recommend

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early identification and intervention for ADHD symptoms and emotional/behavior problems in children with a history of enterovirus 71 CNS infection.

Increased risk of ADHD following CNS infection is not specific to enterovirus 71, but occurs with a variety of microorganisms. A recent review of etiologic factors, especially environmental causes, found an increased prevalence of ADHD in children born to women with a viral exanthematous rash of measles, varicella, or rubella during pregnancy. Other viral infections invoked include HIV, varicella zoster encephalitis, and influenza. (Millichap JG. **Pediatrics** 2008;121:e358-e365). A possible relation between ADHD and streptococcal infection, Borrelia burgdorferi and Lyme disease, or otitis media requires confirmation.

Clinical manifestations of enterovirus 71 infection are protean and include hand-foot-and mouth disease, brainstem encephalitis and polio-like paralysis. Isolation of the virus in cell culture is the standard diagnostic method, and stool and throat specimens produce the highest yield (AAP Redbook, 27th ed, 2006). In a previous report of a long-term study of neurologic sequelae in 142 children with enterovirus 71 CNS infection by the same group of investigators in Taiwan, children with cardiopulmonary complications had a significantly higher incidence of delayed neurodevelopment and lower IQ scores than children with CNS involvement alone. (Chang L-Y et al. **N Engl J Med** 2007;356:1226-1234).

ADHD is a highly heritable disorder, but various environmental factors, including viral infection may play a role in etiology. The recognition, prevention, and treatment of environmental causes may provide more effective management and reduce reliance on symptom modification with medication.

ROUTINE ECG AND STIMULANT MEDICATIONS FOR ADHD

The American Academy of Pediatrics (AAP) has issued a statement contradicting the recommendation of the American Heart Association (AHA) for routine electrocardiograms (ECGs) before starting medication to treat ADHD. The AAP and the American Academy of Child and Adolescent Psychiatry (AACAP) have concluded that sudden cardiac death (SCD) in persons taking medications for ADHD is a very rare event, occurring at rates no higher than in the general population. There is no evidence that routine ECG screening would prevent SCD. The AAP recommends careful assessment by a targeted cardiac history and examination, and a cardiac consultation only if clinically indicated. The AAP urges further research on risk factors for SCD, and improved methods for detecting hidden cardiac disease. (Perrin JM, Friedman RA, Knilans TK, the Black Box Working Group and the Section on Cardiology and Cardiac Surgery. **Pediatrics** August 2008;122:451-453).
(Reprint orders: http://www.pediatrics.org/misc/reprints.shtml).

COMMENT. This AAP statement is endorsed by AACAP, Society for Developmental and Behavioral Pediatrics, and National Association of Pediatric Nurse Practitioners. The AAP recommends careful cardiac assessment of children with a history of cardiac disease, palpitations, syncope, or seizures; family history of sudden death; hypertrophic cardiomyopathy; long QT syndrome; or Wolff-Parkinson-White syndrome.

Risks of not treating ADHD include: 1) academic failure; 2) driving and other accidental injuries; 3) loss of self-esteem; 4) nicotine use and substance abuse; and 5) obesity. (see **Ped Neur Briefs** August 2008;22:64).

NEUROBEHAVIOR AND MRI IN 22q13.3 DELETION SYNDROME

Neuromotor, sensory, language, communication and social development, and cerebral MRI and PET studies were performed in 8 children with 22q13.3 deletion syndrome, at the National Institutes of Health, Necker-Enfants Malades Hospital, and other centers in Paris, France. A common developmental profile was characterized by hypotonia, sleep disorders, excessive crying, poor response to the environment suggestive but not diagnostic of autism, expressive language delay, sensory processing and neuromotor disorders. Cognitive tests revealed mild-to-severe delay in all developmental milestones, verbal and imitation more than motor skills. Episodic symptoms prompting an EEG included acute hypotonia, repetitive rolling of tongue, eyelid flutter, vagal syncope, and standing still at attention. One had bifrontal spikes but none had epilepsy. Brain MRI was normal or showed a thin corpus callosum, and PET studies identified a localized dysfunction of the left temporal lobe and hypoperfusion in the amygdala, as compared to a group of mentally retarded control children. This description of an underdiagnosed syndrome should lead to more frequent recognition. (Philippe A, Boddaert N, Vaivre-Douret L, et al. Neurobehavioral profile and brain imaging study of the 22q13.3 deletion syndrome in childhood. **Pediatrics** August 2008;122:e376-e382). (Respond: Anne Philippe MD, PhD, INSERM U781, Hopital Necker-Enfants Malades, 149 Rue de Sevres, 75015 Paris, France. E-mail: anne.philippe@necker.fr).

COMMENT. The neurobehavioral description of the 22q13.3 deletion syndrome resembles that of pervasive developmental disorders but is distinct from autism. The 8 children in this study shared a common developmental course characterized by hypotonia, sensory and sleep disorders, global developmental delay, lack of emotion and inappropriate facial expression, episodic and stereotyped movements and postures. These symptoms should prompt a chromosome analysis with special attention to the 22qter deletion.

SEIZURE DISORDERS

KETOGENIC DIET FOR EPILEPSY AND FOCAL MALFORMATION

The efficacy and long-term treatment outcome of a classic ketogenic diet (KD) add-on treatment (4:1 lipid/nonlipid ratio, without initial fasting and fluid restriction) were evaluated retrospectively in 47 children with intractable epilepsy and focal malformation of cortical development, in a study at Severance Children's and Sanggye Park Hospitals, Seoul, Korea. At 3 months after diet initiation, 21 (44.7%) were seizure free, and 29 (62%) had >50% seizure reduction. Of 21 with complete seizure control at 3 months, 16 (76%) continued the diet for 2 years without relapse; 10 (48%) remained seizure-free after discontinuing the diet, at mean follow-up of 3 years 10 months. Diet was discontinued in 2 patients who developed hemorrhagic gastritis, and diet intolerance occurred in 5 patients. Of 19 patients whose seizures were not completely controlled during the KD and in 3 who had recurrences after diet withdrawal, 13 (59%) became seizure-free after undergoing epilepsy surgery. All patients were followed for at least 12 months after completion of the KD. In the management of intractable seizures due to focal cortical maldevelopment, patients who

become seizure free within 3 months of initiating the KD have an excellent long-term outcome. (Jung DE, Kang HC, Kim HD. Long-term outcome of the ketogenic diet for intractable childhood epilepsy with focal malformation of cortical development. **Pediatrics** August 2008;122:e330-e333). (Respond: Heung Dong Kim MD, PhD, Yonsei University College of Medicine, Brain Research Institute, Severance Children's Hospital, 134 Shinchon-dong, Seodaemun-gu, Seoul 120-752, Korea. E-mail: hdkimmd@yuhs.ac).

COMMENT. The ketogenic diet (KD) was first introduced for the treatment of epilepsy at the Mayo Clinic (Wilder RM. **Mayo Clin Bull** 1921;2:307). Unlike the later Johns Hopkins protocol (Livingston S. **Postgrad Med** 1951;10:333-336; Freeman JM et al. **Pediatrics** 1998;102:158-1363), the classic Mayo KD is introduced without initial fasting (NFKD) and usually, without admission to hospital. In my experience using the NFKD, a smaller ratio of ketogenic to antiketogenic items than that employed by the present authors has usually been successful in younger children, the higher 4:1 ratio being necessary only in older children (Millichap JG et al. **Am J Dis Child** 1964;107:593-604; **JAMA** 1966;198:210). In a Korean multicenter study involving 199 patients, a comparison of the modified Mayo non-fasting KD and the Hopkins fasting KD, found that by omitting the fasting period, especially in young children, acute dehydration was prevented, with no difference in the time to ketosis or in the efficacy of the diet. However, by employing the relatively high 4:1 ratio, favored by the Hopkins method, serious adverse effects were not avoided, including 5 deaths related to lipoid aspiration pneumonia, serious infection, and nutritional problems. (Kang HC et al. **Epilepsia** 2005;46:272-279; **Ped Neur Briefs** Feb 2005:19:12-13).

RISK OF MORTALITY IN CHILDREN WITH FEBRILE SEIZURES

Mortality after febrile seizures was studied in a large population-based cohort of children in Denmark followed from 3 months of age up to 25 years or until death, by researchers at Institute of Public Health, and National Centre for Register-based Research, Aarhus University; and University Hospital, Aarhus, Denmark; and School of Public Health, UCLA, USA. Of 1.6 million children born between 1977 and 2004, 8172 died, including 232 deaths in 55,215 children with a history of febrile seizures. The mortality rate ratio (1.80) was 80% higher during the first year and 90% higher (1.89) during the second year after the first febrile seizure; 132 of 100,000 children died within 2 years of a febrile seizure compared with 67 deaths per 100,000 without a history of febrile seizures. The increase in mortality (rate ratio 1.99) was restricted to patients with complex febrile seizures (>15 min or recurrence within 24 hr); children with simple febrile seizures (<15 min and no recurrence within 24 hr) had a mortality rate similar to the background population (rate ratio 1.09). The cause-specific cumulative mortality within 2 years of a febrile seizure per 100,000 children was 13 for seizures, 11 for pneumonia, 11 for sudden unexpected death, and 11 for congenital malformation of the nervous system. The development of epilepsy was not the explanation for increased mortality in all cases. The risk of sudden unexpected death was five times greater during the 2 years after a first febrile seizure than in the background population. (Vestergaard M, Pedersen MG, Ostergaard JR, Pedersen CB, Olsen J, Christensen J. Death in children with febrile seizures: a population-based cohort study. **Lancet** Aug 9, 2008;372:457-463). (Respond: E-mail: mogens.vestergaard@a.alm.au.dk).

COMMENT. An increased risk of mortality in children with a history of febrile seizures is restricted to patients with complex febrile seizures. The risk though significant is small, but the cause is not completely understood. The occurrence of epilepsy or neurologic abnormality may be contributory in some but not in all deaths. Mazumdar M in a commentary (**Lancet** 2008;372:429-430) recommended further follow-up of complex cases. Kinney H et al. (**Pediatr Dev Pathol** 2007;10:208-223) relates sudden death in 5 toddlers with febrile seizures to developmental hippocampal pathology and possible nocturnal seizures. A shared susceptibility to SIDS and febrile seizures has not been proven. That febrile seizures may be less benign than generally assumed is suggested by the above study and also by the recent report of MRI abnormalities in patients with first simple or complex febrile seizures. (Hesdorffer DC et al. **Epilepsia** 2008;49:765-771). In practice, MRI is not indicated for the evaluation of simple febrile seizures, but neurologic consultation is advisable in children with recurrent febrile seizures and in those with complex seizures. (**Ped Neur Briefs** June 2008;22:47-48).

Omega-3 fatty acids recommended in treatment of refractory seizures and in prevention of sudden unexpected death in epilepsy. (Scorza FA et al. **Epilepsy Behav** Oct 2008;13:279-283). The recommendation is based on clinical and animal studies that have demonstrated anticonvulsant properties of omega-3 supplementation and a reduction in cardiac arrhythmias and sudden cardiac deaths, the proposed mechanism of sudden death in epilepsy.

SPECTRUM OF BENIGN OCCIPITAL EPILEPSIES OF CHILDHOOD

The clinical, electroencephalographic and genetic characteristics of Panayiotopoulos and Gastaut syndromes were explored, using twin and multiplex family studies, by researchers at The University of Melbourne, Australia, and Tel Aviv University, Israel. Sixteen probands including 7 twins were classified into early, late or mixed benign occipital epilepsy of childhood (BOEC) syndromes, and 9 non-twin probands with a family history of epilepsy were included. One-third of the children in this selected series of BOEC had a mixed syndrome with features of both Panayiotopoulos (early) and Gastaut (late) syndromes. Monozygotic twin pairs had a similar concordance rate to that of dizygotic twin pairs, suggesting that BOEC may not be a purely genetic disorder. A mixed pattern of focal and generalized epilepsies, mainly focal, was found in relatives with epilepsy. Panayiotopoulos and Gastaut syndromes are not distinct genetic entities, but part of an electro-clinical BOEC spectrum, with shared genetic and environmental determinants. (Taylor I, Berkovic SF, Kivity S, Scheffer IE. Benign occipital epilepsies of childhood: clinical features and genetics. **Brain** September 2008;131:2287-2294). (Respond: Prof Ingrid E Scheffer, Epilepsy Research Centre, Austin Health, West Heidelberg, Victoria 3081, Australia. E-mail: scheffer@unimelb.edu.au).

COMMENT. The syndromes of Panayiotopoulos and Gastaut are not distinct, but part of a continuum of BOEC syndromes, with overlapping electro-clinical features, and largely undetermined, shared genetic and environmental factors in etiology. SCN1A missense mutation, identified with generalized epilepsy with febrile seizures plus and Dravet

syndromes, has recently been reported in a family with atypical Panyiotopoulos syndrome (Grosso S et al. **Neurology** 2007;69:609-611).

GOURMAND SYNDROME IN A CHILD WITH EPILEPSY

A preoccupation with food, increased appetite and a preference for fine food had developed in a 10-year-old obese boy soon after the onset of refractory seizures at 8 years of age, in a report from University Hospital of Geneva, Switzerland. He had streptococcal B sepsis and hemorrhage in the right temporoparietal lobes during the neonatal period. Seizures were stereotyped, with loss of contact and oral automatisms or dystonic posturing of the left hand. Their frequency was once a week to 7 times a day. They were uncontrolled despite trial of 5 different antiepileptic drugs. He preferred to cook meals for himself rather than eat at fast food restaurants. He had no history of emotional disorder, binge eating, bulimia, or preoccupation with his weight. Neurological examination revealed a left inferior quadrantanopia and left dysdiadochokinesia. In presurgical evaluation, the EEG showed a right posterior focus, and diffuse bilateral parasaggital seizure activity in sleep. MRI revealed a porencephaly, periventricular gliosis and hemosiderin deposits in the right parietal lobe. Neuropsychological examination showed visuospatial memory deficits, discrete signs of neglect, more pronounced in the postictal phase, with perseveration and confabulation. (Kurian M, Schmitt-Mechelke T, Korff C, Delavelle J, Landis T, Seeck M. "Gourmand syndrome" in a child with pharmacoresistant epilepsy. **Epilepsy Behav** August 2008;13:413-415). (Respond: Dr M Kurian, Presurgical Epilepsy Evaluation Unit, Department of Neurology, University Hospital of Geneva, 24 rue Micheli-du-Crest, 1211 Geneva 14, Switzerland. E-mail: mary.kurian@hcuge.ch).

COMMENT. "Gourmand" syndrome" reported in adults with right hemisphere lesions is often associated with epilepsy, and the eating disorder may be reversible when epilepsy is controlled. (Levine R et al. **Epilepsy Behav** 2003;4:781-3; cited by Kurian et al). The authors recommend brain imaging to rule out right hemisphere lesion in a patient who develops disturbed eating habits following a head injury or seizures.

RISK OF DROWNING IN EPILEPSY

The risk of drowning in patients with epilepsy is quantified by a meta-analysis of published reports, in a study at the Institute of Neurology, Queen Square, London UK. The number of deaths from drowning and the number of person-years at risk were estimated in 51 cohorts of people with epilepsy. Standardized mortality ratios (SMRs) (observed deaths divided by the expected deaths) were calculated for each cohort and for the total population. Compared with 4.7 expected deaths, 88 drowning deaths were reported in people with epilepsy, giving an SMR of 18.7 (95% CI 15-23). The 51 cohorts combined had 206,596 patient-years of follow-up. In people with epilepsy and learning disability, the SMR was 25.7, and in those in institutional care, 96.9. In those with temporal lobectomy for epilepsy, the SMR was 41.1. Using National Registries for estimation of drowning deaths in people with epilepsy in England and Wales (1999-2000), the SMR was 15.3. (Bell GS, Gaitatzis A, Bell CL, Johnson AL, Sander JW. Drowning in people with epilepsy. How great is the risk. **Neurology** Aug 19 2008;71:578-582). (Reprints: Prof Ley Sander, Box 29, Department of

Clinical & Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK. E-mail: lsander@ion.ucl.ac.uk).

COMMENT. Compared to the general population, people with epilepsy have a 15- to 19- fold increase in risk of drowning, according to this meta-analysis of published articles. The actual number of drownings in children is small, only 4 of the 15 articles involving predominantly children including deaths due to drowning. Inadequate supervision was a frequent factor. One previous study suggested that the relative risk of drowning in the bath is 96 for children with epilepsy compared to those without, and for drowning in a swimming pool is 23 (Diekema DS et al. **Pediatrics** 1993;91:612-616). One in 20 deaths from drowning was due to seizures (Ryan CA et al. **CMAJ** 1993;148:781-784).

GENETICS OF AUTOSOMAL DOMINANT PARTIAL EPILEPSY WITH AUDITORY FEATURES (ADPEAF)

Data from 24 previously published ADPEAF families with mutations in the leucine-rich, glioma inactivated 1 gene (*LGI1)* were analyzed, in a study at Columbia University, New York. Penetrance is 67%, it tends to be greater in families with more affected individuals, does not differ with gender, and may increase with advancing generation. (Rosanoff MJ, Ottman R. Penetrance of *LGI1* mutations in autosomal dominant partial epilepsy with auditory features. **Neurology** Aug 19, 2008;71:567-571). (Dr Ruth Ottman, GH Sergievsky Center, Columbia Univcrsity, 630 W 168th St, P&S Box 16, New York, NY 10032. E-mail: ro6@columbia.edu).

COMMENT. Autosomal dominant (AD) partial epilepsy with auditory features, also known as AD lateral temporal epilepsy, is an idiopathic focal epilepsy syndrome manifested by auditory symptoms (humming, buzzing, or ringing, volume changes, specific songs or voices) or receptive aphasia. Ictal receptive aphasia is a sudden inability to understand language without general confusion. Mutations in the *LGI1* gene located on chromosome 10 occur in approximately 50% of families with ADPEAF, but not in families with other familial temporal lobe epilepsies.

Symptomatic temporal lobe auditory seizures. Many examples of seizures secondary to temporal lobe tumor and manifested by auditory illusions and hallucinations are included in the classic book by Penfield W, and Jasper H (**Epilepsy and the Functional Anatomy of the Human Brain.** Boston; Little, Brown & Comp. 1954;459-467). One patient, a housewife of 43 years, complained of ringing in the ears and of hearing voices or music, a song she had heard previously, an hallucination sometimes she described as a dream. Another, a girl aged 16 years, heard a lullaby that her mother used to sing to her as an infant. In some attacks she complained of a change in volume or fading away of sounds, considered an illusional seizure. Stimulation of the cortex in the superior gyrus of the left temporal lobe illicited hallucinations of voices, saying words, repeated music (accompanied by humming), and "There was singing" response. Penfield referred to these as "psychical seizures." In children, temporal lobe seizures often begin with a sense and look of fear, the child clinging to mother, although unable to describe a possible associated hallucination.

VASCULAR DISORDERS

PRESENTATION OF NEONATAL SINOVENOUS THROMBOSIS

Signs, risk factors, comorbidities, and radiographic findings in 59 neonates presenting with sinovenous thrombosis are reported from Indiana University School of Medicine, Indianapolis, IN. Thirty-nine (66%) patients presented early, within 48 hours after birth, and 20 (34%) presented late, between 2 and 28 days (median 7.5 days). Presenting signs were respiratory distress in 43 (73%), hypoxia (69%), seizures (59%), weight loss (58%), and hypotonia (58%). Early presentation was significantly associated with respiratory distress, hypoxia, hypotonia, preterm delivery, and low Apgar score; maternal preeclampsia/hypertension showed a trend toward early association. Late presentation was significantly associated with dehydration. Neonatal comorbidities included congenital cardiac disorders in 37%, anemia in 29%, cyanosis in 27%, and dehydration in 17%. Diagnosis of sinovenous thrombosis was established by CT scan in 28, MRI in 20, MR venography in 10, and ultrasound in 1. Superior sagittal sinus was involved most commonly (75%); 71% had multiple thrombosed sinuses. Infarction occurred in 54%, with associated hemorrhage in 42%. Multiple thromboses, complications and radiographic severity were not significantly correlated with time of presentation. Refractory seizures were marginally associated with hemorrhage (P=0.09). (Nwosu ME, Williams LS, Edwards-Brown M, Eckert GJ, Golomb MR. Neonatal sinovenous thrombosis: Presentation and association with imaging. **Pediatr Neurol** September 2008;39:155-161). (Respond: Dr Golomb, Division of Pediatric Neurology, Indiana University School of Medicine, 575 West Dr, Building XE, Room 040, Indianapolis IN 46202. E-mail: mgolomb@iupui.edu).

COMMENT. Two thirds of neonates with cerebral sinovenous thrombosis have symptoms within 48 hours after birth. Early presentation is associated with respiratory distress, hypoxia, hypotonia, and low Apgar scores; late presenters frequently have dehydration, a preventable causative factor.

DEMYELINATING DISORDERS

SUN EXPOSURE AND REDUCED RISK OF MULTIPLE SCLEROSIS

The association between red hair color (RHC) melanocortin 1 receptor genotype, past environmental sun exposure, and risk of multiple sclerosis (MS) was investigated in a population-based case-control study in Tasmania, Australia, involving 136 cases with MS and 272 controls. Increasing summer sun exposure at ages 6 through 10 years was associated with reduced MS risk among those with no RHC variant (p=0.03), but not among those with RHC variant genotype (p=0.15). The association was more evident for women than for men. (Dwyer T, van der Mei I, Ponsonby A-L, et al. Melanocortin 1 receptor genotype, past environmental sun exposure, and risk of multiple sclerosis. **Neurology** Aug 19, 2008;71:583-589). (Reprints: Dr Terry Dwyer, Murdoch Childrens Research Institute, Royal Children's Hospital, Parkville Victoria 3052, Australia. E-mail: terry.dwyer@mcri.edu.au).