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

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HEADACHE DISORDERS

DIAGNOSTIC UTILITY OF CT SCAN FOR ACUTE HEADACHE

ED records for 364 children 2 to 5 years of age who presented to the Children's National Medical Center ED, Washington, DC, between July 1, 2003, and June 30, 2006, with headache as their chief complaint, were examined to determine whether CT scans led to better acute management, justifying the risk of radiation. On the basis of initial history and physical examination findings, 306 children (84%) had secondary headache (nonneurologic viral/respiratory/febrile illness in 222 (72%), trauma in 47 (15%), v-p shunt in 14 (4.5%), brain tumor in 7 (2.3%), meningitis 4 (1.3%), seizures 2 (0.7%), and misc. Primary headaches accounted for 57 (15.7%) cases; of these, 5 (8.7%) were migraine, and 52 (91.3%) unclassified. No family history was recorded for 59% of children with primary headache. Of 58 children (16%) with no recognized CNS disease or systemic illness at presentation, 16 (28%) had CT scans performed. One scan was abnormal (6%), showing a brainstem glioma, and this patient's neurologic exam was abnormal at presentation. For 15 (94%) cases, CT scans were normal, and did not contribute to the diagnosis or management. (Lateef TM, Grewal M, McClintock W, Chamberlain J, Kaulas H, Nelson KB. Headache in young children in the emergency department: Use of computed tomography. **Pediatrics** July 2009, 124:e12-e17). (Respond: Tarannum M Lateef M D, Department of Neurology, Children's National Medical Center, 111 Michigan Ave, Washington, DC 20010. E-mail: tlateef@cnmc.org).

COMMENT. CT scan is not useful in the diagnosis and management of young children presenting with headache in the ED. The test is rarely contributory in patients with normal neurologic examination, it is expensive and not without risk. The majority of acute headaches are caused by nonneurologic febrile illness. In the rare case having an abnormal

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CT scan, the history and neurologic examination are abnormal, pointing to a neurologic cause with symptoms and signs of raised intracranial pressure. The value of a thorough neurologic history and examination outweighs that of a CT scan. In patients with primary headaches, the family history is frequently positive for migraine and provides reassurance in a decision to defer neuroimaging of young children with headache in the ED.

Brain imaging in children referred to a pediatric neurology clinic for headache was also found of very limited value, in a retrospective study of 133 patients ages 3 to 18 years at Schneider Children's Hospital, NY. (Maytal J et al. **Pediatrics** 1995;96:413-416). The indications for brain imaging in 78 patients were atypical headache pattern in 12, parental concern in 12, physician concern about cerebral tumor in 11, systemic symptoms of fatigue and weight loss in 11, focal symptoms or signs during headaches in 7, neurologic or ocular abnormalities in 6, increasing severity or frequency of headache in 5, and unspecified in 17. Abnormal scans in 11 (14%) patients included evidence of chronic sinusitis in 7, neuroepithelial cyst near the foramen of Monroe in 1, temporal lobe arachnoid cyst in 1, cerebral hemiatrophy in 1, and Dandy-Walker malformation in 1. None of the scans showed lesions requiring neurosurgical intervention. MRI indications proposed by the authors include 1) atypical recurrent headaches, 2) recent change in character of headache, 3) persistent vomiting, 4) abnormal neurologic findings, and 5) occurrence in younger age groups. Headache associated with abnormal EEG should also be considered for MRI. In a young child with recurrent headache seen by a neurologist in a single consultation, without prospect of follow-up, deferral of imaging may not be practical or judicious.

SEIZURE DISORDERS

SINGLE-PULSE ELECTRICAL STIMULATION IN IDENTIFICATION OF EPILEPTOGENIC CORTEX

Single-pulse electrical stimulation (SPES) was evaluated in 35 children who underwent intracranial subdural electroencephalographic (EEG) monitoring at Great Ormond Street Hospital for Children and King's College Hospital, London, UK. Median age was 14 yrs 2 mos (range 9 mos to 17 yrs 7 mos). Using a series of 10 or more single, brief (1 ms) electrical stimuli, the cortical responses were examined for associations between response type, ictal onset zone, lesion boundary, and seizure outcome. Studies were conducted during interictal periods, while the patient was awake, and in parallel with video-EEG. Subdural grids (in 25 patients), subdural strips (in 30 patients), or depth electrodes (9 patients) covered a number of areas in each patient. The median number of electrodes in each patient was 54 (range 17-78). Abnormal responses to SPES indicative of epileptic cortical excitability were present in 54% of cases, and were "delayed"(DR) or "repetitive"(RR) in type. The DR is a sharp wave or spike, occurring later than 100 ms after stimulus, and corresponding with the area of seizure onset. The RR has the form of a successive repetition of an early response (ER), a sharp wave followed by a slow wave, typically lasting for a second or longer. Removal of the entire area responsible for abnormal responses to SPES was associated with good outcomes. (Flanagan D, Valentin A, Seoane JJG, Alarcon G, Boyd SG. Single-pulse electrical stimulation helps to identify epileptogenic cortex in children. **Epilepsia** July

2009;50:1783-1803). (Respond: Dr Gonzalo Alarcon, Dept Clinical Neurophysiology, King's College Hospital, Denmark Hill, London SE5 8ED, UK. E-mail: gonzalo.alarcon@iop.kcl.ac.uk).

COMMENT. Cortical responses to SPES in children are similar to those observed in adults. Abnormal SPES responses (DRs and RRs) correlate with epileptogenic cortex, and are useful in the presurgical evaluation and positioning of electrodes. The method may be used with or without anesthesia (Valentin et al, King's College Hospital, unpublished observation).

KETOGENIC DIET AND HORMONAL THERAPY IN PREVENTION OF EVOLUTION OF WEST SYNDROME TO LENNOX-GASTAUT

Medical records of 98 patients diagnosed with West syndrome and monitored at Sanggye Paik Hospital, Seoul, Korea, for at least 3 years were retrospectively reviewed to assess etiology, age at onset, value of various therapies, and the rate of evolution from West syndrome to Lennox-Gastaut syndrome. During follow-up, West syndrome evolved to Lennox-Gastaut syndrome in 48 of the 98 (49%) patients. Etiology of West syndrome was cryptogenic in 36 (36.7%) and symptomatic in 62 (63.3%). Patients with normal psychological development before seizure onset were excluded. All patients had hypsarrhythmia and infantile spasms. Treatment of West syndrome varied as follows: antiepileptic drugs in 31 patients, ketogenic diet in 33, prednisolone in 45, ACTH in 15, surgery in 3, and herbal medication or no treatment in 4 patients. Age at onset of seizures (mean, 5.8 +/- 2.4 mos) or disease etiology was not related to development of Lennox-Gastaut syndrome. Risk of evolving to Lennox-Gastaut syndrome in patients treated with anticonvulsant drugs was 17 in 31 (55%). Risk was significantly lower in patients treated with ketogenic diets (10/33, 30%) or hormonal therapy (26/60, 43%) or a combination of both (7/27, 26%), ($P<0.05$). (You SJ, Kim HD, Kang H-C. Factors influencing the evolution of West syndrome to Lennox-Gastaut syndrome. **Pediatr Neurol** Aug 2009;41:111-113). (Respond: Dr Kang, 134 Shinchon Dong, Seodaemun Gu, Seoul 120-752, Korea. E-mail: hipo0207@yuhs.ac).

COMMENT. The ketogenic diet, prednisolone or ACTH or a combination of both diet and hormonal therapy may prevent the development of encephalopathy and Lennox-Gastaut syndrome in patients with West syndrome. It is estimated that 20-50% of West syndrome cases evolve to Lennox-Gastaut syndrome; 70-80% of Lennox-Gastaut cases have no history of West syndrome. The relatively higher risk of development of Lennox-Gastaut after West syndrome in the present study may be related to the exclusion of West syndrome patients with normal neuropsychological development prior to onset of infantile spasms. That the evolution to Lennox–Gastaut syndrome is significantly reduced by treatment with ketogenic diet, hormonal therapy or both suggests that these therapies may modify the underlying encephalopathic process in West and Lennox-Gastaut syndromes. Age and brain maturation are not the primary factors in the development of Lennox-Gastaut syndrome following West syndrome.

SLEEP DISORDERS

KLEINE-LEVIN SYNDROME RESPONSE TO CARBAMAZEPINE

A 16-year-old male adolescent began having recurrent episodes of severe hypersomnia which persisted 5 or 6 times a year up to age 27, when he was treated with carbamazepine at the American University of Beirut, Medical Center, Lebanon. Each episode lasted 4-7 days and recurred every 2-3 months. During the episode his mean daily sleep time was 20 hours; he woke to eat and void and then went back to sleep. He stated that he felt depressed with suicidal thoughts, and displayed abnormal sexual behavior. Hyperphagia or binge eating was not a symptom. At the end of the episode, he described partial amnesia for the event, and functioned normally without daytime drowsiness. Family history was negative for similar symptoms. Neurologic examination, EEG between episodes, and brain MRI were normal. Initially, he was misdiagnosed with complex partial seizures and was treated with valproate. Therapeutic levels of valproate were ineffective, and treatment with carbamazepine was initiated at 400 mg/day, later increased to 600 mg/day, with a level of 9.2 mg/L. Complete freedom from episodic hypersomnia for 2 years was followed by recurrence when carbamazepine was discontinued. After 3 episodes over 4 months, each lasting 4-5 days, carbamazepine was resumed, followed by complete resolution of attacks. The diagnosis of Kleine-Levin syndrome was confirmed by polysomnogram, recording normal sleep architecture between attacks. (Hajj TE, Nasreddine W, Korri H, Atweh S, Beydoun A. A case of Kleine-Levin syndrome with a complete and sustained response to carbamazepine. **Epilepsy & Behav** July 2009;15:391-392) (Respond: Dr Ahmad Beydoun, American University of Beirut, Medical Center, Beirut, Lebanon. E-mail: ab29@aub.edu.lb).

COMMENT. By John J Millichap MD. Discussant. Case report and Review of Kleine-Levin syndrome for Psychiatry Rounds, CMH, July 2009. Hypersomnia, the cardinal symptom of Kleine-Levin syndrome (KLS), was described by Willi Kleine (1925), and hyperphagia added as a frequently associated symptom by Max Levin (1936). The eponym KLS was coined by M Critchley and Hoffman (1942). Approximately 200 cases are reported, male>female, with onset in adolescence. American Academy of Sleep Medicine and International Classification of Sleep Disorders characterize KLS as a rare disorder affecting predominantly adolescent boys, with recurring episodes of hypersomnia (100%), frequently and variably associated with behavioral and cognitive disturbances (96%), compulsive eating behavior (80%), and hypersexuality (43%). The diagnosis is frequently delayed and often labeled incorrectly as an epilepsy. Differential diagnosis includes non-convulsive status epilepticus, narcolepsy, encephalitis, psychotic affective or dissociative disorders, hypothalamic lesion, and migraine. Median sleep duration during episodes is 18 h/day (range 12-24 h/day), median duration of episodes is 10 days, and interval between episodes is 3 months. Hypothetical etiologies include diencephalic-hypothalamic dysfunction, neurotransmitter imbalance, viral infection, autoimmune HLA, and genetic factors. Triggers include stress, sleep deprivation, and alcohol abuse. Cochrane Review of Treatments finds no evidence that pharmacological agents are consistently effective and safe, stimulants improve sleepiness but not other symptoms, antidepressants have no effect in preventing relapses (except one case using MAOI), anticonvulsant carbamazepine, in single case, improved abnormal behavior, and lithium significantly improves abnormal behavior and recovery, but

only in 3 of 12 patients treated. Median duration of KLS is 8 years (range 0.5 to 41 years). Course is longer for women, and shorter in cases with high number of episodes in first year.

ATTENTION DEFICIT DISORDERS

CARDIOVASCULAR EFFECTS OF LONGER-TERM, HIGH-DOSE OROS METHYLPHENIDATE IN ADOLESCENTS WITH ADHD

The short-term and longer-term cardiovascular safety of high daily doses of OROS methylphenidate (MPH) of up to 1.5 mg/kg in 114 adolescents with ADHD is reported from Massachusetts General Hospital, Boston, MA. Small but statistically significant increase in diastolic BP and heart rate were observed at 6 weeks, without further increases up to 6 months' follow-up. The mean total daily dose of OROS-MPH at 6 weeks was 63.1 +/- 25.0 mg; 50% of subjects were taking >72 mg daily; at month 6 these doses were 67.2 +/- 24.3 mg and >72 mg, respectively. A small but statistically significant increase in systolic BP was observed over time. No changes in ECG were observed and no serious cardiovascular adverse events occurred. (Hammerness P, Wilens T, Mick E, et al. Cardiovascular effects of longer-term, high-dose OROS methylphenidate in adolescents with attention deficit hyperactivity disorder. **J Pediatr** July 2009;155:84-89). (Reprints: Dr Paul Hammerness, Pediatric Psychopharmacology, 185 Alewife Brook Parkway, Suite 2000, Cambridge, MA 02138. E-mail: phammerness@partners.org).

COMMENT. Small but statistically significant increases in blood pressure and heart rate were observed in adolescents treated with relatively higher doses of OROS methylphenidate, without changes in the ECG. The CV effects noted in adolescents with higher doses were similar to the previously documented effects in children with lower doses of OROS-MPH. In an editorial, Dr Stephen R Daniels advises caution in patients with BP elevation or tachycardia (**J Pediatr** 2009;155:A3).

COMPARATIVE CARDIAC RISKS OF METHYLPHENIDATE AND AMPHETAMINES IN TREATMENT OF ADHD

The risk for adverse cardiac events in subjects between 3 and 20 years of age treated with methylphenidate or amphetamine salts for ADHD was determined in a retrospective study at University of Florida, Gainesville, FL. Cardiac events were defined as first ED visit for cardiac disease or symptoms. The percentage of patients observed for at least 6 months on stimulants was similar for MPH (54.5%) and amphetamines (52.6%). A total of 456 youth visited the ED for cardiac reasons during 52,783 years of follow-up. The risk for cardiac ED visits was similar among current users of MPH or amphetamines. Periods of former use had a similar risk in subjects exposed. Variables showing positive associations with ED visits with both models were use of bronchodilators, use of antidepressants, antipsychotics at age 15 and older, congenital anomalies, and history of circulatory disease or cardiac symptoms. (Winterstein AG, Gerhard T, Shuster J, Saidi A. Cardiac safety of methylphenidate versus amphetamine salts in the treatment of ADHD. **Pediatrics** July 2009;124:e75-e80). (Respond:

AG Winterstein PhD, College of Pharmacy, University of Florida, PO Box 100496, Gainesville, FL 32610. E-mail: almut@ufl.edu).

COMMENT. Spontaneous reports of adverse drug reactions to the FDA show a higher risk of cardiac events with amphetamines than methylphenidate. (**FDA News**;March 14, 2007). The above authors report a 20% increased risk for ED visits for cardiac symptoms for all stimulants combined (Winterstein AG et al. **Pediatrics** 2007;120(6):e1484). The present study did not confirm the previous report that amphetamines might carry a higher risk of adverse cardiac events than MPH. Further long-term population-based studies are indicated to define the risks of stimulant-induced serious heart events and the prophylactic utility of routine electrocardiograms before and during treatment.

DIFFUSION TENSOR IMAGING ABNORMALITIES IN THE CEREBELLUM OF CHILDREN WITH ADHD AND EPILEPSY/ADHD

Diffusion tensor imaging was used to investigate cerebellar structure in children with combined epilepsy/ADHD and ADHD alone, at the University of Basel, Switzerland. By generating fractional anisotropy (FA) maps, the extent to which water diffusion is greater in one direction compared with others, the organization of white matter in the brain is computed. Healthy controls (n=12) exhibited more FA in the left and right middle cerebellar peduncle compared with 8 boys with combined epilepsy/ADHD, and more FA in the right middle cerebellar peduncle compared with 14 boys with developmental ADHD. Deficient cerebellar connections were demonstrated in both patient groups. Inattention and other ADHD problems in both epilepsy/ADHD and ADHD patients are based on the same neurobiological mechanisms that involve the middle cerebellar peduncle. (Bechtel N, Kobel M, Penner I-K, et al. Decreased fractional anisotropy in the middle cerebellar peduncle in children with epilepsy and/or attention deficit/hyperactivity disorder: A preliminary study. **Epilepsy & Behav** July 2009;15:294-298). (Respond: Dr Nina Bechtel, Dept Cognitive Psychology and Methodology, University of Basel, Missionsstrasse, 60/62, 4055 Basel, Switzerland. E-mail: nina.bechtel@unibas.ch).

COMMENT. One in 5 children with epilepsy has comorbid ADHD (Gross-Tsur et al, 1997). A study involving 203 patients found 60% of children with epilepsy had either ADHD-Inattentive subtype or ADHD-Combined. (Sherman EMS et al, 2007). Quality of life was impaired 2-fold in children with epilepsy complicated by ADHD-I, and 4-fold with ADHD-C comorbidity, when compared to normal controls. Impairment of attention is more likely with generalized epilepsies than with focal epilepsies, in most studies.

Approximately one in 4 children with ADHD has an abnormal EEG, without clinical seizures. The significance of subclinical seizure discharges in children with ADHD is controversial. In addition to EEG abnormalities, a neurobiological basis for ADHD is also demonstrated by MRI brain volume studies, PET studies, and neurological soft signs. MRI volumetric studies have found decreased volume of the total brain, right prefrontal cortex, cerebellar vermis, corpus callosum, and basal ganglia. (Castellanos FX et al. **Arch Gen Psychiatry** 1996;53:607-616). These developmental abnormalities correlate with fronto-striatal-cerebellar circuit dysfunction, neuropsychological deficits, and response to stimulant

medication. (Zametkin AJ, Rapoport JL. Neurobiology of ADHD. **J Am Acad Child Adolesc Psychiatry** 1987;26:676-686).

PERIPHERAL NERVOUS SYSTEM DISORDERS

EARLY- AND LATE-ONSET INHERITED ERYTHROMELALGIA

A genotype-phenotype relationship at the clinical, cellular and molecular levels is shown in a case of erythromelalgia of relatively late onset, in a study at Yale University School of Medicine, and centers in China. The patient, a male age 17 years, began experiencing excruciating pain, warmth and redness in both feet and lower legs at age 14 years. Blood was analyzed for mutations in SCN9A, gain-of-function sodium channel mutations that are preferentially expressed within dorsal root ganglia (DRG) and sympathetic ganglion neurons. The effect of the Q10R mutation on firing of DRG neurons was investigated by current-clamp recording. The hyperexcitability of the DRG neuron induced by Q10R mutation in this adolescent patient was smaller than the change produced by I848T, an early-onset erythromelalgia mutation. (Han C, Dib-Hajj SD, Lin Z et al. Early- and late-onset inherited erythromelalgia: genotype-phenotype correlation. **Brain** July 2009;132:1711-1722). (Respond: Stephen G Waxman, MD PhD, Department of Neurology, LCI 707, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06520. E-mail: Stephen.Waxman@yale.edu).

COMMENT. Inherited erythromelalgia (erythermalgia) (IEM) is an autosomal dominant disorder characterized by severe burning pain and erythema of the extremities triggered by warmth. IEM is linked to gain-of-function mutations in SCN9A, the gene encoding Na, 1.7, a voltage-gated sodium channel that is preferentially expressed in dorsal root ganglion neurons, particularly nociceptors, and sympathetic ganglion neurons. The resultant nociceptor hyperexcitability causes pain in the extremities. Almost all cases reported are linked to families with onset in early childhood (infancy to 6 years of age). The above case report uncovers a new mutation in Na, 1.7, Q10R, from a patient with onset in the second decade of life. Mutations that produce smaller effects on sodium channel activation are associated with a smaller degree of DRG neuron excitability and later onset of clinical signs.

Carbamazepine-responsive erythromelalgia and $Na_v1.7$ mutation. The above team of investigators publish a second article on erythromelalgia (Fischer TZ et al. **Ann Neurol** July 2009;65:733-741), reporting a novel $Na_v1.7$ mutation (V400M) in a three-generation Canadian family with pain relieved by carbamazepine (CBZ). $Na_v1.7$ sodium channels are preferentially expressed within nociceptor ganglia and sympathetic neurons that are involved in the inflammatory and neuropathic pain of inherited erythromelalgia. CBZ has a normalizing effect on mutant $Na_v1.7$ channels in this Canadian kindred, preventing the hyperexcitability of dorsal root ganglia in erythromelalgia.

BRAIN DEVELOPMENTAL LESIONS

COGNITIVE FUNCTION AND PEDIATRIC ARACHNOID CYST

Neurocognitive and psychological functions were investigated in 35 consecutive children with arachnoid cyst (AC) and 35 healthy controls, in a study at Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Korea. Ages ranged from 5 to 15 years (mean 7.94+/-3.12); 28 males and 7 females. Locations of the AC were mainly temporal (n=22), frontal in 6, suprasellar (4), and posterior fossa (3). Tests included the Korean WISC-III, ADHD diagnostic panel, executive function, depression inventory, and anxiety scale. Intelligence scores in AC subjects were not different from controls. Internalization, anxiety, social immaturity, externalization, and aggressive behavior scores were significantly higher in AC subjects. Parenting stress in the AC group was higher than in control group. Of 28 with Sylvian location, 22 had compressed temporal lobes and 6 had compressed frontal lobes. Those with compressed frontal lobes showed more problems with sustained attention and more anxiety than the temporal lobe group. Left hemisphere AC was associated with increased anxiety compared to right hemisphere cyst. The 20 patients who required AC surgery showed no significant differences in IQ, memory or anxiety compared to the nonsurgical group. (Park YS, Eom S, Shim K-W, Kim D-S. Neurocognitive and psychological profiles in pediatric arachnoid cyst. **Childs Nerv Syst** September 2009;25:1071-1076). (Respond: Dr Dong-Seok Kim. E-mail: dskim33@yuhs.ac).

COMMENT. Neurocognitive function is not impaired in children with arachnoid cyst (AC), but AC in the left hemisphere, frontal location is associated with more anxiety. Symptoms of ADHD are more prevalent in children with AC. (Millichap JG. Temporal lobe arachnoid cyst-ADHD syndrome. Role of the EEG in diagnosis. **Neurology** 1997;48:1435-1439).

CSF overdrainage in shunted intracranial AC. Researchers in Murcia, Spain, report 5 patients with acquired Chiari I malformation and 3 with posterior fossa overcrowding due to excessive CSF drainage in shunted intracranial AC. (Martinez-Lage JF et al. **Childs Nerv Syst** Sept 2009;25:1061-1069). Symptoms related to hindbrain herniation developed after an average interval of 5 years following the shunt.

HIPPOCAMPAL AND CONGENITAL BRAIN MALFORMATIONS

Sixty two patients, aged 15 days to 18 years, with congenital brain malformations were evaluated retrospectively to determine the association of various brain malformations with hippocampal abnormalities, in a study at Baskent University, Ankara, Turkey. Indications for MRI included seizures in 26, growth retardation in 10, headache (9), and microcephaly (4). Primary malformations included corpus callosum agenesis in 36, lissencephaly (9), and heterotopias (6), Hippocampal abnormalities were associated in 43 (69%) patients, and especially those with cortical dysplasia (100%), lissencephaly (78%), and corpus callosum agenesis (72%), (Donmez FY, Yildirim M, Erkek N, Karacan CD, Coskun M. Hippocampal abnormalities associated with various congenital malformations. **Childs Nerv Syst** 2009;25:933-939). (FY Donmez. E-mail:fuldemyildirim@yahoo.com).