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

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HEADACHE DISORDERS

OUTCOME OF CHRONIC DAILY HEADACHE IN ADOLESCENTS

A community-based sample of 122 adolescents aged 12-14 years with chronic daily headache (CDH) was established in 2000 at University centers in Taiwan by a survey of 7,900 students in 5 selected public middle schools. CDH was defined as >15 headache days/month, average >4 hours/day for >3 months. At short-term 1 and 2-year follow-up, CDH persisted in 40% subjects in 2001 (average monthly headache frequency of 11.0+/-9.7 days), and in 25% subjects in 2002 (7.7+/-6.5 days). At long-term 8-year follow-up, the headache profile for the past year was determined by the Migraine Disability Assessment (MIDAS) questionnaire. Outcome measures were headache frequency, MIDAS score, and presence of CDH in 2008. When re-interviewed by physicians via telephone, of a total of 103 subjects who completed the study, 26 were male and 77 were female, mean age 21.6+/-0.9 years. Moderate or severe headache disability (MIDAS >11) persisted in 28 (27.2%) subjects. Of 12 (12%) who met CDH criteria in 2008, 10 (83%) had chronic migraine, the most common subtype; 2 (2%) overused medication. Migraine diagnosed at baseline predicted poorer outcome after 8 years follow-up. CDH onset <13 years of age, duration >2 years, and medication overuse were predictive of either higher headache frequencies or CDH in 2008. (Wang S-J, Fuh J-L, Lu S-R. Chronic daily headache in adolescents: An 8-year follow-up study. **Neurology** August 11, 2009;73:416-422). (Respond: Dr Shuu-Jiun Wang, The Neurological Institute, Taipei Veterans General Hospital, Taipei, 112, Taiwan. E-mail: sjwang@vghtpe.gov.tw).

COMMENT. Chronic daily headache in adolescents resolves in 75% subjects at 2-year follow-up, but the 25% with persistent CDH still have a headache disability at 8-year follow-up and 12% have CDH, the majority diagnosed with chronic migraine. Factors

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predicting persistence of CDH into young adulthood include a history of migraine, early onset, longer duration than 2 years, and medication overuse. Of interest, only 5 (5%) subjects in this study used preventive agents, and neurology consultation was obtained by only 4%. Only 30% subjects used painkillers, the majority over-the-counter medications.

In an Editorial (**Neurology** 2009;73:412-413), Mack KJ and Hershey AD at the Mayo Clinic emphasize the variability of symptoms of CDH between patients and in an individual. CDH presents as severe intermittent migraine attacks, intermittent low severity headaches, continuous headache, or as a combination of these headache types. CDH affects 1 – 2% of middle-school children. A family history of migraine is common. Most patients are headache-free within 1 to 2 years. A small proportion has a continuing problem, usually an episodic migraine.

TOPIRAMATE IN PEDIATRIC MIGRAINE

Efficacy and tolerability of topiramate in the treatment of pediatric migraine is studied by retrospective analysis of records of 37 children treated at St Christopher's Hospital for Children, Philadelphia, PA. The mean age was 14 years; the range, 7.3-20.5 years. The majority (30 [81%]) had migraine without aura, 4 (11%) had migraine with aura, and the remaining 3 had abdominal, ophthalmoplegic, and catamenial migraine in one each. Mean follow-up was 12 +/- 5 months. The mean dose of topiramate was 1.7 +/- 1 mg/kg/day (range, 0.5-5.5 mg/kg/day), or 50-200 mg/day. Headache frequency per month was 15 +/- 7 before treatment and 3 +/- 3.4 after treatment. Response was excellent or good, with >50% migraine reduction, in 28 (76%) patients. Adverse effects occurred in 10 (27%) patients; 5 had cognitive deficits, 3 drowsiness, 1 paresthesias, and 1 anhidrosis. No patient had significant weight loss. Side effects were directly related to dosage, and occurred especially in patients taking doses >2 mg/kg/day (mean toxic dose 2.8 +/- 1.5 mg/kg/day). The mean dose not associated with adverse events was 1.27 +/- 0.7 mg/kg/day. Seven (19%) patients discontinued treatment because of side effects, 5 (14%) with cognitive issues. The authors conclude that topiramate is an effective, safe prophylactic therapy for pediatric migraine. The acceptable risk/benefit maintenance dose is <2 mg/kg/day. (Cruz MJ, Valencia I, Legido A, et al. Efficacy and tolerability of topiramate in pediatric migraine. **Pediatr Neurol** Sept 2009;41:167-170). (Respond: Dr Harold G Marks, Section of Neurology, St Christopher's Hospital for Children, Erie Avenue at Front Street, Philadelphia, PA 19134. E-mail: Harold.marks@drexelmed.edu).

COMMENT. In this retrospective, uncontrolled study, topiramate at one-year follow-up appeared to be an effective prophylactic therapy for pediatric migraine. Cognitive deficit was a significant adverse event, however, leading to withdrawal of therapy in 14% patients. Since headache disorders in children and adolescents tend to resolve spontaneously in a large proportion of patients, as shown in the previous study (Wang S-J et al, 2009), double-blind, placebo-controlled studies of migraine prophylaxis are essential.

Other anticonvulsants, including phenytoin and valproate, are effective in the prophylaxis of migraine, but the side-effects tend to outweigh the benefits. In an early study of the EEG and response to phenytoin in 30 children with migraine, 77% had headaches controlled (Millichap JG. **Child's Brain** 1978;4:95-104). Response to phenytoin was not

correlated with an abnormal EEG. In 13 patients with abnormal and 17 with normal EEGs, the beneficial response rates were 61% and 88%, respectively. Epileptiform EEGs were found in 18% of a total 100 consecutive children with recurrent headache, and with the same frequency in those with migraine. Kramer U, Harel S and associates found an 11% incidence of epileptiform EEGs in children with migraine or tension headaches; the incidence was 26% and significantly higher in children with chronic "very brief" headaches (**Brain Dev** 1994;16:304-308).

SEIZURE DISORDERS

TOPIRAMATE MONOTHERAPY IN EPILEPSY

The dosing, effectiveness, patient characteristics predictive of effectiveness, and safety of topiramate monotherapy in treatment of epilepsy were evaluated in a 6-month, multicenter, open-label study at UCLA School of Medicine, Mattel Children's Hospital, Los Angeles; and University of Miami School of Medicine, FL. Of 244 patients meeting requirements for evaluation (>12 weeks of treatment and stabilized topiramate dose during final 28 days), 213 were taking topiramate monotherapy at end of trial. The mean stabilized daily dose of topiramate over the last 28 days of treatment (primary endpoint) was 191 mg in patients with 1-3 seizures (low seizure frequency, n=147) and 239 mg in those with >3 seizures (high seizure frequency, n=66) ($P<0.003$). Patients with low seizure frequency reached a stable topiramate dose after a median of 36 days, compared with 53 days for patients in the high-seizure-frequency group. Baseline seizure frequency and lifetime seizure count were significant ($P<0.05$) predictors of the required stabilized dosage. Treatment-emergent adverse events (TEAEs) that occurred with cumulative incidence rates >10% in either seizure frequency group included paresthesia, fatigue, anorexia, dizziness, somnolence, headache, and hypoesthesia. Most adverse events were considered mild to moderate, 5.1% were serious, and 18.2% of patients discontinued therapy because of a TEAE (16.6% of the low-seizure-frequency, lower dose group compared with 21.4% in the high-seizure-frequency higher dose group). (Sankar R, Ramsay E, McKay A, Hulihan J, Wiegand, CAPSS-311 study group. **Epilepsy Behav** Aug 2009;15:506-512). (Respond: Dr Raman Sankar, David Geffen School of Medicine at UCLA, Mattel Children's Hospital, PO Box 951752, Los Angeles, CA 90095. E-mail: RSankar@ucla.edu).

COMMENT. Lower topiramate monotherapy doses (200 mg/kg day in 2 divided doses, am and pm) are adequate for patients with low baseline seizure frequency, and seizure control is associated with a lower incidence of adverse effects.

VALPROIC ACID AND SLEEP DURATION IN CHILDREN WITH EPILEPSY

Sleep duration and behavior were assessed in 46 children (age range 1.7-17.4 years) before and after tapering valproic acid (VPA) administered for more than 6 months for epilepsy, in a study at University Children's Hospital, Zurich, Switzerland. Actigraphy data obtained for 7 consecutive days and nights showed that after termination of VPA 33 children

slept less (>30 min in 9 patients) and 13 children slept longer (>30 min in 1). Mean Actual Sleep Time per Day was significantly reduced after VPA termination (-10.7 min) in children older than age 6 years. Gender and dose of VPA were not contributing factors. Questionnaire data showed no significant difference in bed and wake time, duration of sleep, and time to fall asleep before and after ending VPA treatment. (Schmitt B, Martin F, Critelli H, Molinari L, Jenni OG. Effects of valproic acid on sleep in children with epilepsy. **Epilepsia** Aug 2009;50:1860-1867). (Respond: Bernard Schmidt MD, Department of Pediatric Neurology, University Children's Hospital, Steinwiesstrasse 75, CH-8032 Zurich, Switzerland. E-mail: bernard.schmidt@kispi.uzh.ch).

COMMENT. Termination of VPA after long-term treatment for epilepsy is associated with a small but significant reduction of sleep duration, but only in children older than 6 years of age. The reason given for initiating this study was frequent parental reports that sleep duration increases during VPA treatment and decreases when medication is suspended. The results partly confirm the parental observations.

CONCURRENT ANTICONVULSANT/KETOGENIC DIET EFFICACY

Researchers at the Johns Hopkins Hospital, Baltimore, studied retrospectively the comparative efficacy of six most frequently used anticonvulsants when employed in combination with the ketogenic diet (KD) for treatment of 115 children with epilepsy. Mean age at initiation of the KD was 4.7 years. Patients had tried unsuccessfully a median of 4 anticonvulsants, and at KD initiation were receiving a median of 2 anticonvulsants (range 1-5). At KD onset, the most common anticonvulsants included valproic acid (n=38), topiramate (31), levetiracetam (27), lamotrigine (25), zonisamide (21), and phenobarbital (14). Only 4 children received vigabatrin. Most common seizure types treated with drug/KD combination included Lennox-Gastaut syndrome or mixed/multiple seizures (n=56), infantile spasms (18), and complex partial seizures (19). After 3 months on the diet and no change in the anticonvulsant dose, 72% had a >50% seizure reduction. Patients receiving zonisamide and KD were more likely to have a >50% reduction in seizures than the other children combined who were receiving the other 5 anticonvulsants (P=0.04). Nineteen of the 21 children (90%) receiving zonisamide had a >50% seizure reduction. Children receiving phenobarbital and KD were less likely to have a >50% seizure reduction (P=0.003). The difference in the interaction between KD and zonisamide or phenobarbital was not explained by seizure type or age. Patients responding with a >90% seizure reduction or seizure freedom showed no significant correlation with a specific anticonvulsant/KD combination. (Morrison PF, Pyzik PL, Hamdy R, Hartman AL, Kossof EH. The influence of concurrent anticonvulsants on the efficacy of the ketogenic diet. **Epilepsia** Aug 2009;50:1999-2001). (Respond: Eric H Kossof MD, Pediatric Epilepsy Center, The Johns Hopkins Hospital, Baltimore, MD 21287. E-mail: ekossof@jhmi.edu).

COMMENT. Zonisamide is not approved for use in children, and its mechanism of action is not definitely known. It is thought to increase seizure threshold by effects on sodium and calcium channels. As a carbonic anhydrase inhibitor, zonisamide is less active than acetazolamide, but this mechanism may have a contributory anticonvulsant effect.

Controlled clinical balance studies of the effects of anticonvulsant drugs and the ketogenic diet (KD) on acid-base, electrolyte, and amino acid metabolism in children with absence seizures (Millichap JG et al. **Epilepsia** 1964;5:239-255; **Am J Dis Children** 1964;107:593-604) found that the KD and acetazolamide, studied as monotherapies, had similar metabolic effects. They both caused a metabolic acidosis, with decreased pH, pCO2, and standard bicarbonate, and a negative balance of electrolytes. In contrast, trimethadione, mephobarbital, and methsuximide as monotherapies (anti-'petit mal' medications available in the 1960s), caused a metabolic alkalosis, with an elevation of pH and standard bicarbonate, and compensatory rise in pCO2; the urinary excretion of sodium and potassium and fecal excretion of calcium, magnesium and phosphorus were reduced, and the balance of electrolytes was positive. The effects of the ketogenic diet and acetazolamide on acid-base and electrolyte balance were the reverse of those obtained during treatment with conventional antiepileptic medications and corticotropin. Apart from an increase in serum leucine during treatment with the KD, levels of serum amino acids showed no significant changes. In this study, while all therapies were beneficial, the KD was most effective in the control of absence seizures and reduction of epileptiform discharges in the EEG. Concurrent use of a carbonic anhydrase inhibitor (acetazolamide or zonisamide) and KD would result in accentuated effects on acid-base and electrolyte metabolism and potential improvement in seizure control, but not without an anticipated increase in adverse side effects.

QUANTITATIVE EEG, COGNITIVE DEFICITS, AND BECTS

Researchers at Pontificia Universidade Catolica, Campinas, Brazil studied the relationship between educational problems and clinical/EEG aspects of benign childhood epilepsy with centrotemporal spikes (BECTS) in 38 children, ages 8 to 11 years (average age 9.29 +/- 1.27). Educational problems assessed by the School Performance Test, Parent and Teacher Questionnaires on learning difficulties, and the WISC-III test were observed in 7 (18.4%) children with BECTS. In this subgroup of educationally handicapped children, relative alpha amplitudes at the central and parietal electrodes were lower as compared with the BECT subgroup with normal educational performance and a control group matched for age and gender. Alterations in background brain electrical activity appeared to be related to a tendency toward educational disorders in children with BECTS. Quantitative EEG is a possible means of assessment of cognitive deficits in children with BECTS. (Tedrus GMAS, Fonseca LC, Melo EMV, Ximenes VL. Educational problems related to quatitative EEG changes in benign childhood epilepsy with centrotemporal spikes. **Epilepsy & Behav** Aug 2009;15:486-490). (Respond: Dr Lineu C Fonseca, Dept of Neurology, Pontificia Universidade Catolica de Campinas, Brazil. E-mail: lineu.fonseca@uol.com.br).

COMMENT. Deonna T, Roulet E and associates, of Lausanne, Switzerland, in one of the earlier prospective neuropsychological and EEG studies of 22 children with BECTS (19) and occipital spikes (3), found 21 had average IQ, 8 had school difficulties, 4 delayed language development, and 8 had transient impairments in verbal, visuospatial, or memory function. Cognitive deficits improved or normalized on follow-up, with concomitant EEG improvement or normalizaton. Transient cognitive difficulties in some children with BECTS were directly related to the paroxysmal EEG activity (Deonna T et al. **Dev Med Child Neurol** 2000;42:595-603). Wolff M et al (**Epilepsia** 2005;46:1661-1667), in a combined

MEG/EEG study of children with benign partial epilepsy, reported a correlation between location of focal interictal spikes and selective cognitive deficits. Massa R et al (**Neurology** 2001;57:1071-1079) found that EEG interictal patterns and their persistence were the hallmarks of neuropsychological impairments in 10 of 35 patients (28%) with BECTS followed from onset to complete recovery. While these studies focused on the correlation between epileptiform discharges and cognitive impairments in children with BECTS, the current study from Brazil notes a relation between alterations in amplitude of background EEG activity and educational problems.

Ictal EEG and BECTS. Tedrus et al, the Brazil research team, also report details of an ictal EEG during oropharyngeal seizures in an 8-year-old boy with BECTS (**Clinical EEG and Neuroscience** July 2009;40(3):200-203). Seizure onset during sleep correlated with an increase in centrotemporal spikes followed by slow waves in the right hemisphere. A brief decrease in amplitude of background activity preceded rhythmic, diffuse sharp waves in the right centrotemporal region. Finally, high potential spikes reappeared in the central and temporal regions of the right hemisphere with normalization of background activity. The EEG changes occurred concurrently with clonic lip movements, pouting, and throat noises.

COGNITIVE DEFICITS AT ONSET OF EPILEPSY

Neuropsychological functioning and academic achievement were determined at the time of the first seizure in a prospective study of 282 children (ages 6-14 years, with IQ >70) and compared with 147 healthy siblings examined at Indiana University, Case Medical Center, and Cincinnati Children's Hospital. Children with seizures scored lower than siblings on all neuropsychological tests, especially involving attention/executive/construction, but academic achievement was unaffected. Neuropsychological deficit was exhibited by 27.4% of children with seizures vs 18.2% of healthy siblings (p=0.04). Almost twice as many with seizures showed deficits in attention/executive/construction, verbal memory and learning, language and processing speed. Only symptomatic/cryptogenic seizure etiology was a risk factor for cognitive deficit. Children taking valproic acid scored lower for processing speed vs no-AED group (p=0.009). Among children with seizures, those on AEDs performed worse than no-AED group on all neuropsychological factors, but not on academic achievement. EEG epileptiform activity was associated with slower processing speed (p=0.004) but not with academic achievement. Risk factors for cognitive deficits were multiple seizures, AEDs, symptomatic/cryptogenic etiology, and epileptiform activity on initial EEG; a child with all 4 risk factors is 3 times more likely than healthy siblings to have neuropsychological deficits by the first clinic visit. Absence epilepsy was an added risk factor. (Fastenau PS, Johnson CS, Perkins SM, et al. Neuropsychological status at seizure onset in children. Risk factors for early cognitive deficits. **Neurology** Aug 12, 2009;73:526-534). (Respond: Philip S Fastenau PhD, Department of Neurology, University Hospitals Case Medical Center, 11100 Euclid Ave, HAN 5040, Cleveland. OH 44106. E-mail: Philip.Fastenau@uhhospitals.org).

COMMENT. Children identified with a first seizure exhibit neuropsychological deficits in 27% cases. In those with risk factors, up to 40% have cognitive deficits. Children with multiple seizures, symptomatic/cryptogenic seizure etiology, those on AEDs, or with epileptiform discharges on the initial EEG should be referred for neuropsychological and educational evaluation.

DEMYELINATING AND INFLAMMATORY CNS DISORDERS

MRI CHANGES COMPARED IN CHILD AND ADULT ONSET MS

Initial brain MRI characteristics of 41 children (<18 years) and 35 adults (>18 years) at multiple sclerosis (MS) onset were analyzed retrospectively in a study at UCSF Regional Pediatric and Adult MS Centers, and University of California, San Francisco. Children had a higher number of total T2- and large T2-bright areas than adults. Children more frequently had T2-bright foci in the posterior fossa and enhancing lesions than adults. Age was the main independent predictor for infratentorial involvement. (Waubant E, Chabas D, Okuda DT, et al. Difference in disease burden and activity in pediatric patients on brain magnetic resonance imaging at time of multiple sclerosis onset vs adults. **Arch Neurol** Aug 2009;66:967-971). (Respond: E Waubant MD PhD, UCSF Regional Pediatric MS Center, 350 Parnassus Ave, Ste 908, San Francisco, CA 94117. E-mail:emmanuelle.waubant@ucsf.edu).

COMMENT. Higher disease burden, posterior fossa involvement, and rate of new lesions in pediatric-onset MS are characteristics associated with worse disability progression in adults.

ACUTE CEREBELLITIS AND HYDROCEPHALUS

Two children, a girl aged 5 years and a boy aged 11 years, with acute cerebellitis, tonsillar herniation and hydrocephalus are reported from Schneider Children's Medical Center of Israel, Petah Tikva, Tel Aviv. The 5-year old presented with vomiting, occipital pain, and right torticollis of 1 week's duration. Two weeks previously, she had cough and rhinorrhea. Neurological examination revealed hyperactive reflexes, truncal ataxia, and dysmetria. MRI showed diffuse edema (hyperintensity on T2-weighted images) of the right cerebellar hemisphere and vermis, compression of 4th ventricle and brainstem, tonsillar herniation, compatible with cerebellitis. Serology for *Mycoplasma pneumoniae* was immunoglobulin M-positive and G-negative. Following treatment with dexamethasone, diuretics and vibramycin, signs resolved after 1 week. Follow-up MRI after 7 weeks showed regression of cerebellar edema, correction of cerebellar tonsils, and normal ventricles. The 11-year-old boy recovered after ventriculostomy; the cause for his cerebellitis was unknown. (Shkalim V, Amir J, Kornreich L, Scheuerman O, Straussberg R. Acute cerebellitis presenting as tonsillar herniation and hydrocephalus. **Pediatr Neurol** Sept 2009;41:200-203). (Respond: Dr Shkalim, Department of Pediatrics C, Schneider Children's Medical Center of Israel, 14 Kaplan St, Petah Tikva 49202, Israel. E-mail: shine6@walla.co.il).

COMMENT. Fulminant cerebellitis, a fatal, clinically isolated syndrome, is reported in a 9-year-old boy treated at Jawaharlal Nehru Medical College, Belgaum, India. (Kamate M, Chetal V, Hattiholi V. **Pediatr Neurol** Sept 2009;41:220-222). He presented with severe occipital headache, vomiting, and ataxic gait, associated with intermittent fever. Neurological examination showed a conscious, oriented, irritable child with papilledema, bilateral lateral rectus palsy, brisk reflexes, neck retraction and ataxia. CT head scan revealed hydrocephalus

secondary to 4th ventricle obstruction. MRI after ventricular shunt showed bilateral cerebellar swelling and brainstem compression secondary to cerebellitis. PCR studies for herpes simplex virus and varicella were negative. Despite methylprednisolone and shunt, the patient died on day 2 of admission. Posterior fossa decompression was refused.

Cerebellitis, an inflammatory process, is caused by primary infectious, postinfectious, or postvaccination disorder. The authors cite varicella zoster, Epstein-Barr virus, measles, pertussis, diphtheria, Coxsackie, mumps, herpes simplex virus 1, and parvovirus as most frequently involved infectious agents.

EMERGING CNS VIRAL INFECTIONS

In a 2-part review, a neuroinfectious disease specialist at the University of Colorado Denver Health Sciences Center and Veterans Medical Center describes emerging viral infections as diseases that infect new hosts, spread into new geographic areas, alter their pathogenesis, or are caused by agents not recognized as pathogenic. Of 1415 species of infectious organisms known to be pathogenic in humans, 175 are considered to be emerging, with viruses and prions accounting for 77 (44%) of the total, and 80% having a primary nonhuman animal source (zoonotic). Animals, particularly wild animals, are significant risk factors for emerging infectious diseases (EIDs), and 40% of viral zoonotic EIDs are vectorborne. Exposure to mosquitoes and common arthropod vectors is another major factor in disease emergence. Host factors also play a key role in EIDs, an increased susceptibility resulting from AIDS, immunosuppression with cancer chemotherapy, organ transplant-associated, and drugs used to treat autoimmune and immune-mediated disorders. Viral EIDs cause severe neurological symptoms such as encephalitis in 39% of cases, and occasionally in an additional 10%. The review of various viruses includes 76 references. (Tyler KL. Emerging viral infections of the central nervous system. **Arch Neurol** Aug 2009;66:939-948). (Respond: Kenneth L Tyler MD, Neurology B-182, Research Complex-2, University of Colorado Denver Health Sciences Center, 12700 E 19th Ave, Aurora, CO 80045. E-mail: ken.tyler@ucdenver.edu).

COMMENT. Millichap JJ and Epstein LG in their recent publication, neuroinfectious disease as an emerging subspecialty in neurology (**Neurology** July 28 2009;73:e14-e15), discuss career prospects for neurologists interested in the field. Accredited fellowships are in the developing stage, but non-accredited training is available at several institutions. Close identification with a mentor in neuro-ID and collaboration with medicine or pediatrics-based ID specialists are essential requirements. Important roles for pediatric neurology ID subspecialists include consultant to an ID service for acute CNS infections, and diagnosis and management of chronic neuroinfectious disorders, including postinfectious epilepsy. Development of new antimicrobial and anti-inflammatory agents is an area of future research, especially in the management of emerging viral infections. Dedicated textbooks and reviews on neuro-ID cited by Millichap and Epstein include:

Barton LL, Friedman NR, eds. *The Neurological Manifestations of Pediatric Infectious Diseases and Immunodeficiency Syndromes.* Totwa, NJ: Humana Press, 2008.

Roos KL, ed. *Principles of Neurologic Infectious Diseases: Principles and Practice.* New York: McGraw-Hill, 2004.

Neuroinfections: celebrating the past, discussing the present. *Lancet Neurol* 2008;7:975.