

PEDIATRIC NEUROLOGY BRIEFS

A MONTHLY JOURNAL REVIEW

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

Vol. 22, No. 12

December 2008

SEIZURE DISORDERS

SEIZURES AND ANTI-NMDA-RECEPTOR ENCEPHALITIS

The clinical and immunological features of 100 patients with encephalitis associated with antibodies against NR1-NR2 heteromers of the NMDA receptor were analyzed in a study at the Children's Hospital of Philadelphia, and University of Pennsylvania. Median age was 23 years (range 5-76 years), and 91 were female. One boy (11 years old, without tumor) and 21 girls (12 with ovarian tumor) were a median age of 15 years (range 5-18 years). Prodromal symptoms in 86% consisted of headache, low-grade fever, or a non-specific viral-like illness within 2 weeks before hospital admission. Presenting symptoms were psychiatric or memory problems in 100%, seizures in 76%, decreased consciousness in 88%, dyskinesias, chiefly orofacial (86%), autonomic instability (69%), and hypoventilation (59%). Seizures were generalized tonic-clonic in 45 and partial complex in 10. EEG was abnormal in 92, and showed slow activity in 71 and epileptic activity in 21. Brain MRI was abnormal in 55, with increased FLAIR or T2 signal, and limited to the medial temporal lobes in 16. CSF was abnormal in 95, with pleocytosis in 91, increased protein in 32, and oligoclonal bands positive in 26 of 39 tested. Brain biopsy in 14 patients was nonspecific. Ovarian teratoma or other tumors were associated in 59%. Seventy-five patients recovered or had mild deficits, and 25 had severe deficits or died. Among those who recovered with mild deficits, 64 (85%) had signs of frontal lobe dysfunction including poor attention, impulsivity, and behavioral disinhibition. Patients with better outcomes and fewer neurological relapses had received early tumor treatment, usually with immunotherapy ($P=0.04$). Improvement was associated with a decrease of serum antibody titers. The effect of antibodies on neuronal cultures was determined by quantitative analysis of NMDA-receptor clusters. Patients' antibodies decreased the numbers of cell-surface NMDA receptors and clusters in postsynaptic dendrites. (Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. **Lancet Neurol**

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.

Dec 2008;7:1091-1098). (Respond: Dr Josep Dalmau, Division of Neuro-Oncology, Department of Neurology, 3 W Gates, University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104; E-mail: josep.dalmau@uphs.upenn.edu).

COMMENT. Anti-NMDA-receptor encephalitis is a new category of immune-mediated disorders of adolescents or young adults, often paraneoplastic (60%), diagnosed serologically, and amenable to surgical and/or immunotherapy. This disorder is not uncommon, almost 100 cases identified at the Univ Pennsylvania in 2 years. CSF findings are helpful in diagnosis but MRI abnormalities are nonspecific. Seizures, attention and behavior disorders are common sequelae in the 75% patients who recover. The role of prodromal viral infection or other event in triggering the immune response requires further study. The antibody-induced modulation of the target antigens is similar to the Lambert-Eaton myasthenic syndrome that occurs with or without tumor association. In Lambert-Eaton syndrome the presence of small-cell lung cancer confers a poor neurological outcome, whereas in anti-NMDA-receptor encephalitis, cases associated with teratoma of the ovary or testis and treated early have a good prognosis. (see Reflection and Reaction. Vincent A, Bien CG. *Lancet Neurol* 2008;7:1074-1075).

HEAD NODDING SEIZURES AND *O.VOLVULUS* INFESTATION

Head nodding (HN) syndrome, a new epilepsy disorder in sub-Sahara Africa, is described in 62 patients studied prospectively at the University of Ulm, Germany; Haydom Lutheran Hospital, Tanzania; and other centers in Austria, Tanzania, and Canada. The onset of HN attacks was at 6 to 10 years in 50% cases, and at 11-15 years in 37%. At the time of diagnosis and evaluation, most patients were between 11 and 15 years of age. Twenty-eight (45%) patients had only HN attacks, and 28 had HN plus one other type of seizure, usually generalized or partial complex. HN was associated with loss of neck tone, and 37 (60%) patients had additional loss of tone of upper extremities. Consciousness was impaired in 11 (18%). Food was a provoking factor in 9 patients, and bathing in cold water caused HN in 2. A family history of epilepsy was present in 90%. EEGs in 10 patients were normal in 4 and showed abnormal slowing in 6, with sharp waves in 2. MRIs in 12 patients were normal in 4, and showed hippocampal sclerosis in 5 and gliotic changes in 5. Thirty-one (61%) of 51 patients had microfilariae visible on microscopic examination of the skin. Traces of *Onchocerca volvulus* DNA in the skin were identified by PCR in 12 of 20 without microscopically visible microfilariae. Skin PCR positivity was significantly associated with MRI abnormalities. Neutrophil counts were elevated in 14 (27%) patients and eosinophils in 28 (55%). *O. volvulus* serum ELISA test was positive in 44 (86%). CSF PCR was negative in all patients. HN seizures were 50% controlled by conventional antiepileptic drugs. (Winkler AS, Friedrich K, König R, et al. The head nodding syndrome – clinical classification and possible causes. *Epilepsia* Dec 2008;49:2008-2015). (Respond: Dr Andrea S Winkler, Department of Neurology, University of Ulm, Oberer Eselsberg 45, 89081 Ulm, Germany. E-mail: drawinkler@yahoo.com.au).

COMMENT. The prevalence of epilepsy is reportedly higher in areas where onchocerciasis is endemic, eg Mexico, Sudan, Uganda, Tanzania, and S America, but meta-analysis fails to show a significant association between *O. volvulus* and epilepsy (Druet-

Cabanac et al, 2004; cited by authors). The cause of the head nodding epilepsy syndrome in Tanzania and Sudan remains unclear. Alternative explanations offered include hippocampal sclerosis, and genetic susceptibility. Evidence of CNS invasion by *O. volvulus* was not supported by CSF PCR tests.

Onchocerciasis (River Blindness, Filariasis) involves skin, subcutaneous tissue, lymphatic vessels and the eyes. The AAP Red Book, 27th ed. 2006 makes no mention of CNS invasion or epilepsy as a complication of onchocerciasis. Ivermectin, a microfilarial agent, and doxycycline are the drugs of choice for treatment of the infestation. Only anticonvulsant drug treatment is discussed in the article on HN syndrome. The effect of treatment with ivermectin on seizure frequency might be of interest.

CARBAMAZEPINE-INDUCED HYPERSENSITIVITY SYNDROME AND ROLE OF HHV-6 REACTIVATION

A 14-year-old Japanese boy with localization-related epilepsy and carbamazepine (CBZ)-induced hypersensitivity syndrome is reported from Ehime University School of Medicine, Japan. He developed a maculopapular rash and low-grade fever after 3 weeks of CBZ therapy. CBZ was discontinued and systemic corticosteroid (1 mg/kg/day) started. The rash spread to become diffuse, WBC increased with 19% atypical lymphocytes and 24% eosinophils. Improvement started on day 11, but relapse followed on day 15 with high fever, purpura, abdominal discomfort and liver dysfunction. AST and ALT were markedly elevated. On day 19, blood PCR was positive for HHV-6 DNA, and HHV-6 was isolated from peripheral blood mononuclear cells. On day 26, the anti-HHV-6 immunoglobulin G (IgG) titer was increased by 5,120-fold. Symptoms gradually subsided, and corticosteroid was discontinued without sequelae. Seizures did not recur during a 6-month follow-up and alternative anticonvulsant therapy was not required. (Suzuki Y, Fukuda M, Tohyama M, Ishikawa M, Yasukawa M, Ishii E. Carbamazepine-induced drug-induced hypersensitivity syndrome in a 14-year-old Japanese boy. *Epilepsia* Dec 2008;49:2118-2121). (Respond: Dr Yuka Suzuki, Department of Pediatrics, Ehime University School of Medicine, Shitsukawa, Toon, Ehime 7910295, Japan. E-mail: yusuzuki@m.ehime-u.ac.jp).

COMMENT. The treatment of anticonvulsant drug-induced hypersensitivity syndrome (DIHS) is controversial, except for the discontinuance of the drug. The association with HHV-6 reactivation may discourage the use of immunosuppressive therapy that may worsen the infectious complications of DIHS. Alternative treatments, especially in patients with liver dysfunction, include immunoglobulin and plasmapheresis. The successful use of N-acetylcysteine and intravenous immunoglobulin is reported in an adult with DIHS and liver dysfunction induced by phenytoin. (Cumbo-Nacheli G, Weinberger J, Alkhalil M, Thati N, Baptist AP. Anticonvulsant hypersensitivity syndrome: Is there a role for immunomodulation? *Epilepsia* Dec 2008;49:2108-2112).

ANTICONVULSANT SUPPRESSION OF POSTNATAL NEUROGENESIS IN LABORATORY ANIMALS

The effects of phenobarbital and diazepam on cell proliferation and neurogenesis were studied in newborn rats followed for 6 months, in a study at University of Dresden, Germany; Medical University, Lublin, Poland; University Medicine Berlin, Germany; and Solvay Research Laboratories, Weesp, The Netherlands. The N-methyl-D-aspartate antagonist MK801, and the GABA subtype A agonists phenobarbital and diazepam administered to infant rats on postnatal days 6-10 caused reduced numbers of neurons in the hippocampal dentate gyrus at postnatal day 15. No apoptosis was demonstrated. At age 6 months, phenobarbital-treated rats had fewer neurons in the dentate gyrus and performed worse than saline-treated littermates in water maze learning and memory task. Blockade of N-methyl-D-aspartate receptor-mediated excitation and enhancement of GABA subtype A receptor activation impair cell proliferation and inhibit neurogenesis in the immature rat brain. These findings raise concerns about the frequent use of phenobarbital in the treatment of neonatal seizures. (Stefovska VG, Uckermann O, Czuczwar M, et al. Sedative and anticonvulsant drugs suppress postnatal neurogenesis. *Ann Neurol* Oct 2008;64:434-445). (Respond: Dr Ikonomidou, Department of Pediatric Neurology, Children's Hospital, Medical Faculty Carl Gustav Carus, University of Technology Dresden, Fetscherstrasse 74, 01307 Dresden, Germany).

COMMENT. Neurogenesis in the hippocampal dentate gyrus is at its peak during the first week of postnatal life and declines progressively after day 9 in newborn rats. Phenobarbital administered in the first week to 10 days results in reduced neurogenesis at 2 weeks postnatally and impairment of learning and memory at 6 months, equivalent to adult life. These effects result in decreased hippocampal volume, reduced neuronal densities in the dentate gyrus, the CA1-hippocampus, and the cingulate cortex. These observations call for caution regarding the use of NMDA receptor antagonists and GABA-a agonists in neonatal, pediatric, and obstetric medicine.

SLEEP DISORDERS

SLEEP TERRORS IN TWINS

In an attempt to clarify the genetic and environmental causes of sleep terrors in childhood, researchers in Canada followed 390 pairs of monozygotic and dizygotic twins by assessing the frequency of sleep terrors at 18 and 30 months of age using a questionnaire administered to the biological mothers. The prevalence of sleep terrors was 36.9% at 18 months and 19.7% at 30 months. Boys and girls were affected equally. The polychoric correlations were 0.63 monozygotic and 0.36 dizygotic at 18 months and 0.68 and 0.24 at 30 months. Sleep terrors were best explained by a genetic and non-shared environmental, 2-component model. At 18 months, genetic factors accounted for 43.7% and non-shared environmental factors for 56.3% of the phenotypic variance; at 30 months, these proportions were 41.5% and 58.5%, respectively. (Nguyen BH, Perusse D, Paquet J, et al. Sleep terrors in children: a prospective study of twins. *Pediatrics* Dec 2008; 122:e1164-e1167). (Respond:

Jacques Montplaisir MD, PhD, Sleep Disorders Center, Sacre-Coeur Hospital, Montreal, Quebec, Canada H4J 1C5).

COMMENT. The prevalence of sleep terrors is high in infants (37% at 18 months) and decreases by one half to approximately 20% by 30 months of age. Genetic factors play an important role in the etiology of this early childhood parasomnia, accounting for >40% of the phenotypic variance for both 18- and 30-month-old twins. The role of non-shared environmental factors is also significant, >55% of the variance at both 18 and 30 months. Night terrors have a combination genetic-environmental etiology, but to date, no specific genes have been identified.

GENETICALLY DETERMINED EEG FINGERPRINT OF SLEEP

The influence of genetic factors on the individual profile of sleep electroencephalographic (EEG) power spectra at the 8 to 16 Hz frequency range during non-rapid eye movement (NREM) sleep was determined by recording 40 monozygotic and dizygotic twins during sleep. The study performed at the University of Rome and various international centers found that this EEG fingerprint of sleep showed a greater similarity in monozygotic than dizygotic pairs, with a 96% estimate of heritability. (De Gennaro L, Marzano C, Fratello F, et al. The electroencephalographic fingerprint of sleep is genetically determined: a twin study. *Ann Neurol* Oct 2008;64:455-460). (Respond: Dr De Gennaro, Department of Psychology, Section of Neuroscience, University of Rome "Sapienza," Via dei Marsi, 78, 00185 Rome, Italy. E-mail: luigi.degennaro@uniroma1.it).

COMMENT. Healthy humans have a unique profile of the sleep electroencephalographic (EEG) power spectra at the 8 to 16 Hz frequency range during non-rapid eye movement (NREM) sleep. This fingerprint allows discrimination between individuals with a probability of 92% (De Gennaro L et al, 2005). These authors have shown that individual differences in this EEG fingerprint of NREM sleep are genetically determined. A genetic contribution has already been demonstrated for the awake-resting EEG alpha power, and also, for many sleep disorders, including night terrors, narcolepsy, obstructive sleep apnea, restless legs syndrome, and Kleine-Levin syndrome.

NEUROMUSCULAR DISORDERS

HAND INVOLVEMENT IN CHARCOT-MARIE-TOOTH DISEASE 1A

Hand strength, function and disease-related symptoms were determined in 84 children, aged 2-16 years, with Charcot-Marie-Tooth disease type 1A (CMT1A) at University of Sydney, Children's Hospital at Westmead, and Royal Children's Hospital, Parkville, Australia. Hand weakness and dysfunction was present from the earliest stages of the disease and tended to worsen with age throughout childhood. Poor handwriting, weakness, pain and sensory symptoms also worsened with age. (Burns J, Bray P, Cross LA, North KN, Ryan MM, Ouvrier RA. Hand involvement in children with Charcot-Marie-Tooth disease type 1A. *Neuromuscul Disord* Dec 2008;18:970-973). (Respond: Dr Joshua Burns,

Institute for Neuromuscular Research, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW 2145, Australia. E-mail: joshuab2@chw.edu.au.

COMMENT. CMT1A is a demyelinating neuropathy characterized by progressive muscle weakness and atrophy. The peroneal muscles are involved first, causing a striking stork-like gait, and weakness and atrophy of the upper extremities is initially limited to the intrinsic muscles of the hands. The authors comment that the hand involvement is frequently under-recognized in the early stages.

HEARING LOSS IN FACIOSCAPULOHUMERAL DYSTROPHY

The clinical presentation of facioscapulohumeral dystrophy (FSHD) with unusual large 4q35 deletions was studied with attention to hearing loss. Hearing function was examined by otoscopy, audiometry and auditory-evoked brainstem responses. Data obtained from 6 patients with EcoRI 4q35 fragment size, ranging from 10 to 13 kb, were compared with those of 28 similar subjects reported in the literature. Sensorineural hearing loss occurred in 4 patients who had an infantile-onset dystrophic phenotype. Hearing loss was associated with mental retardation in 3 and epilepsy in 2. Hearing was mildly impaired in the remaining 2 of 6 patients. When the data from 28 similar cases reported in the literature were combined with that from the 6 patients examined, 68% had auditory impairment. Hearing loss is a characteristic feature of FSHD patients with a large 4q35 deletion. When considering only cases with 10-11 kb fragment size, FSHD is associated with early-onset dystrophic phenotype, mental retardation in 92% and epilepsy in 58%. (Trevisan CP, Pastorello E, Tomelleri G et al. Facioscapulohumeral muscular dystrophy: hearing loss and other atypical features of patients with large 4q35 deletions. *Eur J Neurol* Dec 2008;15:1353-1358 (Abstract)).

COMMENT. Facioscapulohumeral dystrophy with sensorineural hearing loss and Coats' syndrome was described by Taylor DA et al (*Ann Neurol* 1982;12:395). Coats' syndrome includes congenital retinal dysgenesis with telangiectasia and retinal detachment. A PubMed search of the literature found 8 reports of FSHD and sensorineural deafness, dating from 2008 to 1985. One case with epilepsy was complicated by infantile spasms at 6 months of age, the dystrophy presenting at 3 years, and sensorineural deafness noted later (Akiyama C et al. *No To Hattatsu* 1991;23:395-399). All 6 patients reported with facial diplegia in the first year of life and subsequent development of FSHD had sensorineural deafness (Korf BR et al. *Ann Neurol* 1985;17:513-516).

NEONATAL DISORDERS

HIPPOCAMPAL VOLUMES IN PRETERM INFANTS

The relation between neonatal regional brain volumes and working memory deficits at age 2 years was investigated in 156 very preterm children born at the Royal Women's Hospital, Melbourne, Australia, prior to 30 weeks gestation or weighing <1250g. Very preterm children who perseverated on the working memory task had significantly smaller

hippocampal volumes than controls with intact working memory. (Beauchamp MH, Thompson DK, Howard K, et al. Preterm infant hippocampal volumes correlate with later working memory deficits. **Brain** Nov 2008;131:2986-2994). (Respond: Dr Peter J Anderson, School of Behavioural Science, The University of Melbourne, Melbourne, VIC 3010, Australia. E-mail: peterja@unimelb.edu.au).

COMMENT. Children born preterm have smaller hippocampal volumes that correlate with working memory deficits measured at 2 years of age. Further research will determine the longterm effect of altered hippocampal volumes on cognitive function of premature infants.

NEUROGLIAL HETEROTOPIA AND NASOPHARYNGEAL OBSTRUCTION IN A NEONATE

The clinical presentation, imaging, treatment, and pathology of a case of neuroglial heterotopia in the nasopharynx causing airway obstruction in a newborn are reported from Columbus Children's Hospital, OH. MRI and CT showed a cystic mass filling the nasopharynx with a midline bony defect in the sphenoid bone above the clivus. Posterior nasal endoscopy visualized the cystic lesion prior to surgical removal. Connection with CSF and subarachnoid space was excluded. At 6-month follow-up, developmental milestones were normal, and repeat CT showed no evidence of recurrence of the mass. Histopathology of the lesion showed choroid plexus, glial, and respiratory-like epithelial cells. (Husein OF, Collins M, Kang DR. Neuroglial heterotopia causing neonatal airway obstruction: presentation, management, and literature review. **Eur J Pediatr** Dec 2008;167:1351-1355). (Respond: OF Husein, 1414 N Houk Rd, Suite 208, Spokane, WA 99216. E-mail: tiffhusein@yahoo.com).

COMMENT. Reviewing the literature, the authors found reports of 30 cases of pharyngeal neuroglial heterotopia. Both CT and MRI are recommended in the assessment of nasopharyngeal masses. CT visualizes any bony deformities of the skull base, and MRI detects intracranial connections through the skull defect. Encephalocele has a similar histology but differs from neuroglial heterotopia by maintaining a connection to the subarachnoid space.

ATTENTION DEFICIT DISORDERS

NEUROANATOMICAL ABNORMALITIES IN ADOLESCENT ADHD

Twenty-four adolescents with familial ADHD and 10 control youths underwent high-resolution structural MRI, and frontal lobe gyri and caudate were compared in a study at Stanford University and other US centers. Youths with ADHD had larger right caudate and right inferior frontal lobe volumes than control subjects. An increase in left caudate volume in a subgroup of ADHD youths was correlated with decreasing functional activation in this region. The findings were thought to reflect neurodevelopmental changes specific to late adolescence in familial ADHD. (Garrett A, Penniman L, Epstein JN et al. Neuroanatomical abnormalities in adolescents with attention-deficit/hyperactivity disorder. **J Am Acad Child**

Adolesc Psychiatry Nov 2008;47:1321-1328). (Repond: Amy Garrett PhD, Department of Psychiatry, 401 Quarry Rd, Stanford, CA 94305. E-mail: agaarrett@stanford.edu).

COMMENT. Neuroanatomical abnormalities detected in patients with ADHD support the neurobiological basis for this symptom complex. The authors cite a meta-analysis of structural imaging research that indicates regions most frequently affected include total cerebral volume, caudate nucleus, splenium of the corpus callosum, cerebellum and frontal lobes. Differences in findings may be attributable to differences in age of subjects selected and the weight of hereditary compared to environmental causes of ADHD (Millichap JG. Etiological classification of attention-deficit/hyperactivity disorder. **Pediatrics** 2008;121:e358-e365). The selection of cases with familial ADHD by the Stanford group is a more homogeneous sample than some, emphasizing the neural correlates of inherited forms of the disorder. The possible influence of associated environmental factors is not excluded, however.

ADHD SYMPTOMS AND LIKELIHOOD OF CHILD MALTREATMENT

The relationship between inattentive and hyperactivity symptoms and child maltreatment was studied among a sample of 14,322 participants in the National Longitudinal Study of Adolescent Health at the Centers for Disease Control and Prevention, Atlanta, GA. The weighted percentage of respondents reporting ADHD symptoms was 8.3%. Self-reported rates of child maltreatment were 40.5% for supervision neglect, physical neglect (11.6%), physical abuse (28.4%), and contact sexual abuse (4.5%). Forty six percent reported no child maltreatment. The age of subjects sampled was 18 to 28 years (average 21.8 years). Type of maltreatment was not correlated with age. Respondents with ADHD symptoms were more likely to report maltreatment. Compared with non-ADHD subjects, those with ADHD of any type reported all 4 types of child maltreatment. The *inattentive type* was associated with elevated risks of all 4 types of maltreatment whereas the *hyperactive/impulsive type* was associated only with an increased likelihood of supervision neglect and physical abuse. The *combined type* was associated with elevated risks of physical neglect and contact sexual abuse, and a significant risk of supervision neglect. The number of reported ADHD symptoms was also associated with the severity of child maltreatment. Each additional inattentive symptom was significantly associated with elevated risks of more severe child maltreatment of all 4 types. Each additional hyperactive/impulsivity symptom was associated with an increased likelihood of more severe supervision neglect or physical abuse. (Ouyang L, Fang X, Mercy J, Perou R, Grosse SD. Attention-deficit/hyperactivity disorder symptoms and child maltreatment: a population-based study. **J Pediatr** Dec 2008;153:851-856). (Reprints: Lijing Ouyang PhD, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Mail-Stop E-88, Atlanta, GA 30333. E-mail: eop9@cdc.gov).

COMMENT. Physicians should be alerted to the potential for child maltreatment in children with ADHD. Those with the inattentive type of ADHD are particularly vulnerable. The more severe the ADHD, the greater is the likelihood of child maltreatment.