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DEVELOPMENTAL DISORDERS

EPILEPTOGENICITY OF CORTICAL DYSPLASIAS AND TUMORS

The epileptogenic characteristic of focal cortical dysplasias and dysembryoplastic neuroepithelial tumors explored by depth electrodes and stereoelectroencephalography is quantified using an epileptogenicity index, in a study of 36 patients with focal drug-resistant epilepsy at Universite de la Mediterranee and other centers in Marseille and Rennes, France. The epileptogenic zone is organized as a simple focal lesional site or as a complex 'epileptogenic network' extending beyond the lesion. Epileptogenicity index (EI) values range from 0 (none) to 1 (maximal epileptogenicity). The mean EI in lesional regions was 0.87, and 0.29 in non-lesional structures. A single focal lesion was found in 31% of patients, and more than one epileptogenic region in 25 patients (64%) (a network organization in 61% and bilateral epileptogenic zone organization in 8%). Distant structures are often involved, and in mesio-temporal epilepsy, the number of epileptogenic structures increases with epilepsy duration. None patient with bilateral organization became seizure-free, while 87% with focal organization and 57% with network organization were seizure-free. The EI is of value in the delineation of the epileptogenic zone with brain lesions and in the definition of the extent of surgical resection. (Aubert S, Wendling F, Regis J, et al. Local and remote epileptogenicity in focal cortical dysplasias and neurodevelopmental tumours. **Brain** Nov 2009;132:3072-3086). (Respond: Pr Fabrice Bartolomei, MD, PhD, Service de la Neurophysiologie Clinique, CHU Timone-264 Rue st Pierre, 13005-Marseille, France. E-mail: fabrice.bartolomei@ap-hm.fr).

COMMENT. The epileptogenicity index (EI) is a method of quantifying and defining the epileptogenicity in and around focal cortical dysplasias and neurodevelopmntal tumors during stereo-EEG with depth electrodes. Defining the extent of the epileptogenic zone is

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important in prognosis and in surgical resection. The November 2009 issue of **Ped Neur Briefs** reviews a report of a novel immunocytochemical test for epileptogenic brain tissue, independent of the histological findings (Sarnat HB, Flores-Sarnat L. **Can J Neurol Sci** 2009;36:566-574). With this added quantification of the epileptogenicity zone by stereo-EEG and the EI, surgical resection for refractory epilepsies should become more accurate and effective.

EPILEPSY IN ANGELMAN'S SYNDROME

The natural history and response to treatment of epilepsy in a large population of Angelman syndrome (AS) patients were studied by detailed electronic survey conducted through the AS Foundation by pediatric neurologists at Massachusetts General Hospital, Boston; Texas Southwestern Medical Center; and Rady Children's Hospital, San Diego, CA. Approximately 1000 families of individuals with AS were asked to complete a questionnaire online. The survey was available for 3 months, Feb–May 2007, and questions included the description of seizures, and response to various medications and their side effects. Responses were obtained from family members of 461 individuals with AS, a 40-50% response rate. The average age of patients was 11.8 years (1.3-45 years) at time of survey, and an average age of 5.3 years (<1-35 years) at diagnosis; 56% were male. Multiple seizure types were reported, most commonly atonic seizures (41%), generalized tonic-clonic (40%), atypical absence seizures (37%), and complex partial (32%). Myoclonic seizures occurred in 12% and infantile spasms in 2%. Control of seizures was reported in 34% for a median period of 3.2 years, usually beginning at 8.8 years of age. Of 396 with current epilepsy, only 46% of those age <3 years had seizures, whereas 53-64% ages 3-18 years had seizures; 35% had regression in development, and 12% had experienced convulsive status epilepticus. In 64% of subjects with epilepsy, emergency lorazepam or diazepam was used for prolonged seizures or clusters of seizures.

Rates of epilepsy differed among genetic subtypes; those with maternal deletions (89%) and unknown subtypes (90%) had the highest rates of epilepsy, whereas those with imprinting defects (55%) were least affected. Of all subjects, 65% had a maternal deletion, and 18% had an unknown subtype. Most commonly prescribed anticonvulsant medications (AED) were valproic acid (63%) and clonazepam (34%), but lamotrigine (24%) and levetiracetam (20%) had similar efficacy and tolerability. Only 15% responded to the initial AED, and an additional 8% responded to the second agent; 77% had refractory seizures. Ketogenic diet was effective in 11 of 31 subjects, and vagus nerve stimulation in 8 of 16. (Thibert RL, Conant KD, Braun EK, et al. Epilepsy in Angelman syndrome: A questionnaire-based assessment of the natural history and current treatment options. **Epilepsia** Nov 2009;50(11):2369-2376). (Respond: Dr Elizabeth Thiele MD PhD, Pediatric Epilepsy Program, Department of Neurology, Massachusetts General Hospital, 175 Cambridge Street No 340, Boston, MA 02114. E-mail: ethiele@partners.org).

COMMENT. Epilepsy is a common problem in AS and is refractory to treatment. Although often considered a generalized form of epilepsy, partial seizures are fairly frequent. Newer AEDs, lamotrigine and levetiracetam, are as effective as conventional medications and have fewer serious side effects. Genetic analyses are correlated with response to therapy.

Sleep problems associated with epilepsy in AS may be related to the severity of seizures and the use of anticonvulsant mdication. In 290 individuals with AS, decreased nightly hours of sleep, and a difficulty initiating sleep were significantly correlated with epilepsy. (Conant KD, Thibert RL, Thiele EA. Epilepsy and the sleep-wake patterns found in Angelman syndrome. **Epilepsia** Nov 2009;50(11):2497-2500).

Genetic testing in AS demonstrates a molecular mechanism causing lack of expression of the UBE3A gene with abnormalities of chromosome 15, inherited from the mother. (Dan B. Angelman syndrome: Current understanding and research prospects. **Epilepsia** Nov 2009;50(11):2331-2339). Three characteristic EEG patterns are described: A. high amplitude delta with spikes anteriorly without clinical correlation; B. diffuse theta not associated with drowsiness; and C. high amplitude delta mixed with spikes in posterior regions on eye closure. Boyd SG and associates described the EEG features in early diagnosis of AS. (**Eur J Pediatr** 1988;147:508-513).

LANGUAGE DISORDERS

LANGUAGE AND READING DISORDERS IN EPILEPSY

The severity and range of linguistic impairments in youths with epilepsy were studied at UCLA, Los Angeles, State Fullerton University, and UC at Irvine, California. Tests of language, intelligence, achievement, and psychiatric interviews were administered to 182 youths with epilepsy, ages 6.3-8.1, 9.1-11.7, and 12.0-15.2 years, and to 102 normal children. Parents provided demographic, seizure-related and behavioral information. Language scores 1 SD below average were significantly more frequent in epilepsy subjects than in controls. Intermediate and adolescent epilepsy groups had significantly lower mean language scores compared to controls. The older group had more language impairment. Longer duration of epilepsy, absence epilepsy, psychiatric diagnosis, and socioeconomic status were associated with linguistic deficits in the young group. Prolonged seizures, lower Peformance IQ and minority status predicted low language scores in the intermediate age epilepsy group. Poor seizure control, decreased Performance IQ, and lower socioeconomic status correlated with language impairment in the adolescent group. Linguistic and reading deficits were significantly related in each epilepsy group. (Caplan R, Siddarth P, Vona P, et al. Language in pediatric epilepsy. **Epilepsia** Nov 2009;50(11):2397-2407). (Respond: Rochelle Caplan MD, Semel Institute for Neuroscience and Human Behavior, 760 Westwood Plaza, Los Angeles, CA 90024. E-mail: rcaplan@ucla.edu).

COMMENT. Linguistic and reading impairment in pediatric and adolescent epilepsy increases with age, and predictors of impairment vary with each age goup. Language assessment and intervention are important in children with epilepsy.

EFFECT OF TEMPORAL LOBECTOMY FOR EPILEPSY ON LANGUAGE DEVELOPMENT

Language development was examined in 24 children (mean age 11 years; range 5.8-15.7 years) with AED intractable epilepsy before and 6, 12, and 24 months after anterior temporal lobectomy, in a study by the Dutch Collaborative Epilepsy Surgery Programme (DuCESP) at University Medical Center Utrecht, The Netherlands. Before surgery, the mean language delay varied from 1.7 years to 3.5 years and after surgery, language development was slower than normal, except for receptive syntax (execution of oral commands). Productive lexicon (oral response to visually presented objects) was slowed when surgery and language mediation were both in the left hemisphere. (de Koning T, Versnel H, Jennekens-Schinkel A, et al. Language development before and after temporal surgery in children with intractable epilepsy. **Epilepsia** Nov 2009;50(11):2408-2419). (Respond: Huib Versnel, FO2.504, Department of Otorhinolaryngology, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands. E-mail: h.versnel@umcutrecht.nl).

COMMENT. Intractable temporal lobe epilepsy is a risk factor for delay in language development, and surgery does not result in improved language. Some language components are slowed when surgery and language mediation both involve the left hemisphere. Temporal lobectomy of the non-dominant hemisphere is not expected to affect language development.

PAROXYSMAL DISORDERS

FRONTAL-TEMPORAL BRAIN VOLUMES IN ABSENCE EPILEPSY

Fronto-temporal brain volumes and their association with clinical and psychological variables in children, aged 7.5-11.8 years, with childhood absence epilepsy (CAE) were compared to age and gender-matched children without epilepsy. The CAE group (n=26) had significantly smaller gray matter volumes of the left orbital frontal gyrus and both temporal lobes vs controls (n=37). Brain volumes in CAE children were related to age, gender, ethnicity, and pregnancy complications but not to seizure, IQ, and psychopathology variables. In controls without epilepsy, brain volumes were related to IQ. (Caplan R, Levitt J, Siddarth P, et al. et al. Frontal and temporal volumes in childhood absence epilepsy. **Epilepsia** Nov 2009;50(11):2466-2472). (Respond: Rochelle Caplan MD, Semel Institute for Neuroscience and Human Behavior, 760 Westwood Plaza, Los Angeles, CA 90024. E-mail: rcaplan@ucla.edu).

COMMENT. This study supports the theory of an orbital frontal focus for CAE spikes (Holmes et al **Epilepsia** 2004;45:1568-1579), and a symptomatic localization related cause for CAE, Lack of an association between orbital frontal gyrus gray matter volumes and seizure variables suggests that an underlying neuropathology, not seizures, affects brain development in children with CAE.

OPSOCLONUS MYOCLONUS PRESENTING AS STATUS EPILEPTICUS

Two cases of non-epileptic opsoclonus presenting as status epilepticus are reported fom the John Radcliffe Hospital, Oxford, UK. Jerking of eyes and limbs were initially explained as suspected encephalitis, and the patients were treated for seizures with anticonvulsants and anesthetic intubation, but without benefit. EEGs showed no epileptic discharges. A diagnosis of opsoclonus myoclonus was made in both cases, and treatment with adrenocorticotropic hormone (40 IU/day) in one and prednisolone (4 mg/kg/day) in the other resulted in rapid resolution of symptoms. No neoplasm or infectious agent was identified, and neither patient has relapsed or shown developmental delay. Video footage of both patients showing florid jerking suggestive of status epilepticus is presented on line. (Haden SV, McShane MA, Holt CM. Opsoclonus myoclonus: a non-epileptic movement disorder that may present as status epilepticus. **Arch Dis Child** 2009;94:897-899). (Respond: Dr Sarah V Haden, Community Paediatrics Department, Level LG 1, Children's Hospital, John Radcliffe Hospital, Headley Way, Oxford OX3 9DG, UK. E-mail: sarah.haden@orh.nhs.uk).

COMMENT. The electroencephalogram is indispensable in the distinction of non-epileptic paroxysmal disorders from epileptic seizures and in the diagnosis of nonconvulsive status epilepticus and an encephalopathic process. (Markand ON. Pearls, perils, and pitfalls in the use of the electroencephalogram. **Semin Neurol** 2003;23(1):7-46).

Outcome of opsoclonus-myoclonus studied in 11 patients at Children's Memorial Hospital, Chicago found that 9 of 10 treated with ACTH had recurrence of symptoms during a gradual withdrawal of ACTH; prednisone in one patient was ineffective in controlling opsoclonus-myoclonus. Eight had developmental delay with motor incoordination and speech delay (7 with neuroblastoma and 1 without). Tumor removal did not improve symptoms. One of 8 with tumor and 2 of 3 with no tumor had normal neurologic development. (Hammer MS, Larsen MB, Stack CV. **Pediatr Neurol** 1995;13(1):21-24).

INFANTILE CONVULSIONS AND RETINAL HEMORRHAGES

The prevalence of retinal hemorrhages in infants presenting with convulsions was studied at Hospital Universitari Sant Joan de Deu, Barcelona, Spain. Of 389 children seen in the accident and emergency epartment with convulsions, 182 aged 15 days to 2 years were admitted with a first convulsion over a 2-year period (May 2004-May 2006), and 2 had retinal hemorrhages. All infants were examined within 72 hours of admission by an ophthalmologist using indirect ophthalmoscopy. Both infants with retinal hemorrhages were diagnosed with shaken baby syndrome. Convulsions alone are unlikely to cause retinal hemorrhages in children <2 years of age. (Curcoy AI, Trenchs V, Morales M, Serra A, Pineda M, Pou J. Do retinal hemorrhages occur in infants with convulsions? **Arch Dis Child** 2009;94:873-875). (Respond: Dr Ana Isabel Curcoy, Paseig Sant Joan de Deu, 2, 08950 Esplugues de Llobregat, Barcelona, Spain. E-mail: acurcoy@hsjdbcn.org).

COMMENT. A similar prospective study at Sackler School of Medicine, Tel Aviv University. Israel examined 153 children (aged 2 months to 2 years) in the ED after a

convulsive episode. One child was found with unilateral retinal hemorrhages following a simple febrile convulsion. No other reason for the hemorrhage was uncovered. It was concluded that retinal hemorrhages following a convulsive episode are rare and should trigger a search for other causes, including child abuse. (Mei-Zahav M et al. Convulsions and retinal hemorrhages: should we look further? **Arch Dis Child** 2002;86(5):334-335).

In 2 cases of infants with hyponatremic seizures examined at Franklin Square Hospital, Baltimore, MD, retinal hemorrhages were an unexpected finding. Long bone fractures and subdural hematoma were associated in one case of shaken baby syndrome, and cerebral edema in case 2 was presumed to be the result of child abuse. Children with hyponatremic seizures are often neglected and are at risk of other forms of child abuse. (Krugman SD, et al. **Pediatr Emerg Care** 2000;16(6):432-434).

BENIGN ROLANDIC EPILEPSY AND LEARNING DISABILITIES

Neuropsychological impairments in 35 children with rolandic epilepsy, and the relationship to electroencephalographic findings, were studied at Ege University, Izmir, Turkey. Patients showed significant impairments of visuomotor and reading ability and attention to verbal stimuli compared to controls. Reading disability persisted on follow-up, despite resolution of EEG seizure discharges and remission of seizures. Cognitive disorders were not related to antiepileptic drugs, and occurred in untreated subjects. Patients should be followed to identify learning problems. (Ay Y, Gokben S, Serdaroglu G, et al. Neuropsychological impairment in children with rolandic epilepsy. **Pediatr Neurol** Nov 2009;41:359-363). (Respond: Dr Ay, Department of Pediatrics, Faculty of Medicine, Ege University, 35100 Izmir, Turkey. E-mail: dryilmazay@yahoo.com).

COMMENT. Contrary to the so-called benign nature of BECTS, the disorder is sometimes associated with learning disabilities, especially reading problems, while a normal IQ is preserved.

Impairment in attention in rolandic epilepsy evaluated in 14 studies published between 1990 and 2006, in a study at Columbia University, NY, found at follow-up when the EEG had normalized, that attention problems had almost completely resolved. (Kavros PM et al. **Epilepsia** 2008;49:1570-1580; **Ped Neur Briefs** Oct 2008;22(10):77-78). Rolandic spikes may aggravate the course of ADHD and predispose to increased impulsivity (Holtmann M et al. **Brain Dev** 2006;28:633-640).

ATTENTION DEFICIT DISORDERS

RATINGS OF ATTENTION PROBLEMS IN ADHD: A CONTINUUM

To determine whether ADHD should be classified in three distinct DSM-IV diagnostic subtypes or a continuum of attention problems, maternal ratings of attention on the Child Behavior Check List (CBCL), in Durch boys at age 7, 10, and 12 years, were fitted to class models, assuming either subtype or severity differences. The fit of the models to the data is compared, to determine which model is appropriate. Researchers at the Universities of Notre Dame, IN; Vermont; Utrecht; and Amsterdam conducted the study. At all three ages

tested, models that distinguish between 3 quantitative classes (mild, moderate, and severe attention problems) provide the best fit to the data. The attention problem (AP) severe class contains all the subjects diagnosed with ADHD-combined subtype. Some subjects with ADHD-predominantly inattentive type are in the moderate AP class. Factor mixture analyses show that the CBCL AP syndrome varies along a severity continuum of mild to moderate to severe attention problems. Children with ADHD are at the extreme of the continuum. Framers of DSM-V will need these data in considering a change in classification to a continuum rather than discrete diagnostic categories of ADHD. (Lubke GH, Hudziak JJ, Derks EM, van Bijsterveldt TCEM, Boomsma DI. Maternal ratings of attention problems in ADHD: Evidence for the existence of a continuum. **J Am Acad Child Adolesc Psychiatry** Nov 2009;48(11):1085-1093). (Respond: Gitta Lubke PhD, Department of Psychology, University of Notre Dame, 18 Haggar Hall, Notre Dame, IN 46556. E-mail: glubke@nd.edu).).

COMMENT. The proposed continuum of attention problems is not a novel concept for ADHD. Epstein MA, Shaywitz SE and associates (**J Learn Disabil** 1991;24(2):78-86) examined distinctions between ADD, LD, and ODD/CD. Children referred to mental health settings differ from those referred to child neurologists, and "may be considered an extreme of the continuum of ADD." Many children with ADD will be represented by those referred primarily for ADD and LD, rather than those with ADHD and comorbid aggression referred for child psychiatry evaluation. Shaywitz BA and associates, defining and classifying learning disabilities and ADHD (**J Child Neurol** 1995;10(Suppl 1):S50-7), report several lines of investigation showing reading ability and reading disability as a continuum. Awareness of this relationship of the norm to abnormal in a seamless relationship is critical to our understanding of the basis for reading disability (and ADHD). This concept might also provide evidence of a decreasing severity pattern with increasing age, and gender differences.

The present DSM criteria for diagnosis of ADHD rely on symptoms alone, and criteria dependent on signs (perceptual and neurological deficits, including EEG epileptiform discharges in 25% cases) are not admitted. Perhaps the new DSM-V diagnostic criteria dependent on grading of severity will include a reference to the neurobiological and genetic nature of ADHD and objective signs. A genetic overlap between measures of hyperactivity/inattention and mood is demonstrated in twins with comorbid ADHD and depression (Cole J et al. **J Am Acad Child Adolesc Psychiatry** 2009;48(11):1094-1101). Gene-environment interaction (genetic sensitivity to environmental factors) should also be considered in diagnosis and treatment. (Thapar A, Lewis G. Editorial. **J Am Acad Child Adolesc Psychiatry** 2009;48(11):1051-1052).

CEREBRAL NEOPLASMS

INFANTILE INTRACRANIAL TUMORS

Patients presenting to the Children's Hospital of Eastern Ontario (CHEO) through the last 34 years with intracranial tumor in the first year of life were reviewed retrospectively for symptoms, management, and functional outcome. Of 18 cases identified, 12 were supratentorial (8 benign) and 6 infratentorial (all malignant histology). They represented 4.8% of all pediatric brain tumors seen over that period. Eight were of glial origin (7

supratentorial), 4 neuroectodermal, 2 teratoid rhabdoid, 2 choroid plexus, 1 meningioma, and 1 teratoma. Median age of presentation differed by lesion location, but not duration of symptoms. Raised intracranial pressure was more than twice as prevalent with posterior lesions and increased head circumference. Seizures occurred in 9 (50%); the tumor was supratentorial in 67% and infratentorial in 17% (p=0.04). Torticollis occurred in 4 (67%) of infratentorial and none of supratentorial tumors (p<0.01). Total resection was performed in 47%, and CSF shunt was more frequent with infratentorial tumor. Adjuvant chemotherapy was given in 44%, and radiotherapy in 17%, mainly in infratentorial tumors. Eight survived, 7 with supratentorial tumor, 5 to adulthood. Six are functionally independent. (Mehrotra N, Shanji MF, Vassilyadi M, Ventureyra ECG. Intracranial tumors in first year of life: the CHEO experience. **Childs Nerv Syst** Dec 2009;25:1563-1569). (Respond: Dr Michael Vassilyadi, Division of Neurosurgery, The Ottawa Hospital, Ottawa, Canada. E-mail: vassilyadi@cheo.on.ca).

COMMENT. In this young age group (<1 year of age), seizures occurred in 50% of patients, mainly with supratentorial tumors. In a study of 291 children with intracranial tumors treated at the Mayo Clinic over a ten-year period, seizures occurred in 17%; the tumor was supratentorial in 62% and infratentorial in 38%. Average age at seizure onset and at diagnosis was 4.9 and 6.7 years, respectively, in patients with supratentorial, and 4.8 and 5.1 years in those with infratentorial tumors. EEG was of localizing value in 75% of supratentorial tumors (88% of cortical tumors). A generalized dysrhythmia, maximal in the occipital regions and compatible with a lesion in the posterior fossa, was present in 44% of patients with infratentorial tumor. A delta pattern, indicative of an expanding lesion, occurred in 57% patients. (Millichap JG et al. The electroencephalogram in children with intracranial tumors and seizures. **Neurology** 1962;12:329-336).

NEUROMUSCULAR DISORDERS

ASCORBIC ACID IN CHARCOT-MARIE-TOOTH DISEASE

Ascorbic acid has been shown to reduce demyelination and improve muscle function in a transgenic mouse model of Charcot-Marie-Tooth disease (CMT1A). Aberrant expression of the myelin protein 22 gene, PMP22 is the cause of CMT1A, and large doses of ascorbic acid are shown to inhibit cAMP-mediated stimulation of human PMP22 expression. A 12-month, randomized, double-blind, placebo-controlled study of ascorbic acid in 117 adult patients compared to 62 receiving placebo found no significant difference between groups in neuropathy scores. Doses of ascorbic acid were 1 g and 3 g daily. The occurrence of adverse events did not differ between groups. (Micallef J, Attarian S, Dubourg O, et al. Effect of ascorbic acid in patients with Charcot-Marie-Tooth disease type 1A: a multicentre, randomized, double-blind, placebo-controlled trial. **Lancet Neurology** Dec 2009;8:1103-1110). (Respond: Dr Olivier Blin, CHU La Timone, Marseille, France.E-mail: Olivier.blin@ap-hm.fr).

COMMENT. Similar negative results were obtained in a placebo-controlled trial of ascorbic acid (30 mg/kg/day) in 81 children with CMT1A (2-16 years of age). (Burns J, Ouvrier RA, Yiu EM, et al. **Lancet Neurol 2009;**8(6):537-544).