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SEIZURE DISORDERS

DACRYSTIC SEIZURES: A MULTICENTER VIDEO-EEG STUDY

Researchers at Children's Hospital, Boston; Boston University; Mayo Clinic, Jacksonville, FL; Northwestern University, Chicago; and the Cleveland Clinic in the USA; and centers in Germany and Spain studied the frequency of dacrystic seizures (DS) identified in video-EEG long-term monitoring units and the relationship of their clinical presentation to the underlying pathophysiology and etiology. Nine patients (5 male, 4 female) with DS were identified and included 1) stereotyped lacrimation, sobbing, grimacing, yelling, or sad facial expression; 2) long-term video-EEG recordings (at least 12 hrs.); and 3) at least one brain MRI study. Age at onset of seizures ranged from 0.08 – 70 years (mean 14.9 years). DS were identified in 0.06-0.53% of patients admitted for long-term video-EEG. DS occurred alone in only 1 patient; they were accompanied by gelastic seizures in 5 cases, and generalized tonic-clonic seizures in 5. Hypothalamic hamartoma was diagnosed in the 5 patients with DC and gelastic seizures. Left mesial temporal sclerosis was the etiology for 3 of the 4 patients with DC without gelastic seizures; and frontal glioblastoma was the underlying pathology in 1 patient.

Seizures were generally refractory to medication; at least 3 different AEDs were tried and only 2 of 9 patients responded. Six patients were considered for surgery and 3 underwent a surgical/radiosurgical or radioablative procedure that was successful in 1 who remains seizure-free after 3 years. (Blumberg J, Fernandez IS, Vendrame M, et al. Dacrystic seizures: demographic, semiologic, and etiologic insights from a multicenter study in long-term video-EEG monitoring units. **Epilepsia** 2012 Oct;53(10):1810-1819). (Respond: Dr Tobias Loddenkemper, Division of Epilepsy and Clinical Neurophysiology, Fegan 9, Children's Hospital Boston, 300 Longwood Ave, Boston, MA 02115. E-mail: tobias.loddenkemper@childrens.harvard.edu).

COMMENT. The term "dacrystic epilepsy," from the Greek *dakryon,* tear, was

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proposed in 1976 (Offen ML, et al. **J Neurol Neurosurg Psychiatry** 1976 Sep;39(9):829-34). Hypothalamic hamartoma is the most likely cause when dacrystic seizures (DC) are accompanied by gelastic epilepsy. When DS occur alone, the lesion is commonly in the temporal lobe cortex. DS are refractory to treatment with AEDs and frequently require surgery for removal of a structural lesion. Whereas involuntary laughter is an accepted expression of epilepsy, especially as a symptom of hypothalamic hamartoma, involuntary crying is a relatively rare form of epilepsy. The current article adds to the sparse literature suggesting that DS are symptomatic of structural brain lesions, and demonstrates that patients with DS without gelastic epilepsy frequently present with mesial temporal sclerosis. Symptoms leading to the diagnosis of a hypothalamic-pituitary or temporal lobe lesion are usually neurological, including increased intracranial pressure and seizures. Endocrine symptoms (changes in weight, height, puberty, or diabetes insipidus) and their occurrence prior to the onset of neurologic symptoms may help to diagnose the hypothalamic-pituitary lesions earlier than the appearance of gelastic seizures (Taylor M, et al. **J Pediatr** 2012 Nov;161(5):855-863.e3; see **Pediatr Neurol Briefs** 2012 Dec;26(12):95-96).

UTILITY OF SHORT-TERM VIDEO-EEG MONITORING

Researchers at Monash University Medical Center, Melbourne, Australia evaluated the yield and clinical utility of outpatient, short-term video-EEG monitoring (OVEM) as a diagnostic tool in routine clinical practice. Of a total of 175 patients with records examined retrospectively, 111 were female and 64 male, with an age-range of 16-87 years (mean 36 years). Mean length of recording was 3.8 hrs (range 1-6.8 hrs). Pre-test frequencies of clinical events were <1 per week (30.1%), 2-6 per week (48.7%), and >7 per week (21.2%). Focal slowing occurred in 24 recordings (13.7%) and background and generalized slowing in 18 (10.3%). Interictal epileptiform discharges (IED) were focal in 15 (8.6%) and generalized in the same frequency. Epileptic seizures were captured in 12 patients (6.9%). Psychogenic nonepileptic seizures (PNES) occurred in 65 (37.1%) patients. The diagnostic yield for PNES was 37.1%, for IED 17.2%, and for epileptic seizures 6.9%. Before OVEM, a provisional diagnosis of epilepsy was made in 136 (77.7%) patients; after OVEM, the diagnosis of epilepsy was changed to PNES in 28.6%, and from PNES to epilepsy in 2.3%. OVEM has a higher yield for PNES than epileptic seizures and IED. The yield of PNES was >5 times that of epileptic seizures, and diagnosis was changed from epilepsy to PNES in > one-fourth of patients. (Seneviratne U, Rahman Z, et al. The yield and clinical utility of outpatient short-term video-electroencephalographic monitoring: A five-year retrospective study. **Epilepsy Behav** 2012 Nov;25(3):303-6). (Respond: Dr Udaya Seneviratne, Dept. of Neuroscience, Monash Medical Centre, Australia. E-mail: udaya.seneviratne@monash.edu).

COMMENT. Outpatient short-term VEM changes the pre-test diagnosis in 30.9% of patients. It is a useful diagnostic test for PNES and has a higher yield for PNES than epilepsy. OVEM is relatively cheaper than inpatient long-term VEM, but the shorter recording duration may miss some patients with epileptic seizures. OVEM is considered in the diagnostic work-up of suspected PNES prior to an inpatient long-term VEM.

COGNITIVE FUNCTION AND ABSENCE EPILEPSY

Researchers at the University of Rome, Italy studied executive function and attention in 15 children with childhood absence epilepsy (CAE) (8 boys, 7 girls), under treatment with valproic acid, compared to healthy controls. Age at onset of CAE was 6-11 years. Seizures were completely controlled and their EEG after seizure remission showed no ictal or interictal epileptiform activity. Tests of neuropsychological function included planning and problem solving (Tower of London, TOL), verbal fluency (phonological fluency, FAS; category fluency, CAT), verbal short-term memory (digit span, DSForward), verbal working memory (digit span backward, DSB), visuo-spatial memory (Corsi block tapping test, CBTT), and sustained and divided attention (Trail making visual search test, TMT-A, TMT-B). CAE and control groups showed no differences on measures of intellectual functioning, verbal short-term memory and visuospatial memory. In contrast, significant differences were found in total time of planning task (TOL), phonological (FAS) and category (CAT) fluency and sustained and divided attention (TMT). (D'Agati E, Cerminara C, Casarelli L, Pitzianti M, Curatolo P. Attention and executive functions profile in childhood absence epilepsy. **Brain Dev** 2012 Nov;34(10):812-7). (Respond: Dr Elisa D'Agati, Department of Neuroscience, Child Neurology and Psychiatry Unit, "Tor Vergata" University of Rome, Viale Oxford 81, 00133 Rome, Italy. E-mail: elisadagati@gmail.com).

COMMENT. CAE and control groups show no significant differences in *scores* of tests of intellectual functioning and memory but large differences in *total time* of planning, verbal fluency, and attention. The authors suggest that, based on neuroimaging studies, the task slowness of children with absence epilepsy could be due to dysfunction of dorsolateral prefrontal circuits and other frontal regions, including the anterior cingulate, orbito-frontal and motor/premotor regions. This study involves patients whose clinical and EEG seizures are completely controlled.

In a study of impairment of consciousness during absence and other epileptic seizures, the cerebral cortex and subcortical structures were involved in maintaining consciousness. Alterations of consciousness during epileptic seizures may be produced by subcortical, i.e. reticular formation and/or cortical dysfunction. These authors propose that an impairment of consciousness during absence seizures may be due mainly to cortical dysfunction, whereas complex partial seizures may be associated with dysfunctional subcortical structures. (Yamauchi T. **Epilepsia** 1998;39 Suppl 5:16-20).

RECOGNITION MEMORY AFTER FEBRILE SEIZURES

Researchers at the Institute of Child Health, London; Epilepsy Center, University of Edinburgh; and Dartmouth Medical School, New Hampshire, US studied memory abilities in 26 children (mean age 23 months, SD 12.6 months) after prolonged febrile seizures (median, 37.5 days), and compared to 37 normal controls. Fifteen patients were reassessed after a mean of 12.5 months. The visual paired comparison task, dependent on functional hippocampi, was used to test memory abilities. Recognition memory was impaired when tested at a median of 37.5 days following prolonged febrile seizure (> 30 min). The deficits were not related to the seizure itself or to the anticonvulsant

medication. The magnitude of the decline in performance from the immediate to the delayed paradigm was linked to the size of the hippocampi at time of testing. One year later, the prolonged febrile seizure group still showed impairments in remembering a face after a 5 min delay. Age at the time of the seizure was not a factor. (Martinos MM, Yoong M, Patil S, et al. Recognition memory is impaired in children after prolonged febrile seizures. **Brain** 2012 Oct;135(Pt 10):3153-64). (Respond: Rod C Scott PhD, Dartmouth Medical School, Lebanon, NH. E-Mail: Rodney.C.Scott@Dartmouth.edu).

COMMENT. In this study concerning the effects of prolonged febrile seizures on recognition memory, a visual paired comparison task employing faces was used to test memory abilities in small infants. Prosopagnosia, an inability to recognize faces, is congenital and genetic or acquired. The congenital form may be inherited by ~2.5% of the population. The brain region associated with prosopagnosia is usually stated as the fusiform gyrus or an occipito-temporal location, contiguous with the hippocampal gyrus, the location emphasized in the above study. Congenital prosopagnosia is not rare. Oliver Sacks himself confused the faces of his brothers and learned that his relatives were similarly affected (Sacks O. A Neurologist's Notebook: Face-blind. Why are some of us terrible at recognizing faces? **The New Yorker** 2010 Aug 30:36). A PubMed search of the literature uncovered reports of significant improvements in familiar face recognition following training of a 4-year-old child with congenital prosopagnosia (Schmalzl L, et al. **Cogn Neuropsychol** 2008 Jul;25(5):704-29). Training focused on directing visual attention to specific characteristics of the face, particularly the eye region. The performance became flawless immediately after training as well as at a follow-up assessment 1 month later. Since the visual paired comparison task uses the face in repetitive tests of memory, practice effects on an inherent prosopagnosia are a possible modifying factor in studies of the effect of prolonged febrile seizure on face recognition and memory in infants.

ATYPICAL FACE SHAPE AND GENOMIC VARIANTS IN EPILEPSY

Researchers at the Institute of Neurology, Queen Square, London; Children's Hospital, Florence, Italy; and other centers in the UK, Belgium, and the Netherlands studied face shape abnormalities in 118 children and adults attending three European epilepsy clinics, using an objective measure called Face Shape Difference to show that those with pathogenic structural variants have a significantly atypical face shape. In a second group of 63 patients the predictive accuracy of the measure showed high sensitivity (80% for whole face, 60% for periorbital and perinasal regions) and specificity (78% for whole face and perinasal regions, 69% for periorbital region). Computer-based stereophotogrammetry and dense surface models were effective in detecting subtle relevant face shape abnormalities or dysmorphisms in patients with epilepsy and pathogenic structural genomic variants, as determined by chromosome microarray. (Chinthapalli K, Bartolini E, Novy J, et al. Atypical face shape and genomic structural variants in epilepsy. **Brain** 2012 Oct;135(Pt 10):3101-14). (Respond: Dr Sanjay M Sisodiya, Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK, E-mail: s.sisodiya@ucl.ac.uk).

COMMENT. Patients with epilepsy and pathogenic structural genomic microarray variants have an objectively more atypical face shape compared with those without. The authors suggest that an evaluation for facial dysmorphism should be part of the clinical work-up for epilepsy. The concept of a "facies epileptica" as defined by Turner (Turner WA. **Epilepsy: A Study of the Idiopathic Disease**. London: Macmillan and Co; 1907.), is now regarded as unacceptable. Given the heterogeneity of epilepsy, 3D stereophotogrammetry and dense surface models are not expected to identify a specific "face" associated with epilepsy, and actual facial shapes are as varied as the underlying pathogenic structural variants. An objective measure of face shape variation might be used in clinical selection of patients with epilepsy who should be considered for microarray chromosome analysis.

GENETIC NEUROLOGICAL SYNDROMES

EPILEPSY IN MUENKE SYNDROME

Researchers at the National Institutes of Health, Bethesda, MD; Children's National Medical Center; and George Washington University, Washington, DC present 7 patients with Muenke syndrome complicated by epilepsy. A review of 789 published cases of Muenke syndrome with neurological complications identified epilepsy in 6 cases, with intracranial anomalies in 5. The intracranial anomalies were agenesis of the corpus callosum, hemimegalencephaly, and porencephaly. In the review of 58 patients with Muenke syndrome in the Washington, DC cohort, 7 (12%) had epilepsy and 4 survived neonatal apnea. Patients with Muenke syndrome should be monitored for apnea and seizures. Those with seizures or febrile seizures should undergo neuroimaging, preferably MRI. (Agochukwu NB, Solomon BD, Gropman AL, Muenke M. Epilepsy in Muenke syndrome: FGFR3-related craniosynostosis. **Pediatr Neurol** 2012 Nov;47(5):355-61). (Respond: Dr Muenke, Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bldg 35, Bethesda, MD 20892. E-mail: mamuenke@mail.nih.gov).

COMMENT. Muenke syndrome has an autosomal dominant inheritance and is characterized by craniosynostosis, most commonly coronal uni- or bilateral, asymmetry of skull and face, sensorineural hearing loss, developmental delay, broad toes and thumbs, fusion of carpal and tarsal bones, hypertelorism, ptosis, strabismus, midface hypoplasia, and fronto-temporal bossing. The syndrome is caused by a mutation in the FGFR3 gene, with variable expressivity and phenotype. (Doherty ES, et al. Muenke syndrome (FGFR3-related craniosynostosis): expansion of the phenotype and review of the literature. **Am J Med Genet A** 2007 Dec 15;143A(24):3204-15). Other craniosynostosis syndromes associated with the fibroblast growth factor receptors (FGFR) include Crouzon, Apert, and Pfeiffer syndrome. (Millichap JG. **Neurological Syndromes. A Compendium for Clinicians.** New York: Springer; 2013. In press).

VICI SYNDROME WITH SENSORINEURAL HEARING LOSS AND LARYNGOMALACIA

Researchers at Baskent University, Adana, and other centers in Turkey report a 3-month-old Turkish girl with Vici syndrome complicated by stridor and laryngomalacia. They also review the clinical features of 15 Vici syndrome patients published in the literature. The Turkish girl was the second child of consanguineous parents, she was admitted with bronchopneumonia, stridor, and failure to thrive, and examination revealed microcephaly, hypopigmentation of the skin, silvery hair, high-arched palate and micrognathia. Neurologic abnormalities included hypotonia, areflexia, cataracts, ocular albinism, and cranial MRI revealed agenesis of the corpus callosum, delayed myelination of cerebral white matter, and hypoplasia of the cerebellar hemisphere and brain stem. EEG showed paroxysmal, bifrontal discharges during sleep. Chest X-ray showed cardiomegaly, echocardiography demonstrated hypertrophic cardiomyopathy, and audiology exam revealed deafness in the left ear. The patient died of a recurrence of bronchopneumonia at 6 months of age.

Of the total 15 patients with Vici syndrome, 6 were girls and 9 boys, and 8 were siblings. Common manifestations include agenesis of the corpus callosum (100%), hypotonia (100%), developmental delay (100%), cerebellar and cortical defects (60%), cataracts (60%), seizures (60%), cardiomyopathy, hypopigmentation (albinism), recurrent infections, immunological abnormalities, and sensorineural hearing loss (20%). Vici syndrome should be considered in the differential diagnosis of an infant with agenesis of the corpus callosum. (Ozkale M, Erol I, Gumus A, Ozkale Y, Alehan F. Vici syndrome associated with sensorineural hearing loss and laryngomalacia. **Pediatr Neurol** 2012 Nov;47(5):375-8). (Respond: Dr Erol, Division of Neurology, Department of Pediatrics, Adana Teaching and Medical Research Center, Faculty of Medicine, Baskent University, Baraj Yolu 1 Durak, Seyhan 01120, Adana, Turkey. E-mail: ilknur_erol@yahoo.com).

COMMENT. Vici syndrome is a rare phenotypically heterogeneous, autosomal recessive disorder of unknown cause. Also called immunodeficiency with cleft lip/palate, cataract, hypopigmentation and absent corpus callosum. The diagnosis is based on a cluster of clinical symptoms and MRI evidence of structural cerebral defects, typically agenesis of the corpus callosum. The prognosis is poor because of immunological abnormalities and recurrent severe infections. (Vici CD, Sabetta G, Gambarara M, et al. Agenesis of the corpus callosum, combined immunodeficiency, bilateral cataract, and hypopigmentation in two brothers. **Am J Med Genet** 1988 Jan;29(1):1-8).

GROWTH FAILURE AND OUTCOME IN RETT SYNDROME

Researchers at the Miami Children's Hospital and other centers in the US studied growth patterns among children with Rett syndrome compared to unaffected children. Growth charts for classic and atypical Rett were created from 9,749 observations of 816 female subjects. Mean growth in classic Rett decreased below that for the normative population at 1 month for head circumference, 6 months for weight, and 17 months for length. Mean BMI was unchanged. Pubertal increases in height and weight were absent in classic Rett patients. Classic Rett was associated with more growth failure than

atypical Rett cases. In classic Rett, poor growth was associated with worse development, higher disease severity, and certain MECP2 mutations. (Tarquinio DC, Motil KJ, Hou W, et al. Growth failure and outcome in Rett syndrome. Specific growth references. **Neurology** 2012 Oct 16;79(16):1653-61). (Response and reprints: Dr Tarquinio; E-mail: danieltarq@aol.com).

COMMENT. More than 200 mutations identified in MECP2 are associated with growth velocity in Rett syndrome, and specific mutations are associated with developmental outcome. In a study of MECP2 mutations and clinical correlations in Greek children with Rett syndrome, mutations were detected in ~70% of classic and ~21% of variant Rett syndrome cases. MECP2-positive females had more problems in ambulation, muscle tone, tremor and ataxia, respiratory disturbances, head growth, hand use and stereotypies. (Psoni S, Sofocleous C, Traeger-Synodinos J, et al. **Brain Dev** 2012 Jun;34(6):487-95).

BRAIN TUMORS

ENDOCRINE SYMPTOMS IN HYPOTHALAMIC-PITUITARY TUMORS

Researchers at Universite Paris Descartes and other centers in Paris, France performed a retrospective, study of 176 patients (93 boys) aged 6 years (range 0.2-18 years) with hypothalamic-pituitary lesions to determine whether the time to diagnosis could be shortened by analyses of clinical and endocrine presenting symptoms. The lesions were craniopharyngioma in 56, optic pathway glioma (n=54), supracellar arachnoid cyst (25), hamartoma (22), germ cell tumor (12), and hypothalamic-pituitary astrocytoma (7). The most common presenting symptoms were neurologic (50%) and/or visual complaints (38%). Endocrine symptoms occurred alone in 28%. Precocious puberty triggered the diagnosis in 19% of 131 prepubertal patients, and occurred earlier in patients with hamartoma than those with optic glioma ($P<0.02$). Isolated diabetes insipidus led to diagnosis of all germ cell tumors. In 122 patients presenting with neuro-ophthalmic symptoms, the mean interval from symptom to diagnosis was 0.5 year, although 66% of patients had abnormal body mass index or growth velocity, which preceded the presenting symptom onset by 1.9 years ($P<0.0001$) and 1.4 years ($P<0.0001$), respectively. Among this subgroup of patients with neuro-ophthalmic presenting symptoms, endocrine symptoms were present before onset of presenting symptoms in two-thirds of cases. Obesity occurred prior to diagnosis in 41 (38%) of 108 patients evaluated for BMI. Abnormal BMI or BMI progression was observed in 67 (62%) patients at a median time of 2.5 years prior to diagnosis. The French guidelines for the management of obese children state that endocrine or brain tumor should be suspected in case of poor growth velocity with obesity, and the AAP recommendations state that an exogenous cause of obesity (e.g. tumor) can lead to poor linear growth. In the cohort studied, 71% maintained normal growth velocity after onset of the presenting symptom and up to diagnosis of tumor. The guidelines failed to identify 61% to 85% of obese patients with a hypothalamic-pituitary lesion. (Taylor M, Couto-Silva A-C, Adan L, et al. Hypothalamic-pituitary lesions in pediatric patients: Endocrine symptoms often

precede neuro-ophthalmic presenting symptoms. **J Pediatr** 2012 Nov;161(5):855-863.e3). (Reprints: Dr Melissa Taylor, E-mail. melissa.taylormarchetti@gmail.com).

COMMENT. Endocrine disorders precede the onset of neuro-ophthalmic presenting symptoms in two-thirds of patients. Greater attention and identification of changes in weight, height, BMI and endocrine symptoms in children with hypothalamic-pituitary lesions should lead to earlier diagnosis and treatment. (Rogol AD. Editorial. **J Pediatr** 2012 Nov;161(5):778-80).

In a study of endocrine and growth features in 32 children with craniopharyngioma, neuro-ophthalmic presenting symptoms (headache, vomiting, visual impairment) were most common. Some patients presented with signs or symptoms of endocrine disorder (polyuria, polydipsia, growth failure, precocious puberty, and obesity). The growth pattern was heterogeneous. After tumor treatment, growth hormone deficiency required hormonal therapy, but 8 grew normally without growth hormone. (Di Battista E, Naselli A, et al. **J Pediatr Endocrinol Metab** 2006 Apr;19 Suppl 1:431-7).

HEADACHE DISORDERS

MIGRAINE AND SCHOOL PERFORMANCE IN PREADOLESCENT CHILDREN

Researchers at the Glia Institute, Brazil; Albert Einstein College of Medicine, NY; and other centers conducted a population-based study of school performance in children in Brazil with migraine. Episodic migraine occurred in 9%, probable migraine in 17.6%, and chronic migraine in 0.6% of 5, 671 children from 87 cities and 18 Brazilian states. Teachers provided information and measurements of the overall scholastic achievement for the school year. Parents were interviewed using a headache questionnaire and the Strengths and Difficulties Behavior Questionnaire. Poor performance in school was significantly more likely in children with episodic and chronic migraine, in terms of severity and duration of attacks, abnormal scores of mental health, and by nausea, headache frequency, use of analgesics, and gender. (Arruda MA, Bigal ME. Migraine and migraine subtypes in preadolescent children. **Neurology** 2012 Oct 30;79(18):1881-8). (Response: Dr Bigal. E-mail: marcelo_begal@merck.com).

COMMENT. Children with migraine are more likely to have below average school performance relative to children without headaches and more likely to have missed school days. These associations are correlated with the severity of pain, presence of associated symptoms, and frequency of pain. The associations are predicted by behavior and emotional symptoms.

A current study to assess cognitive functioning of Italian children with migraine without aura and those with tension-type headache finds no difference in FS IQ between the groups, but children with tension-type headache have a lower verbal IQ and a higher performance IQ than healthy controls and children with migraine. Children with migraine have lower perceptual organization than those affected by tension-type headache. (Esposito M, Pascotto A, Gallai B, et al. **Neuropsychiatr Dis Treat** 2012;8:509-13).