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SEIZURE DISORDERS

EEG FOLLOWING FEBRILE STATUS EPILEPTICUS

Investigators at Lurie Children's Hospital of Chicago; Albert Einstein College of Medicine, NY; Columbia University, NY, and 7 additional members of the FEBSTAT study team report the results of a prospective evaluation of the consequences of febrile status epilepticus (FSE) on the EEG of 199 children (median age 15.8 months; range 12-24 months). Median peak temperature at FSE was 102.7°F and median duration of FSE was 70 minutes. The majority (96%) of EEGs were obtained within 72 hours of status; of the remainder, 2.5% were obtained within a week and 1.5% within a month of FSE. Ninety (45.2%) EEGs were abnormal, including 85 (42.7%) nonepileptiform and 13 (6.5%) epileptiform (temporal in 6 and central in 4). Significant focal nonepileptiform abnormalities occurred in 60 (30.2%) EEGs; focal slowing involving the temporal region was seen in 47 (right-sided in 36; left-sided in 11) and attenuation occurred in 25, always unilateral and more common on the right. Diffuse background slowing was seen in 22 EEGs, and focal slowing was associated in 11 cases (23.4%). The odds of focal slowing were significantly increased by focal FSE and hippocampal T2 signal abnormality on MRI. High temperature with FSE was associated with significantly decreased odds of focal slowing. Low peak temperature, focal FSE, and hippocampal T2 signal abnormality increased the odds of focal slowing. Focal EEG attenuation was associated with hippocampal T2 signal abnormality. (Nordli DR Jr, Moshe SL, Shinnar S, et al. Acute EEG findings in children with febrile status epilepticus. **Neurology** 2012 Nov 27;79(22):2180-2186). (Response: Dr Nordli: E-mail: dnordli@luriechildrens.org).

COMMENT. EEGs obtained within 72 hours of FSE show focal slowing or attenuation in 30% and these abnormalities are associated with evidence of acute hippocampal injury on MRI. In contrast, epileptiform abnormalities occur infrequently. The FEBSTAT investigators conclude that the EEG performed immediately after febrile

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status epilepticus is more sensitive than the MRI as a biomarker for the prediction of subsequent epilepsy.

Previous studies of the EEG in children with febrile seizures, some performed in the 1950s-60s and cited by the FEBSTAT investigators, also emphasize the frequency and significance of slow wave abnormalities. In addition, Lennox-Buchthal M (**Ugeskr Laeger** 1964 Feb 13;126:203-6) extended her research and performed serial EEGs on children with febrile seizures at varying time intervals after the first seizure as follows: on the third, fourth, or fifth day of admission, 10 days to 2 weeks after admission, and at 3, 6, and 12 months and every year at follow-up visits. The EEGs showing slow frequencies at the third to fifth day after a febrile convulsion had a trace of slowing in some after 10 days to 2 weeks, but the record was normal after an interval of 3 months. Compared to the patients with normal initial EEGs, those with pronounced slow frequencies had a greater incidence of recurrence of febrile seizures and of paroxysmal abnormalities in subsequent records, but the differences in incidence were not significant. Perhaps the larger cohort of the FEBSTAT study will show a more robust correlation between slowing and subsequent epilepsy at follow-up. Repeated EEGs at intervals are advised in some febrile seizure patients with recurrent seizures or other complications so that delayed emergence of paroxysmal abnormalities and susceptibility to epilepsy with increasing age may be excluded.

CSF IN FEVER-ASSOCIATED STATUS EPILEPTICUS

Investigators at Children's Hospital of the King's Daughters, Eastern Virginia Medical School, Norfolk, VA; Albert Einstein College of Medicine, Bronx, NY; Columbia University, NY; and other centers on behalf of the FEBSTAT Study Team assessed CSF findings in 154 (77%) of 200 patients with fever-associated status epilepticus (FSE). LP was performed at the discretion of the attending physicians, and 136 children had a nontraumatic LP (<1000 red blood cells; 116 (96.2%) of the 136 had </= 3 white blood cells/mm^3). Likelihood of an LP performed in the ED was significantly higher in younger children, in those with the first FS, a longer median duration of FSE, febrile status epilepticus, and a focal FSE. Mean CSF protein level was 22 mg/dL (range, 8-137 mg/dL); 3 (2.3%) had a protein level >60 mg/dL. Mean CSF glucose level was 89.6 mg/dL (range, 46-201 mg/dL). Excess WBCs in the CSF should not be attributed to the seizure (Frank LM, Shinnar S, Hesdorffer DC, et al. Cerebrospinal fluid findings in children with fever-associated status epilepticus: Results of the Consequences of Prolonged Febrile Seizures (FEBSTAT) Study. **J Pediatr** 2012 Dec;161(6):1169-1171.e1). (Reprint requests: L. Matthew Frank MD. E-Mail: matthew.frank@chkd.org).

COMMENT. LP performed at the discretion of the attending physician confirms that the CSF is usually normal in children with FSE. Abnormal CSF results should not be attributed to the seizure and should prompt close investigation and treatment for suspected meningitis.

Clinical manifestations and complex seizures are the principal indications for lumbar puncture, not patient age, in a study of 100 consecutive febrile seizure patients treated in a tertiary hospital ED. (Millichap JJ et al. **Pediatr Neurol** 2008 Dec;39(6):381-6). Eleven (78.6%) patients undergoing LP had complex FS, 3 manifesting prolonged

seizures and FSE, with durations of 43, 45, and 60 minutes. CSF findings were normal and bacterial cultures were negative. A child aged 3 months to 5 years who presents with a first or recurrent FS should be considered for LP if one or more of the following indications are present: neurologic signs of meningitis, systemic signs of toxicity, complex seizure with prolonged postictal obtundation of consciousness, or pretreatment with antibiotics. Complex FS alone is not an absolute indication for LP.

In a retrospective study at Children's Hospital Boston to assess the rate of acute bacterial meningitis among 526 children who present with their first complex febrile seizure, 2.7% had CSF pleocytosis and 3 patients (0.9%) had acute bacterial meningitis. One appeared well clinically; of 2 with Streptococcus pneumoniae cultured from CSF, 1 was nonresponsive clinically, and the other had a bulging fontanel and apnea. (Kimia A, et al. **Pediatrics** 2010 Jul;126(1):62-9).

THALAMOCORTICAL STRUCTURAL AND FUNCTIONAL CONNECTIVITY IN JUVENILE MYOCLONIC EPILEPSY

Researchers at King's College, Institute of Psychiatry, London and other centers in the UK, US, and Germany discovered changes in an anterior thalamo-cortical bundle during tests of structural connectivity, as measured by diffusion tensor imaging, in a cohort of 28 subjects with juvenile myoclonic epilepsy. An alteration in task-modulated connectivity was detected in a region of frontal cortex connected to the thalamus via the same anatomical bundle, and overlapping with the supplementary motor area. In patients with active seizures, the degree of abnormal connectivity is related to disease severity in those with active seizures. These results point to abnormalities in a specific thalamo-cortical circuit, with reduced structural and task-induced functional connectivity that underlies this idiopathic epilepsy. (O'Muircheartaigh J, Vollmar C, Barker GJ, et al. Abnormal thalamocortical structural and functional connectivity in juvenile myoclonic epilepsy. **Brain** 2012 Dec;135(Pt 12):3635-44). (Response: Dr Mark P Richardson, E-mail: mark.richardson@kcl.ac.uk).

COMMENT. The characteristic generalized spike and wave discharges in the EEG of juvenile myoclonic epilepsy implicate thalamo-cortical interactions, and the discharges are most prominent in frontal regions. The functional and diffusion MRI and diffusion tensor imaging used above provide anatomic evidence for the role of the thalamus and a specific thalamo-cortical circuit dysfunction in JME. JME is a lifelong disorder and a structural cerebral defect may explain the necessity to continue treatment indefinitely. (Wandschneider B, et al. Frontal lobe function and structure in juvenile myoclonic epilepsy: a comprehensive review of neuropsychological and imaging data. **Epilepsia** 2012 Dec;53(12):2091-8).

MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY AND EPILEPSY

Investigators from the University of Catania, and other centers in Europe have identified a novel genetic glycosylation disorder, DPM2-CDG (part of the DPM synthase complex) in 3 infants with severe hypotonia, progressive muscle weakness and wasting, elevated CK, absent psychomotor development, intractable epilepsy with onset at 1 week

to 5 months, and early mortality. (Barone R, Aiello C, Race V, et al. DPM2-CDG: a muscular dystrophy-dystroglycanopathy syndrome with severe epilepsy. **Ann Neurol** 2012 Oct;72(4):550-8). (Respond: Dr Dirk J Lefeber. E-mail: D.Lefeber@neuro.umcn.nl or Dr Gert Matthijs. E-mail: Gert.Matthijs@uzleuven.be).

COMMENT. Serum N-glycosylation screening and/or enzyme analysis of DPM synthase are recommended in the workup of infants born with unsolved dystroglycanopathies.

INFECTIOUS DISORDERS

SUBDURAL EMPYEMA IN BACTERIAL MENINGITIS

Researchers at the University of Amsterdam, the Netherlands, evaluated the occurrence, treatment, and outcome of subdural empyema as a complication of community-acquired bacterial meningitis in 28 (2.7%) adults. Predisposing conditions in 26 (93%) patients included spread of otitis or sinusitis to the subdural space in 21 (75%). Presenting symptoms in 23 patients (82%) were neurologic and consisted of paresis, focal seizures, and dysesthesia contralateral to the empyema. The organism cultured from the CSF was Streptococus pneumoniae in 26 patients (93%) and Streptococcus pyogenes in 1 (3%). One patient had negative CSF cultures. Complications leading to an unfavorable outcome in 68% cases were seizures (50%), focal neurological abnormalities (54%), and hearing impairment (39%). Five patients with empyema causing midline shift were treated by neurosurgical evacuation of the empyema. (Jim KK, Brouwer MC, van der Ende A, van de Beek D. Subdural empyema in bacterial meningitis. **Neurology** 2012 Nov 20;79(21):2133-9). (Response and reprints: Dr van de Beek, E-mail: d.vandebeek@amc.uva.nl).

COMMENT. Symptoms or signs indicative of subdural empyema in adults with meningitis are otitis or sinusitis, focal neurologic deficits, or seizures. In patients suspected of having developed subdural empyema, the diagnosis was confirmed by MRI with diffusion-weighted imaging. Lumbar puncture may be associated with a risk of brain shift and sudden clinical deterioration and requires careful monitoring.

In a pediatric study of intracranial empyema at the University of Paris Descartes, 33 of 38 patients presented with subdural empyema and 5 with extradural empyema. Ten were infants <1year of age, all related to bacterial meningitis, and 28 were children mainly associated with otitis or sinusitis infections. In children with subdural empyema, factors associated with poor prognosis were neurological deficit and cerebral herniation on admission CT scan. (Legrand M, et al. **Eur J Pediatr** 2009 Oct;168(10):1235-41).

BRAIN ABSCESS FROM A PERITONSILLAR ABSCESS

Researchers at Louisiana State University, Shreveport, LA, report the case of a 9-year-old immunocompetent girl diagnosed with a left frontal brain abscess accompanied by fever, headache, and weight loss for a 3-month period. A left-sided peritonsillar abscess was the presumptive source of the brain abscess. A review of the literature

uncovered only one similar case report. (Sankararaman S, Riel-Romero RMS, Gonzalez-Toledo E. Brain abscess from a peritonsillar abscess in an immunocompetent child: A case report and review of the literature. **Pediatr Neurol** 2012 Dec;47(6):451-4). (Response: Dr Sankararaman; E-Mail: drsskumar@gmail.com).

COMMENT. Predisposing risk factors for pediatric brain abscess include congenital cyanotic heart disease, immunocompromised state, or septic foci in teeth, paranasal sinuses, middle ear, mastoid and tonsils. Cranial MRI in diagnosis of suspected brain abscess should include a possible source of infection in sections of the neck.

AAN GUIDELINE ON STEROIDS AND ANTIVIRALS FOR BELL PALSY

The Guideline Development Subcommittee of the AAN provides an update of the 2001 evidence-based practice guideline for the treatment of Bell palsy. A search of Medline and the Cochrane Database of Controlled Clinical Trials for articles published since January 2000 identified 9 studies (2 rated Class I) of patients with new-onset Bell palsy who received steroids/antiviral agents. The committee concludes as follows: 1) Steroids are highly likely to be effective and should be offered to increase the probability of recovery of facial nerve function; 2) antiviral agents in combination with steroids do not increase the probability of facial functional recovery by >7%. Antivirals may be offered in addition to steroids because of a possible modest increase in recovery, but patients should be counseled that a benefit from antivirals has not been established. (Gronseth GS, Paduga R. Evidence-based guideline update: steroids and antivirals for Bell palsy. Report of the Guideline Development Subcommittee of the American Academy of Neurology. **Neurology** 2012 Nov 27;79(22):2209-13). (Response and reprints: American Academy of Neurology. E-mail: guidelines@aan.com).

COMMENT. The committee suggests for further research, large randomized trials comparing outcomes after steroids with or without antivirals, including patients with zoster sine herpete. The optimal dose and timing of steroids and their effects in children should be determined.

MOVEMENT DISORDERS

THALAMIC METABOLISM AND RESTLESS LEGS SYNDROME

Researchers at University of Bologna, Italy, evaluated medial thalamus metabolism and structural integrity in 23 patients with restless legs syndrome and 19 healthy controls. Proton magnetic resonance spectroscopy (PMRS) disclosed a significantly reduced N-acetylaspartate creatine ratio and N-acetylaspartate concentrations in the medial thalamus of patients with restless legs syndrome compared to controls ($P<0.01$). Lower N-acetylaspartate concentrations were significantly associated with a family history of restless legs syndrome ($P=0.018$). Dysfunction of the medial thalamus and limbic system plays a role in the pathophysiology of idiopathic restless legs syndrome. In contrast, thalamic volume studies using diffusion tensor imaging, and voxel-based morphometry showed no structural thalamic changes. (Rizzo

G, Tonon C, Testa C, et al. Abnormal medial thalamic metabolism in patients with idiopathic restless legs syndrome. **Brain** 2012 Dec;135(Pt 12):3712-20). (Respond: Raffaele Lodi MD, PhD. E-mail: raffaele.lodi@unibo.it).

COMMENT. RLS is heterogeneous, some cases symptomatic of iron deficiency, uremia, pregnancy and polyneuropathy, and others idiopathic, especially patients with onset before age 30 years. Genetic risk variants have also been identified. (Paulus W, et al. Update of the pathophysiology of the restless-legs-syndrome. **Mov Disord** 2007;22 Suppl 18:S431-9).

Investigation of unmedicated early onset restless legs syndrome by voxel-based morphometry, T2 relaxometry, and functional MR imaging during the night-time hours reveals no regional brain volume changes but indicates increased iron content in the globus pallidus and substantia nigra, suggesting dysfunction of the basal ganglia. Activation of the striatofrontolimbic area may represent the neurofunctional substrate mediating RLS. (Margariti PN, et al. **AJNR Am J Neuroradiol** 2012 Apr;33(4):667-72).

HEMI-CHOREA AND BRAINSTEM GLIOMA

A case-report from Baroda Medical College, India, concerns a 9-year-old girl who complained of difficulty in walking and involuntary movements of the left upper and lower limbs. On neurological examination she had chorea involving the left side, bilateral lateral rectus palsy, and spasticity of the right upper and lower limbs. CT scan and MRI showed a focal glioma involving the upper pons and midbrain. Following surgery for removal of the tumor, hemi-chorea decreased in intensity. Histopathological examination showed a pilocystic astrocytoma grade 1. (Patankar AP. Hemi-chorea: an unusual presentation of brainstem glioma. **Br J Neurosurg** 2012 Nov 21. [Epub ahead of print]). (Response: Dr Patankar, Baroda Medical College, Vadodara, Gujarat, India).

COMMENT. Brain tumor is an unusual cause of extrapyramidal signs and symptoms. In children treated at the Mayo Clinic between 1950 and 1960, 4% of brain tumors involved the basal ganglia but <1% were associated with involuntary movements. In a report of 2 children, ages 6 and 12 years, presenting with choreiform movements and dystonia, the tumor involved the right thalamus in one and was caudad to the thalamus, in the mesencephalon and upper pons, in the other. (Millichap JG, et al. **JAMA** 1962 Feb 24;179:589-93). The localization of the lesion involved with involuntary movements often shows discrepancies, and only lesions in the subthalamic nucleus of Luys are attended by a consistent clinical disorder, usually a contralateral hemichorea or hemiballism. (Denny-Brown D, Christian HA. **Diseases of Basal Ganglia and Subthalamic Nuclei**. New York: Oxford University Press; 1946. p. 261). Tumor as a cause of choreiform disorder should be considered when the involuntary movements are progressive and are associated with cranial nerve lesions and crossed hemiparesis and/or ataxia. (Ropper AH, Adams RD, Victor M, Samuels MA, Eds. **Adams and Victor's Principles of Neurology**. 9th ed. New York: McGraw-Hill Medical; 2009).

CNS MALFORMATIONS

COWDEN SYNDROME WITH CORTICAL MALFORMATION AND EPILEPSY

Investigators at the Institute for Research on Mental Retardation and Brain Aging, Troina, and University of Naples, Italy report a case of Cowden syndrome presenting with unilateral perisylvian dysplasia and with drug resistant focal seizures. A 14-year-old girl was born with hemiparesis and at 4 months she presented with seizures. Birth weight, height, and head circumference were above the 90th centile. MRI showed a dysplastic cleft and polymicrogyria in the right Sylvian region. The left cerebellar hemisphere was enlarged with dysplastic and hamartomatous appearance characteristic of Lhermitte-Duclos disease, part of the Cowden syndrome. At 7 years of age she developed obstructive hydrocephalus with herniation of cerebellar tonsils, relieved by a VP shunt and removal of the cerebellar hamartoma, histologically a cerebellar gangliocytoma. Seizures involving left side were refractory to medications. Intestinal examination showed small duodenal polyps. PTEN sequence analysis showed a de novo missense mutation. (Elia M, Amato C, Bottitta M, et al. An atypical patient with Cowden syndrome and PTEN gene mutation presenting with cortical malformation and focal epilepsy. **Brain Dev** 2012 Nov;34(10):873-6). (Respond: Dr Marco Carotenuto, Second University of Naples, Napoli, Italy. E-mail: marco.carotenuto@unina2.it).

COMMENT. Cowden (or multiple hamartoma) syndrome, named after the first patient reported (Lloyd KM, Dennis M. **Ann Intern Med** 1963 Jan;58:136-42), is characterized by macrocephaly, intestinal hamartomatous polyps, benign skin tumors, and dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease). The occurrence of drug resistant epilepsy with Cowden syndrome is explained by an associated cortical dysplasia.

EPIDERMAL NEVUS SYNDROME ASSOCIATED WITH BRAIN MALFORMATIONS AND MEDULLOBLASTOMA

Researchers at Juntendo University and Tokyo Women's Medical University, Japan; and University of California, San Francisco, Ca, report a male infant with epidermal nevus syndrome associated with brainstem and cerebellar malformations and neonatal medulloblastoma. Macrocephaly and enlarged fourth ventricle were noted on fetal ultrasound. At birth the patient had epidermal nevi, brain malformations including polymicrogyria, dysmorphic and enlarged midbrain tectum, and enlarged cerebellar hemispheres. The patient died after surgical resection of a medulloblastoma, diagnosed on MRI at 51 days of age. At autopsy, the cerebellum had many foci of heterotopia and the brainstem showed multiple anomalies, including enlarged superior colliculi, hypoplastic pyramidal tracts and dysplasia of inferior olivary nuclei. These malformations extend the spectrum of epidermal nevus syndrome. (Okumura A, Lee T, Ikeno M, et al. A severe form of epidermal nevus syndrome associated with brainstem and cerebellar malformations and neonatal medulloblastoma. **Brain Dev** 2012 Nov;34(10):881-5). (Respond: Dr Akihisa Okumura, Department of Pediatrics, Juntendo University Faculty of Medicine, Tokyo, Japan. E-mail: okumura@juntendo.ac.jp).

COMMENT. Epidermal nevus syndrome (or Solomon syndrome) is characterized by various epidermal nevi, including ichthyosis, acanthotic, and sebaceous, mental retardation, epilepsy, ocular abnormalities, including coloboma, microphthalmos, cataracts, and skeletal, cardiac, and urogenital abnormalities. Associated abnormalities include hemihypertrophy, hemimegalencephaly, seizures, including infantile spasms, sensorineural deafness, spastic hemiparesis, kyphoscoliosis, and polydactyly. A tendency to malignant transformation of nevi and associated visceral malignancies (Wilms tumor, astrocytoma, intrathoracic teratoma) are reported. (Egan CA, et al. Neurologic variant of epidermal nevus syndrome with a facial lipoma. **Int J Dermatol** 2001 Mar;40(3):189-90).

CNS NEOPLASMS

CLINICO-RADIOLOGICAL PROFILE OF PEDIATRIC GLIOBLASTOMA

Researchers at Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India, studied the clinico-radiological profile, pathology, treatment and outcome of 65 pediatric patients (age < 18 years) with histopathologically proven diagnosis of intracranial glioblastoma. Male-to-female ratio was 2.6:1, with a mean age at diagnosis of 13.3 years (range 2-18 years). Most common presenting symptoms were headache with or without vomiting (n=51, 78%), seizures (n=42, 65%), and focal deficits (n=31, 47%). The tumor was supratentorial in 62 (95.4%) patients, frontal in 30%, and temporal in 9%; it was located deeply in 16 (25%), in the thalamus in 10 (12%). Obstructive hydrocephalus occurred in 13 (20%) patients and intratumoral bleeding in 5 (7.7%). Total tumor excision was achieved in 43 (66%) patients, and the remainder had incomplete excisions (n=22, 34%). Mean progression-free and overall survivals were 10 and 20 months, respectively; 3 patients survived for >5 years. Extent of resection was the independent predictor of survival (p=0.002). (Das KK, Mehrotra A, Nair AP, et al. Pediatric glioblastoma: clinico-radiological profile and factors affecting the outcome. **Childs Nerv Syst** 2012 Dec;28(12):2055-62). (Response: Dr Raj Kumar. E-mail: rajkumar1959@gmail.com).

COMMENT. Glioblastoma is an uncommon brain tumor in children compared to the prevalence in adults. Of all CNS tumors in children glioblastoma accounts for ~3–9%; the higher figure is that of Bailey P, Buchanan DN, and Bucy PC, in their classic study in Chicago (Bailey P, Buchanan DN, Bucy PC. **Intracranial Tumors of Infancy and Childhood.** Chicago: University of Chicago Press; 1939). The relative frequencies of the pathological varieties of intracranial space occupying lesions in children have changed over time; almost a century ago, tuberculoma was the most common lesion (Critchley M. Brain tumours in children: Their general symptomatology. **Br J Child Dis** 1925; 22:251-264).

The prevalence estimates for primary brain tumors in the United States are 35.4 per 100,000 person-years for children <20 years old and 278/100,000 for adults. (Porter KR, et al. **Neuro Oncol** 2010 Jun;12(6):520-7). The prevalence for malignant brain tumors in children is 25/100,000 and for non-malignant tumors, 11/100,000.