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FEBRILE SEIZURES

HIPPOCAMPAL SCLEROSIS AND FEBRILE STATUS EPILEPTICUS

The FEBSTAT study team of investigators determined whether febrile status epilepticus (FSE) produces acute hippocampal injury that evolves to hippocampal sclerosis. FSE was defined as a febrile seizure (FS) lasting 30 minutes or longer or repetitive FSs, lasting at least 30 minutes without regaining alertness. Acute MRI performed after FSE in 226 children aged 1 month to 6 years showed hippocampal T2 hyperintensity in 22 (10%) children, maximum in Sommer's sector, and in association with increased hippocampal volume. Follow-up MRI obtained ~1 year later on 14 of the 22 with acute hyperintensity showed hippocampal sclerosis (HS) in 10 and reduced hippocampal volume in 12. In contrast, follow-up of 116 children without acute hyperintensity showed abnormal T2 signal in only 1 (after another episode of FSE). Compared to controls with simple FS, FSE subjects with normal acute MRI had abnormally low right to left hippocampal volume ratios, small hippocampi initially, and reduced hippocampal growth. Impaired growth of normal-appearing hippocampi suggests subtle injury after FSE, even in the absence of T2 hyperintensity. The relationship of these findings to temporal lobe epilepsy requires longer follow-up. (Lewis DV, Shinnar S, Hesdorffer DC, et al. Hippocampal sclerosis after febrile status epilepticus: The FEBSTAT study. **Ann Neurol** 2014 Feb;75(2):178-85).

COMMENTARY. The combined MRI findings of increased hippocampal signal and atrophy are considered reliable indicators of HS [1]. In 1964, Falconer MA,

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neurosurgeon, and associates at Maudsley Hospital, London, UK, recorded the pathological findings in 100 consecutive surgical patients with temporal lobe epilepsy and found a possible association between mesial temporal sclerosis and febrile convulsions in childhood [2]. Sixty years later we are still uncertain of the exact relationship between temporal lobe epilepsy and febrile seizures. Multiple epileptogenic factors may be involved, including HHV6/HHV7 viremia, developmental delay, and pre-existing congenital abnormalities. It is difficult to determine whether HS predates or is the consequence of febrile seizure. As concluded in an invited commentary (Can febrile status cause HS?), the chicken or egg controversy remains unsettled [3]. Of the 9 patients (4% of 226) who developed changes suggestive of HS, 5 had other MRI abnormalities. Longer follow-up should determine the outcome and occurrence of TLE in this cohort.

References.
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2. Falconer MA, et al. Arch Neurol. 1964 Mar;10(3):233-48.
3. French JA, Kuzniecky R. Ann Neurol. 2014 Feb;75(2):173-4.

EMERGENCY TREATMENT OF FEBRILE STATUS EPILEPTICUS

The FEBSTAT study investigators reviewed the charts of 199 patients with FSE, age 1 month to 6 years, recruited from multiple centers from 2002 to 2010. More than one AED was required to terminate FSE in 140 patients (70%). Median time from seizure onset to first AED administered by emergency medical services (EMS) or emergency department (ED) was 30 min. Mean seizure duration was 81 min for subjects who received AED prior to arrival at ED and 95 min for those who did not ($p=0.1$). Median time from the first dose of AED to the end of seizure was 38 min. Initial dose of lorazepam or diazepam was suboptimal in 32 (19%) of 166 patients. Respiratory support was required by 95 subjects (48%). Median seizure duration in the respiratory support group was 83 min whereas for the nonrespiratory support group, seizure duration was 58 min ($p<0.001$). Reducing the time from seizure onset to AED initiation was significantly related to shorter seizure duration. A standard prehospital treatment protocol is recommended with education of EMS responders. (Seinfeld S, Shinnar S, Sun S, et al. Emergency management of febrile status epilepticus: Results of the FEBSTAT study. **Epilepsia** 2014 Mar;55(3):388-95).

COMMENTARY. EMS care of children participating in FEBSTAT studies varied considerably, some being allowed to administer treatment only when ordered by an ED physician. Delay in AED administration may lead to prolonged FSE and an associated increased risk of respiratory distress. Early treatment of seizures with benzodiazepines does not increase the need for prehospital or ED intubation and respiratory support [1] but rather, results in shorter total seizure duration [2].

References.
1. Alldredge BK, et al. Pediatr Neurol. 1995 Apr;12(3):213-6.
2. Seinfeld S, et al. Epilepsia. 2014 Mar;55(3):388-95.

GENETIC FACTOR IN ETIOLOGY OF FEBRILE SEIZURES

Investigators from Istanbul, Turkey, studied R43Q mutations of the gamma-aminobutyric acid A receptor (GABRG2) gene, located on the long arm of chromosome 5, in 44 children with febrile seizure (FS) and 49 without. FSs were simple in 28 (63.6%) and complex in 16 (36.4%). Heterogeneous R43Q mutation of gamma-aminobutyric acid A receptor g2 subunit occurred significantly more often in the patient group (36%) than in the control group (2%); $p<0.001$. The homozygous mutation carrier status was not different in the 2 groups. Family history of febrile convulsion and epilepsy was significantly higher in the study group than in controls ($p<0.01$). (Hancili S, Onal ZE, Ata P, et al. The GABAa receptor g2 subunit (R43Q) mutation in febrile seizures. **Pediatr Neurol** 2014 Apr;50(4):353-6).

COMMENTARY. The febrile seizure trait is inherited as a polygenic or multifactorial model or an autosomal dominant pattern with reduced penetrance [1]. Mutations of several genes have been linked to febrile seizures, including voltage-gated sodium, calcium, and potassium, and ligand-gated ion channels, nicotinic cholinergic receptor and gamma-aminobutyric acid A (GABAa) receptor. R43Q mutation of the GABAa receptor g2-subunit is involved in the cause of absence epilepsy and febrile seizure [2]. Twin studies reveal distinct genetic factors for different FS subtypes and sub-syndromes, especially FS+ [3].

References.

1. Nakayama J. Brain Dev. 2009 May;31(5):359-65.
2. Wallace RH, et al. Nat Genet. 2001 May;28(1):49-52.
3. Eckhaus J, et al. Epilepsy Res. 2013 Jul;105(1-2):103-9.

ENVIRONMENTAL FACTORS ASSOCIATED WITH FEBRILE SEIZURES

Investigators from Taichung, Taiwan, conducted a nationwide population-based retrospective study of the association between febrile seizure (FS) and allergic rhinitis. During an average 6.7 years follow-up of 1304 children with FSs, the incidence of allergic rhinitis in the FS group was higher, and after 11 years, the allergic rhinitis incidence was 4% higher than controls ($p<0.0001$). Risk of allergic rhinitis in the FS group is 1.21 times higher than in the control group, and the risk is even higher (18.9) in patients with more than 3 FS-related medical visits. Both disorders have similar cytokine profiles and viral infection association. (Lin W-Y, Muo C-H, Ku Y-C, Sung F-C, Kao C-H. Increased association between febrile convulsion and allergic rhinitis in children: a nationwide population-based retrospective cohort study. **Pediatr Neurol** 2014 Apr;50(4):329-33).

COMMENTARY. Fever and height of the body temperature as a measure of the FS threshold have an essential role in the mechanism of the FS. The cause of fever is almost always viral, most frequently HHV-6 in the United States and influenza in Japan. Some viruses have neurotropic properties, leading to the theory of a transient encephalitic

or encephalopathic process in some cases. Additional factors involved in the mechanism of the FS include a genetic susceptibility, age and maturation, and cytokine and immune response to infection [1]. The association of allergic rhinitis and FS in the present study was significantly higher in children 0.5 to 2 yrs of age (the age of susceptibility to FS), of male sex, and with frequent FS-related clinic visits. Children with FS had a higher association with other atopic comorbidities, including asthma (8.08% vs 5.62%, p=0.006) [2].

Allergies and immune reactions are proposed as factors in the etiology of FS [3]. In 1953, Dees, reporting on EEG observations in so-called "allergic epilepsy," emphasized the significance of occipital dysrhythmia in children with allergies complicated by convulsions [4]. Allergic disorders may also increase the risk of ADHD [5], and the risk of ADHD is increased in children with FS [6]. A significant association between proinflammatory cytokine, IL-1B, and both ADHD and FS may be a link in the mechanism of these disorders [6].

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4. Dees S. South Med J. 1953 Jun;46(6):618-20.
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SEIZURE DISORDERS

IV METHYLPREDNISOLONE FOR INTRACTABLE EPILEPSY

Investigators at King Abdulaziz University, Jeddah, Saudi Arabia, report their experience with IV pulse methylprednisolone in the treatment of children with severe drug-resistant epilepsy. Patients with infantile spasms, progressive degenerative, or metabolic disorders were excluded. Of 17 children aged 2-14 (mean 5.3) years, 88% had daily seizures and 13 (76%) had been admitted previously with status epilepticus. Cognitive and motor deficits were recognized in 82%. The epilepsy was cryptogenic in 47% and seizures were mixed in 41% (Lennox Gastaut in 4 (23%) and Doose syndrome in 2 (12%)). EEG showed focal or multifocal epileptiform discharges in 7 (41%) and generalized epileptiform discharges in 10 (59%). IV methylprednisolone 15 mg/kg/day, divided every 6 hours for 3 days was followed by oral prednisolone at 1-1.2 mg/kg/day once am for 1 week, then weaned slowly over 2 to 8 weeks (mean 3 wks). After follow-up for 6-24 months (mean 18), 6 (35%) became completely seizure free but 3 relapsed later, and 10 (59%) were improved. Those with mixed seizures were more likely to have a favorable response than those with one seizure type. No major side effects were noted, and 35% had improved alertness and appetite. (Almaabdi KH, Alshehri RO, Althubiti AA, et al. Intravenous methylprednisolone for intractable childhood epilepsy. **Pediatr Neurol** 2014 Apr;50(4):334-6).

COMMENTARY. A trial of add-on steroid therapy may be effective in children with intractable seizures of mixed type, apart from those with infantile spasms. Multiple

antiepileptic medications were ineffective; the ketogenic diet was unavailable in this center and had not been tried.

Of 314 children enrolled in the Far-East Asia Catastrophic Epilepsy (FACE) study group, age of onset of epilepsy was <12 months in 239 cases (80%), epileptic spasms were the most frequent seizure type (in 42%), followed by generalized tonic seizures (in 20%) [1]. Epileptic syndromes included West syndrome (in 37%), unclassified (21%), Lennox-Gastaut (12%), Dravet (4%), and Rasmussen (2%). Cortical dysplasia and chromosomal anomalies were the two most frequent causes of epilepsy, in 16% and 6%, respectively; in almost one half of patients, the cause was unknown. Psychomotor development was retarded in 62% cases.

References.

1. Oguni H, et al. Brain Dev. 2013 Sep;35(8):786-92.

PSYCHOGENIC NON-EPILEPTIC SEIZURES

Investigators at the National Institute of Mental Health and Neurosciences, Bangalore, India, conducted a retrospective analysis of semiologic patterns of psychogenic non-epileptic seizures (PNES) diagnosed by video EEG in 56 children aged < 18 years (mean age 12.3 yrs; range 2-17 yrs). Age at onset of PNES was 8.9 yrs (range 0.4-15.8 yrs); age at diagnosis 11.9 yrs (range 2-17 yrs); delay in diagnosis 3.2 yrs (range 0-15 yrs). Associated diagnoses included anxiety in 16%, stress in 10%, and depression (10%). Coexistent epilepsy in 16% patients was complex partial in 8.9%, generalized tonic-clonic in 5.4%, and simple partial in 1.8%. Prior to VEEG, 33 (59%) patients were initially misdiagnosed as epilepsy and were treated with AEDs; in 14 patients (25%) the initial diagnosis of PNES was unchanged after VEEG. EEG during a PNES showed various artifacts, depending on the type of movement or coma-like state. MRI performed in 14 patients with PNES alone was normal in 12 (86%) and showed non-specific white matter signal changes or UBOs in 2. Characteristic signs of PNES were flexion/extension movements, moaning and gasping, tremors, flaccidity, vocalization, hyperventilation, and pelvic thrusting. Eyes were closed in 25 (45%) and remained open during the PNES in 55%. The EEG technician's simple motor commands were followed by 55% during the event. PNES was classified in 5 categories: I. Abnormal motor (hypermotor (23%) and partial (14%)); II. Affective/emotional behavior 3.6% (moaning, grunting); III. Dialeptic 14% (coma-like state, flaccidity); IV. Aura 5.4% (subjective feeling, dizziness); V. Mixed (39%). (Dhiman V, Sinha S, Rawat VS, et al. Children with psychogenic non-epileptic seizures (PNES): a detailed semiologic analysis and modified new classification. **Brain Dev** 2014 Apr;36(4):287-93).

COMMENTARY. Video-EEG is important in the diagnosis and differentiation of epileptic seizures from PNES. Epilepsy and PNES are coexistent in 16% of cases. In a previous semiologic analysis of 27 childhood PNES cases based on video-EEG monitoring, mean duration of PNES was longer compared to epileptic seizures, eyewitnesses were almost always present, eyes were closed at the onset in only 15% of events, tremor was the most frequent motor sign, and dialeptic PNES was most frequent among younger children [1].

References.
1. Szabo L, et al. Epilepsia. 2012 Mar;53(3):565-70.

HUMAN METAPNEUMOVIRUS AND STATUS EPILEPTICUS

Investigators at Cincinnati Children's Hospital, OH, report 2 toddlers, ages 15 and 18 months, with human metapneumovirus (hMPV) infection who presented in status epilepticus and later developed respiratory failure. Both patients recovered over 2 weeks with no sequelae. Infection with hMPV should be considered as a cause of seizures or encephalitis with respiratory symptoms in infants and children. (Webster DL, Gardner AH, Dye TJ, Chima RS. Status epilepticus: a possible association with human metapneumovirus infection. **Pediatrics** 2014 Mar;133(3):e747-50).

COMMENTARY. Neurological complications of human metapneumovirus infection are not mentioned in the 2012 edition of the AAP Redbook [1], and a review of seizures and hMPV in PubMed uncovers few reports. One earlier study reports an incidence of 6.3% of hMPV cases associated with seizures compared to 0.7% of patients infected with RSV (p=0.031). hMPV may be associated with a spectrum of CNS disease ranging from febrile seizure to status epilepticus and severe, fatal encephalitis [2].

References.
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ENCEPHALITIDES

HERPES SIMPLEX AND NMDA ENCEPHALITIDES

Investigators at University of Texas Southwestern Medical Center, Dallas, TX, report 2 male patients, an infant and adult, with confirmed herpes simplex encephalitis (HSE) and anti-NMDA receptor antibody encephalitis. Testing for anti-NMDA receptor antibodies and autoimmune disorder is recommended in patients with persistent encephalopathy, regression after initial improvement, or persistent movement disorders. Neuronal infections such as HSV may trigger subsequent anti-NMDA receptor antibody formation. Concomitant treatment or testing for immune-mediated encephalitis is indicated when treating viral encephalitis. (DeSena A, Graves D, Warnack W, Greenberg BM. Herpes simplex encephalitis as a potential cause of anti-N-methyl-D-aspartate receptor antibody encephalitis report of 2 cases. **JAMA Neurology** 2014;71(3):344-6).

COMMENTARY. The association of herpes simplex and anti-NMDA receptor antibody encephalitides is reported in 5 prospectively diagnosed patients (2 female) with relapsing post-herpes simplex encephalitis [1]. In 3 further retrospectively studied patients with HSE and NMDAR antibodies the frequency of autoantibodies increased over time, suggesting that HSE triggers NMDAR antibodies and brain autoimmunity [1].

All prospectively identified patients were treated with a second course of IV acyclovir, and 4 received immunotherapy with improvement in 3.

References.

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CONTINUOUS EEG IN ENCEPHALITIS

Investigators from Rady Children's Hospital of San Diego, CA, reviewed records from all 217 children enrolled in the California Encephalitis Project 2004-2011. At least one seizure was observed clinically or recorded on EEG in 100 (46%) children. Diffuse slowing occurred in 88.9%, focal abnormalities in 63.2%, and epileptiform abnormalities in 57.3%. Continuous EEG for at least 1 day in 54 (25%) patients recorded a seizure in more than half of patients. In 22 (10%) children, a seizure was recorded by continuous EEG after routine EEG had failed to record a seizure. Overall, a continuous EEG was more likely to capture a seizure, capture a subclinical seizure, or rule out an event as a seizure than routine EEG ($p<0.0001$). (Gold JJ, Crawford JR, Glaser C, Sheriff H, Wang S, Nespeca M. The role of continuous electroencephalography in childhood encephalitis. **Pediatr Neurol** 2014 Apr;50(4):318-23).

COMMENTARY. Continuous EEG is an important diagnostic tool in the ICU, to identify nonconvulsive seizures or status epilepticus, aid in management of AED treatment, and to identify seizures in children with suspected encephalitis. An online survey of pediatric neurologists from 50 US and 11 Canadian institutions conducted in 2011 found the following common cEEG indications: altered mental status after status epilepticus (97%), altered mental status of unknown cause (88%). Median number of patients with cEEG per month per center increased from 6 per month in 2010 to 10 per month in 2011 in the US [1].

References.

1. Sanchez SM, et al. J Clin Neurophysiol. 2013 Apr;30(2):156-60.

BRAIN TUMORS

COGNITIVE OUTCOME OF CRANIOPHARYNGIOMA

Investigators from Carl von Ossietzky University, Oldenburg, and other centers in Germany, compared cognitive performance in a group of 15 patients with childhood craniopharyngioma and hypothalamic involvement and a group of 24 age- and intelligence-matched control subjects. IQ scores were mostly in the average range and not significantly different in patients and controls. Patients had significantly lower performance scores in tests of memory and executive functioning. Delayed recall performance was severely impaired in one-third of the patients. Compared with patients with low-grade hypothalamic involvement, those with high-grade involvement showed worse performance in executive functions and reduced functional aptitude for daily life actions. Preoperatively, only 1 patient was severely obese; postoperatively, most patients

were obese, a sign of hypothalamic dysfunction. (Ozyurt J, Thiel CM, Lorenzen A, et al. Neuropsychological outcome in patients with childhood craniopharyngioma and hypothalamic involvement. **J Pediatr** 2014 Apr;164(4):876-881).

COMMENTARY. Craniopharyngioma, a histologically benign tumor, may invade the hypothalamus, mammillary bodies, pituitary, and optic nerves. Sequelae of the tumor or its removal include visual field defects, obesity, and neurobehavioral deficits. Hypothalamic obesity in 46% of 24 cases of craniopharyngioma treated at the Phoenix Children's Hospital was refractory to current management options and accounted for increased mortality [1]. The development of obesity is influenced by premorbid obesity, genetics, and therapy received, especially radiation.

References.

1. Rosenfeld A, Arrington D, Miller J, et al. Pediatr Neurol 2014 Jan;50(1):4-10.

RISK OF FAMILIAL INTRACRANIAL ANEURYSM

Investigators at University Medical Center Utrecht, Netherlands, studied the yield of long-term (up to 20 years) screening for intracranial aneurysms in individuals with a positive family history (2 or more first-degree relatives) of aneurysmal subarachnoid hemorrhage (aSAH) or unruptured intracranial aneurysm (1993-2013). MRI or CT was performed from age 16-18 to 65-70 years. Aneurysms were identified in 51 (11%) of 458 individuals at first screening, in 21 (8%) of 261 at second screening, in 7 (5%) of 128 at third screening, and 3 (5%) of 63 at fourth screening. Five (3%) individuals with 2 negative screens had a de-novo aneurysm in follow-up screens. Smoking, history of previous aneurysm, and familial history of aneurysms were significant risk factors for aneurysms at first screening. History of previous aneurysms was the only significant risk factor for aneurysms at follow-up screening. Aneurysms were identified in 6 (5%) of 129 individuals screened before age 30 years. Long-term serial screening is advocated in individuals with a family history of aSAH. (Bor ASE, Rinkel GJE, van Norden J, Wermer MJH. Long-term, serial screening for intracranial aneurysms in individuals with a family history of aneurysmal subarachnoid hemorrhage: a cohort study. **Lancet Neurol** 2014 Apr;13(4):385-92).

COMMENTARY. Of 77 children (mean age 12 years) with 103 intracranial aneurysms treated at University California San Francisco (1981 and 2008), 25 (32%) presented with subarachnoid hemorrhage. The aneurysms were saccular in 35 (45%), fusiform in 25, traumatic in 12 patients, and infectious in 6. Treatment of 59 patients was conservative in 18. Mortality was 1.3% [1].

In a long-term study of 114 pediatric patients with aneurysms at Helsinki University, Finland, the mean patient age was 14.5 years (range 3 months to 18 years) and the male:female ratio was 3:2. The most common location was the internal carotid artery bifurcation (28%). A family history of aneurysms was present in 14 (12%) [2].

References.

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