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SEIZURE DISORDERS

RISK FACTORS FOR EPILEPSY AFTER FEBRILE SEIZURES

Investigators from Aristotle University of Thessaloniki, Greece, identified prognostic factors for subsequent epilepsy in a prospective study of 501 children with a first febrile seizure (FS). Patients were followed for a median of 5.3 years. Age at onset of FS ranged between 3 months and 5 years old (median age at onset 23 months +/- 12 months). Viral infection was the cause of the fever in 88.6% cases; bacterial infections were associated in 10.4%, and immunizations in 1%. EEG at the first episode of FS was pathologic in 105 (21%) of 501 children; 58 had generalized S/W complexes, 32 had focal epileptiform discharges (mostly centrotemporal and occipital); and 15 showed nonepileptiform abnormalities; epilepsy occurred in 4 patients with abnormal EEGs.

Epilepsy occurred in 27 (5.4%) of 501 FS patients. A median of 30 months (range 6 – 42 months) elapsed between the time of first FS and occurrence of epilepsy. Of 221 children with a first FS recurrence, 23 (10%) developed epilepsy; of 106 with a second FS recurrence, 19 (18%) had later epilepsy. Significant prognostic markers for subsequent epilepsy were as follows: 1) positive family history of epilepsy, especially maternal, 2) complex FS, 3) focal FS, 4) Todd paresis, 5) short duration of fever before FS, 6) late age at onset of FS (>3 years), and 7) multiple FSs (4 or more). Multiple FS increased the risk of epilepsy 10 times, positive family history of epilepsy 7.3 times, age at onset of FS after third year of life 3.8 times, and complex FS 3.6 times. Focality at the first and second FS recurrence increased the risk of epilepsy about 9.7 and 11.7 times, respectively. From the third FS recurrence and beyond, only focality of FS continued to have prognostic value. (Pavlidou E, Panteliadis C. Prognostic factors for subsequent epilepsy in children with febrile seizures. **Epilepsia** 2013 Dec;54(12):2101-7).

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COMMENTARY. A review of the World literature concerning febrile convulsions found 37 reports dating from 1929 to 1964, totalling 5,576 patients with febrile convulsions; a mean of 20% had frequent recurrence of afebrile seizures or epilepsy (range, 2.6% - 100%), and a mean of 27% had electrographic seizure discharges (range, 3% - 86%) [1]. The wide variations in incidence of epilepsy are explained by differences in diagnostic criteria and selection of patients. Those with short febrile seizures were mainly in prospective studies and rarely developed spontaneous seizures, whereas patients with complicated febrile seizures had often presented at a later age with epilepsy, and 17% had records of brain injury at birth [2]. In a prospective study of 110 unselected FS patients followed for ~2 years by the author, spontaneous nonfebrile seizures occurred in 17%, they were recurrent in 12%, and were frequent in 4% [3]. The duration of the FS, a factor not analyzed specifically in the Pavlidou study, and abnormal EEG were most predictive of subsequent epilepsy.

In 1706 children in the US who had experienced at least one FS and were followed to the age of 7 years, epilepsy developed in 2%. In children whose first seizure was complex febrile, epilepsy developed at a rate 18 times higher than in children with no febrile seizures. In patients with simple FS, epilepsy developed in 11 per 1000 (1.1%) [4].

In a UK national population based study of 14,676 children, 398 (2.7%) had at least one FS. The first FS was simple in 80% and complex in 20%. Epilepsy developed in 9 (2.3%), at a rate similar to that in the US [5]. The early recognition of a heightened susceptibility to epilepsy in a child with FS should lead to the introduction of seizure precautions and EEG surveillance at intervals.

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EPILEPSY COMORBIDITIES

Investigators at Children's Hospital of Pittsburgh, PA; UCLA; and Univ Wisconsin, Madison, WI, draw attention to the lack of attention to comorbidities in the treatment of epilepsy. Comorbidities include depression, anxiety disorders, ADHD, interictal psychosis, autism, and suicidal behavior. Despite studies that demonstrate the frequency of cognitive, psychiatric, linguistic, and social problems, the translation of research data to clinical practice is frequently hindered by limited access to critical cognitive and psychological evaluations and counseling. The NINDS Epilepsy Benchmarks and other national initiatives emphasize the need for comprehensive care for patients with epilepsy, yet there is a continuing lack of interest in support of these goals. (Asato MR, Caplan R, Hermann BP. Epilepsy and comorbidities – What are we waiting for? **Epilepsy Behav** 2014 Feb;31:127-8).

COMMENTARY. ADHD is a common comorbidity of epilepsy, occurring in one of 5 children with epilepsy [1]. Quality of life was impaired twofold in children with epilepsy complicated by ADHD-inattentive subtype (ADHD-I), and fourfold with

ADHD-hyperactive-Impulsive subtype (ADHD-C) comorbidity, when compared to non-ADHD/epilepsy patients. Methylphenidate with AEDs may be beneficial in treatment of ADHD and AED refractory epilepsy [2][3].

References.
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TOBACCO SMOKE, NICOTINE AND EPILEPSY

Investigators at University of South Florida, Tampa, FL, review the literature on the differences between tobacco smoke and nicotine, and their roles in causing or protecting against seizures in animal studies and in humans with epilepsy. In addition to nicotine, tobacco smoke contains many harmful constituents, including carbon monoxide, associated with increasing levels of carboxyhemoglobin (CO-Hb) in the blood, a potential cause of seizures. The level of CO-Hb in non-smokers is 1-2%, in heavy smokers 5-6%, while in patients with seizures it can be as high as 10%. Other chemicals in tobacco smoke that can trigger seizures include ammonia, lead, hexane, toluene, cresol, arsenic, and acetone. Some constituents of tobacco smoke, such as carbon dioxide, have anticonvulsant effects. Even nicotine is reported to control seizures in patients with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), the first partial epilepsy syndrome in humans caused by a single gene mutation in the nicotinic acetylcholine receptor (nAChR) gene subunits. For people with a past history of smoking, there is no association between epilepsy risk and the number of cigarettes smoked daily. The etiologies of seizures in chronic smokers are numerous, and include noncompliance with taking AEDs, and multisystem disorders such as COPD. Seizure risks are higher in acute secondhand smokers, chronic active smokers, and babies whose mothers smoke. Tobacco smoking agents can be inactive, proconvulsant, or in some cases, anticonvulsant. (Rong L, Frontera AT Jr, Benbadis SR. Tobacco smoking, epilepsy, and seizures. **Epilepsy Behav** 2014 Feb;31:210-8).

COMMENTARY. The use of a nicotine patch, gum or inhaler in the treatment of drug refractory ADNFLE is of interest, but the risk of nicotine addiction may be a contraindication. The efficacy and safety of nicotine as an anticonvulsant for severe pharmacoresistant frontal lobe epilepsy requires further study [1][2][3].

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INTRACRANIAL EEG SEIZURE-ONSET PATTERNS

Investigators at Montreal Neurological Institute and Hospital, Canada, studied intracranial electroencephalographic seizure-onset patterns associated with different epileptogenic lesions, and defined high-frequency oscillation correlates of each pattern.

MRI-documented lesions included mesial temporal sclerosis, focal cortical dysplasia, periventricular nodular heterotopia, tuberous sclerosis complex, polymicrogyria, and cortical atrophy. Seizure-onset patterns (n=7) identified across the 53 seizures sampled were as follows: low-voltage fast activity (43%); low-frequency high-amplitude periodic spikes (21%); sharp activity at -/<13Hz (15%); spike and wave activity (9%); burst of high amplitude polyspikes (6%); burst suppression (4%); and delta brush (4%). Periodic spikes were only observed with mesial temporal sclerosis, and delta brush was exclusive to focal cortical dysplasia. Otherwise, each pattern occurred across several pathologies. Compared to other patterns, low voltage fast activity was associated with a larger seizure-onset zone (P=0.04). Four patterns (sharp activity, low voltage fast, spike and wave, and periodic spikes) were also found in regions of seizure spread. Each of the 7 patterns was accompanied by a significant increase in high-frequency oscillations at seizure-onset. In periodic spikes and spike and wave activity, ripple and fast ripple densities continued to increase after seizure-onset. (Perucca P, Dubeau F, Gotman J. Intracranial electroencephalographic seizure-onset patterns: effect of underlying pathology. **Brain** 2014 Jan;137(Pt 1):183-96).

COMMENTARY. The authors conclude that (1) biologically distinct epileptogenic lesions share intracranial electroencephalographic seizure-onset patterns, suggesting that different pathological substrates can affect similarly networks or mechanisms underlying seizure generation; (2) certain pathologies are associated with EEG signatures at seizure-onset, eg. periodic spikes may reflect mechanisms specific to mesial temporal sclerosis; (3) some seizure-onset patterns (eg periodic spikes) are found in regions of spread and may not always define the epileptogenic zone; and (4) high-frequency oscillations increase at seizure-onset, independently of the pattern. Delta brush, previously described as the EEG signature of the premature infant [1], and with ANMDA encephalitis [2], the association of delta brush with epilepsy and focal cortical dysplasia appears to be a novel finding.

References.

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METABOLIC DISORDERS

FOLINIC ACID RESPONSIVE EPILEPSY IN OHTAHARA SYNDROME

Investigators at Queen Mary Hospital, Hong Kong, report a case of Ohtahara syndrome with transient folinic acid responsiveness but without evidence of antiquitin dysfunction in a girl later found to have a known STXBP1 mutation. At day 3 of life she had a cluster of epileptic spasms lasting less than 2 min. Ultrasound showed grade 1 intraventricular hemorrhage, but MRI was normal. EEG showed electrographic seizures from both frontal and anterior temporal regions without clinical seizures, unresponsive to 100mg iv pyridoxine. Seizures were controlled with phenobarbital. At day 70, the infant presented with clusters of flexion or extension epileptic spasms with generalized

myoclonic seizures not related to sleep. EEG showed burst suppression pattern, refractory to medication and typical of Ohtahara syndrome. Seizures were unresponsive to pyridoxal phosphate and AEDs. Finally, folinic acid 5 mg/kg per day was added with dramatic response. The child was seizure-free in 1 day, and the EEG showing only generalized slowing had no burst-suppression pattern 4 days later. She was seizure-free for 6 months but relapsed at 10 months of age during a febrile illness. Seizures were finally controlled with sodium valproate and clobazam, but she had severe global developmental delay. Mutation analysis of the ALDH7A1 (antiquitin) gene was negative. Mutation screening revealed a missense mutation in exon 16 of the STXBP1 gene. Analysis of parental DNA confirmed the mutation as de novo. (Tso WWY, Kwong AKY, Fung CW, Wong VCN. Folinic acid responsive epilepsy in Ohtahara syndrome caused by STXBP1 mutation. **Pediatr Neurol** 2014 Feb;50(2):177-80).

COMMENTARY. In addition to Ohtahara syndrome, STXBP1 mutations are associated with West syndrome, and learning disabilities. For Ohtahara syndrome caused by STXBP1 mutations, a trial of folinic acid is indicated. Folinic acid responsive seizures are identical to pyridoxine-dependent epilepsy, and both are caused by a-AASA dehydrogenase deficiency with mutations in the ALDH7A1 (antiquitin) gene [1]. Two patients with neonatal epileptic encephalopathy are reported whose CSF showed the marker of folinic acid-responsive seizures, but who responded to pyridoxine [1]. Treatment with both pyridoxine and folinic acid is recommended for infants with alpha-AASA dehydrogenase deficiency. The Hong Kong patient's seizures caused by mutations in the STXBP1 gene showed transient folinic acid responsiveness and no response to pyridoxine.

References.

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EARLY NEUROIMAGING IN MOLYBDENUM COFACTOR DEFICIENCY

Investigators at Wakayama Medical University, Japan, report the neuroimaging features soon after birth in 2 siblings with molybdenum cofactor deficiency (MoCoD) type A. Seizures occurred soon after birth. Brain ultrasound revealed subcortical multicystic lesions in the frontal white matter, and brain MRI at 4-24 hours after birth showed restricted diffusion on diffusion-weighted images, with severe atrophy of the entire cortex within 1 month. The corpus callosum was absent or underdeveloped in both infants. (Higuchi R, Sugimoto T, Tamura A, et al. Early features in neuroimaging of two siblings with molybdenum cofactor deficiency. **Pediatrics** 2014 Jan;133(1):e267-71).

COMMENTARY. MoCo is a coenzyme common to sulfite oxidase, xanthine dehydrogenase and aldehyde oxidase. Encephalopathy in MoCoD may result from isolated sulfite oxidase deficiency. MoCoD presents with intractable seizures in the neonatal period and MRI findings are similar to those of hypoxic ischemic encephalopathy (HIE). Since MoCoD progresses rapidly after birth, early diagnosis suspected by MRI findings can be confirmed with low plasma uric acid, positive sulfite

dipstick in fresh urine, and elevated urine and plasma s-sulfocysteine. In infants with HIE these markers are absent and the plasma uric acid is elevated. On diffusion weighted imaging within 1 week after birth, patients with HIE show an increased signal in all cortical and subcortical areas, whereas in patients with MoCoD these findings are not uniform.

In addition to HIE, infants with MoCoD may present with neonatal hyperekplexia, unresponsive to clonazepam [1], and as pyridoxine-dependent epilepsy [2]. Two siblings with pyridoxine-responsive seizures and increased urinary excretion of a-AASA were diagnosed with MoCoD and a mutation in the MOCS2 gene. A trial of pyridoxine is recommended in patients with MoCo or sulfite oxidase deficiencies [2].

References.
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DEGENERATIVE DISEASES

ALZHEIMER GENE LINKED TO BRAIN DEVELOPMENT

Investigators at Brown University, Providence, RI, and other imaging genetic centers in the US, compare MRI measurements of white matter myelin water fraction (MWF) and gray matter volume (GMV) in healthy infant carriers and noncarriers of the apolipoprotein E (APOE) e4 allele, the major susceptibility gene for late-onset Alzheimer disease (AD). Infant e4 carriers, ages 2–25 months, had lower MWF and GMV measurements than noncarriers in precuneus, posterior/middle cingulate, lateral temporal, and medial occipitotemporal regions, areas affected by AD, whereas these measures were greater in frontal regions, and an attenuated relationship between MWF and age was evident in posterior white matter regions. The study demonstrates some of the earliest brain changes associated with a genetic predisposition to AD, and the role of APOE in normal human brain development and AD pathology. (Dean DC 3rd, Jerskey BA, Chen K, et al. Brain differences in infants at differential genetic risk for late-onset Alzheimer disease: a cross-sectional imaging study. **JAMA Neurol** 2014 Jan 1;71(1):11-22).

COMMENTARY. In a comment (Alzheimer gene APOE e4 linked to brain development in infants), Drs McDonald and Krainc of Northwestern University Feinberg School of Medicine find that this study highlights compelling evidence of the influence of the APOE e4 allele on brain structure in young infants. It remains to be determined whether these neurodevelopmental observations specifically influence AD pathogenesis in later life [1]. In an editorial, Growdon JH, and Hyman BT allude to data emphasizing effects of B-amyloid on neural plasticity during brain development, a peptide elevated in Down syndrome where trisomy 21 leads to an extra copy of the amyloid precursor protein and early onset AZ [2].

A study of effect of age and APOE genotype on neuropathological changes in Down syndrome hippocampal formation found that individuals who had inherited the APOE e4 genotype contained more than twice the amyloid burden of non-carriers. The level of amyloid deposition in Down syndrome patients is higher than in sporadic AZ

disease [3]. Inheritance of the APOE e4 genotype is an independent risk factor for developing higher levels of amyloid accumulation.

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RIBOFLAVIN IN BROWN-VIALETTO-VAN LAERE SYNDROME

Investigators at Great Ormond Street Hospital, London, UK, and multiple centers internationally report the response to high-dose oral riboflavin therapy in 18 patients from 13 families with mutations in SLC5ZA2, encoding riboflavin transporter RTVT2, a new causative gene for Brown-Vialetto-Van Laere syndrome (BVVLS), a progressive neurodegenerative disorder leading to death in childhood. BVVLS is characterized by cranial neuropathies, pontobulbar palsy, sensorimotor neuropathy manifesting with sensory ataxia, weakness of upper limbs and axial muscles, with preserved strength of lower limbs, optic atrophy, sensorineural hearing loss, and respiratory insufficiency. Riboflavin therapy resulted in significant sustained clinical and biochemical improvement in 2 patients and preliminary response in 13 patients. (Foley AR, Menezes MP, Pandraud A, et al. Treatable childhood neuronopathy caused by mutations in riboflavin transporter RFVT2. **Brain** 2014 Jan;137(Pt 1):44-56).

COMMENTARY. BVVLS is a similar disorder to Fazio Londe syndrome caused by subtly different mutations of the same gene, and with the additional clinical feature of sensorineural deafness [1][2]. Diagnosis requires mutation analysis of transporter genes. The simple treatment with riboflavin supplementation may halt progression of both neurodegenerative disorders. An invited comment by Dr. John Wilson, Emeritus Chief of Neurology, Great Ormond Street Hospital, London, UK, and an authority on Fazio-Londe disease [2], is paraphrased as follows: “as our understanding of the basic concepts of disease become more complex, so we are lead to a beautiful simplicity (in the form of vitamin therapy) that brings light into dark places.” How many similar degenerative diseases may in the future be found responsive to a simple vitamin?

References.
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AUTISM SPECTRUM DISORDERS

ABNORMAL MOTOR FUNCTION AND AUTISM

Investigators from Albert Einstein College of Medicine, Bronx, NY, recorded the gait characteristics and prevalence of toe walking, the range of passive joint mobility, and age at walking in children with DSM IV autism spectrum disorders (ASDs) and in age- and gender-matched healthy peers (mean age 4 years 6 months, range 22 months – 10

years 9 months). Children with ASD had significantly greater passive joint mobility, more gait abnormalities, and walked on average 1.6 months later than their non-autistic peers. Gait abnormalities included wide-based, apraxic, posturing, clumsy and toe walking. This study indicates that ASDs affect a broader range of central nervous system circuitry than often appreciated. (Klein MS, et al. Abnormalities of joint mobility and gait in children with autism spectrum disorders. **Brain Dev** 2014 Feb;36(2):91-6).

COMMENTARY. Motor abnormalities in addition to sociability, communication, and restricted and repetitive behaviors should be examined in the clinical evaluation of a child suspected of having autism spectrum disorder. Hypotonia is commonly recorded in the neurological examination of a child with ASD. The most reliable estimation of tone is the resistance to passive movement of a limb [1]. The authors emphasize that hypotonia has multiple potential causes, and in children with ASD the relative contribution of peripheral ligamentous joint laxity, muscle disorder or central nervous system dysfunction was not determined.

References.

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SLEEP PATTERNS AND AUTISM

Investigators from University of Bristol, and other centers in the UK and Canada conducted a prospective study of sleep duration of children with an autism spectrum disorder (ASD) diagnosis at age 11 years (n=73). Parental reports of sleep duration collected by questionnaires at 8 time points from 6 months to 11 years showed that from age 30 months to 11 years, children with ASD slept for 17-43 min less each day than contemporary controls. In infancy, no significant difference in total sleep duration was apparent, but from 30 months of age, children with ASD had less nocturnal sleep than their peers. Night-time sleep duration was shortened by later bedtimes, earlier waking times and frequent waking (3 or more times a night). Age specific decreases of >1 SD in sleep duration was a predictor of ASD between 18 months and 30 months of age ($p=0.04$) and from 30 months to 42 months ($p=0.02$). (Humphreys JS, Gringras P, Blair PS, et al. Sleep patterns in children with autistic spectrum disorders: a prospective cohort study. **Arch Dis Child** 2014 Feb;99(2):114-8).

COMMENTARY. Sleep duration in children with ASD is reduced from 30 months of age and persists until adolescence. Changes in sleep patterns are most noticeable between 18 months and 3 and one half years. Children with ASD are reported to have reduced levels of circulating melatonin and disrupted circadian rhythms [1]. Melatonin should be considered in the treatment of sleep patterns in ASD children [2].

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