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SEIZURE DISORDERS

EPILEPSY AND BEHAVIOR

Investigators at Georgia Regents University, Augusta, GA, and multiple centers (25) in the USA and UK, studied the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD Study) in 195 children of pregnant women with epilepsy who had received AED monotherapy (carbamazepine, lamotrigine, phenytoin, or valproate) from 1999 to 2004. Epilepsy was localization-related in 59%, idiopathic generalized in 31%, and GTCS in 10%. Adaptive and emotional/behavioral functioning at 6 years of age were evaluated by parental and teacher completion of Adaptive Behavior Assessment System (ABAS-II) and Behavior Assessment System for Children (BASC). BASC clinical symptoms included hyperactivity, conduct, anxiety, depression, withdrawal, and attention disorders.

Adjusted mean scores for the four AED groups were in the low average to average range for parent rating of ABAS-II and for parent and teacher ratings of BASC. Children of mothers taking valproate during pregnancy had significantly lower General Adaptive Composite scores than the lamotrigine and phenytoin groups. The significant decline in performance was dose related for both valproate and phenytoin. Children exposed to fetal valproate exhibited significantly more atypical behaviors and inattention than those in the lamotrigine and phenytoin groups. BASC parent and teacher ratings of attention span and hyperactivity showed that children of mothers who took valproate during pregnancy had a significantly greater risk of a diagnosis of ADHD by age 6 years. (Cohen MJ, Meador KJ, et al. Fetal antiepileptic drug exposure: Adaptive and emotional/behavioral functioning at age 6 years. **Epilepsy Behav** 2013 Nov;29:308-315).

COMMENTARY. Cohen and associates [1] examine the behavioral effects of prenatal AED exposure, and especially valproate, on adaptive and behavioral functioning of children at age 6 years. In the NEAD prospective study of children at 3 years of age,

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fetal valproate exposure was shown to significantly impair cognitive function [2], and verbal and nonverbal abilities [3]. At the completion of the study, six-year cognitive outcome of valproate fetal-exposed children continued to exhibit significantly lower IQ than those exposed to other AEDs examined [4].

Adverse outcomes in children born to mothers with epilepsy may be caused by AEDs, maternal epilepsy, socioeconomic or genetic factors, maternal cigarette smoking, alcohol consumption, folate deficiency, or may occur by chance. Even after adjustments for these potential confounders, a follow-up study of a Danish National Birth Cohort found that preschool children exposed prenatally to AEDs had a behavioral disorder [5]; 133 children (age 4-5 years) whose mothers had received AEDs were compared to 304 unexposed and 1193 whose mothers did not have epilepsy.

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EPILEPSY AND FINE MOTOR FUNCTION

Investigators at Kocaeli University, Pediatric Neurology OP Clinic, Turkey, studied the relationship between fine motor skills and seizure and treatment parameters in 44 children with rolandic epilepsy (RE) and compared to 44 healthy controls. The children were aged 8 to 14 years, mean age 10 years, 64% males and 36% females, matched in age, gender and level of education in each group. WISC-R total scores were normal in both groups but the mean score in the RE group was lower than controls ($p<0.006$). Fine motor skills as measured by the Purdue Pegboard Test (PPT) were lower in the RE group than in controls. Epileptic focus, treatment, type of treatment, age at onset of seizures, time since last seizure, and total number of seizures did not affect motor skills. RE negatively affected fine motor skills regardless of level of IQ. (Ayaz M, Kara B, Soylu N, Ayaz AB. Fine motor skills in children with rolandic epilepsy**. Epilepsy Behav** 2013 Nov;29(2):322-5).

COMMENTARY. Although RE is regarded as a benign disorder, several reports emphasize development of cognitive, behavioral and psychiatric disorders during the active seizure phase, sometimes persisting after the epilepsy remits [1]. Early seizures in RE may interfere with brain development, causing deficits in executive function despite a normal IQ. Cognitive and behavioral abnormalities may outlast the RE [2].

Month to month fluctuations in cognitive abilities and the frequency and lateralization of interictal EEG spikes are reported, potentially impacting academic performance [3]. Clinical seizure remission was achieved 4-5 years earlier than the recovery of cognitive function. No significant correlations were found between lateralization of EEG changes and the character of the cognitive dysfunction, although age-related lateralization of focal epileptiform activity was present [4]. One study suggests that valproate, ethosuximide or levetiracetam is effective in treatment of transitory cognitive disorders [4] whereas one other found that medication and duration

of epilepsy had no significant effect on language reorganization and performance [5]. RE is associated with negative effects on fine motor skills as well as negative effects on other cognitive functions, although these may be transitory.

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HYPOXIC-ISCHEMIC ENCEPHALOPATHY AND INFANTILE SPASMS

Investigators at UCSF, British Columbia, and Toronto studied the pattern and areas of brain injury on MRI at third day of life of children with infantile spasms following neonatal hypoxic-ischemic encephalopathy (H-IE). Among a cohort of 176 term newborns with H-IE, 8 (4.5%) developed infantile spasms (hypsarrhythmia in 5 or modified hypsarrhythmia in 3). Neonatal seizures occurred in 6 (75%) patients who developed infantile spasms and in 9 (56.3%) controls that did not. Patients with infantile spasms showed no significant differences in perinatal and neonatal course when compared with 16 controls without spasms. Development of infantile spasms after neonatal H-IE was significantly associated with basal ganglia/thalamus and total brain injury (p=0.001), extent of cortical injury greater than 50% (p=0.01), injury to the midbrain (p=0.007) and hypothalamic abnormalities (p=0.01). Infantile spasms were significantly associated with medically refractory epilepsy and moderate to severe developmental delay. Spasms were diagnosed at a median age of 3.5 months (range 2-9 months); and at 3 months of age or younger in half of the infantile spasm patients. (Gano D, Sargent MA, Miller SP, et al. MRI findings in infants with infantile spasms after neonatal hypoxic-ischemic-encephalopathy. **Pediatr Neurol** 2013 Dec;49(6):401-5).

COMMENTARY. Neonatal H-IE is a relatively common precursor of infantile spasms and hypsarrhythmia. Several studies have shown that the earlier the diagnosis of infantile spasms and treatment with ACTH, the better the response and prognosis [1][2]. The MRI is of value in the early diagnosis of infantile spasms following H-IE. Injury to the basal ganglia/thalamus and total brain injury on the third day of life are significantly associated with infantile spasms and outcome, particularly in patients with extensive cortical injury and/or injury to the midbrain. Injury to the pons or medulla is not associated with development of infantile spasms [3].

The predictive value of the EEG during early infancy for later development of West syndrome in premature infants with cystic periventricular leukomalacia (PVL) is demonstrated in a study of 19 infants with EEGs recorded at 3 months of corrected age [4]. Paroxysmal discharges during early infancy are correlated with later development of West syndrome. Prolonged EEG depression at > 21 days of age in term and near-term infants with H-IE is a predictor of the later development of West syndrome [5].

In an ongoing investigation at Lurie Children's Hospital, Chicago, the predictive value of a pre-hypsarrhythmia pattern in serial EEGs during the first 6 months following

H-IE is in progress, with a view to prevention of West syndrome by early administration of ACTH [Millichap JJ, prepublication observations].

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LONG-TERM OUTCOME OF JUVENILE MYOCLONIC EPILEPSY

Investigators at Epilepsy Centers in Berlin, Germany, performed a retrospective study of seizure outcome in 66 patients with juvenile myoclonic epilepsy (JME) after a mean follow-up time of 44.6 years (20-69 years); 59.1% of patients remained seizure-free for at least 5 years before the last contact. Of seizure-free patients, 28 (71.8%) remained on AEDs and 11 (28.2%) were off medication for at least the last 5 years. Absence seizures at onset were an independent predictor of an unfavorable outcome and JME persistence. (Senf P, et al. Prognosis of juvenile myoclonic epilepsy 45 years after onset. Seizure outcome and predictors. **Neurology** 2013 Dec 10;81(24):2128-33).

COMMENTARY. JME is usually described as a chronic disorder requiring lifelong therapy [1]. In contrast, recent long-term follow-up studies point to a more favorable prognosis, allowing cautious withdrawal of medication after long seizure control [2]. In an editorial comment, a trial of older medications, including primidone and acetazolamide, is recommended in patients with refractory JME [3].

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ENCEPHALOPATHIES

ENCEPHALOPATHIC SUSAC SYNDROME

Investigators from Tubingen and Munster, Germany, report the case of a 32-year-old woman who at 32 weeks of pregnancy developed a change in personality, disorientation, ataxia, dysarthria, and hemispasticity. MRI showed multiple diffuse T2-intense lesions, many involving the corpus callosum. CSF showed mild lymphocytic pleocytosis (13 cells/mcl) and elevated protein (1,800 mg/l) and no oligoclonal bands. A bluish, net-like exanthema on trunks and legs was diagnosed as livedo racemosa. Weeks later, she was readmitted with visual field loss and ischemic damage to both retinae, and bilateral hearing loss. With a diagnosis of Susac syndrome, IV cyclophosphamide, the standard treatment, was not instituted because of risk of permanent infertility. A combination of prednisolone, IV immunoglobulins, mycophenolate mofetil, and methotrexate provided a sustained control of symptoms. (Engeholm M, et al.

Encephalopathic Susac's syndrome associated with livedo racemosa in a young woman before the completion of family planning. **BMC Neurol** 2013 Nov 25;13:185).

COMMENTARY. Susac syndrome (SS)[1] consists of a triad of encephalopathy, branch retinal artery occlusions and hearing loss. Associated abnormalities include multifocal corpus callosal lesions on MRI [2], resembling a vasculitis, and autoimmune disorder such as juvenile dermatomyositis. Headache is usually constant but was absent in the above case. Women are affected more often than men (3:1); the age of onset ranges from 7 to 72 years, but ages 20-40 are most vulnerable [3]. SS is an autoimmune endotheliopathy that responds to treatment with immunosuppressants, steroids, cyclophosphamide, and IV immunoglobulin, with aspirin as an adjunct [2][4].

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INTERFERON BIOMARKERS IN AICARDI-GOUTIERES SYNDROME

Investigators at University of Manchester, UK, and multiple international centers studied interferon-related biomarkers in patients with Aicardi-Goutieres syndrome (AGS). Of 82 patients with AGS, 74 (90%) had a positive interferon score. The measurement of an interferon score might be used to assess efficacy of anti-inflammatory therapy. (Rice GI, Forte GMA, Szynkiewicz M, et al. Assessment of interferon-related biomarkers in Aicardi-Goutieres syndrome associated with mutations in TREX1 (and any of six genes): a case-control study. **Lancet Neurol** 2013 Dec;12(12):1159-69).

COMMENTARY. Aicardi-Goutieres syndrome is an early-onset familial encephalopathy characterized by brain atrophy, microcephaly, spasticity, dystonia, psychomotor retardation, chronic CSF lymphocytosis, basal ganglia calcification, autoimmune disorders such as chilblains (pernio), and increased interferon-alpha in the CSF and serum [1][2]. High mortality in the first year is common. An early active stage of the disease followed by a period of attenuation correlates with higher levels of interferon activity in infancy and lower levels with increasing age.

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TRAUMATIC BRAIN INJURY

NEUROLOGICAL DETERIORATION AFTER MILD TBI

Investigators from UMDNJ-New Jersey Medical School, Newark, NJ, studied the cause, course, and outcomes of 757 patients who were admitted over 54 months following mild head injury (MHI) complicated by intracranial hemorrhage (ICH). Of these, 31 (4.1%) experienced delayed neurological deterioration (DND)(Glasgow Coma Scale score decrease >2); 87% deteriorated within 24 hours of admission, 68% had progressive ICH, 32% had medical causes for DND, and 23% died. Factors associated with mortality included age >60 years, coagulopathy, and change in Marshall CT classification. In adolescents and adults the incidence of DND is low but carries significant morbidity and mortality if it results from progressive ICH. (Choudhry OJ, et al. Delayed neurological deterioration after mild head injury: Cause, temporal course, and outcomes. **Neurosurgery** 2013 Nov;73(5):753-60).

COMMENTARY. This study shows that the majority (96%) of adult and adolescent patients with mild head injury plus ICH has a good prognosis and remains stable without neurological decline. In the 4% with delayed neurological deterioration, 87% deteriorated within the first 24 hours, mainly because of a progressive ICH. Coagulopathy is an important risk factor and the diagnosis and correction during transmission to a trauma center improves prognosis [1]. Since age (>60 years) is found to be a risk factor [2], children and adolescents may be expected to carry a low risk of delayed neurological deterioration. The following study, however, emphasizes a residual cognitive disability in TBI children aged 7-18 years.

Residual Cognitive Disability in Children with TBI. On admission to inpatient rehabilitation, patients with TBI had more cognitive disability than those with other injuries, and TBI patients had significant residual cognitive disability on discharge [3].

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HYPOPITUITARISM, A SEQUEL TO TBI

Investigators at Cincinnati Children's Hospital, OH, studied the prevalence of hypopituitarism in children with inflicted traumatic brain injury. Of 14 patients evaluated, 86% had at least one endocrine dysfunction, and 50% had 2 or more, a significant increase compared to the general population, estimated to have 2.5% with endocrine abnormality. Elevated prolactin occurred in 64%, abnormal thyroid in 33%, short stature (29%), and low nocturnal growth hormone peak (17%). A child with a history of inflicted TBI should be followed closely for growth velocity and pubertal changes. If growth velocity is slow, prolactin level and full endocrine evaluation are indicated. (Auble BA, Bollepalli S, Makoroff K, et al. Hypopituitarism in pediatric survivors of inflicted traumatic brain injury. **J Neurotrauma** 2013 Nov 23).

COMMENTARY. Hypopituitarism after traumatic brain injury occurs frequently in adults, whereas in children the reported prevalence is variable. In a large study of 89 adults, aged 18-65 years (mean age 36 years), hormonal function evaluated at the time of injury and at 3, 6, and 12 months postinjury showed primary hormonal dysfunction in 19 patients (21%). Major deficits included growth hormone dysfunction, hypogonadism, and diabetes insipidus. MR imaging demonstrated increased frequency of empty sella syndrome in patients with hormonal dysfunction [1].

In children, endocrine dysfunction after TBI is common, but most cases resolve by 1 year. In one study of 31 children, average age 11.6 years, the incidence of endocrine dysfunction was 15% at 1 month, 75% at 6 months, and 29% at 12 months. At 12 months postinjury, 14% had precocious puberty, 9% had hypothyroidism, and 5% had growth hormone deficiency. Endocrine dysfunction does not correlate with severity of injury [2]. In a retrospective study of 33 children with accidental head injury (27 boys), only minor pituitary hormone abnormalities were observed, unrelated to the severity of TBI, and no clinically significant endocrinopathy was identified [3].

Age of occurrence of the TBI appears to be a significant risk factor for postinjury endocrinopathy. In children and adults, endocrine surveillance at 6 and 12 months following moderate or severe TBI is recommended, but in contrast to adults, systematic screening for hormonal dysfunction in children is generally unnecessary [2][3]. A child with a history of inflicted TBI is an exception, and if on follow-up growth velocity is slowed, prolactin level and a full endocrine evaluation should be performed [4].

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DEMYELINATING DISORDERS

PROGNOSIS OF ACUTE TRANSVERSE MYELITIS

Investigators at Children's Hospital of Chongqing Medical University, China, reviewed children diagnosed with acute transverse myelitis (ATM) between 1995 and 2008 and selected 39 patients diagnosed according to the new Johns Hopkins Consortium criteria [1]. At a mean follow-up period of 102.7 months, 31 had a good outcome and 8 did poorly. Risks of poor prognosis included secondary infection, increased CSF protein, short time to maximal deficit, long time to peak neurological impairment, and initial duration of treatment. Children with these risk factors were more likely to have residual neurological deficits, resulting in lower qualities of life. Conversion to multiple sclerosis occurred in 2 patients (5.1%). Additional poor prognostic factors included flaccid paraparesis, respiratory failure, age < 6 months, and spinal shock. Good prognostic factors were a plateau shorter than 8 days, supraspinal symptoms, independent walking at <1 month, hyperreflexia and Babinski reflex. (Chen L, et al. Prognostic indicators of acute transverse myelitis in 39 children. **Pediatr Neurol** 2013 Dec;49(6):397-400).

COMMENTARY. In a follow-up study of 47 children with ATM at Johns Hopkins, Baltimore, a febrile illness had occurred in 47% and vaccination in 28%. At the nadir of the illness, 89% were unable to walk, required assisted ventilation, or both. At a median of 3.2 years after the acute illness, 43% were unable to walk 30 ft, 68% had urinary urgency, 55% had dysesthesias, and 75% had numbness. Age at onset <3 years was associated with a worse functional outcome. [2]. A longer follow-up period and effect of rehabilitation may explain the better prognosis in the Chinese study group.

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ATTENTION DEFICIT DISORDERS

DOPAMINERGIC MECHANISMS IN ADHD

Investigators at Addenbrooke's Hospital, University of Cambridge, UK, and centers in Germany and France examined the neural mechanisms underlying attention deficits associated with ADHD and their reversal with a single dose of methylphenidate (MPH). Sixteen adults with ADHD and 16 controls were scanned by PET and MR imaging while performing a computerized sustained attention task after oral MPH (0.5 mg/kg) and placebo, in a double-blind, cross-over design. Patients with ADHD showed significant attention deficits and reduced grey matter volume in fronto-striato-cerebellar and limbic networks. Compared to controls, ADHD patients had equivalent D2/D3 receptor availability and equivalent increases in endogenous dopamine after MPH treatment. Poor attention performers from both the ADHD and control groups had reduced left caudate dopamine activity. MPH significantly increased dopamine levels in all nigrostriatal regions, normalizing dopamine levels in the left caudate in low performers. Behaviorally, MPH improved sustained attention with increased dopamine release in the midbrain. Midbrain dopamine autoreceptor regulation is reduced in low performers, and MPH-induced increases in midbrain dopamine levels are smaller in low compared to high performers. The findings confer midbrain dopamine autoreceptors an important role in the therapeutic effects of MPH in ADHD. (del Campo N, et al. A positron emission tomography study of nigrostriatal dopaminergic mechanisms underlying attention: implications for ADHD and its treatment. **Brain** 2013 Nov;136(Pt 11):3252-70).

COMMENTARY. In a study at the Karolinska Institute of 12 adolescents with ADHD and 10 young adults as controls, attention and motor behavior were investigated with a continuous performance task and motion measurements. In the midbrain, the binding potential values for density of dopamine transporter (DAT) determined by PET were significantly lower in children with ADHD. Dopamine D2 receptor binding (D2R) in the right caudate nucleus correlated significantly with increased motor activity [1][2].

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