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DEMYELINATING DISORDERS

Axonal Damage in Pediatric Multiple Sclerosis

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Related Article: Pfeifenbring S, Bunyan RF, Metz I, Rover C, Huppke P, Gartner J, et al. Extensive acute axonal damage in pediatric multiple sclerosis lesions. Ann Neurol. 2015;77(4):655-67.
Keywords: Pediatric; Multiple Sclerosis; Axonal Damage

Investigators from Georg August University, Gottingen, Germany, analyzed axonal pathology in brain biopsy and autopsy samples from 19 children with early multiple sclerosis (MS). As compared to adults with MS, children present with polyfocal onset of symptoms, have a higher relapse rate during early years of the disease yet have shorter time to recovery and a higher rate of remission.

Histopathologic features of CNS biopsies (and 1 autopsy specimen) from children with pediatric MS collected over 18 years (1997-2014) at two academic medical centers were assessed and compared to features of CNS tissue from adults with MS. Nineteen of 64 pediatric specimens contained sufficient tissue sample for analysis of axonal damage. Markers of axonal injury included reduction in axonal density and presence of axonal spheroids positive for amyloid precursor protein (APP).

A 49% reduction in axonal density within demyelinating lesions in pediatric biopsies was calculated in comparison to periplaque white matter. Acute axonal damage was increased in early active demyelinating lesions in children as compared to adult biopsies and was negatively correlated with age of the subject at time of biopsy. An increased density of APP-positive axons in pediatric early demyelinating lesions was noted particularly in biopsies of children who were < 11 years of age (pre-pubertal) in whom the counts were 50% higher than those in post-pubertal or adult biopsies. Expanded Disability Status Scale at onset of the attack correlated with the number of APP positive spheroids in the biopsy. The amount of macrophage infiltration correlated with the degree of axonal injury in both pediatric and adult biopsies. [1]

COMMENTARY. The authors point out one of the potential limitations of their report: the selection bias relating to which clinical cases of CNS demyelinating disease were biopsied. In the cases with histology available, an atypical or unusual feature of presentation (clinical, imaging, or severity) had been distinctive enough to warrant biopsy to exclude an alternative diagnosis. Clinical cases in which the clinical, imaging and diagnostic parameters all cleanly fit within an expected range of findings would be diagnosed and treated without biopsy. However, the care with which these authors staged the acuity and phase of demyelinating lesions, their comparison of the axonal density within the lesion to that in the periplaque white matter and the contrast of all of these parameters with adult biopsies from clinically similar events makes these findings independently credible and important.

Other biomarkers have been noted to be different in children (particularly pre-pubertal children) with pediatric MS. CSF has been noted to have more inflammatory cells such as neutrophils and lower likelihood of oligoclonal bands or elevation in IgG index in children [2]. The authors here point out that this likely indicates prominent activation of the innate immune system as compared to the adaptive immune system post puberty. MRI in children with pediatric MS has shown an increased number and size of T2 lesions in the CNS in early disease [3].

Despite the greater degrees of acute axonal damage noted in CNS demyelinating lesions in prepubertal children, their rate of clinical recovery from clinical events is greater than in adults [2]. MR studies support this by noting a greater tendency for demyelinating lesions to "vanish" over time in prepubertal children [4].

This article begins the important process of elucidating the differences in pathophysiology of CNS demyelinating disease in children, particularly young or prepubertal children.

Disclosures

The author(s) have declared that no competing interests exist.

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TRAUMATIC DISORDERS

Vestibular Deficits Following Concussion

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Related Article: Corwin DJ, Wiebe DJ, Zonfrillo MR, Grady MF, Robinson RL, Goodman AM, et al. Vestibular Deficits following Youth Concussion. J Pediatr. 2015;166(5):1221-5.
Keywords: Pediatric; Concussion; Vestibular Deficits; Cognitive Testing

Investigators from the Division of Emergency Medicine, Sports Medicine, and Department of Pediatrics, Children's Hospital of Philadelphia, PA, and Sports Medicine, Somerset, NJ, performed a retrospective cohort study of 247 patients ages 5-18 years with concussion referred from July 2010 to Dec 2011; 81% of patients showed a vestibular abnormality on initial clinical examination. The Vestibular/Ocular Motor screening assessment includes tests for dysmetria, nystagmus, smooth pursuits, fast saccades, and gaze stability, near-point convergence, and gait/balance testing. Vestibular deficits included either abnormal vestibular ocular reflex (VOR) or abnormal tandem gait testing. Patients with vestibular clinical signs initially took a significantly longer time to return to school (median 59 days vs 6 days, P=.001) or to be fully cleared (median 106 days vs 29 days, P=.001). They scored more poorly on initial neurocognitive testing and they took longer to recover from neurocognitive deficits. Patients with 3 or more previous concussions had a greater prevalence of vestibular deficits, and it took longer for those deficits to resolve. Vestibular rehabilitation therapy is recommended. [1]

COMMENTARY. While vestibular deficits as symptoms of concussion are well recognized [2], the correlation of persistent signs of vestibular dysfunction with extended recovery times and neurocognitive deficits are not previously reported. Vestibular dysfunction is a prevalent sequel to sports and recreation-related concussions in children and adolescents, and vestibular rehabilitation is important in their management. Since recovery is often slow and prolonged, causes of vertigo and ataxia other than trauma may need to be considered in diagnosis and treatment. These include infection (otomastoiditis, labyrinthitis, vestibular neuritis, herpes zoster oticus), vertebrobasilar insufficiency, and benign paroxysmal positional vertigo. The injury to the vestibular system may be central (vestibular nuclei and cerebellum) or peripheral (semicircular canals, otoliths, vestibular nerve). The location of the injury may lead to a specific form of therapy.

Vestibular paroxysmia is a rare but treatable cause of short vertigo attacks related to arterial compression of the eighth cranial nerve. Usually found in adults, a report of three pediatric cases, ages 8, 9, and 12 years, is noteworthy. Brief, vertiginous attacks with nystagmus occurred several times a day. MRI revealed arterial compression of the vestibular nerve. Attacks were controlled by low-dose carbamazepine (2-4 mg/kg daily) [3].

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The author(s) have declared that no competing interests exist.

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VASCULAR DISORDERS

Prognosis of Neonatal Arterial Ischemic Stroke

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Keywords: Cerebral Palsy; Epidemiology; Neonate; Outcome; Stroke

Investigators from University Children's Hospitals in Bern, Zurich, Aarau, and multiple other centers in Switzerland evaluated prospectively the epidemiology, manifestations, and treatment of all full-term neonates with neonatal arterial ischemic stroke (NAIS) and born 2000-2010. The NAIS incidence in Switzerland was 13 per 100,000 live births. Median age was 2.0 days (range 1-26 days); median birth weight 3380 g (range 2370-4520 g). Of 100 neonates (67 boys) with NAIS all but 3 (97%) presented with seizures, and 50 (52%) had seizures as the only presenting symptom. Increased or decreased tone abnormalities were present in 32% and movement abnormalities in 11%; 81% had unilateral (80% left-sided) infarcts and 19% had bilateral lesions. The anterior circulation only (internal carotid, anterior cerebral, and middle cerebral arteries) was affected in 89%. Risk factors for NAIS were maternal risk conditions (32%), birth complications (68%), and neonatal comorbidities (54%). Genetic testing abnormalities included factor V Leiden mutation in 5%, heterozygous prothrombin mutation in 11%, and heterozygous methylene tetrahydrofolate reductase mutation in 36%. Seventeen percent received antithrombotic and antiplatelet therapy without serious side effects. At aged 2 years follow-up, 39% were diagnosed with cerebral palsy, 7 (9%) were treated for epilepsy (4 had infantile spasms), and 31% had delayed motor development. Children with normal mental performance at 2 years after birth may develop deficits later in life. [1]

COMMENTARY. A comparison of the incidence of NAIS in this population-based, prospective study with that in 9 previously published studies, 5 of which were population-based and 4 were hospital-based [1], the incidence varied widely from a low of 5 per 100,000 live births (a population-based study) to a high of 43 per 100,000 (a hospital-based study). The greater susceptibility of boys to NAIS is unexplained; boys and men have a higher incidence of stroke through life, and elevated testosterone levels increase the risk of cerebral thromboembolism [2].

Neonatal seizures are most commonly the clinical finding that triggers assessment in neonates with stroke. In children with NAIS without early-onset seizures, perinatal stroke is recognized retrospectively, with emerging hemiparesis or late-onset seizures presenting >14 days after the stroke. Risk factors for perinatal stroke include hereditary or acquired thrombophilia and environmental factors [3].

Disclosures

The author(s) have declared that no competing interests exist.

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VASCULAR DISORDERS

Long-term Outcome of Arterial Stroke in Children

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Related Article: Goeggel Simonetti B, Cavelti A, Arnold M, Bigi S, Regenyi M, Mattle HP, et al. Long-term outcome after arterial ischemic stroke in children and young adults. Neurology. 2015;84(19):1941-7.
Keywords: Pediatrics; Stroke; Outcomes

Investigators at University Children's Hospital, Inselspital, and Universities of Bern, Geneva, Basel, and Zurich, Switzerland compared long-term outcome of children (1 month-16 years) and young adults (16.1-45 years) with arterial ischemic stroke (AIS) using prospective data from the Swiss Neuropediatric Stroke Registry and the Adult Bernese stroke registry, between Jan 2000 and Dec 2008. Follow-up information was available in 95/116 children and 154/187 young adults. Median follow-up was 6.9 years (range 4.7-9.4). Long-term functional outcome was similar; 53 (56%) children and 84 (55%) young adults had a favorable outcome. Mortality in children was 14% and in young adults 7% (p=0.121), and recurrence rate did not differ (p=0.759). Except for more behavioral problems among children (13% vs 5%, p=0.040) and more effects of AIS on everyday life in adults (27% vs 64%, p<0.001), overall psychosocial impairment and quality of life did not differ. Low Pediatric NIH Stroke Scale/NIH Stroke Scale score was the most important predictor of favorable outcome (p<0.001). No major differences in mortality, disability, quality of life, psychological, or social variables were found in long-term outcome after AIS in children and young adults. [1]

COMMENTARY. Do children recover better from AIS than young adults? A question posed in an editorial, given the commonly held opinion among neurologists of a greater plasticity of the child's brain [2]. While commending the authors for the multiple strengths of the long-term study, they point to different interpretations of the findings. The plasticity in children might be more apparent if children are compared with older adults. The groups varied in terms of stroke etiology, a factor that may influence outcome. In the majority of patients the severity of residual symptoms did not change significantly within the year prior to follow-up. However, 23% of children and 14% of young adults reported ongoing improvements. While the study lends support to the concept of neuroplasticity, the results also introduce doubts that can be answered only by further long-term outcome studies.

Seizures are reported in 12 (15%) of 82 children and 15 (11%) of 139 young adults (p=0.403); active seizures in 1 (8%) and 1 (7%), (p=1.0). Poststroke seizures are of 2 types, early-onset (<14 days after the stroke) and late-onset (>14 days after). In a Taiwan study of 78 survivors of AIS in children aged 1 month to 18 years, 25% had early-onset seizures, and 13 (65%) of 20 survivors of early-onset seizures had late-onset seizures after the acute stage, of which 12 had post-stroke epilepsy [3]. A comparison of epilepsy following AIS in children and young adults would require records of the types of seizures and EEG.

Disclosures

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HEREDO-DEGENERATIVE DISORDERS

Risk Factors for Late Diagnosis of Rett Syndrome

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Related Article: Tarquinio DC, Hou W, Neul JL, Lane JB, Barnes KV, O'Leary HM, et al. Age of diagnosis in rett syndrome: patterns of recognition among diagnosticians and risk factors for late diagnosis. Pediatr Neurol. 2015;52(6):585-91.e2.
Keywords: MECP2; Rett Syndrome; Early Diagnosis; Prognosis; Risk Factors

Investigators at Emory University, Atlanta, GA; Stony Brook, New York; University of California, San Diego; and other centers determined the type of physician who makes the Rett syndrome (RTT) diagnosis and identified risk factors for delayed diagnosis. Among 919 classic and 166 atypical female RTT participants recruited between 2006 and 2014, the median age at diagnosis was 2.7 years (range 2.0-4.1) in classic and 3.8 years (range 2.3-6.9) in atypical RTT. Pediatricians rarely made the diagnosis of classic RTT (5.2%), but the proportion increased since 2006. Odds of a pediatrician making the diagnosis of classical RTT were higher if a child stopped responding to parental interaction, and lower if they had gastroesophageal reflux, specific stereopathies, or if they lost babbling or ability to follow commands. Earlier diagnosis was associated with delay in gross motor skills or finger feeding. Late diagnosis risk factors were delay in fine motor skills, late onset of supportive features (GE reflux, bruxism, breath-holding, hyperventilation, self-abuse) and normal head circumference; 33% with microcephaly before 2.5 years were diagnosed with RTT after the median age of 2.7 years. Age of RTT diagnosis has improved among subspecialists, and pediatricians made the diagnosis of classic RTT more frequently since 2006. [1]

COMMENTARY. Children with Rett syndrome, almost exclusively female, have delayed milestones. Regression occurs after 12 months in >90%, and is followed by phase of recovery or stagnation. A high index of suspicion between ages 6 months to 3 years, and greater awareness of the diagnostic importance of delay in advanced skills should lead to improvement in the age of diagnosis [1]. The absence of some characteristic clinical signs, especially head circumference deceleration, should not lead to delay in diagnosis. In the present study, of 83% who had microcephaly, 19% were not diagnosed until after 4.1 years. Early diagnosis is important in family planning, and emphasis on intervention services.

Epilepsy is a core symptom of Rett syndrome, occurring in 60 – 70% of patients, with uncontrolled seizures in 30% [2]. Mean age of onset of epilepsy is 4.68 +/-3.5 years, the younger age of onset correlating with severity of epilepsy. Various mutations in the MECP2 gene have a different influence on epilepsy, unrelated to the severity of the Rett phenotype. The p.R255X mutation confers an increased risk for epilepsy and severe epilepsy [2]. Attempts to correlate clinical stages of Rett syndrome with epileptic activity in the EEG have mixed results. Some typical symptoms of Rett syndrome (hand stereotypies, vacant spells) are difficult to differentiate from seizures [3]. EEG abnormalities reported in Rett syndrome patients include continuous spike and wave in slow-wave sleep [4] and diffuse paroxysmal alpha activity [5].

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ATTENTION DEFICIT DISORDERS

Indications for an EEG in a Child with ADHD

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Related Article: Zaimoglu S, Turkdogan D, Mazlum B, Bekiroglu N, Tetik-Kabil A, Eyilikeder S. When Is EEG Indicated in Attention-Deficit/Hyperactivity Disorder? J Child Neurol. Epub 2015 Apr 20.
Keywords: Attention-Deficit/Hyperactivity Disorder; Digit Span; Rolandic Spikes

Investigators at Departments of Child Neurology, Neuroscience, Biostatistics, Marmara University, Istanbul, Turkey studied the parameters for prediction of epileptiform abnormalities in the EEG of 148 children diagnosed with ADHD, according to DSM-IV criteria, aged between 6 and 13 years (mean 8.76 +/- 1.26; 25.7% female). Wake and sleep EEGs lasting about one hour were obtained in 89.2% patients and a WISC-R in 100%. The coexistence of speech sound disorder and higher Digit Span test performance predicted the occurrence of epileptiform discharges in the EEG. The prevalence of epileptiform abnormalities was 26.4%; they were frequently localized in the frontal (41%) and centrotemporal (28.2%) regions. Speech sound disorder co-occurrence (64%) with rolandic spikes suggests that the pathophysiology of epileptiform abnormalities in ADHD might be genetically determined. [1]

COMMENTARY. The utility of the EEG in a child presenting with ADHD is a frequent and sometimes hotly debated subject. The American Academy of Pediatrics (AAP), in their 2000 clinical practice guideline for diagnosis of ADHD [2], found no reliable differences between the EEG in children with ADHD and normal controls. Higher rates of abnormal EEGs in some studies lack consistency, and "the current literature is not supportive of routine EEG in the diagnosis of ADHD." Two references are provided, one showing that the EEG of children diagnosed with ADHD in psychiatry clinics in Japan, China, and Korea are significantly different from those of normal and deviant behavior groups, showing more delta and theta and fewer alpha waves [3]. A second reference to a study using quantitative EEG showed differences in the ADHD, ADD, and control groups [4]. ADHD is associated with increased fronto-central theta and theta/beta ratio compared to controls [5].

Whereas the studies in the 1990s, in agreement with the AAP guideline, are not supportive of the routine use of the EEG in diagnosis of ADHD, subsequent research regarding the utility of the EEG in the management of patients with ADHD shows that an increased susceptibility to epilepsy is sufficiently strong to warrant investigation. Of 624 records (94.5% sleep-deprived) of nonepileptic children evaluated for ADHD in our clinic and laboratory, 163 (26.8%) were abnormal, 42.9% only focal spikes, chiefly central, frontal, and temporal [6]. Seven studies, 2000-2011, found epileptiform abnormalities in an average of 25.1% of children with ADHD. The prevalence of EEG seizure discharges does not warrant a trial of AED but caution in the use of stimulants is advised. An ADHD child who exhibits episodic altered awareness or a family history of epilepsy should be considered for an EEG. The present report adds the coexistence of speech sound disorder and higher digit span to the indications for an EEG in ADHD. The 2000 AAP guidelines may require revision based on more current literature [5-7].

Disclosures

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INFECTIOUS/AUTOIMMUNE DISORDERS

Role of HHV-6B Infection in Mesial Temporal Lobe Epilepsy

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Related Article: Kawamura Y, Nakayama A, Kato T, Miura H, Ishihara N, Ihira M, et al. Pathogenic Role of Human Herpesvirus 6B Infection in Mesial Temporal Lobe Epilepsy. J Infect Dis. 2015. Epub 2015 Apr 3.
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Investigators from Fujita Health University, Toyoake, and National Epilepsy Center, Shizuoka, Japan, studied the pathogenic role of HHV-6B in patients with mesial temporal lobe epilepsy (MTLE). Of 75 intractable MTLE patients, 52 had mesial temporal sclerosis (MTS) and 23 were non-MTS patients. Resected samples of hippocampus, amygdala, and mixed samples of amygdala and uncus were examined by real-time polymerase chain reaction (PCR) and reverse-transcriptase PCR to detect viral DNA and messenger RNA (mRNA), respectively. Detection of HHV-6 DNA was higher in MTS patients than non-MTS patients. Of 9 herpes viruses analyzed, HHV-6 was the most frequently detected. DNA was determined in 12/27 HHV-6 DNA-positive samples and no HHV-6B mRNA were detected in all samples. In MTS patients, expression of monocyte chemotactic protein-1 and glial fibrillary acidic protein were significantly higher in the amygdala samples with HHV-6 DNA than those without viral DNA. The number of prolonged febrile seizures early in life was higher in the MTS patients than the non-MTS patients. HHV-6B may play an important role in the pathogenesis of MTS via modification of host gene expression. Latent infection rather than reactivation of HHV-6 probably contributes to the development of MTS. [1]

COMMENTARY. Prolonged febrile seizures or febrile status epilepticus (FSE) are associated with an increased risk of MTS and TLE, the subject of an ongoing, prospective multicenter study, the FEBSTAT study [2]. In 1964 and 1968, Falconer MA, Neurosurgeon at the Maudsley Hospital, London, UK, investigating the etiology of TLE, reported 13 (28%) of 47 cases with a history of infantile convulsions ascribed to fever [3,4]. In comparison, 7 (15%) had a history of difficult birth. As early as 1956, Cavanagh and Meyer noted the high incidence of febrile convulsions preceding onset of TLE [5]. In the recent FEBSTAT study, HHV-6B viremia is reported in 54 of 169 subjects (32%) at the time of FSE [2].

A relationship between MTS and a history of febrile seizures and HHV-6B positivity is demonstrated in the current study [1]. Further, the viral load of HHV-6B correlates with markers that reflect inflammatory injury. Neuroinflammation is recognized as a key component of epilepsy pathogenesis [6]. If HHV-6-related febrile seizures are involved in the etiology of temporal sclerosis and TLE, antivirals that penetrate the blood-brain barrier administered at a young age for treatment of prolonged febrile seizures could prevent the development of MTLE [6].

Disclosures

The author(s) have declared that no competing interests exist.

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