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SEIZURE DISORDERS

Investigations in West Syndrome: Which, When and Why

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Related Article: Wirrell E, Shellhaas, RA, Joshi C, Keator C, Kumar S, Mitchell WG and Pediatric Epilepsy Research Consortium (PERC). How should children with West Syndrome be efficiently and accurately investigated? Results from the National Infantile Spasms Consortium. Epilepsia 2015; 56: 617-625
Keywords: Infantile Spasms; West syndrome; Investigations

Investigators from the National Infantile Spasms Consortium (NISC) in the USA studied the etiology of new-onset infantile spasms (IS) in 251 infants (mean age at onset, 7.1, range, 0.1-22.7 months). The study aim was to evaluate the yield of genetic and/or metabolic investigations in the identification of an etiology of IS within three months of diagnosis when no cause had been found after an initial clinical assessment and brain MRI. Clinical evaluation and brain MRI identified a specific etiology in 138 of 250 (55%) children. Additional etiologies were identified in another 23 cases following genetic (18) and "metabolic" (5) studies. No correlation was found between type of health insurance and the genetic and metabolic testing. The NISC proposed a cost-effective workup for those children in whom initial clinical assessment and brain MRI failed to identify a cause: array comparative genomic hybridization followed by an epilepsy gene panel, and, if genetic testing is not "definitive", metabolic studies. [1]

COMMENTARY: West syndrome (WS) remains one of the most iconic but also enigmatic of the 'epileptic encephalopathies'. The focus over the past 40 years has been on treatment, and prognosis – for both the epilepsy and developmental (cognitive) outcome. Debate continues as to which is(are) the most important prognostic factor(s), particularly for developmental outcome. The principal ones are the time to diagnosis (and treatment), and the underlying cause. Most studies evaluating outcome (spasm-suppression and development) by time to diagnosis or by specific treatments have largely failed to correct by the underlying cause [2,3,4], other than in children with tuberous sclerosis complex [5] or Down syndrome [6]. Wirrell *et al.* take an interesting and refreshing approach to etiology. Overall, the results are predictable, at least to clinicians that have been managing children with WS for many years. Undoubtedly, more of the iceberg-tip of 'cryptogenic' WS will melt with advances in molecular genetics and possibly more routine higher-resolution (e.g. 5T MRI) neuroimaging. It is also likely that genetic results will be more rapidly available than the three-month census used in this study [1]. Consequently, this should improve counselling and may obviate the need for additional and potentially more invasive investigations as has been shown in Dravet syndrome [7].

The issue of the cost-effectiveness of investigations in WS is important. The cumulative cost of all potential investigations is significant, particularly for those families with no or only limited health insurance, as in the US. Despite the NHS in the UK, there is a financial impact of repeat neuro-imaging and particularly next generation sequencing (epilepsy gene panel), which though small is a contributing factor in the spiraling costs of the NHS. This will be even more relevant to developing countries.

Disclosures

The author has declared that no competing interests exist.

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SEIZURE DISORDERS

Timing of Anticonvulsant Administration in Status Epilepticus

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Related Article: Sanchez Fernandez I, Abend NS, Agadi S, An S, Arya R, Brenton JN, et al. Time from convulsive status epilepticus onset to anticonvulsant administration in children. Neurology. 2015;84(23):2304-11.
Keywords: Pediatrics; Status Epilepticus; Anticonvulsant

Investigators from the Pediatric Status Epilepticus Research Group studied the time elapsed from onset of pediatric convulsive status epilepticus (SE) to administration of antiepileptic drugs (AED). This prospective observational cohort study enrolled pediatric patients (1 month–21 years) with convulsive SE. In order to study timing of AED administration during all stages of SE, the investigators restricted their study population to patients who failed 2 or more AED classes or needed continuous infusions to terminate convulsive SE. Eighty-one patients were enrolled (44 male) with a median age of 3.6 years. The first, second, and third AED doses were administered at a median (p25–p75) time of 28 (6–67) minutes, 40 (20– 85) minutes, and 59 (30–120) minutes after SE onset. Considering AED classes, the initial AED was a benzodiazepine in 78 (96.3%) patients and 2 (2–3) doses of benzodiazepines were administered before switching to non-benzodiazepine AEDs. The first and second doses of non-benzodiazepine AEDs were administered at 69 (40–120) minutes and 120 (75–296) minutes. In the 64 patients with out-of-hospital SE onset, 40 (62.5%) patients did not receive any AED before hospital arrival. In the hospital setting, the first and second in-hospital AED doses were given at 8 (5–15) minutes and 16 (10–40) minutes after SE onset (for patients with in-hospital SE onset) or after hospital arrival (for patients with out-of-hospital SE onset). The authors concluded that the time elapsed from SE onset to AED administration and escalation from one class of AED to another is delayed, both in the pre-hospital and in-hospital settings. [1]

COMMENTARY. Current status epilepticus (SE) treatment protocols recommend a timely administration of AED doses and a rapid escalation between different classes of AED's [2]. The rationale for this recommendation includes results from clinical studies suggesting better seizure control and reduction of brain injury with earlier AED administration [3]. Results from animal models showed that prolonged SE causes brain damage [4], and the response to benzodiazepines decreases with seizure duration [5, 6]. While these data suggest the importance of rapid AED administration in SE, there is limited literature on the timeliness of AED administration in clinical practice. Additionally, there are no series that have systematically studied the time of AED administration at all stages of SE treatment. This study addresses these gaps in knowledge. In the pre-hospital setting, more than half of the patients did not receive any AED until hospital arrival. Interestingly, lack of pre-hospital AED administration also occurred in patients with a prior diagnosis of epilepsy or prior SE episode, a group in whom a plan should have been devised. Although the study does not address what causes delays in drug administration, the authors identified several areas for improvement including earlier detection and treatment of seizures, more widespread use of home rescue BZD's, and rapid escalation of AED treatment or early poly-pharmacotherapy. Their results support the implementation of policies that optimize timing and escalation of AED administration for seizures at the family, EMS, and hospital levels.

Disclosures

The author has declared that no competing interests exist.

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SEIZURE DISORDERS

GRIN1 Mutations in Early-Onset Epileptic Encephalopathy

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Related Article: Ohba C, Shiina M, Tohyama J, Haginoya K, Lerman-Sagie T, Okamoto N, et al. GRIN1 mutations cause encephalopathy with infantile-onset epilepsy, and hyperkinetic and stereotyped movement disorders. Epilepsia. 2015;56(6):841-8.
Keywords: NDMA receptors; GluN1; Epilepsy

Investigators from Yokohama City University and other medical centers in Israel and Japan reported mutations on N-methyl-D-aspartate (NMDA) receptors subunit *GRIN1* (GluN1) identified in patients with nonsyndromic intellectual disability and early-onset epileptic encephalopathy. Next generation sequencing analysis of 88 unsolved epileptic encephalopathies revealed 4 patients with 4 *de novo* missense *GRIN1* mutations. In these 4 patients, initial symptoms appeared within 3 months of birth, including hyperkinetic movements (2/4), and seizures (2/4). All developed different types of seizures during first year of life including spasms, myoclonic and focal. EEG showed nonspecific focal and diffuse epileptiform abnormality, and never showed suppression-burst or hypsarhythmia during infancy. Involuntary movements, severe developmental delay, and intellectual disability occurred in all four patients. Brain MRI images of all four patients showed cerebral cortex atrophy, and/or ventriculomegaly, and/or thin corpus callosum. Three mutations were located in the transmembrane domain, and 1 in the extracellular loop near transmembrane helix 1; all were predicted to impair the function of the NMDA receptor. [1]

COMMENTARY. Dramatic advances in next-generation sequencing technologies have led to a rapid increase in the amount of exome sequencing data, which has advanced our understanding of the genetic basis of neurologic diseases, including epilepsy. In recent years, a surprising number of missense mutations and deletions/truncations (>140) have been identified in NMDA receptors through whole exome sequencing [2]. These mutations are scattered across all domains in NMDA receptor subunits, including the *GRIN1* gene, which encodes the GluN1 subunit. Moreover, these mutations appear associated with multiple neuropathological conditions, for which epilepsy/seizures comprise the largest group [2]. *GRIN2A*/GluN2A subunit constitutes a locus for mutations in a subset of patients with early-onset epilepsy [2]. This report suggests that the *GRIN1*/GluN1 subunit may be another locus for early-onset seizures.

Despite the identification of new NMDA receptor mutations, there are still only minimal functional data available for a handful of *de novo* mutations [2]. One noteworthy example is GluN2A(L812M), which was identified in a patient with intractable seizures and early-onset epileptic encephalopathy [3]. Functional studies of this mutation suggested that a profound increase in receptor function likely contributes to the patient's phenotype. Evaluation of the potency of FDA-approved drugs that can block mutant NMDA receptors raised the possibility of personalized therapies. When the NMDA receptor channel blocker memantine was introduced into the treatment regimen for this patient, it significantly reduced seizure frequency [4]. While this effect remains to be replicated in other patients and rigorously tested in clinical trials, the example emphasizes the need and potential promise of functional analysis of the rapidly expanding list of NMDA receptor mutations revealed by gene sequencing programs for patients. Locations of the reported *GRIN1* mutants were in pre-M1 helix (D552E), M3 transmembrane domain (M641I and N650K), and M4 transmembrane domain (G815R), all which are considered as important elements/domains that are likely to influence NMDA receptor gating. We expect that future studies of the effects of these *GRIN1* mutations on NMDA receptor functions will be useful not only for clarifying molecular mechanism underlying these patients' phenotype, but also for exploring the potential targeted therapies.

Disclosures

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

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NEONATAL DISORDERS

Epilepsy Following Neonatal Seizures Symptomatic Of Stroke

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Related Article: Suppiej A, Mastrangelo M, Mastella L, Accorsi P, Grazian L, Casara G, et al. Pediatric epilepsy following neonatal seizures symptomatic of stroke. Brain Dev. 2015. Epub 2015 Jun 6.
Keywords: Stroke; Epilepsy; Neonates

Investigators from Child Neurology and Clinical Neurophysiology, Pediatric University Hospital, Padua, Italy studied the long term risk of developing epilepsy in patients with EEG confirmed neonatal seizures and arterial ischemic stroke.

This was a retrospective study where patients were recruited from a multi-center prospective registry. Patients with EEG confirmed seizures, arterial ischemic stroke confirmed by neuroimaging and follow-up $\geq$ 3.5 years were included.

55 patients from 10 centers were selected for the study. Mean gestational age was 40 weeks; 56% were males. The most frequent vascular territory involved was that of the left middle cerebral artery (49%), followed by the right middle cerebral artery (24%). Neonatal seizures occurred within the first week of life in all but 2 infants. 45% of infants had status epilepticus. Phenobarbital was an effective first-line medication in 56% of patients, while 36% needed more than one anti-epileptic drug. Phenobarbital was stopped prior to discharge in all patients. Mean follow-up was 8 years and 5 months. Development of epilepsy was noted in 16.4 % of children at a mean age of 4 years 2 months. The risk of developing epilepsy was higher with involvement of the right middle cerebral artery and multiple arterial territories. [1]

COMMENTARY. Neonatal seizures occur in 1 per 1000 live births [2]. Etiology of neonatal seizures is diverse and includes vascular injury and metabolic and genetic disorders. Previous studies have reported higher rates of epilepsy following neonatal seizures. For example, a study by Clancy and Legido showed that 56% of neonates with seizures develop epilepsy; however, their study included patients with diverse etiologies of intracranial injury [3]. There is increasing awareness of the importance of examining the etiology of seizures in predicting outcome with respect to developing epilepsy. A recent study evaluating epilepsy after hypoxic ischemic injury in selectively head cooled infants found 18 % of infants developed epilepsy and higher risk of epilepsy was associated with injury involving subcortical regions [4].

This study finds 16.4% of infants with neonatal seizures and perinatal arterial ischemic stroke developed epilepsy [1]. A retrospective study by Golomb et al., found that 67% of infants with perinatal arterial stroke developed epilepsy after 6 months of age; however, epilepsy resolved in a significant subset of patients and 25% of children with epilepsy continued to have epilepsy in longer term follow-up. Age at follow-up ranged from 9 – 179 months [5]. A retrospective study by Wusthoff et al. followed patients for a mean duration 31.3 months and found that the probability of remaining seizure-free at 3 years was 73% [6].

These studies suggest that the risk of developing epilepsy following perinatal arterial stroke is lower than previously thought. Future studies that continue to identify risk factors for development of epilepsy will allow us to implement improved vigilance, guidance and potentially preventive treatment. There are currently no guidelines on discontinuing anti-epileptic medications in neonates with perinatal arterial stroke who present with seizures. Accumulating data suggest that prolonged prophylactic therapy may not be needed in neonates.

Disclosures

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DEMYELINATING DISORDERS

Prognostic Factors of MS Conversion in Optic Neuritis

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Related Article: Heussinger N, Kontopantelis E, Gburek-Augustat J, Jenke A, Vollrath G, Korinthenberg R, et al. Oligoclonal bands predict multiple sclerosis in children with optic neuritis. Ann Neurol. 2015;77(6):1076-82.
Keywords: Optic Neuritis; Multiple Sclerosis; Oligoclonal Bands

Investigators from Children's Hospital Aschaffenburg, Germany; University of Manchester, Manchester, United Kingdom; University Children's Hospital Tübingen, Tübingen, Germany; and other international centers studied prognostic factors in optic neuritis. They retrospectively reviewed 357 children treated at 27 different hospitals presenting with isolated optic neuritis and with a median follow up of 4 years to evaluate for factors predicting eventual conversion to multiple sclerosis. Factors they reviewed included baseline abnormal MRI, presence of cerebrospinal fluid immunoglobulin G oligoclonal bands, sex, and laterality of optic neuritis (unilateral versus bilateral). They used Multiple Cox proportional-hazards regressions to identify abnormal MRI and CSF oligoclonal bands as independent predictors of conversion to multiple sclerosis, (cMRI: hazard ratio [HR]= 5.94, 95% confidence interval 3.39-10.39, $p < 0.001$; OCB: HR = 3.69, 95% CI = 2.32-5.86, $p < 0.001$), with an even higher risk when both factors were present (HR = 26.84, 95% CI = 12.26-58.74, $p < 0.001$). They also identified age as an independent risk factor, with a hazard ratio of 1.08 per year of age, 95% CI = 1.02-1.13, $p = 0.003$. They found that sex and whether the optic neuritis was unilateral or bilateral at presentation did not have any prognostic value. The authors also found that only 9 of 115 patients without oligoclonal bands and with a negative MRI developed MS within 4 years. Moreover, none of the 5 children with a final diagnosis of neuromyelitis optica had CSF oligoclonal bands during initial presentation. [1]

COMMENTARY. Although patients often improve significantly if not completely, optic neuritis in children often poses a prognostication challenge for the child neurologist. The authors of this study found a multiple sclerosis (MS) conversion rate of 40.6% after median of 4 years follow up, which is greater than prior studies have indicated, including 36% identified after two year follow up in a 2006 study [1,2]. This finding may be related to more sensitive diagnostic criteria for MS than in past studies or a change in the natural history of childhood optic neuritis and MS [1,3]. Regardless, this indicates that often, optic neuritis is not a benign self-limited event, and children who present with unilateral or bilateral optic neuritis may develop MS in the future.

Various studies have shown a benefit to prophylactic immunotherapy for adults with a clinically isolated syndrome [4], but similar data is not available for children [5]. It is then helpful for the clinician to have reliable prognostic evidence available to aid in decision making about when to initiate prophylactic treatment for MS. This study suggests that a thorough evaluation that includes CSF analysis for the presence of oligoclonal bands may be indicated in the initial evaluation of a pediatric patient presenting with optic neuritis, especially if MRI is not diagnostic of MS. Furthermore, this study reiterates the importance of following children with optic neuritis over time, with serial neuroimaging.

Disclosures

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NEURODEVELOPMENTAL DISORDERS

Cognitive Development of Children with Craniosynostosis

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Related Article: Speltz ML, Collett BR, Wallace ER, Starr JR, Cradock MM, Buono L, et al. Intellectual and academic functioning of school-age children with single-suture craniosynostosis. Pediatrics. 2015;135(3):e615-23.
Keywords: Craniosynostosis; Intelligence; Learning

Investigators from University of Washington, Seattle, WA; Harvard U, MA; St Louis, MO; Atlanta, GA; Northwestern U, and Shriner's Hospital, Chicago, compared the development of school-aged children with single-suture craniosynostosis (sagittal, metopic, unicoronal, lambdoid) and unaffected children. Tests of intelligence, reading, spelling, and math were administered in 182 case participants and 183 controls. Case participants' average scores were lower than controls on all measures. Full-Scale IQ and math computation showed the largest differences; case participants' adjusted mean scores were 2.5 to 4 points lower than those of control participants (Ps ranged from .002 to .09). Mean case-control differences on other measures of achievement (reading and spelling), partially evident at school age, were only slightly lower, but case deficits were more pronounced after adjusting for participation in developmental interventions. The frequency of specific learning problems in case and control participants was comparable; among case participants, 58% had no learning problem. Children with metopic, unicoronal and lambdoid synostosis tended to score lower on most measures than those with sagittal fusion (P<.001 to .82). In patients with single-suture fusions, neurodevelopmental screening in preschool years is especially important in those with unicoronal and lambdoid synostosis, with more selective screening of children with isolated sagittal fusions. [1]

COMMENTARY. This 10-year, multi-site study of the cognitive development of children with single-suture craniosynostosis shows that children born with the disorder are on average more likely to develop learning problems in early elementary school. Developmental delays are generally mild and vary significantly, those with unicoronal or lambdoid synostosis being most vulnerable, whereas sagittal synostosis cases, the most common variety of synostosis, are spared. Boys with single-suture craniosynostosis score lower on academic and IQ tests than girls; and males are more likely than females to have learning problems (50 vs 30%); males with unicoronal synostosis have a 86% risk of learning disorder [2].

The cause of neurodevelopmental and cognitive delay of infants with single-suture craniosynostosis remains unclear [3]. Craniosynostosis is frequently complicated by other neurological abnormalities constituting various syndromes, eg Apert syndrome (acrocephalopolysyndactyly), sometimes associated with cerebral malformation and hydrocephalus [4]. Various cognitive profiles are described in patients with Apert syndrome [5]. Other syndromes that list craniosynostosis as a major abnormality include Crouzon, Pfeiffer, Carpenter, Jackson-Weiss, Saethre-Chotzen, Beare-Stevenson, Vogt, Waardenburg, and Muenke syndrome. The characteristics of Muenke syndrome are a unilateral coronal craniosynostosis with anterior plagiocephaly, asymmetry of skull and face, developmental delay and learning disorder. This unilateral craniosynostosis is explained by a mutation in the gene FGFR3 [6].

Disclosures

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

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INFECTIOUS/AUTOIMMUNE DISORDERS

Clinical Features of NMDAR Ab-mediated Encephalitis

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Related Article: Wright S, Hacohen Y, Jacobson L, Agrawal S, Gupta R, Philip S, et al. N-methyl-D-aspartate receptor antibody-mediated neurological disease: results of a UK-based surveillance study in children. Arch Dis Child. 2015;100(6):521-6.
Keywords: NMDAR Ab; Encephalitis; Steroids; Immunoglobulin; Plasma Exchange

Investigators from University of Oxford, Birmingham Children's Hospital, Guy's and St Thomas', London, UK, performed a prospective surveillance study in children with NMDAR-Ab-mediated neurological disease reported from Nov 2010 to Dec 2011. Over the study period (13 months) 1526 email responses were received from 171 clinicians reporting 33 known and 10 new cases. The incidence was calculated at 0.85/million children/year. The majority of patients were female (23/31, 74% with a median age of 8 years (range 22 months-17 years). Male patients were older (median 11 years, range 6-17 years, p=0.03). None had a family history of autoimmune disease. Behavioral change and neuropsychiatric features were present in 90% of the 31 children who fulfilled selection criteria. Seizures and movement disorders each occurred in 67%. EEG was encephalopathic in 28/30 (93%); extreme delta brush was not recognized. CSF showed pleocytosis in 45%; 67% had oligoclonal bands. Antibodies detected included antistreptolysin O, IgM Epstein-Barr, antinuclear, antibasal ganglia, and voltage-gated potassium channel-complex. MRI was normal in 65% and showed high signal changes in cortical and subcortical areas in 23%. Typical NMDAR-Ab encephalitis was reported in 24 children and a partial phenotype without encephalopathy in 7. Autonomic features included cardiac arrest in one and hypoventilation in 3. Steroids were prescribed for all patients, 22 (71%) received IV immunoglobulin, 9 (29%) received plasma exchange, and 10 (32%) received second-line immunotherapy. Of 23 diagnosed early, 18 (78%) made a complete recovery compared with only 1 of 8 (13%) diagnosed late (p=0.002). Seven patients relapsed with 4 needing additional second-line immunotherapy. One (1 of 31, 3%) patient diagnosed late, after 6 months, responded to initial immunotherapy and was subsequently diagnosed and treated for ovarian teratoma with no relapse. [1]

COMMENTARY. Pediatric NMDAR-Ab encephalitis often presents with neurological rather than psychiatric symptoms, the more common presentation in adults with the disease. Patients diagnosed and treated early with immunotherapy have a better prognosis than those treated late [1]. Anti-NMDAR Abs in CSF is the diagnostic marker for NMDAR encephalitis, and the diagnosis may be supported by the EEG pattern "extreme delta brush."[2]. This pattern named because of its resemblance to the EEG of premature infants is reported in 30% of adult patients with NMDAR encephalitis. Extreme delta brush is associated with more severe neurological/behavioral symptoms, prolonged hospitalization and increased days of cEEG monitoring.

In pediatric patients with behavioral disorders and abnormal movements, early EEG patterns may be suggestive of anti-NMDAR encephalitis. Consecutive polygraphic video-EEG recordings in 9 children with NMDAR encephalitis were analyzed and in 6 patents, the waking EEG showed preserved background activity and either focal or unilateral hemispheric slowing. The outcome with focal EEG slowing was more favorable than in the 3 children with diffuse slowing. Unilateral abnormal movements contralateral to the hemispheric slowing were also indicative of milder clinical severity when compared with generalized abnormal movements and diffuse slowing [3].

Disclosures

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

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