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NEUROCUTANEOUS SYNDROMES

Predictive Power of EEG in Infants with Tuberous Sclerosis

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Related Article: Wu JY, Peters JM, Goyal M, Krueger D, Sahin M, Northrup H et al. Clinical Electroencephalographic Biomarker for Impending Epilepsy in Asymptomatic Tuberous Sclerosis Complex Infants. Pediatr Neurol 2016 Jan;54:29–34.
Keywords: Epileptic Spasms; EEG; Tuberous Sclerosis

Investigators from University of California- Los Angeles and collaborators from across the country report on the use of prospective EEGs in infants with tuberous sclerosis complex (TSC) to predict evolution to seizures. They prospectively enrolled infants with TSC in an observational study which included regularly scheduled exams and research one-hour video EEGs. These infants were diagnosed on the basis of clinical features (i.e. cardiac rhabdomyomas, intracranial MRI findings, skin findings) or genetic diagnosis. The infants were younger than 7 months at enrollment, were seizure free, and had not been treated with TS specific medications (vigabatrin or inhibitors of the mammalian target of rapamycin [mTOR].) If the child developed seizures, EEG was performed to confirm the diagnosis and an appropriate anti-epileptic drug was initiated. This was an interim publication of findings, with 28/40 enrolled patients older than a year at the time of analysis. Of those, 19 (67.8%) had developed seizures, with epileptic spasms being the most frequent seizure type (52.6%.) All children with epileptiform discharges on EEG went on to develop epilepsy (100% positive predictive value). [1]

COMMENTARY. This study suggests that serial EEGs may be used as a biomarker for subsequent epilepsy in infants with early diagnosis of TSC [1].

TSC is an autosomal dominant hamartomatous condition affecting various organ systems, but most consistently presenting with CNS symptoms. These may include epilepsy (85%), intellectual disability or other neuropsychiatric condition. The genes implicated code for hamartin and tuberin (TSC1 and 2), which control cell proliferation through mTOR pathways in cells. CNS lesions may include subependymal nodules, cortical tubers, and subependymal giant cell astrocytomas. Cardiac rhabdomyomas may be detected on second trimester ultrasounds and lead to prenatal diagnosis. Renal angiomyolipomas and renal cysts are also prevalent. Two-thirds of infants with TSC develop seizures before a year of age, and earlier seizures lead to more significant neuropsychiatric sequelae [2].

Increased mTOR activity is believed to increase epileptogenicity in multiple ways, including leading to dysplastic neurons, abnormal astrocytes, loss of normal cortical structure, abnormal dendritic arborization, decreased GABAergic inhibition and increasing glutamatergic excitation. Because of specific effects of GABA systems and some inhibition of mTOR signaling pathways, vigabatrin is first line treatment for infantile spasms and focal seizures in TSC patients before a year of age. Early diagnosis of seizures and initiation of vigabatrin is particularly important for intellectual development and achieving seizure control [3]. The referenced article from Wu et al suggests that interictal epileptiform discharges may be detectable prior to seizure onset in many children with TSC and their presence reliably predicts the later development of seizures [1]. In the future mTOR inhibitor treatment may be initiated when EEGs indicate epileptogenicity and prior to seizure onset to improve neurodevelopmental outcomes and long-term prognosis of epilepsy in patients with TSC, however studies are still in progress [4].

Disclosures

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

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NEUROCUTANEOUS SYNDROMES

Visual Processing in Infants with Tuberous Sclerosis Complex

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Related Article: Varcin KJ, Nelson CA 3rd, Ko J, Sahin M, Wu JY, Jeste SS. Visual Evoked Potentials as a Readout of Cortical Function in Infants With Tuberous Sclerosis Complex. J Child Neurol 2016 Feb;31(2):195–202.
Keywords: VEP; Tuberous Sclerosis Complex; Visual Processing

Investigators from Harvard University and UCLA have reported that despite evidence of structural abnormalities in the visual pathway of animal models and children with tuberous sclerosis complex (TSC), visual evoked potentials (VEPs) in 12-month old children with TSC compared to an age-matched control group are not significantly altered. This study is motivated by the high rates of autism spectrum disorder in children with TSC, which the authors posit may be due to delayed visual processing.

This multisite, longitudinal case-control study compares 16 infants with TSC (including a majority with retinal hamartomas, occipital tubers, and intractable epilepsy on vigabatrin) to 18 "typically-developing infants." Infants were presented a black and white phase-reversing checkerboard during which visual fixation was tracked, and 50-100 trials were recorded. Peak amplitude and latency of the N1, P1, and N2, the primary components of the visual evoked potential, were measured and were found to be not significantly different in a non-parametric analysis. [1]

COMMENTARY. This paper seeks to identify an early and easily-tested surrogate for neurodevelopmental impairment in children with TSC, as increased rates of autism in the TSC population suggest the increased prevalence in this population might warrant early therapeutic interventions in the future if possible. In Drosophila lacking *TSC1* in the retina, both the photoreceptor layer itself and the axon bundle are severely disrupted [2]; similarly, *TSC2* gene mutation leads to enlarged photoreceptor and support cell units (ommatidia) with failure to prune synaptic connections [3]. Further study of heterozygous *TSC2* mice has implicated ephrin-EphA receptor signaling in abnormal development of retinogeniculate connections [4], presumably through activation of the mTOR pathway via ERK1/2 inhibition and thus *Tsc2* activation. When taken in the context with studies of patients with TSC showing that a delay in nonverbal ability, primarily visual processing, was an early biomarker for cognitive impairment [5], the authors' hypothesis that visual connectivity is altered early in life in TSC is logical and warrants further testing.

As measurement of a visual evoked potential (VEP) surveys the visual pathway from retina to primary visual cortex, any aberration in synaptic connectivity along this pathway would be expected to impact latency or amplitude in a population-based fashion. VEPs would also prove useful in a clinical setting, as infants with limited ability to cooperate could be tested at different age intervals. However, despite known MRI abnormalities in the occipital region and concurrent diagnosis and treatment of an epileptic encephalopathy, infants in this study did not manifest any systematic difference in VEPs. Potential explanations for this interesting yet unexpected negative finding include the level of visual processing studied - for example, while a previous study noted specifically a deficit in face processing in individuals with TSC [6], this higher-order deficit would not be obvious on VEP. Replication of these results at other developmental stages, for example as autistic behaviors or learning disabilities become more clinically apparent, would also provide valuable information. Nevertheless, the idea that the minimal visual substrate is intact in symptomatic TSC infants represents an important observation in understanding the nature of deficient visual processing.

Disclosures

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

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NEUROCUTANEOUS SYNDROMES

Diffusion Tensor Imaging of Epileptogenic Lesions in TSC

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Related Article: Yogi A, Hirata Y, Karavaeva E, Harris RJ, Wu JY, Yudovin SL et al. DTI of tuber and peritubeal tissue can predict epileptogenicity in tuberous sclerosis complex. Neurology 2015 Dec;85(23):2011–5.
Keywords: Surgical Epilepsy; Tuberous Sclerosis; Diffusion Tensor Imaging

Investigators from University of California Los Angeles, studied whether epileptogenic tubers in Tuberous Sclerosis Complex (TSC) can be identified by diffusion tensor imaging (DTI). The group used retrospective analysis of 23 pediatric patients with TS who underwent epilepsy surgery. This population had extensive pre-operative data including video EEG, MRI, and PET scans. MRI and PET data were co-registered. Magnetic dipoles were also identified in some patients. Surgical decisions were made by a multidisciplinary group that included epileptologists, neurosurgeons, neuroradiologists and psychologists. Tubers were considered epileptogenic if there was a "meaningful reduction" in seizure frequency after resection.

By using specific diffusion tensor parameters such as axial diffusion (AD), apparent diffusion coefficient (ADC), fractional anisotropy (FA) and restricted diffusivity (RD) the authors show a difference in diffusivity values between epileptogenic and non-epileptogenic regions, specifically for ADC and RD. The methods used include an expanded area beyond the tuber itself, termed the "peri-tubular" region, which also shows a significant difference in ADC and RD from non-epileptic pre-tubular regions. Finally, receiver-operator curves were used to establish tuber+peritubular cutoff values for both ADC and RD. Together these imaging findings across 543 tubers, of which 6% were epileptogenic, indicate a potential method for delineating epileptogenic sites in tuberous sclerosis. The study is limited in that it is a retrospective analysis of patients who underwent surgery, and does not discuss the potential epileptogenicity of tubers in non-surgical candidates. [1]

COMMENTARY. TSC is a multi-lesional epileptic disorder, in which not all tubers are epileptogenic. Identifying epileptogenic surgical candidate lesions is critical for any chance of seizure freedom. Current imaging methods that are used in conjunction with electrophysiology include MRI, fMRI, PET, SPECT and MEG. Of these methods, MRI is the most widely available.

The current pre-surgical identification of epileptogenic loci includes a gold standard of intracranial EEG, although this is not routine for TSC due to limited capabilities at surgical centers [3]. FDG-PET and magnetic source imaging may be utilized for pre-surgical evaluation, but both are highly specialized tests with limited availability, even for epilepsy surgical centers [4,5].

DTI is a powerful MRI tool that uses the movement of water molecules to describe three dimensional aspects of white matter tracts and intracranial structures in more detail than standard MR images [2]. DTI holds promise as a method for better evaluation of three dimensional structures like the tubers of TSC. In particular, a long-standing controversy in TSC is whether the tuber alone is epileptogenic or whether the peritubular region also has epileptogenicity [3].

A multi-disciplinary approach to TSC surgery remains the optimal and safest route to surgical planning, given that no single method adequately proves epileptogenicity of tubers. Although still investigatory, the findings presented by Yogi A. et al [1] are promising in that a widely available methodology may at some point be applicable for pre-surgical evaluation.

Disclosures

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

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SEIZURE DISORDERS

Language after Hemispherotomy in Rasmussen Syndrome

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Related Article: Bulteau C, Grosmaitre C, Save-Pédebos J, Leunen D, Delalande O, Dorfmüller G et al. Language recovery after left hemispherotomy for Rasmussen encephalitis. Epilepsy Behav 2015 Dec;53:51–7.
Keywords: Rasmussen Syndrome; Hemispherotomy; Hemispherectomy; Language

Investigators from Rothschild Foundation Hospital in Paris report language outcome in children after (left) dominant-hemisphere hemispherotomy for Rasmussen Syndrome. Six children underwent surgery at ages 4.1 to 8.4 years. Preceding duration of epilepsy was short, mean of 1.2 years. Four experienced pre-operative aphasia with decreased verbal comprehension indices (VCI) (4/6) and performance reasoning index (5/6). Mean duration of follow-up was 5.6 years. Longitudinal follow-up of cognition and speech is reported. Post-operatively VCI normalized over 3-8.3 years. The authors describe a specific linguistic profile: normal verbal comprehension, and weakness of grammatical judgment, word repetition, statement production, semantic verbal fluency and metaphonological abilities. Working memory scores were also weak, though not meeting statistical significance.

The authors suggest this study emphasizes the ability of the right hemisphere to functionally reorganize language over a long period of time following surgery, support decision making toward hemispherotomy in left-sided Rasmussen syndrome and can aid post-operative follow-up and rehabilitation strategies. [1]

COMMENTARY. Rasmussen syndrome is a rare chronic progressive neurological disease of presumed immune basis characterized by unilateral inflammation and atrophy of a cerebral hemisphere, drug-resistant focal epilepsy, progressive hemiplegia and cognitive decline [2]. To date medical therapies are imperfect and can but alleviate symptoms. Only surgery, specifically hemispherotomy (disconnection of the affected hemisphere) halts the disease. Surgery gives a high chance of seizure freedom (70-80%) and cognitive stabilization, but at the cost of inflicting hemiplegia, homonymous hemianopia and in language-dominant hemisphere disease, aphasia. These deficits may be present preoperatively, with variable severity and alacrity. Children adapt to hemianopia, walk again though with an ankle splint, but do not recover upper limb fine-motor function. Though it is known that language function can be sub-served by one non-dominant hemisphere alone, decisions around timing of surgery with regard to language recovery are more difficult.

Careful pre-operative neuropsychological testing and in the cooperative child language functional MRI can lateralise language, making Wada testing, long deemed the gold-standard, no longer essential. Interval imaging may show transfer/re-localisation of language dominance to the contra-lateral hemisphere over the disease course, giving the epilepsy surgery team more confidence in the prospects of post-hemispherotomy language recovery and more confidence to proceed. Earlier onset seizures may increase the chances of this transfer but it is not known if earlier surgery could better drive this at a younger age with more retained neural plasticity, or whether it is better to allow function to become established naturally in the unaffected hemisphere, accepting that cognitive decline proceeds inexorably [3].

The present study is encouraging; all children regained speech and long-term follow-up demonstrated on-going language recovery. Rehabilitation is essential after surgery and the patterns of language recovery delineated here can also inform therapy programs and goal-setting. Further, the parallel to the cognitive gains 5-years out from temporal lobe surgery, remind us the importance of long-term follow-up studies in informing our decision-making in the acute disease setting [4].

Disclosures

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

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GENETIC DISORDERS

Clinical and Molecular Characterization of ALG1-CDG

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Related Article: Ng, BG., Shiryaev, SA., Rymen, D., Eklund EA., et al. ALG1-CDG: Clinical and Molecular Characterizattion of 39 Unreported Patients. H Mutat. 2016 March 2. [Epub ahead of print].
Keywords: Asparagine-Linked Glycosylation Protein 1; CDG; Carbohydrate-Deficient Transferrin; Xeno-Tetrasaccharide

Investigators from the Human Genetics Program, Sanford Burnham Prebys Medical Discovery Institute, La Jolla, California and a large study group utilized a combination of exome sequencing, targeted gene panels, and Sanger sequencing to identify thirty-one pathogenic variants in thirty-nine affected individuals with ALG1-CDG from 32 families. Congenital disorders of glycosylation (CDGs) cause impaired synthesis of glycoconjugates and are genetically heterogeneous with pathogenic variants in over one hundred genes that can cause it. ALG1 mutations cause a rare autosomal recessive disorder called ALG1-CDG. Of the thirty-one pathogenic variants reported, twenty-two (65%) are novel variants. This study has tripled the number of known patients with ALG1-CDG.

Pathogenicity of each mutation was confirmed based on its inability to rescue impaired growth or hypoglycosylation of a standard biomarker in an alg1-deficient yeast strain. ALG1-CDG patients are known to accumulate a novel N-linked xeno-tetrasaccharide. Since this tetrasaccharide does not normally occur in mammals and is primarily detected in ALG1-CDG cases, it serves as a biomarker for either detecting or confirming a diagnosis of ALG1-CDG. This biomarker was identified in all 27 patients tested.

This study also expands the clinical phenotype of ALG1-CDG patients. All ALG1-CDG patients have substantial neurological involvement; however other systems are variably affected. Several factors may cause this variability, including how ALG1 mutations affect residual mannosyltransferase activity or GDP-Man binding efficiency, complex formations with other proteins, tissue specific expression, or even protein stability. [1]

COMMENTARY. Congenital disorders of glycosylation are a group of predominantly autosomal recessive diseases with multi-system affects ranging from developmental delay and hypotonia with multiple organ system involvement to hypoglycemia and enteropathy [1]. Congenital disorders of N-linked glycosylation are of two types. Type I involve defects in either the synthesis or transfer of a dolichol lipid – linked oligosaccharide to proteins in the endoplasmic reticulum while type II result from golgi dependent processing of protein bound oligosaccharide. The most common type of CDG is PMM2-CDG, while the other types are rarer. The screening test for almost all types of CDG-N-linked is transferrin isoform analysis; however molecular testing is needed for confirmation [2,3]. Next generation sequencing technology (NGS) has enabled novel disease gene discoveries and was used in this study to identify cases with this are disorder (ALG1-CDG).

The clinical features in this group of 39 patients included developmental delay, hypotonia, epilepsy, microcephaly, cerebral and cerebellar atrophy, strabismus, dysmorphic facial features, gastrointestinal abnormalities and hypoalbuminemia [1]. Thus a diagnosis of CDG's should be considered in a child presenting with developmental delay and multi-system organ involvement. For genetically and phenotypically heterogeneous disorders like CDG's, targeted panel based sequencing should be done if the screening transferrin isoform analysis is abnormal. If negative, it can be followed by exome sequencing to increase the diagnostic yield. This principle has helped find a genetic basis in a variety of undiagnosed neurological disorders in a cost effective manner. This approach also helps overcome some unique diagnostic challenges in CDG's such as: genetic heterogeneity (large number of causative genes) and phenotypic heterogeneity (multiple genes with overlapping) [1-3].

Disclosures

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

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ATTENTION DEFICIT DISORDERS

ADHD as Sequel to Acute Disseminated Encephalomyelitis

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Keywords: Attention-Deficit Hyperactivity Disorder; Acute Disseminated Encephalomyelitis; Behavioral Problems; Learning Disabilities

Investigators from Ruth Children's Hospital, Haifa, and Schneider Medical Center, Petah Tikuah, Israel, evaluated the long-term motor and neurocognitive outcome of 43 children hospitalized during 2002-2012 with acute disseminated encephalomyelitis (ADEM), and identified prognostic risk factors. Patients were treated with IV methylprednisolone 30 mg/kg for 3-5 days, followed by oral corticosteroids. Full neurological examinations and comprehensive neurocognitive and behavioral assessments identified different degrees of neurological sequelae in 26 children (61%) after a mean follow-up of 5.5 +/-3.5 years. Persisting symptoms occurred in 44%. The most common residual impairments included attention-deficit hyperactivity disorder (44%), behavioral problems (32%), and learning disabilities (21%). A full-scale IQ of 70 or less was found as a sequel to ADEM in five (12%) children, compared to 2.2% in the general population. Neurocognitive sequelae were found even in children considered fully recovered at time of discharge. The EEG performed in 16 patients was abnormal in 12 (75%); epilepsy developed in only 3 patients (7%). MRI revealed cortical and subcortical hemispheric lesions in 49% of patients, basal ganglia and thalamus in 31%, brain stem in 26%, spinal cord in 20%, and cerebellum in 15%. Complete resolution on follow-up MRI was found in 65% and partial resolution in 35%. Risk factors for severe neurological sequelae and poor long-term outcome were older age at presentation (p=0.025) and male gender (p=024). Neuropsychological testing and long-term follow-up is recommended for all children with ADEM, even in those with no neurological deficits at discharge. [1]

COMMENTARY. The cause of ADHD is highly genetic and involves the dopamine receptor and transporter genes. Environmental factors are also important and a gene-environmental interplay is frequently recognized [2]. Among acquired environmental etiologies for ADHD, viral infections linked to an increased risk of ADHD include measles, varicella, rubella, HIV, and enterovirus [2]. ADEM is uncommon. Apart from the above Israel study, only one similar study is listed in Pubmed. This involves 19 patients (10 with ADEM before the age of 5 years), reported from Australia. A brief neuropsychological assessment of children with ADEM compared to 19 controls showed that those with ADEM admitted before 5 years of age were particularly vulnerable to impairments in both cognitive and social domains, and had higher incidence of severe behavioral and emotional problems [3]. A further patient with severe deficits in arousal and sustained attention, associated with hemispatial neglect, were secondary to ADEM that involved the medial nuclei and pulvinar of the thalamus. Treatment with the noradrenergic agonist guanfacine was associated with a significant amelioration of impairments of both spatial and sustained attention [4]. Guanfacine XR is effective in treatment of ADHD [5], especially when stimulants are contraindicated.

Disclosures

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

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NEONATAL DISORDERS

School-Aged Outcomes After Neonatal Arterial Ischemic Stroke

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Related Article: Chabrier S, Peyric E, Drutel L, Deron J, Kossorotoff M, Dinomais M, et al. Multimodal Outcome at 7 Years of Age after Neonatal Arterial Ischemic Stroke. J Pediatr. 2016 Mar 9. [Epub ahead of print]
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Investigators from the Accident Vasculaire Cérébral de nouveau-né (AVCnn) Study Group, a multicenter registry in France, examined outcomes at 7 years of age in children previously identified with neonatal arterial ischemic stroke (NAIS). 100 patients were enrolled in this cohort, 80 patients completed at least part of the total assessment. Investigators obtained the patient's medical history, assessment of his/her developmental profile, and parental opinions on their child's medical sequelae from NAIS. Outcomes studied were presence of epilepsy, academic performance, presence and severity of cerebral palsy, presence of intellectual disability, presence of impaired spoken language, co-occurrence of deficits and parental opinion of outcomes. Impaired language was the most common problem, affecting 49% of children studied. The prevalence of the other outcomes was as follows: cerebral palsy 32%, low academic skills 28%, active epilepsy 11% and global intellectual impairment 8%. The investigators conclude that 59% of the patients in this cohort had any type of disability and that co-occurrence of disabilities is high. The investigators found a higher prevalence of speech impairment in comparison with other previously reported studies. This cohort presents a cross section of outcomes of school children presenting with NAIS in the neonatal period. [1]

COMMENTARY. Neonatal arterial ischemic stroke (NAIS) is by definition a symptomatic arterial ischemic infarct which presents within the first 28 days of life [2]. NAIS affects approximately 1 in 1600 to 1 in 5000 neonates [3]. It is likely that the total incidence of perinatal stroke is much higher than these quoted statistics since some children who are asymptomatic in the newborn period are later identified as having a presumed neonatal stroke by imaging when they present with early handedness, hemiplegia, epilepsy, or learning difficulties. The evolution of imaging findings and the variability of presenting symptoms makes it more difficult to study those children with presumed perinatal stroke cohort as compared to those identified with NAIS. Children with NAIS have been previously identified as being at risk for future development of motor deficits, cognitive disorders, and epilepsy [3]. This current study adds information on the prevalence of these issues at age 7 years in children with NAIS. While the overall occurrence of outcomes such has cerebral palsy, epilepsy, and intellectual impairment was similar to that reported in previous studies [3], this study explored in more detail the severity of impairment in each case. It is interesting to see that although many children have disabilities, most cases are mild. It is encouraging that all patients in this cohort are able to walk independently and only 8% have global intellectual disability. Previously reported data have shown an association between mixed infarctions and cerebrospinal tract involvement with worse motor outcomes [4]. This study adds important information that may be provided to caretakers regarding the long term outcome of infants presenting with NAIS. Additional studies would be needed to determine differences in long-term outcomes between children with a neonatal presentation and those with later presentation.

Disclosures

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

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