EEG and Clinical Features of Childhood Absence Predict Clinical Outcomes

Pretreatment EEG in Childhood Absence Epilepsy: Associations With Attention and Treatment Outcome.

Dlugos D, Shinnar S, Cnaan A, Hu F, Moshé S, Mizrahi E, Masur D, Sogawa Y, Le Pichon JB, Levine C, Hirtz D, Clark P, Adamson PC, Glauser T; for the Childhood Absence Epilepsy Study Team. *Neurology* 2013;81:150–156.

OBJECTIVE: In children with newly diagnosed childhood absence epilepsy (CAE), determine pretreatment EEG features and their associations with baseline neuropsychological function and short-term treatment outcome. METHODS: In a multicenter, randomized clinical trial, patients with CAE underwent a pretreatment, 1-hour video-EEG and neuropsychological testing with freedom-from-failure and seizure-freedom (SF) outcome assessed at the 16- to 20-week visit.

RESULTS: Detailed evaluation of the pretreatment EEG was possible for 99.8% of participants (445/446). Median time to first seizure was 6.0 minutes (range 0–59 minutes), median number of seizures was 5 (range 1–60), and median seizure duration was 10.8 seconds (range 3.3–77.6 seconds). Median duration of shortest seizure per EEG was 7.5 seconds (range 3.0–77.6 seconds). Seizure frequency was not associated with baseline measures of attention, executive function, or treatment outcome. Presence of a seizure lasting ≥20 seconds was noted in 29% of subjects (129/440); these children had higher median omissions T score on the Conners Continuous Performance Test (56.3 vs 51.6, $p = 0.01$). Patients with a shortest seizure of longer duration were more likely to demonstrate treatment success by both freedom-from-failure ($p = 0.02$) and SF ($p = 0.005$) criteria, even after controlling for age, treatment group, and number of seizures, with good predictive value (area under the curve 78% for SF). CONCLUSIONS: CAE is reliably and quickly confirmed by EEG. Occurrence of a seizure ≥20 seconds, but not overall seizure frequency, was associated with differential baseline measures of attention. Patients whose shortest pretreatment EEG seizure was longer in duration were more likely to achieve SF, regardless of treatment.

Commentary

Childhood absence epilepsy (CAE) is a common pediatric epilepsy syndrome, accounting for approximately 10 to 17 percent of childhood epilepsy (1, 2). The EEG pattern in CAE is an approximate 3-Hz bilateral synchronous, symmetric spike and slow wave, with seizures often activated by hyperventilation (HV). Treatment of CAE is not optimal, with many children having incomplete seizure control (3, 4). A recent multicenter, double-blind, randomized clinical trial aimed to compare the effectiveness of commonly used antiepileptic drugs (AEDs) (ethosuximide, valproate, and lamotrigine) among 446 children with newly diagnosed CAE (3, 4). Valproate and ethosuximide were found to be more effective than lamotrigine, and ethosuximide was better tolerated. These subjects had pretreatment EEG obtained as part of recruitment criteria. EEG is typically used to diagnose CAE. In addition to seizures, children with CAE are at risk for deficits in attention (3, 4). Better understanding of CAE EEG characteristics and its utility in diagnosis will help direct clinical care. Determining if there is a relationship between EEG findings and clinical outcome, including response to treatment and neuropsychologic parameters, may help identify those potentially at greater risk for adverse outcomes.

Dlugos and colleagues performed an analysis of pretreatment EEG features among children with newly diagnosed CAE enrolled in the previously reported multicenter, double-blind, randomized, clinical trial. Associations between neuropsychologic function as well as treatment outcome were determined. Subjects aged between 2.5 and 13 years with the clinical diagnosis of CAE were enrolled. Entry criteria included an EEG revealing 2.7- to 5-Hz generalized spike wave (GSW) with a normal background and at least one GSW burst lasting ≥3 seconds. Subjects had a 1-hour baseline video-EEG as well as a battery of neuropsychologic tests. The specific neuropsychologic tests included the Conners Continuous Performance Test to assess attention and the Wisconsin Card Sorting Test for executive function.

Video-EEG recordings were standardized with a predetermined protocol. The protocol included a 5-minute waking baseline period, first HV trial of 3 to 4 minutes, photic stimulation at 2 to 20 Hz, second HV trial if no electroclinical seizures were detected during first HV trial, and additional wakefulness for 1 hour total. Standard EEG recording allowed

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investigators to assess effectiveness of a 1-hour recording as well as investigate associations with both clinical response and neuropsychologic outcomes. Prior studies have used EEGs ranging from 20 minutes to 24 hours. Of 446 subjects, 445 had detailed evaluation of the pretreatment EEG, and 406 had the standardized EEG protocol. EEGs were reviewed locally and then centrally. Predefined criteria for normal background and seizures were established and used for the analysis.

The primary outcomes were time to first seizure, number of seizures, seizure duration, total seizure exposure, and presence/absence of any seizure ≥20 seconds. Data were summarized and analyzed on patient level, not seizure. Medians, minimum, maximum, and quartiles were used to describe EEG because of high skewness. Spearman correlations were calculated between EEG and cognitive variables. Logistic regression was used to evaluate whether EEG characteristics predicted treatment outcome.

The median time to first seizure was 6.0 minutes (range, 0–58.9 minutes). The first seizure was recorded within the first 30 minutes in 94% of subjects. This finding demonstrates the sensitivity of a 1-hour EEG study and the limited benefit of more prolonged studies. The median number of seizures was 5 (range, 1–60). Median seizure duration was 10.8 seconds (range, 3.3–77.6 seconds). The median duration of the shortest seizure per EEG was 7.5 seconds (range, 3.0–77.6 seconds). A seizure lasting ≥20 seconds was seen in 129 of 440 subjects (29%). Of interest, there was no association between seizure frequency, median seizure duration, or total seizure exposure and baseline measures of attention, executive function, or treatment outcome. Further analysis did reveal, however, that patients with seizure duration longer than 20 seconds performed worse on baseline measures of attention by being more likely to commit errors of omission on attention testing. One very interesting finding was that patients whose shortest seizure had a longer duration before treatment responded better to treatment. Seventy-four percent with longer seizures were seizure free at the 16- to 20-week visit compared with 63% whose seizures were consistently shorter (<7.5 seconds). This was significant after controlling for multiple factors, including age group and treatment group.

The EEG findings of this study clarify that CAE can be reliably diagnosed across multiple sites with a 1-hour EEG. In fact, only 6% of studied subjects required more than 30 minutes of EEG. Why subjects with the shortest seizure of longer seizure duration responded more favorably to treatment is not entirely clear. Longer electrographic seizure duration may function as a biomarker for clinical response. In addition, subjects with longer seizure duration (>20 seconds) performed more poorly on attention measures. Although this finding is more intuitive, overall the findings do suggest different groups of CAE. As the authors discuss, it is likely that these groups may have unique genetic etiologies. Understanding the genetics behind various epilepsy phenotypes will in the future significantly direct care.

Another detailed analysis by the same group using the same cohort revealed that as a group, children with CAE are at significant risk for disorders of attention (5). Using multiple neurocognitive tests, 36% of the cohort had attention deficits despite intact neurocognitive functioning. These deficits persisted even after treatment, particularly for children treated with valproate. Taken together, children with longer baseline electrographic seizure duration need to be monitored closely for deficits of attention.

The multicenter, randomized, clinical trail of CAE was a well-designed and implemented study. This analysis and its results further demonstrate the utility of this study and will guide clinical practice for patients with CAE.

By Alison M. Pack, MD, MPH

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