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Journal Club: Pretreatment EEG in childhood absence epilepsy

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Childhood absence epilepsy (CAE) is defined by absence seizures in a normally developing child, with onset between 4 and 10 years of age.[1] Typical absence seizures consist of behavioral arrest with or without automatisms, usually last 30–60 seconds, and demonstrate a characteristic 3-Hz generalized spike-wave (GSW) pattern on EEG, often in response to hyperventilation.[2] Children may have hundreds of episodes daily, many of them subclinical, which can impair sustained attention and memory processing. There is a strong association between CAE and disorders of attention and executive function. This association persists even when seizures are well-controlled. An underlying structural or functional abnormality of the brain has been postulated to explain both observations.[3,4] This article by Dlugos et al.[5] is a post hoc analysis of a randomized, double-blinded trial[6] that seeks to characterize the relationship between EEG characteristics prior to treatment, measures of attention, and the outcome of initial antiepileptic treatment.

HYPOTHESIS AND DESIGN The authors used data from a recently completed randomized trial to determine the associations among EEG characteristics, measures of attention, and response to treatment by agents typically used for CAE.

METHODS The study population consisted of 440 children with a clinical diagnosis of CAE aged between 2.5 and 13 years at time of study entry. Demographic information is presented in table 1.[5] Inclusion criteria required an EEG demonstrating GSW with frequency between 2.7 and 5 Hz, a normal background, and at least 1 GSW with duration greater than or equal to 3 seconds. EEGs were obtained by local providers and reviewed by local investigators as well as a central EEG reader. Exclusion criteria included antiepileptic medication for more than 7 days prior to randomization, history of other nonfebrile seizures, history of severe dermatologic reaction to medication, or history of major psychiatric disease, autism spectrum disorder, or significant medical condition.[6]

Baseline assessment included a 1-hour awake-only video-EEG with photic stimulation and 1 or 2 trials of hyperventilation for 3–4 minutes. Seizures were defined as at least 3 seconds of GSW even without clinical changes. Thirty-nine children did not follow established EEG protocol due to delay in hyperventilation trial or inability to cooperate with hyperventilation. EEG outcomes were time to first seizure, number of seizures, seizure duration, total seizure time per hour ("seizure exposure"), and presence of any seizure lasting greater than 20 seconds.

Attention was evaluated with the Conners Continuous Performance Test (CPT; K-CPT under 6 years or CPT-II over 6 years). This task requires participants to sustain attention to identify targets (i.e., avoid errors of omission) while inhibiting nontarget responses (errors of commission).[7] Executive function was assessed with the Wisconsin Card Sorting Test (WCST), in which participants must match cards according to prior trials stored in working memory and then activate regions of the frontal lobe to "set-shift" between different rules or conditions in response to feedback.[8] Both tests are frequently used to study these measures, and both provide a score that is compared to normative data from nonreferred healthy individuals and from symptomatic groups.[9,10]

Patients were randomized to treatment with ethosuximide, lamotrigine, or valproic acid titrated to clinical effect.[4] Freedom from failure (FFF) and seizure freedom (SF) were assessed in follow-up at 16–20 weeks. SF was assessed clinically and by EEG, and only for the 329 patients (75%) who remained on medication at follow-up. FFF was a composite endpoint defined as "no clinical or EEG absence seizures at the 16- to 20-week visit, no generalized tonic-clonic seizures at any time, no drug-related systemic toxicity, no intolerable drug-related side effects, and no study withdrawal."

Multivariate logistic regression was used to create a prediction model for FFF and SF. Logistic regression is used to predict a binary dependent variable (e.g., seizure freedom yes/no) using one or multiple independent (predictor) variables, even if each individual variable is not predictive in isolation. Observations from logistic regression are expressed as odds ratios.

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RESULTS **Baseline EEG characteristics.** Median time to first seizure for the entire sample was 6.0 minutes (range 0–58.9). Median number of seizures per 1-hour study was 5 (range 1–60). Median seizure duration was 10.8 seconds. Median total seizure exposure was 54 seconds per hour, with a broad range from 3.6 seconds to 28 minutes 12 seconds. Twenty-nine percent of subjects (129/440) had a seizure lasting 20 seconds or more. Shortest and longest seizure durations were also noted for each individual.

Measures of attention. The baseline prevalence of attentional dysfunction was 35%.[4] There were no significant correlations between seizure number, median duration, or total seizure exposure during pretreatment EEG and any CPT or WSCT results. However, there was a correlation between the presence of a seizure >20 seconds and the omissions T-score on the CPT, which is a measure of the number of target prompts missed (56.3 vs 51.6, $p < 0.01$). There was no correlation between presence of a seizure >20 seconds and any other subscores or overall scoring on CPT or WCST.

Treatment outcome. No statistically significant relationship was found between treatment outcome and number of seizures, seizure exposure, length of a patient's longest seizure, or presence of seizure >20 seconds on baseline EEG. The duration of a patient's shortest seizure was predictive: patients whose shortest seizures had shorter durations had a poorer treatment response by FFF and SF (odds ratio 1.04 and 1.07, p values 0.018 and 0.0045); however, patients whose shortest seizures were longer had better treatment response. This was true even when controlling for treatment group or age (table 2).[5] These models are shown in figure 3[5] and can be used to predict outcomes based on individual data points. For example, a vertical line drawn from the x-axis at 7.5 seconds meets the overall regression curve for seizure freedom at approximately 0.65 on the y-axis. Clinically, this translates to a patient whose shortest seizure was 7.5 seconds long having a 65% probability of SF. Overall, patients whose shortest seizures were shorter than 7.5 seconds had a 63% probability of SF, while those whose shortest seizures were longer than 7.5 seconds had a 74% probability of SF.

The quality of models like the one in this article can be assessed by discrimination (how well a model predicts the outcome variable) and calibration (how the incidence predicted by the model compares to the actual outcome). Both are measures of internal validity. Area under the curve (AUC) is a measure of discrimination and is derived from the receiver operating characteristic curve, which represents the sensitivity against the false-positive rate. The AUC for duration of shortest seizure predicting FFF was 67.6% and for predicting SF was 77.9%; in general, greater than 70% is considered adequate. Calibration was assessed through the Hosmer-Lemeshow goodness of fit test, which had p values of 0.76 and 0.20, suggesting no significant difference between actual and predicted outcome incidence.

INTERPRETATION This study's primary finding was of a predictive relationship between the duration of a patient's shortest seizure and response to treatment, with longer seizures associated with better treatment outcomes. This counterintuitive finding may reflect that the group more prone to longer seizures is also more treatment-responsive for underlying genetic or biochemical reasons. Application of this predictive model to future study populations may provide validation of the model and also may delineate further subgroups within CAE. Providers may find this study helpful in counseling families on the prognosis for antiepileptic drug treatment based on a child's baseline EEG characteristics.

An important note is that only 75% of patients (329 of 445) stayed on medication until the 16- to 20-week follow-up visit. There were no significant differences in demographic characteristics or measures of attention between those who discontinued medication and those who remained on treatment at follow-up. However, patients who discontinued medication had shorter duration of their shortest, median, and longest seizures than those who remained on treatment. Does this indicate a higher likelihood of discontinuing medication among cases with shorter seizures in whom the perceived benefits of treatment were less? Or were families noticing a lack of treatment response in these children, consistent with the study finding?

This study found significant differences in attentional measures only in patients with seizures lasting longer than 20 seconds and only on one area of the CPT, specifically, with errors of omission. These errors could have been produced by either inattention or absence seizures occurring during testing. Further research is needed to elucidate the relationship between CAE and inattention separate from transient impairment produced by the absence seizures themselves.

By developing a prediction model from a study's own data, with double-blinded treatment groups and multivariate analysis to address confounding, internal validity in this study is high. By contrast, the applicability of a study to a provider's clinical practice depends on the study's external validity, or how well the study population (see table 1[5]) reflects the one seen by the provider. As with any study, care must be taken in applying these findings to patients who are dissimilar to the study population.

AUTHOR CONTRIBUTIONS

Dr. Bernson-Leung drafted the manuscript and approved all final changes. Dr. Mazumdar edited the manuscript and approved all final changes.

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DISCLOSURE

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