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Clinical and EEG factors associated with antiseizure medication resistance in idiopathic generalized epilepsy

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Summary:

Objective:

We sought to determine which combination of clinical and EEG characteristics differentiate between an antiseizure medication (ASM)-resistant versus ASM-responsive outcome for patients with idiopathic generalized epilepsy (IGE).

Methods:

This was a case-control study of ASM-resistant cases and ASM-responsive controls with IGE treated at five epilepsy centers in the United States and Australia between 2002-2018. We recorded clinical characteristics and findings from the first available EEG study for each patient. We then compared characteristics of cases versus controls using multivariable logistic regression to develop a predictive model of ASM-resistant IGE.

Results:

We identified 118 ASM-resistant cases and 114 ASM-responsive controls with IGE. First, we confirmed our recent finding that catamenial epilepsy is associated with ASM-resistant IGE (OR 3.53, 95% CI 1.32-10.41, for all study subjects) after covariate adjustment. Other independent factors seen with ASM-resistance include certain seizure type combinations (absence, myoclonic, and generalized tonic-clonic seizures [OR 7.06, 95% CI 2.55-20.96]; absence and generalized tonic-clonic seizures [OR 4.45, 95% CI 1.84-11.34]), as well as EEG markers of increased generalized spike-wave discharges (GSW) in sleep (OR 3.43, 95% CI 1.12-11.36 for frequent and OR 7.21, 95% CI 1.50-54.07 for abundant discharges in sleep) and the presence of generalized polyspike trains (GPT; OR 5.49, 95% CI 1.27-38.69). The discriminative ability of our final multivariable model, as measured by area under the receiving operating characteristic curve, was 0.80.

Significance:

Multiple clinical and EEG characteristics independently predict ASM-resistance in IGE. To improve understanding of a patient's prognosis, clinicians could consider asking about specific seizure type combinations and track whether they experience catamenial epilepsy. Obtaining prolonged EEG studies to record the burden of GSW in sleep and assessing for the presence of GPT may provide additional predictive value.

Keywords: prognosis, case-control study, epidemiology, outcome, catamenial

Key Points Box:

1. Clinical characteristics associated with ASM-resistant IGE include catamenial epilepsy and certain seizure-type combinations.
2. EEG characteristics associated with ASM-resistant IGE include increased GSW in sleep and the presence of GPT.
3. Prospective studies are needed to refine diagnostic and treatment strategies for ASM-resistant IGE.

Introduction:

Idiopathic generalized epilepsy (IGE) syndromes—childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and generalized tonic-clonic seizures (GTCS) alone—are commonly encountered in the clinic and are estimated to comprise 15-20% of all epilepsy diagnoses.[1, 2] Up to 15-36% of patients with IGE exhibit antiseizure medication (ASM)-resistance and experience ongoing seizures despite appropriate ASM treatment.[3-7] Patients with ASM-resistant IGE have relatively fewer treatment options compared to those with focal epilepsy. They are ineligible for treatment with narrow spectrum ASMs and are also not candidates for resective epilepsy surgery or neurostimulation device placement outside of the research trial setting. Consequently, attaining seizure freedom for patients with ASM-resistant IGE can be challenging once multiple ASMs have failed.

Several studies have investigated clinical and EEG factors that predict a ASM-resistant course in IGE.[4, 8, 9] In a previous study,[10] we attempted to develop a predictive model of ASM-resistant IGE by assessing various clinical factors seen with an ASM-resistant course. While the discriminative model only ranged between 0.58 to 0.65 (area under the curve), we found that catamenial epilepsy, i.e., a change in seizure frequency in conjunction with the menstrual cycle, is significantly associated with ASM-resistant IGE.[10] This predictive model's merely moderate ability to discriminate between those with ASM-resistant and ASM-responsive IGE could be due to unmeasured variables, such as EEG findings. EEG markers of ASM-resistance have included higher densities of generalized epileptiform discharges and the presence of generalized polyspike trains.[11, 12] In the present study, we hypothesized that a combination of clinical and EEG findings will more accurately predict an ASM-resistant course in patients with IGE. We also hoped to verify our recent study findings that catamenial epilepsy is associated with ASM-resistant IGE in an independent patient sample. A clearer understanding of these factors will lead to earlier diagnosis and better treatment options for patients with ASM-resistant IGE.

Methods:

Study Design, Setting, and Participants

We conducted this retrospective case-control study utilizing existing clinical and EEG records for patients treated at the Columbia University (New York, NY, USA), Rutgers University (New Brunswick, NJ, USA), Cornell University (New York, NY, USA), Alfred Hospital (Melbourne,

VIC, AU), and Royal Melbourne Hospital (Melbourne, VIC, AU) comprehensive epilepsy centers between January 1, 2002 through July 31, 2020. This study was approved by the institutional review board for each center.

Study participants were selected using the same clinical criteria described in our recent paper.[10] Specifically, we identified adult (age $\geq$ 18 years) patients with 1) a diagnosis of IGE as per the treating epileptologist and 2) a normal brain MRI (defined as the absence of an epileptogenic lesion). We also included only those patients with at least one EEG study available for direct review. We did not exclude patients with normal EEG findings if the diagnosis of IGE was clearly documented in the medical record by the treating epileptologist. For example, this may include patients for whom IGE was diagnosed based on outside EEG studies, follow-up EEG studies, or on clinical grounds alone. However, we did exclude patients who had EEGs with grossly abnormal background slowing or focal epileptiform discharges inconsistent with a diagnosis of IGE. Approximately 1400 medical records of patients with IGE were reviewed for inclusion in this study among all five centers.

We then identified two groups of IGE patients: 1) ASM-resistant cases and 2) ASM-responsive controls. We defined ASM-resistant cases as those patients who have failed two or more trials of broad-spectrum ASMs or those otherwise indicated in IGE syndromes (e.g., clobazam, clonazepam, ethosuximide, felbamate, lamotrigine, levetiracetam, perampanel, topiramate, valproate, zonisamide) specifically due to inefficacy. We defined inefficacy as ongoing/uncontrolled seizures despite appropriate ASM dosing and clear documentation of treatment failure in the chart. We required each ASM trial to last at least six months prior to determination of inefficacy, as in our previous study.[10] ASM-responsive controls were defined as patients with controlled seizures on either their first or second appropriate ASM trial. We chose not to use the International League Against Epilepsy (ILAE) definition of sustained seizure freedom (i.e., freedom from all seizure types for 12 months or three times the longest preintervention inter-seizure interval, whichever is longer)[13] to define ASM-responsiveness because we wanted to include in the ASM-responsive group those patients with rare breakthrough seizures due to missed doses of medication and occasional non-disabling myoclonic seizures if these did not necessitate a change in management. We included both

prevalent and incident ASM-resistant IGE cases during the study period. We included approximately one ASM-responsive control for each case. We selected controls to include similar participant numbers based on sex, EEG study duration, and age at the time of EEG to minimize confounding due to these variables. However, patients were not individually matched due to insufficient numbers of study subjects.

Data Collection

Data collection was conducted between March 1, 2018 and July 31, 2020. We relied on the most recent clinical document available for each patient to ascertain case versus control status and seizure control. Five investigators (B.K.K., M.J., P.K., C.E., H.C.) collected the following clinical variables from the medical record: study site, sex, date of birth, IGE syndrome, seizure types experienced, concomitant intellectual disability (as per review of records), nocturnal epilepsy (defined as >90% of seizures occurring out of sleep), prior status epilepticus, concomitant psychiatric condition, concomitant diagnosis of psychogenic non-epileptic seizures, history of febrile seizures, family history of epilepsy, and catamenial epilepsy (defined as a change in seizure frequency associated with menses documented by the treating physician).

We operationalized concomitant intellectual disability, nocturnal epilepsy, status epilepticus, psychiatric condition, psychogenic non-epileptic seizures, history of febrile seizures, and family history of epilepsy as binary response variables (yes/no). We classified IGE syndromes as one of the following, relying on the treating epileptologist's diagnosis: 1) CAE, 2) JAE, 3) JME, or 4) GTCS alone/generalized epilepsy not otherwise specified. Seizure types were defined as one of the following combinations: 1) GTCS + absence seizures + myoclonic seizures, 2) GTCS + myoclonic seizures, 3) GTCS + absence seizures, 4) Absence seizures only or myoclonic seizures only or absence + myoclonic seizures, or 5) GTCS alone, as in our prior study.[10] Lastly, we combined variables for sex and catamenial epilepsy and classified subjects as one of the following: 1) men, 2) women without catamenial epilepsy, and 3) women with catamenial epilepsy.

Board-certified epileptologists or epilepsy fellows (B.K.K., M.J., P.K., C.E., H.C.) directly reviewed an EEG study for each patient. If a patient had multiple EEG studies available for review, we chose to review the first EEG study performed at each center. We classified EEGs as

either short (< 4 hours in duration) or long recordings (4-24 hours in duration). For studies that lasted multiple days, we reviewed the first 24 hours of the study. We recorded each patient's age and ASM medication regimen at the time of the study. A codebook of standardized EEG terms and definitions was provided to each EEG reviewer. We then collected information on the following EEG variables: 1) the burden of generalized spike-wave discharges (GSW) in wakefulness, 2) the burden of GSW in sleep, if sleep was recorded, 3) the presence of generalized polyspike trains (GPT, yes/no), and 4) the presence of generalized paroxysmal fast activity (GPFA, yes/no). Here, GSW refer to bilaterally symmetric (<30% amplitude difference between hemispheres) surface-negative spikes lasting 20-80 miliseconds in duration or polyspikes (fewer than five associated spikes) followed by a surface-negative slow wave.[11, 12, 14] We defined sleep by the presence of a K-complex or sleep spindle, i.e., stage N2 sleep.[14, 15] We determined the burden of GSW in wakefulness and sleep using the American Clinical Neurophysiology (ACNS) critical care EEG terminology for sporadic epileptiform discharges as follows: 1) none, 2) rare (fewer than 1 GSW per hour), 3) occasional (more than 1 GSW per hour but fewer than 1 per minute), 4) frequent (more than 1 GSW per minute but fewer than 1 every 10 seconds), and 5) abundant (more than 1 every 10 seconds).[16, 17] We chose to use ACNS criteria to determine the GSW burden because of its ease of use and widespread adoption among clinical neurophysiologists.[16-19] We assessed for GPT according to the recent description by Sun and colleagues as a burst of at least 5 generalized rhythmic spikes lasting less than 1 second in duration in the awake or sleep states.[12] We defined GPFA conventionally as a burst of generalized rhythmic spikes lasting 1 second or longer in duration in the awake or sleep states.[14, 15]

Statistical Analysis

Analysis 1: Catamenial Epilepsy Confirmation

We sought to confirm the recent novel finding that catamenial epilepsy is associated with ASM-resistant IGE.[10] All subjects from Columbia University were excluded from this analysis. Only clinical factors were considered, as in our prior study.[10] First, we performed bivariate analyses to assess which factors were associated with ASM-resistant IGE cases versus controls at $p < 0.1$. We used the chi-square test to compare categorical predictor variables and

the two-sided t-test to compare continuous predictor variables. We then included those factors significantly associated with ASM-resistance in a multivariable logistic regression model. We then performed backward elimination by removing nonsignificant predictor variables that did not significantly alter other predictors to determine a parsimonious final model.

Analysis 2: Predictive Model for ASM-Resistant IGE

We examined both clinical and EEG factors in subjects from all centers (Columbia, Rutgers, Cornell, Alfred, and Royal Melbourne Hospital) to develop a predictive model for ASM-resistant IGE. We first used bivariate analyses to determine which factors were associated with ASM-resistant IGE cases at $p < 0.1$ and then included these factors in a multivariable logistic regression model. Backward elimination was performed to determine a parsimonious final model. We then determined the area under the receiver operator characteristic (ROC) curve (AUC) for the final model, where an AUC value of 0.5 represents a model with no predictive ability and an AUC of 1.0 represents a model with perfect predictive ability.[20, 21] We subsequently compared this AUC with the AUC of our prior model[10] that included three clinical characteristics only (catamenial epilepsy, concomitant psychiatric condition, and seizure type) applied to the current dataset from all five centers using DeLong's method.[22] All data analyses were performed using SAS version 9.4.

Results

Subject Characteristics

A total of 232 patients (118 ASM-resistant cases and 114 ASM-responsive controls) were included for analysis. Clinical and EEG characteristics for study subjects, as well as results from the bivariate analyses are displayed in Tables 1-2. There was no significant difference in the EEG study duration or age at the time of EEG between cases and controls. However, a higher proportion of ASM-resistant cases had sleep recorded on EEG (96/118, 81.4%) when compared to controls (74/114, 64.9%, $p = 0.005$).

Analysis 1: Catamenial Epilepsy Confirmation

Clinical characteristics for IGE cases and controls from all non-Columbia sites are shown in Table 3. After conducting bivariate analyses, we included age of epilepsy onset, sex/catamenial epilepsy, epilepsy syndrome, seizure type combination, intellectual disability,

nocturnal seizures, and prior status epilepticus in the initial logistic regression model. The final parsimonious model included 1) sex/catamenial epilepsy and 2) seizure type.

ASM-resistance was seen with significantly greater frequency (OR = 4.27) in women with catamenial epilepsy compared to women without catamenial epilepsy (Table 4). Compared with individuals with GTCS only, two seizure type combinations were significantly more prevalent among ASM-resistant IGE cases than controls. These combinations were all (a) three seizure types (GTCS, myoclonic, and absence seizures) and (b) GTCS and absence seizure types.

Analysis 2: Predictive Model for ASM-Resistant IGE

We examined the ability of a model including clinical and EEG characteristics to discriminate between ASM-resistant and ASM-responsive IGE among all study subjects. We included age of epilepsy onset, sex/catamenial epilepsy, epilepsy syndrome, seizure types, nocturnal seizures, prior status epilepticus, GSW burden in wake, GSW burden in sleep, GPT, and GPFA in the initial logistic regression model following bivariate analyses of clinical and EEG characteristics (Tables 1-2). The final model included 1) sex/catamenial epilepsy and 2) seizure types, similar to the first stage of analysis, in addition to EEG variables of 3) burden of GSW in sleep and 4) presence of GPT (Table 5). There was no significant interaction between any of these predictor variables.

Again, women with catamenial epilepsy had higher odds of ASM-resistance compared with women without catamenial epilepsy, adjusting for other variables in the model (Table 5). Compared with having only GTCS, seizure type combinations of (a) GTCS, myoclonic, and absence seizures and (b) GTCS and absence seizures were again associated with ASM-resistance. EEG markers seen with ASM-resistant IGE cases included an increased burden of GSW in sleep, specifically in the frequent to abundant range, as well as the presence of GPT. Because there were significantly more cases than controls who had sleep recorded on EEG (Table 2), we performed a secondary analysis only including individuals with sleep EEGs. Results showed that GSW burden in sleep remained a significant independent factor predicting ASM-resistant IGE. Neither the burden of GSW in the awake state, nor the presence of GPFA on EEG were significantly associated with ASM-resistance in any model.

The AUC for the final regression model predicting ASM-resistance among all study subjects was 0.80 (95% CI: 0.74-0.85). By contrast, the AUC for our previously published model[10] was 0.73 (95% CI: 0.68-0.79) when applied to the same dataset, with a statistically significant difference in the AUC between these two models of 0.07 (p = 0.003).

Discussion

In this multi-center case-control study conducted at sites within the US and Australia, we examined which clinical and EEG factors co-occur more frequently in patients with ASM-resistant IGE. First, we confirmed an association between catamenial epilepsy and ASM-resistant IGE in a separate study population.[10] Other independent clinical factors seen with ASM-resistance include certain seizure type combinations (GTCS, myoclonic, and absence seizures; and GTCS and absence seizures) and EEG markers (frequent to abundant GSW in sleep; and GPT). Our final predictive model was able to discriminate between ASM-resistant and ASM-responsive IGE with 80% accuracy (AUC = 0.80) in this dataset. This represents an improvement of around 7% from our previously published model[10], suggesting that the addition of EEG variables improves the model's performance.

The relationship between catamenial epilepsy and ASM-resistant IGE is intriguing and was only recently described. In our prior study, we showed similarly increased odds (3.5-4-fold) of ASM-resistant IGE in patients with catamenial epilepsy.[10] A clear understanding of the relationship between ASM-resistance and the menstrual cycle remains elusive. Herzog et al. showed that cyclic progesterone therapy improved focal seizures in patients with peri-menstrual, but not peri-ovulatory or luteal phase, exacerbations, possibly due to fluctuations of progesterone and other hormone levels during the menstrual cycle.[23] Our assessment of catamenial epilepsy was more limited, as clinical records often do not detail the timing of seizures within the menstrual cycle. Those with ASM-responsive IGE may not experience an adequate number of seizures to recognize a clear association with their menses. Although we excluded patients with five or fewer lifetime seizures in our prior analysis,[10] this information was frequently unavailable in our current study and could contribute to recall bias. Nevertheless, 6.1% of ASM-responsive controls in our study identified a catamenial seizure exacerbation pattern, similar to our prior study (7.5% and 8.2% at the Columbia and Yale

epilepsy centers, respectively).[10] Valproate use may be a confounder. People who can get pregnant are much less likely to be on valproate due to well-documented risks of teratogenicity.[24] On the other hand, valproate is gaining increasing evidence as the most effective ASM in IGE, and treatment failure with valproate was highly specific for ASM-resistant IGE in several cohorts.[25-28] Thus, the higher ratio of women to men among ASM-resistant cases in our study might reflect fewer trials of valproate, and consequently, increased treatment failure. Based on our observed effect size (OR = 3.53) for catamenial epilepsy, the amount of residual confounding by unmeasured factors needed to explain away this association, or E-value, is 3.17 (lower limit: 1.57).[29, 30] Unfortunately, we were unable to determine which patients in our study had been previously treated with valproate, limiting our ability to analyze this question further. In the absence of definitive treatment guidelines for IGE, the choice of initial ASM for these epilepsies is usually individualized based on a patient-centered discussion of side effects and other co-morbidities. However, with more than ten broad-spectrum ASMs in clinical practice, studying their relative efficacies retrospectively is challenging. Future studies could avoid these methodological limitations by recruiting ASM-naïve individuals diagnosed with incident IGE and followed prospectively with documentation of ASM trials, especially valproate.

Two seizure type combinations were associated with ASM-resistant IGE in our study; compared with GTCS alone, the combination of all three seizure types (GTCS + absence + myoclonic seizures) demonstrated the strongest association (OR = 7.06). Other investigators have shown that this seizure type combination is a marker of ASM-resistance in JME and other IGE syndromes.[7, 10, 31, 32] We additionally found that the combination of GTCS and absence seizures was also observed more with ASM-resistant IGE. Interestingly, the combination of seizure types, rather than the IGE syndrome, distinguished ASM-resistance more accurately. Prior studies examining the prognosis of CAE versus JAE found that the presence of GTCS, rather than the age of onset, might be more predictive of ASM-resistance.[33, 34] Similarly, sub-syndromes or evolution within IGE syndromes may complicate the simpler operational classification proposed by the International League Against Epilepsy, as previously discussed by Martínez-Juárez et al.[2, 35] The syndrome of CAE evolving into JME, for example, accompanied a

lack of seizure remission in patients across multiple studies.[8, 35, 36] Because all three seizure types (absence, myoclonic, and GTCS) are seen in CAE evolving to JME, these cases could be driving the relationship seen in our study. Defining the "correct" IGE syndrome may be difficult when features from multiple syndromes co-exist for an individual. The transition from pediatric to adult epilepsy care may further complicate labeling the underlying syndrome, especially if seizures change over time.[34] A better understanding of this relationship requires a detailed characterization of seizure types and their dates of onset. Prospective data collection in this situation is daunting, as it would require years of observation to describe CAE evolving to JME beginning from the onset of epilepsy in childhood. Alternatively, retrospective data collection utilizing past clinical records in conjunction with high-quality patient interviews may help to minimize recall bias. Finally, IGE syndromes represent a subgroup of the genetic generalized epilepsies (GGE) that include other conditions we did not examine in our study.[2]

We also found that an increased burden of GSW in sleep and the presence of GPT are EEG factors independently associated with ASM-resistant IGE. Seneviratne and colleagues recently performed prospective 24-hour ambulatory EEGs on a cohort of patients with IGE and showed that higher densities and longer paroxysms of generalized epileptiform discharges correlated with a shorter preceding duration of seizure freedom.[11] They robustly demonstrated this by counting every epileptiform discharge in each EEG, but we instead utilized ACNS criteria for the burden of sporadic epileptiform discharges. While a much cruder measure, this ordinal scale is less time consuming to determine and already widely used by the clinical neurophysiology community.[11, 17] Future studies could employ automated quantitative EEG techniques to count discharges and reduce human error.[37] Still, it is unlikely that the frequency of GSW could be used in isolation, as nearly 8% of ASM-responsive controls in our study still had frequent to abundant discharges in sleep and 16% of ASM-resistant cases had no discharges. By comparison, GPT was observed in only 21.2% of cases but was highly associated with ASM-resistance (OR = 5.49). A previous study by our Melbourne-based investigators found that GPT on an EEG during sleep was associated with drug-resistant IGE in both a discovery cohort of 85 patients and a replication cohort of 80 patients.[12] Unfortunately, we did not distinguish between GPT in sleep versus wake in the current study to clarify this more precise

relationship. GPT and GPFA are typically thought of as EEG features of Lennox-Gastaut syndrome and other symptomatic generalized epilepsies.[12] We did observe GPFA more frequently in IGE cases than controls (11.9% of cases versus 0.9% of controls), but this was not statistically significant in our model, potentially due to small numbers of patients with this finding, or its co-occurrence with GPT. GPT has now emerged as a promising indicator for ASM-resistant IGE in multiple studies.[38, 39] A limitation of our study is that we relied on previously collected EEG studies for analysis. There was wide variability in EEG study durations between patients, ASM regimens at the time of EEG, and a higher proportion of cases had sleep recorded on EEG. Selection bias may overestimate the importance of GSW in sleep and GPT as markers for ASM-resistant IGE. Future studies would ideally record EEGs of uniform duration, as previously done by Seneviratne et al.[11] Lastly, Szaflarski and colleagues previously demonstrated that focal slowing, focal epileptiform discharges, and differing locations of GSW generators contribute to ASM resistance.[3, 40] We did not assess for focal EEG abnormalities, but these should certainly be examined in future studies.

While we cannot directly calculate the risk, or probability, of ASM-resistance from a traditional case-control study, it can be estimated given the ratio of cases to controls and the prevalence of ASM-resistance.[41] In our prior nested case-control study conducted at two tertiary epilepsy centers, we found an overall ASM resistance prevalence of 21.1% (138/655 patients).[10] We used this prevalence to estimate the risk of ASM resistance for a patient with IGE given a certain set of characteristics via adjustment of the regression coefficients.[41] For example, a patient seen in clinic with catamenial epilepsy, a combination of GTCS and myoclonic seizures, frequent GSW in sleep, and GPT on EEG, has a roughly 47% risk of ASM-resistant IGE based on findings from our study. We emphasize, however, that this model is far from perfect. It may not generalize to settings outside of tertiary epilepsy centers, where patients often present to only after initial consultation with a general neurologist. We did not strictly apply the 2010 ILAE definition of sustained seizure freedom to determine ASM-responsiveness,[13] which may contribute to information bias from misclassification of the outcome. Future studies should apply the more robust ILAE definition. Finally, in contrast with prior work, we did not find an association between underlying psychiatric conditions and ASM-

resistance.[10, 42] While screening for depression and anxiety is currently recommended,[43] it is not the focus of a neurology visit. Furthermore, the direction of causality between psychiatric disorders and epilepsy remains unclear. A better understanding of this relationship requires more granular psychiatric diagnoses and examination of concomitant treatments.

Despite these limitations, our model can begin to provide treating clinicians with useful information on an individual's prognosis. Patients more readily understand absolute risk differences over relative measures of association.[44, 45] A more accurate clinical prediction model could be determined using data from a prospective cohort of patients with incident IGE followed longitudinally until the development of ASM resistance. A prospective study would require time, substantial funding, and recruitment at multiple epilepsy centers based on our patient numbers. Such an undertaking, however, would no doubt add to our understanding of an often frustratingly difficult condition to manage.

In conclusion, we found that a combination of clinical and EEG factors distinguishes between ASM-resistant versus ASM-responsive IGE with 80% accuracy (AUC = 0.80), better than with clinical variables alone. Clinicians should consider obtaining greater detail about a patient's different seizure types and whether they experience changes in seizure frequency with their menstrual cycle. Combining seizure and menstrual calendars should increase our understanding of the relationship between catamenial epilepsy and ASM-resistant IGE. When further prognostic information is desired, we recommend considering an EEG study of sufficient duration to determine the burden of GSW in sleep. Lastly, electroencephalographers should assess for and document the presence of GPT as a reliable marker for ASM-resistant IGE now replicated across multiple studies.[12, 38, 39] Patients "want to know more" and will benefit from meaningful prognostic information that we can provide for this difficult condition.[46]

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Disclosure of Conflicts of Interest

Dr. Perucca has received speaker honoraria or consultancy fees to his institution from Chiesi, Eisai, LivaNova, Novartis, Sun Pharma, Supernus and UCB Pharma, outside the submitted work. He is an associate editor for *Epilepsia Open*. Dr. O'Brien acknowledges his institution has received consultancy and research funding from UCB Pharma, Eisai, ES Therapeutics, Zynerba, Praxis Pharmaceuticals, and BioGen. The remaining authors have no conflicts of interest.

Ethical Publication Statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References:

1. Jallon P, Latour P. Epidemiology of idiopathic generalized epilepsies Epilepsia. 2005;46 Suppl 9:10-14.

2. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology Epilepsia. 2017 Apr;58:512-521.

3. Szaflarski JP, Lindsell CJ, Zakaria T, Banks C, Privitera MD. Seizure control in patients with idiopathic generalized epilepsies: EEG determinants of medication response Epilepsy Behav. 2010 Apr;17:525-530.

4. Mohanraj R, Brodie MJ. Outcomes of newly diagnosed idiopathic generalized epilepsy syndromes in a non-pediatric setting Acta Neurol Scand. 2007 Mar;115:204-208.

5. Seneviratne U, Cook M, D'Souza W. The prognosis of idiopathic generalized epilepsy Epilepsia. 2012 Dec;53:2079-2090.

6. Kharazmi E, Peltola M, Fallah M, Keränen T, Peltola J. Idiopathic generalized epilepsies: a follow-up study in a single-center Acta Neurol Scand. 2010 Sep;122:196-201.

7. Stevelink R, Koeleman BPC, Sander JW, Jansen FE, Braun KPJ. Refractory juvenile myoclonic epilepsy: a meta-analysis of prevalence and risk factors European Journal of Neurology. 2019;26:856-864.

8. Wirrell EC, Camfield CS, Camfield PR, Gordon KE, Dooley JM. Long-term prognosis of typical childhood absence epilepsy: remission or progression to juvenile myoclonic epilepsy Neurology. 1996 Oct;47:912-918.

9. Nicolson A, Appleton RE, Chadwick DW, Smith DF. The relationship between treatment with valproate, lamotrigine, and topiramate and the prognosis of the idiopathic generalised epilepsies J Neurol Neurosurg Psychiatry. 2004 Jan;75:75-79.

10. Choi H, Detyniecki K, Bazil C, Thornton S, Crosta P, Tolba H, et al. Development and validation of a predictive model of drug-resistant genetic generalized epilepsy Neurology. 2020 Oct 13;95:e2150-e2160.

11. Seneviratne U, Boston RC, Cook M, D'Souza W. EEG correlates of seizure freedom in genetic generalized epilepsies Neurol Clin Pract. 2017 Feb;7:35-44.

12. Sun Y, Seneviratne U, Perucca P, Chen Z, Tan MK, O'Brien TJ, et al. Generalized polyspike train: An EEG biomarker of drug-resistant idiopathic generalized epilepsy Neurology. 2018 Nov 6;91:e1822-e1830.

13. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies Epilepsia. 2010 Jun;51:1069-1077.

14. Schomer DL, Lopes da Silva F. Niedermeyer's Electroencephalography: Basic Principles, Clinical Applications, and Related Fields. Philadelphia: Wolters Kluwer Health; 2010.

15. E. Misulis K, Misulis KE. Atlas of EEG, Seizure Semiology, and Management. Oxford: Oxford University Press, Incorporated; 2013.

16. Hirsch LJ, LaRoche SM, Gaspard N, Gerard E, Svoronos A, Herman ST, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version J Clin Neurophysiol. 2013 Feb;30:1-27.

17. Hirsch LJ, Fong MWK, Leitinger M, LaRoche SM, Beniczky S, Abend NS, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version J Clin Neurophysiol. 2021 Jan 1;38:1-29.

18. Tabaeizadeh M, Aboul Nour H, Shoukat M, Sun H, Jin J, Javed F, et al. Burden of Epileptiform Activity Predicts Discharge Neurologic Outcomes in Severe Acute Ischemic Stroke Neurocrit Care. 2020 Jun;32:697-706.

19. Westhall E, Rosén I, Rossetti AO, van Rootselaar AF, Wesenberg Kjaer T, Friberg H, et al. Interrater variability of EEG interpretation in comatose cardiac arrest patients Clin Neurophysiol. 2015 Dec;126:2397-2404.

20. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine Clin Chem. 1993 Apr;39:561-577.

21. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, et al. Assessing the performance of prediction models: a framework for traditional and novel measures Epidemiology. 2010 Jan;21:128-138.

22. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach Biometrics. 1988 Sep;44:837-845.

23. Herzog AG, Fowler KM, Smithson SD, Kalayjian LA, Heck CN, Sperling MR, et al. Progesterone vs placebo therapy for women with epilepsy: A randomized clinical trial Neurology. 2012;78:1959-1966.

24. Meador KJ, Pennell PB, May RC, Gerard E, Kalayjian L, Velez-Ruiz N, et al. Changes in antiepileptic drug-prescribing patterns in pregnant women with epilepsy Epilepsy Behav. 2018 Jul;84:10-14.

25. Cerulli Irelli E, Morano A, Cocchi E, Casciato S, Fanella M, Albini M, et al. Doing without valproate in women of childbearing potential with idiopathic generalized epilepsy: Implications on seizure outcome Epilepsia. 2020 Jan;61:107-114.

26. Gesche J, Khanevski M, Solberg C, Beier CP. Resistance to valproic acid as predictor of treatment resistance in genetic generalized epilepsies Epilepsia. 2017 Apr;58:e64-e69.

27. Marson A, Burnside G, Appleton R, Smith D, Leach JP, Sills G, et al. The SANAD II study of the effectiveness and cost-effectiveness of valproate versus levetiracetam for newly diagnosed generalised and unclassifiable epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial Lancet. 2021 Apr 10;397:1375-1386.

28. Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy N Engl J Med. 2010 Mar 4;362:790-799.

29. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value Ann Intern Med. 2017 Aug 15;167:268-274.

30. Haneuse S, VanderWeele TJ, Arterburn D. Using the E-Value to Assess the Potential Effect of Unmeasured Confounding in Observational Studies Jama. 2019 Feb 12;321:602-603.

31. Gelisse P, Genton P, Thomas P, Rey M, Samuelian JC, Dravet C. Clinical factors of drug resistance in juvenile myoclonic epilepsy J Neurol Neurosurg Psychiatry. 2001 Feb;70:240-243.

32. Matsuoka H. The seizure prognosis of juvenile myoclonic epilepsy Jpn J Psychiatry Neurol. 1992 Jun;46:293-296.

33. Bartolomei F, Roger J, Bureau M, Genton P, Dravet C, Viallat D, et al. Prognostic factors for childhood and juvenile absence epilepsies Eur Neurol. 1997;37:169-175.

34. Bouma PA, Westendorp RG, van Dijk JG, Peters AC, Brouwer OF. The outcome of absence epilepsy: a meta-analysis Neurology. 1996 Sep;47:802-808.

35. Martínez-Juárez IE, Alonso ME, Medina MT, Durón RM, Bailey JN, López-Ruiz M, et al. Juvenile myoclonic epilepsy subsyndromes: family studies and long-term follow-up Brain. 2006 May;129:1269-1280.

36. Trinka E, Baumgartner S, Unterberger I, Unterrainer J, Luef G, Haberlandt E, et al. Long-term prognosis for childhood and juvenile absence epilepsy J Neurol. 2004 Oct;251:1235-1241.

37. Clarke S, Karoly PJ, Nurse E, Seneviratne U, Taylor J, Knight-Sadler R, et al. Computer-assisted EEG diagnostic review for idiopathic generalized epilepsy Epilepsy Behav. 2019 Oct 29:106556.

38. Jensen CD, Gesche J, Krøigård T, Beier CP. Prognostic Value of Generalized Polyspike Trains and Prolonged Epileptiform EEG Runs J Clin Neurophysiol. 2019 Dec 24.

39. Conrad EC, Chugh N, Ganguly TM, Gugger JJ, Tizazu EF, Shinohara RT, et al. Using Generalized Polyspike Train to Predict Drug-Resistant Idiopathic Generalized Epilepsy J Clin Neurophysiol. 2020 Dec 8.

40. Szaflarski JP, Kay B, Gotman J, Privitera MD, Holland SK. The relationship between the localization of the generalized spike and wave discharge generators and the response to valproate Epilepsia. 2013 Mar;54:471-480.

41. Huang Y, Pepe MS. Assessing risk prediction models in case-control studies using semiparametric and nonparametric methods Stat Med. 2010 Jun 15;29:1391-1410.

42. Gomez-Ibañez A, McLachlan RS, Mirsattari SM, Diosy DC, Burneo JG. Prognostic factors in patients with refractory idiopathic generalized epilepsy Epilepsy Res. 2017 Feb;130:69-73.

43. Patel AD, Baca C, Franklin G, Herman ST, Hughes I, Meunier L, et al. Quality improvement in neurology: Epilepsy Quality Measurement Set 2017 update Neurology. 2018 Oct 30;91:829-836.

44. Schrager SB. Five Ways to Communicate Risks So That Patients Understand Fam Pract Manag. 2018 Nov/Dec;25:28-31.

45. Epstein RM, Alper BS, Quill TE. Communicating evidence for participatory decision making Jama. 2004 May 19;291:2359-2366.

46. Prinjha S, Chapple A, Herxheimer A, McPherson A. Many people with epilepsy want to know more: a qualitative study Fam Pract. 2005 Aug;22:435-441.

Table 1. Clinical characteristics of ASM-resistant IGE cases and ASM-responsive IGE controls, all sites

Characteristic		ASM-responsive Controls, n (% of Controls)	ASM-resistant Cases, n (% of Cases)	P-Value
Total		114	118	
Study Site	Rutgers	10	10	
	Columbia	58	58	
	Alfred	17	19	
	RMH	11	13	
	Cornell	18	18	

Age of Epilepsy Onset	<5 years	9 (7.9%)	10 (8.5%)	0.007
	5-9 years	18 (15.8%)	24 (20.3%)	
	10-14 years	28 (24.6%)	48 (40.7%)	
	15-19 years	42 (36.8%)	29 (24.6%)	
	20-24 years	7 (6.1%)	6 (5.1%)	
	>25 years	10 (8.8%)	1 (0.9%)	
Sex / Catamenial Epilepsy	Women without catamenial epilepsy	64 (56.1%)	57 (48.3%)	0.001
	Women with catamenial epilepsy	7 (6.1%)	27 (22.9%)	
	Men	43 (37.7%)	34 (28.8%)	
Epilepsy Syndrome	GTCS alone / Generalized epilepsy, NOS	65 (57.0%)	53 (44.9%)	0.05
	CAE	6 (5.3%)	5 (4.2%)	
	JAE	7 (6.1%)	20 (17.0%)	
	JME	36 (31.6%)	40 (33.9%)	
Seizure Types	GTCS + absence + myoclonic seizures	10 (8.8%)	30 (25.4%)	<0.001
	GTCS + myoclonic seizures	30 (26.3%)	25 (21.2%)	
	GTCS + absence seizures	23 (20.2%)	42 (35.6%)	
	Absence only or myoclonic only or absence + myoclonic seizures	10 (8.8%)	7 (5.9%)	
	GTCS alone	41 (36.0%)	14 (11.9%)	

History of Psychogenic Non-Epileptic Seizures	Yes	3 (2.6%)	8 (6.8%)	0.14
	No	111 (97.4%)	110 (93.2%)	
Intellectual Disability	Yes	4 (3.5%)	7 (5.9%)	0.39
	No	110 (96.5%)	111 (94.1%)	
Nocturnal Seizures	Yes	5 (4.4%)	15 (12.7%)	0.02
	No	109 (95.6%)	103 (87.3%)	
Prior Status Epilepticus	Yes	2 (1.8%)	10 (8.5%)	0.02
	No	112 (98.3%)	108 (91.5%)	
Concomitant Psychiatric Condition	Yes	44 (38.6%)	57 (48.3%)	0.14
	No	70 (61.4%)	61 (51.7%)	
History of Febrile Seizures	Yes	7 (6.1%)	10 (8.5%)	0.50
	No	107 (93.9%)	108 (91.5%)	
Family History of Epilepsy	Yes	25 (21.9%)	33 (28.0%)	0.29
	No	89 (78.1%)	85 (72.0%)	

Key: ASM: antiseizure medication; CAE: childhood absence epilepsy; GTCS: generalized onset tonic-clonic seizures; IGE: idiopathic generalized epilepsy syndrome; JAE: juvenile absence epilepsy; JME: juvenile myoclonic epilepsy; NOS: not otherwise specified; RMH: Royal Melbourne Hospital

Table 2. EEG characteristics of ASM-resistant IGE cases and ASM-responsive IGE controls, all sites

Characteristic		ASM-responsive Controls, n (% of Controls)	ASM-resistant Cases, n (% of Cases)	P-Value
Total		114	118	
Age at EEG, mean		31.0 (14.0) years	32.1 (14.2) years	0.55

(SD)				
Number of ASMs at EEG, mean (SD)		1.0 (0.55)	1.9 (1.0)	<0.001
Duration of EEG Study	Short (< 4 hours)	67 (58.8%)	63 (53.4%)	0.41
	Extended (4-24 hours)	47 (41.2%)	55 (46.6%)	
GSW Burden in Wake	None	59 (51.8%)	36 (30.5%)	0.004
	Rare	6 (5.3%)	13 (11.0%)	
	Occasional	23 (20.2%)	21 (17.8%)	
	Frequent	15 (13.2%)	23 (19.5%)	
	Abundant	11 (9.7%)	25 (21.2%)	
GSW Burden in Sleep	Sleep not recorded	40 (35.1%)	22 (18.6%)	<0.001
	None	26 (22.8%)	19 (16.1%)	
	Rare	12 (10.5%)	5 (4.2%)	
	Occasional	27 (23.7%)	30 (25.4%)	
	Frequent	7 (6.1%)	26 (22.0%)	
	Abundant	2 (1.8%)	16 (13.6%)	
Generalized Polyspike Train	Yes	2 (1.8%)	25 (21.2%)	<0.001
	No	112 (98.3%)	93 (78.8%)	
Generalized Paroxysmal Fast Activity	Yes	1 (0.9%)	14 (11.9%)	<0.001
	No	113 (99.1%)	104 (88.1%)	

Key: ASM: antiseizure medication; EEG: electroencephalogram; GSW: generalized spike-wave discharge [burden defined as none, rare (fewer than 1 GSW per hour), occasional (more than 1 GSW per hour but fewer than 1 per minute), frequent (more than 1 GSW per minute but fewer than 1 every 10 seconds), abundant (more than 1 every 10 seconds)]; IGE: idiopathic generalized epilepsy syndrome; SD: standard deviation

Table 3. Clinical characteristics of ASM-resistant IGE cases and ASM-responsive IGE controls, non-Columbia sites

Characteristic		ASM-responsive Controls, n (% of Controls)	ASM-resistant Cases, n (% of Cases)	P-Value
Total		56	60	
Age of Epilepsy Onset	<5 years	8 (14.3%)	5 (8.3%)	<0.001
	5-9 years	8 (14.3%)	9 (15.0%)	
	10-14 years	9 (16.1%)	30 (50.0%)	
	15-19 years	20 (35.7%)	14 (23.3%)	
	20-24 years	4 (7.1%)	2 (3.3%)	
	>25 years	7 (12.5%)	0 (0.0%)	
Sex / Catamenial Epilepsy	Women without catamenial epilepsy	37 (66.1%)	29 (48.3%)	0.008
	Women with catamenial epilepsy	3 (5.4%)	16 (26.7%)	
	Men	16 (28.6%)	15 (25.0%)	
Epilepsy Syndrome	GTCS alone / Generalized epilepsy, NOS	29 (51.8%)	17 (28.3%)	0.02
	CAE	4 (7.1%)	3 (5.0%)	
	JAE	5 (8.9%)	16 (26.7%)	
	JME	18 (32.1%)	24 (40.0%)	
Seizure Types	GTCS + absence + myoclonic seizures	3 (5.4%)	12 (20.0%)	<0.001
	GTCS + myoclonic seizures	15 (26.8%)	14 (23.3%)	
	GTCS + absence seizures	11 (19.6%)	23 (38.3%)	

	Absence only or myoclonic only or absence + myoclonic seizures	3 (5.4%)	4 (6.7%)	
	GTCS alone	24 (42.9%)	7 (11.7%)	
History of Psychogenic Non-Epileptic Seizures	Yes	3 (5.4%)	5 (8.3%)	0.53
	No	53 (94.6%)	55 (91.7%)	
Intellectual Disability	Yes	1 (1.8%)	6 (10.0%	0.06
	No	55 (98.2%)	54 (90.0%)	
Nocturnal Seizures	Yes	3 (5.4%)	12 (20.0%)	0.02
	No	53 (94.6%)	48 (80.0%)	
Prior Status Epilepticus	Yes	1 (1.8%)	7 (11.7%)	0.04
	No	55 (98.2%)	53 (88.3%)	
Concomitant Psychiatric Condition	Yes	22 (39.3%)	27 (45.0%)	0.53
	No	34 (60.7%)	33 (55.0%)	
History of Febrile Seizures	Yes	3 (5.4%)	7 (11.7%)	0.23
	No	53 (94.6%)	53 (88.3%)	
Family History of Epilepsy	Yes	17 (30.4%)	20 (33.3%)	0.73
	No	39 (69.6%)	40 (66.7%)	

Key: ASM: antiseizure medication, CAE: childhood absence epilepsy; GTCS: generalized onset tonic-clonic seizures; IGE: idiopathic generalized epilepsy syndrome; JAE: juvenile absence epilepsy; JME: juvenile myoclonic epilepsy; NOS: not otherwise specified; RMH: Royal Melbourne Hospital

Table 4. Multivariable logistic regression analysis assessing whether catamenial epilepsy is associated with ASM-resistant IGE for non-Columbia study subjects

Predictor Variable		OR	95% CI for OR	P-Value
Sex / Catamenial Epilepsy	Women without catamenial epilepsy	--	--	--
	Women with catamenial epilepsy	**4.27**	**1.18-20.55**	**0.04**
	Male	1.96	0.75-5.41	0.18
Seizure Types	**GTCS + absence + myoclonic seizures**	**12.25**	**2.69-72.06**	**0.002**
	GTCS + myoclonic seizures	2.99	0.96-10.01	0.06
	GTCS + absence seizures	**6.40**	**2.00-22.92**	**0.003**
	Absence only or myoclonic only or absence + myoclonic seizures	5.83	1.00-38.56	0.05
	GTCS alone	--	--	--

***Bolded variables were statistically significant at p < 0.05**

Key: CI: confidence interval; GTCS: generalized onset tonic-clonic seizures; OR: odds ratio

Table 5. Multivariable logistic regression analysis assessing clinical and EEG variables for study subjects at all sites

Predictor		OR	95% CI for	P-Value

Variable			**OR**	
Sex / Catamenial Epilepsy	Women without catamenial epilepsy	--	--	--
	Women with catamenial epilepsy	**3.53**	**1.32-10.41**	**0.02**
	Male	1.21	0.62-2.38	0.58
Seizure Types	**GTCS + absence + myoclonic seizures**	**7.06**	**2.55-20.96**	**<0.001**
	GTCS + myoclonic seizures	2.07	0.83-5.33	0.12
	GTCS + absence seizures	**4.45**	**1.84-11.34**	**0.001**
	Absence only or myoclonic only or absence + myoclonic seizures	2.41	0.68-8.39	0.17
	GTCS alone	--	--	--
GSW Burden in Sleep	Sleep not recorded	0.74	0.32-1.76	0.50
	None	--	--	--
	Rare	0.92	0.24-3.23	0.90
	Occasional	1.20	0.51-2.88	0.68
	Frequent	**3.43**	**1.12-11.36**	**0.04**
	Abundant	**7.21**	**1.50-54.07**	**0.02**

Generalized Polyspike Train	**Yes**	**5.49**	**1.27-38.69**	**0.04**
	No	--	--	--

***Bolded variables were statistically significant at p < 0.05**

Key: CI: confidence interval; GSW: generalized spike-wave discharge [burden defined as none, rare (fewer than 1 GSW per hour), occasional (more than 1 GSW per hour but fewer than 1 per minute), frequent (more than 1 GSW per minute but fewer than 1 every 10 seconds), abundant (more than 1 every 10 seconds)]; GTCS: generalized onset tonic-clonic seizures; OR: odds ratio