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FULL-LENGTH ORIGINAL RESEARCH

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

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Abstract

Objective: We sought to determine which combination of clinical and electroencephalography (EEG) characteristics differentiate between an antiseizure medication (ASM)–resistant vs 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 and 2018. We recorded clinical characteristics and findings from the first available EEG study for each patient. We then compared characteristics of cases vs 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 (odds ratio [OR] 3.53, 95% confidence interval [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 (GSWs) 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 (GPTs; OR 5.49, 95% CI 1.27–38.69). The discriminative ability of our final multivariable model, as measured by area under the receiver-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

Heiman and Choi contributed equally to this work.

to record the burden of GSWs in sleep and assessing for the presence of GPTs may provide additional predictive value.

KEYWORDS
case-control study, catamenial, epidemiology, outcome, prognosis

1 | 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 an 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. Although the discriminative model only ranged between 0.58 and 0.65 (area under the curve), we found that catamenial epilepsy, that is, 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 electroencephalography (EEG) findings. EEG markers of ASM-resistance have included higher densities of generalized epileptiform discharges (GEDs) and the presence of generalized polyspike trains (GPTs).[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.

Key points

- Clinical characteristics associated with antiseizure medication (ASM)–resistant idiopathic generalized epilepsy (IGE) include catamenial epilepsy and certain seizure-type combinations.
- EEG characteristics associated with ASM-resistant IGE include increased GSWs in sleep and the presence of GPTs.
- Prospective studies are needed to refine diagnostic and treatment strategies for ASM-resistant IGE.

2 | METHODS

2.1 | 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 from 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 article.[10] Specifically, we identified adult (age ≥18 years) patients with (1) a diagnosis of IGE as per the treating epileptologist and (2) a normal brain magnetic resonance imaging (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 EEG studies 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 6 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 nondisabling 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.

2.2 | 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 vs 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 nonepileptic 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 nonepileptic 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) generalized tonic-clonic seizure (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] Finally, 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., and 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 EEG studies as either short (<4 h in duration) or long recordings (4–24 h in duration). For studies that lasted multiple days, we reviewed the first 24 h 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 (GSWs) in wakefulness, (2) the burden of GSWs in sleep, if sleep was recorded, (3) the presence of GPTs (yes/no), and (4) the presence of generalized paroxysmal fast activity (GPFA, yes/no). Here, GSWs refer to bilaterally symmetric (<30% amplitude difference between hemispheres) surface-negative spikes lasting 20–80 msec 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, that is, stage N2 sleep.[14,15] We determined the burden of GSWs in wakefulness and sleep using the American Clinical Neurophysiology Society (ACNS) critical care EEG terminology for sporadic epileptiform discharges as follows: (1) none, (2) rare (<1 GSW per h), (3) occasional (>1 GSW per h but <1 per min), (4) frequent (>1 GSW per min but <1 every 10 s), and (5) abundant (>1 GSW every 10 s).[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 GPTs according to the recent description by Sun and colleagues as a burst of at least five generalized rhythmic spikes lasting <1 s in duration in the awake or sleep states.[12] We defined GPFA conventionally as a burst of generalized rhythmic spikes lasting 1 s or longer in duration in the awake or sleep states.[14,15]

2.3 | Statistical analysis

2.3.1 | 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 vs controls at $p < .1$. 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.

2.3.2 | 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 $p < .1$ 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-operating 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] which included three clinical characteristics only (catamenial epilepsy, concomitant psychiatric condition, and seizure type) applied to the current data set from all five centers using DeLong's method.[22] All data analyses were performed using SAS version 9.4.

3 | RESULTS

3.1 | 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 and 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%, $p = .005$).

3.1.1 | 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 at 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.

3.1.2 | 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 at 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

TABLE 1 Clinical characteristics of ASM-resistant IGE cases and ASM-responsive IGE controls at 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 at epilepsy onset			
<5 years	9 (7.9%)	10 (8.5%)	.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%)	.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%)	.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%)	<.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%)	.14
No	111 (97.4%)	110 (93.2%)	
Intellectual disability			
Yes	4 (3.5%)	7 (5.9%)	.39
No	110 (96.5%)	111 (94.1%)	
Nocturnal seizures			
Yes	5 (4.4%)	15 (12.7%)	.02
No	109 (95.6%)	103 (87.3%)	
Prior status epilepticus			
Yes	2 (1.8%)	10 (8.5%)	.02
No	112 (98.3%)	108 (91.5%)	
Concomitant psychiatric condition			

(Continues)

TABLE 1 (Continued)

Characteristic	ASM-responsive controls, *n* (% of controls)	ASM-resistant cases, *n* (% of cases)	*p*-value
Yes	44 (38.6%)	57 (48.3%)	.14
No	70 (61.4%)	61 (51.7%)	
History of febrile seizures			
Yes	7 (6.1%)	10 (8.5%)	.50
No	107 (93.9%)	108 (91.5%)	
Family history of epilepsy			
Yes	25 (21.9%)	33 (28.0%)	.29
No	89 (78.1%)	85 (72.0%)	

Abbreviations: ASM, antiseizure medication; CAE, childhood absence epilepsy; GTCS, generalized 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 at all sites

Characteristic	ASM-responsive controls, *n* (% of controls)	ASM-resistant cases, *n* (% of cases)	*p*-value
Total	114	118	
Age at EEG, mean (SD)	31.0 (14.0) years	32.1 (14.2) years	.55
Number of ASMs at EEG, mean (SD)	1.0 (0.55)	1.9 (1.0)	<.001
Duration of EEG study			
Short (<4 h)	67 (58.8%)	63 (53.4%)	.41
Extended (4–24 h)	47 (41.2%)	55 (46.6%)	
GSW burden in wake			
None	59 (51.8%)	36 (30.5%)	.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%)	<.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%)	<.001
No	112 (98.3%)	93 (78.8%)	
Generalized paroxysmal fast activity			
Yes	1 (0.9%)	14 (11.9%)	<.001
No	113 (99.1%)	104 (88.1%)	

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

and EEG characteristics (Tables 1 and 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.

TABLE 3 Clinical characteristics of ASM-resistant IGE cases and ASM-responsive IGE controls at non-Columbia sites

Characteristic	ASM-responsive controls, *n* (% of controls)	ASM-resistant cases, *n* (% of cases)	*p*-value
Total	56	60	
Age at epilepsy onset			
<5 years	8 (14.3%)	5 (8.3%)	<.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%)	.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%)	.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%)	<.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%)	.53
No	53 (94.6%)	55 (91.7%)	
Intellectual disability			
Yes	1 (1.8%)	6 (10.0%)	.06
No	55 (98.2%)	54 (90.0%)	
Nocturnal seizures			
Yes	3 (5.4%)	12 (20.0%)	.02
No	53 (94.6%)	48 (80.0%)	
Prior status epilepticus			
Yes	1 (1.8%)	7 (11.7%)	.04
No	55 (98.2%)	53 (88.3%)	
Concomitant psychiatric condition			
Yes	22 (39.3%)	27 (45.0%)	.53
No	34 (60.7%)	33 (55.0%)	
History of febrile seizures			
Yes	3 (5.4%)	7 (11.7%)	.23
No	53 (94.6%)	53 (88.3%)	
Family history of epilepsy			
Yes	17 (30.4%)	20 (33.3%)	.73
No	39 (69.6%)	40 (66.7%)	

Abbreviations: ASM, antiseizure medication; CAE, childhood absence epilepsy; GTCS, generalized 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**	**.04**
Male	1.96	0.75–5.41	.18
Seizure types			
GTCS + absence + myoclonic seizures	**12.25**	**2.69–72.06**	**.002**
GTCS + myoclonic seizures	2.99	0.96–10.01	.06
GTCS + absence seizures	**6.40**	**2.00–22.92**	**.003**
Absence only or myoclonic only or absence +myoclonic seizures	5.83	1.00–38.56	.05
GTCS alone	—	—	—

Note: Bolded variables were statistically significant at $p < .05$

Abbreviations: CI, confidence interval; GTCS, generalized tonic-clonic seizures; OR, odds ratio.

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

Predictor Variable	OR	95% CI for OR	*p*-value
Sex/catamenial epilepsy			
Women without catamenial epilepsy	—	—	—
Women with catamenial epilepsy	**3.53**	**1.32–10.41**	**.02**
Male	1.21	0.62–2.38	.58
Seizure types			
GTCS + absence + myoclonic seizures	**7.06**	**2.55–20.96**	**<.001**
GTCS + myoclonic seizures	2.07	0.83–5.33	.12
GTCS + absence seizures	**4.45**	**1.84–11.34**	**.001**
Absence only or myoclonic only or absence +myoclonic seizures	2.41	0.68–8.39	.17
GTCS alone	—	—	—
GSW burden in sleep			
Sleep not recorded	0.74	0.32–1.76	.50
None	—	—	—
Rare	0.92	0.24–3.23	.90
Occasional	1.20	0.51–2.88	.68
Frequent	**3.43**	**1.12–11.36**	**.04**
Abundant	**7.21**	**1.50–54.07**	**.02**
Generalized polyspike train			
Yes	**5.49**	**1.27–38.69**	**.04**
No	—	—	—

Note: Bolded variables were statistically significant at $p < .05$.

Abbreviations: CI, confidence interval; GSW, generalized spike-wave discharge [burden defined as none, rare (fewer than 1 GSW per h), occasional (more than 1 GSW per h but fewer than 1 per min), frequent (more than 1 GSW per min but fewer than 1 every 10 s), abundant (more than 1 every 10 s)]; GTCS, generalized tonic-clonic seizures; OR, odds ratio.

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 GPTs. 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 EEG studies. 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 was 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% confidence interval [CI]: 0.74–0.85). In contrast, the AUC for our previously published model[10] was 0.73 (95% CI: 0.68–0.79) when applied to the same data set, with a statistically significant difference in the AUC between these two models of 0.07 ($p = .003$).

4 | DISCUSSION

In this multi-center case-control study conducted at sites within the United States 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 GSWs in sleep and GPTs). Our final predictive model discriminates between ASM-resistant and ASM-responsive IGE with 80% accuracy (AUC = 0.80) in this data set. 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 (odds ratio [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 treated previously with valproate, thereby 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 comorbidities. However, with more than 10 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] In addition, we found that the combination of GTCS and absence seizures was also observed more with ASM-resistant IGE. Of interest, the combination of seizure types, rather than the IGE syndrome, distinguished ASM resistance more accurately. Prior studies examining the prognosis of CAE vs JAE found that the presence of GTCS, rather than the age at 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 discussed previously 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 (GGEs) that include other conditions we did not examine in our study.[2]

We also found that an increased burden of GSWs in sleep and the presence of GPTs are EEG factors independently associated with ASM-resistant IGE. Seneviratne and colleagues recently performed prospective 24 h ambulatory EEG studies on a cohort of patients with IGE, and they 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. Although 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 GSWs 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 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 and awake 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 vs 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 and 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 EEG studies of uniform duration, as previously done by Seneviratne et al.[11] Finally, 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.

Although 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 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] Although 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 vs 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. Finally, 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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CONFLICT 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.

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