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Seizure control in patients with idiopathic generalized epilepsies – EEG determinants of medication response

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Abstract

In a minority of patients with IGEs, seizures continue despite appropriate treatment. We sought to determine the clinical and EEG factors associated with medication response in these patients. All patients with IGEs evaluated by epilepsy specialists between 11/17/08 and 11/16/09 were included. We collected information on seizure freedom (dependent variable), EEG asymmetries, response to valproic acid (VPA), MRI characteristics, medication use, demographic information and seizure history (predictors). We identified 322 patients with IGEs; 45 (14%) were excluded from analyses because of either always having normal EEG (N = 26), lack of any EEG data (N = 3) or medication non-compliance (N = 26). JME patients were more likely to respond to VPA when compared to other IGE patients, and VPA response was associated with seizure freedom. When EEG characteristics were considered, presence of any focal EEG abnormalities (focal slowing, focal epileptiform discharges or both) was associated with decreased odds of seizure-freedom. These findings suggest that IGE patients with poor seizure control may have atypical IGE with possibly focal, e.g., frontal rather than thalamic onset.

Keywords

EEG; IGE; JME; medication response; valproic acid

INTRODUCTION

Approximately 30-40% of people with epilepsy have seizures defined by the International League Against Epilepsy as generalized at onset (1,2). These patients experience various

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types of seizures including absences, myoclonic seizures or generalized tonic-clonic seizures. Although idiopathic generalized epilepsies (IGEs) are thought to be relatively easy to control with antiepileptic drugs (AEDs), up to 30% of patients with IGEs have incomplete response to treatment with valproic acid (VPA) or other AEDs (3,4). Some patients continue to have seizures despite best medical therapy and suffer significant long-term consequences including poor quality of life, unemployment, lack of independence, and stigma.(5,6)

The reasons for relative "medication resistance" in IGE patients have been shown to include poor adherence to medication regimens (sometimes called "pseudo-resistance" (3)), presence of psychiatric problems (4,7), early age at epilepsy onset (8), and presence of generalized tonic-clonic seizures (8,9). In patients with JME, multiple seizure types and EEG asymmetries are associated with worse seizure control (10). In childhood or juvenile absence epilepsy, lack of control of absence seizures is a risk factor for persistent generalized tonic-clonic seizures (11). Studies examining treatment resistance in IGEs have been limited to a small number of subjects (3,10), were conducted before newer AEDs became available or were tested in patients with IGEs (3,4,9,10), focus on clinical (12,13) or EEG aspects of IGEs (14,15) sometimes without providing full definitions that were used to describe EEG abnormalities (9,10).

The AED of choice for patients with IGEs is VPA (16). However, some patients remain poorly controlled despite large doses of this or other syndrome-appropriate AEDs. Fernando-Dongas et al., found EEG-asymmetries and intellectual deficiencies were associated with VPA-resistance (10), but the intellectual deficiencies were not well defined suggesting the possibility that some of these patients may have had symptomatic rather than idiopathic generalized epilepsy. Therefore, the main aim of this retrospective study was to explore factors associated with medication resistance in a large sample of patients with IGEs with particular focus on identifying likely predictors for poor medication response in patients with JME, and identifying differences in predictors between patients with JME and other IGEs. The main hypothesis was that patients who respond to VPA and are well controlled show very typical IGEs characteristics including symmetric EEG abnormalities, with the opposite noted in patients with poorly-controlled IGEs. Such findings, if present, could be due at least in part to focal epilepsies presenting clinically as IGEs.

METHODS

Subjects

This retrospective observational study was approved by the Institutional Review Board of the University of Cincinnati. Patients seen in the outpatient clinic of the Cincinnati Epilepsy Center between 11/17/08 and 11/16/09 were eligible to participate if they were treated by epilepsy specialist and had a diagnosis of IGE, as defined by the International League Against Epilepsy (1,2). We focused only on patients treated by epilepsy specialists since epilepsy outcomes have been shown to differ between patients treated by general neurologists and those treated by epilepsy specialists (17,18). Study subjects were identified via review of the electronic health records; paper charts were reviewed for missing data if needed (less than 10% of IGE subjects required additional paper chart review). All charts were reviewed for diagnosis based on the impression of the treating clinician. In cases where the chart entry was not clear, the treating physician was contacted directly with questions and/or a request for additional records (less than 5% of the charts). If the diagnosis was still uncertain (e.g., frontal lobe vs. generalized epilepsy), patients were excluded from the study.

There were 456 patients with a clinical diagnosis of generalized epilepsy identified from 2,522 reviewed charts (2107 with epilepsy, 415 with diagnoses other than epilepsy, e.g., spells or non-epileptic seizures). Of the 456 patients, 134 were excluded since they carried

the diagnosis of symptomatic generalized epilepsy based on the clinical presentation, EEG findings, or presence of cognitive handicaps. Presence of cognitive handicaps was defined as IQ testing less than 70 (if available), need for special education or poor school performance evidenced by the need to repeat grades. The remaining 322 patients were diagnosed with IGEs based on clinical and EEG criteria, and complete review of their charts was conducted (seven of these patients were included in the analyses of their EEG/fMRI data as a part of a larger study evaluating GSWD generators in patients with IGEs (19)).

Data collection and definitions

All charts were abstracted by a single investigator (JPS) using a standardized case report form and data dictionary with explicit, pre-specified data definitions. Disease- and treatment-specific data including type of epilepsy, AED therapy before and during the treatment with VPA, duration of epilepsy, outcomes (as defined below), EEG and neuroimaging were extracted. For the purpose of this study, IGEs were divided into 4 groups: 1. Possible IGE but EEG always normal, 2. Juvenile myoclonic epilepsy (JME), 3. Absence epilepsy (childhood or juvenile; AE), 4. Other IGEs (20). All charts were reviewed within 1 week of a patient's epilepsy clinic visit, and charts of all patients enrolled were re-reviewed on the last day of the study for any new data or findings (seizures, EEGs, study results, medication changes, etc.).

Seizure freedom was the outcome variable. As previously, we assessed charts for the presence/absence of seizures in the 3-month period preceding the last chart review (18). The choice of 3 months cut-off was based on the fact that in our geographic area 3-months seizure-free period is required for driving. Further, this cut-off was chosen to minimize the potential bias due to referral of patients with increased seizure frequency as this time is approximately 3-6 times longer than our current wait time for an initial appointment. Expanding this variable to 12 months would be impractical as many charts do not contain such information. Seizure freedom variable was evaluated at each visit and changed from seizure-free to non-seizure-free if there were calls or reports of seizures, if medication changes were instituted by the treating physician due to possible seizures, or if there was EEG evidence of seizures (e.g., 24 hour ambulatory EEG showing absence seizures or bursts of generalized epileptiform discharges lasting more than 2 seconds) (15,19,21,22). Age of onset was defined as the first age at which seizures were observed (absence, myoclonus or generalized tonic clonic seizures; febrile seizures clearly different from the diagnosis of idiopathic generalized epilepsy were excluded from age of onset calculations). Finally, VPA-response was defined as at least 3 months of seizure-freedom while receiving treatment with this AED. Many patients were either not able to tolerate this AED despite being seizure-free (e.g. due to tremor, weight gain or hair loss) or had other reasons for discontinuation (e.g. women of childbearing age desiring to become pregnant).

Abnormal MRI was defined as any study with focal findings (e.g. medial temporal sclerosis, cortical dysplasia, areas of encephalomalacia) that could potentially have an effect on the diagnosis. All available EEG reports were reviewed for evidence of any abnormalities; attempts were made to review the last performed EEG (routine, ambulatory or video/EEG monitoring). We developed separate definitions for review of the EEG report and for direct review of the EEG itself. For review of the EEG report, we defined the following variables as reported by the interpreting physician: 1. Normal EEG, 2. Focal EEG abnormalities (e.g., focal slowing and/or focal epileptiform discharges), 3. Focal epileptiform discharges or, 4. Generalized epileptiform discharges. For review of the available EEGs themselves, a more precise classification of abnormalities was developed (23,24). This included: 1. Generalized spike and wave discharges or polyspike and wave discharges (GSWD) defined as any epileptiform discharges occurring in bisynchronous fashion with maximum amplitude usually over the F3 and F4 electrodes (possibly with bifrontal and paracentral or bi-occipital

predominance). Focal epileptiform discharges were considered spike fragments if they had clearly the same morphology as GSWD with exception of the more focal (e.g., predominantly over one hemisphere) appearance. 2. Spike fragments were defined as "asymmetric" GSWD, as were any GSWD with more than 30% amplitude difference as measured over the electrodes with the maximum GSWD amplitude. 3. All other epileptiform discharges were labeled as "focal". 4. Focal slowing was defined as any regional EEG abnormality that was not epileptiform in nature. Finally, current AEDs were divided into two groups in order to examine whether AED choices were affected by EEG abnormalities and whether the use of AEDs not indicated for the treatment of IGEs led to better seizure control in patients with asymmetric EEG findings.(25,26) One group of AEDs included syndrome-appropriate AEDs (VPA, lamotrigine, topiramate, zonisamide, levetiracetam, felbamate and benzodiazepines); second group included other AEDs.

Data analyses

Data were initially characterized using descriptive statistics (means and standard deviations or frequencies and percentages as appropriate). We compared groups of patients using Fisher's Exact test or Pearson's Chi-square test for categorical data, and Student's t-test for continuous data. When data departed from normality, the Mann-Whitney U-test was used for between group comparisons and the Wilcoxon Signed-Rank test was used for comparisons within groups. We modeled the effect of EEG abnormalities and VPA use on seizure-freedom using logistic regression. All analyses were a priori, planned comparisons and derived from the main hypotheses, therefore no corrections for multiple comparisons were made and the significance level was set to 5% ($\alpha = 0.05$) for all analyses (see below). All data management and analyses were performed using SPSS V. 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Twenty nine patients (29/322; 9%) with a presumptive diagnosis of IGE were excluded from analyses because of either always having normal EEG (26/29) or lack of any EEG data (3/29). An additional 26 (26/293; 9%) patients were excluded from analyses with a history of medication non-compliance or inadequate life style regulation (e.g., sleep deprivation or alcohol use) leading to possible pseudo-resistance. Hence, the final sample included 267 subjects with IGEs (106 with JME, 55 with AE, and 106 with other IGEs). There were no differences between the included and excluded subjects in the age at epilepsy onset (15.8 years vs. 14.4 years; p=0.07), age at enrollment (34.2 years vs. 32.5 years; p=0.27), gender (p=0.06), or proportion with a JME diagnosis (p=0.57). Finally, these analyses were repeated on all subjects with EEG data including patients with normal EEGs (N=293) in order to eliminate the influence of non-inclusion of IGE patients with normal EEGs (N=26) on the results of the study. No significant differences were noted in the age at epilepsy onset (16.0 vs. 14.4, p=0.379), age at enrollment (34.0 vs. 33.1, p=0.729), gender (p=0.069), or proportion of patients with JME (p=0.687) between the included and excluded patients, respectively; there were no differences in seizure freedom between patients with always normal EEGs vs. other patients (p=0.913) or in VPA response (p=0.682).

Relatively minor differences were noted between patients with JME and other IGEs (Table 1). Patients with IGEs other than JME had a slightly higher chance of having GSWD on their most recent EEG report (69.8% vs. 57.1%; p=0.04) and higher age of epilepsy onset (17.2 years vs. 13.7 years; p=0.001); no differences were noted in the frequency of incidental MRI findings, percentage of females, or family history of epilepsy. Clinical differences were further evaluated. In patients with JME, having absences was associated with decreased odds of seizure freedom (OR 0.100, 95CI 0.021-0.465; p=0.003) and of VPA response (OR 0.241, 95CI 0.078-0.748, p=0.014). Absence seizures were marginally

associated with decreased odds of seizure freedom among all other IGEs (OR 0.419, 95 CI 0.167-1.048, p=0.063), but were not associated with VPA response (OR 0.880, 95CI 0.372-2.084, p=0.771). Generalized tonic-clonic seizures were not included in statistical models as a predictor of seizure freedom because all patients who were free of generalized seizures were also overall seizure-free (JME and other IGEs) and in only one patient who never had generalized seizures VPA was not successful in controlling seizures. Inclusion of patients with normal EEGs resulted in only one minor difference: the family history tended to be more common in those with other IGEs vs. JME (p=0.055). Inclusion of patients with normal EEGs did not significantly change any of the subsequent results hence the results of these analyses are not reported.

In patients with JME, seizure freedom occurred in 85%, and in other IGEs patients seizure freedom occurred in 82% of cases (31/44 JAE patients were successfully controlled by VPA; 70.5%, 95CI 54.6-82.8%). Seizure freedom was not dependent on whether the patient had JME or not (p=0.543). Finally, in patients with JME, VPA was successful in controlling seizures in 78%, and in other IGEs patients it was successful in controlling seizures in 67% of cases. Success of VPA tended to be dependent on whether the patient had JME or not; the odds of VPA being successful were 1.763 times higher for those with JME than those with other IGEs (95%CI 0.923 - 3.370, p=0.086). The success of VPA was a significant predictor of seizure freedom (OR 6.05, 95CI 2.7-13.6; p<0.001) and whether or not the success of VPA predicted seizure freedom was independent of JME (p=0.725). Of note, from among 138 patients initially successfully treated with VPA, 77 had to be weaned off of this AED due to side effects or other reasons. While many remained seizure-free, in 12 this AED change resulted in loss of seizure freedom. For the purpose of this study these patients were labeled “VPA-responders”.

Initial EEG

Results of the first EEG were available in 106 patients (41 with JME). Overall, there were no differences in the first EEG between JME patients and other IGE patients (Table 1). GSWD and focal EEG abnormalities (focal slowing and/or focal epileptiform discharges) were noted more frequently on the first EEG in IGE patients who later did not achieve seizure-free status (p=0.037 and 0.032, respectively); focal EEG abnormalities were also noted more frequently in non-seizure-free JME patients (p=0.004).

All EEGs

Several significant differences between seizure-free vs. not-seizure-free patients were noted when the EEG variables were compared (Table 1). Overall, JME and other IGE patients with focal EEG abnormalities (focal slowing, focal epileptiform discharges or both) were less likely to be seizure-free. Based on EEG reports, focal slowing or focal epileptiform discharges individually did not significantly decrease the odds of seizure freedom (OR 0.776, 95CI 0.311 to 1.94, p=0.588; OR 0.563, 95CI 0.248-1.277, p=0.169, respectively) but, the presence of any focal EEG abnormalities (combined focal slowing and focal epileptiform discharges), was associated with decreased odds of seizure freedom (OR 0.241, 95CI 0.084 to 0.695, p=0.008). Based on the review of the last EEG, asymmetry in GSWD and focal findings (focal slowing or focal epileptiform discharges) were significantly associated with decreased odds of seizure freedom (OR 0.209; 95 CI 0.083 to 0.526, p=0.001; OR 0.244; 95 CI 0.074-0.805, p=0.021, respectively), while GSWD and normal findings were not (OR 0.258, 95CI 0.036 to 1.859, p=0.179; OR 0.386, 95CI 0.045-3.311, p=0.385). Thus the findings indicate that seizure-free patients are more likely to have an EEG that is either normal or shows only symmetric GSWD. Finally, EEG asymmetry variables were not associated with type of AED used based on logistic regression (all

p≥0.093 for all) and the use of non-syndrome-specific AEDs in these patients was not associated decreased seizure control (all p≥0.178).

DISCUSSION

In this retrospective study we explored EEG findings associated with seizure-freedom and medication response in patients with JME and other types of IGEs. Our main finding is that any EEG asymmetries in patients with IGEs, whether focal slowing, focal epileptiform discharges or asymmetric generalized spike and wave discharges (defined as more than 30% amplitude asymmetry) are associated with poor VPA response and decreased chance of seizure-freedom. While these findings may not be surprising as they are supported by literature, they provide additional evidence for clinical and possibly functional differences in patients with medication-responsive and medication-resistant IGEs.

Several studies evaluated factors associated with poor seizure control in patients with IGEs. The concept is that since IGE patients are thought to have the same location and type of seizure and GSWD generators and the seizures and other clinical presentations of IGEs are a continuum that starts in childhood and persists throughout lifetime (27), then these patients should uniformly respond to the same AED. The notion of IGEs continuum is further supported by human EEG triggered functional MRI (EEG/fMRI) data indicating that seizures or GSWDs in either drug-naïve children (28) or AED-treated adult patients (29) are possibly generated in thalami indicating the same underlying etiology as part of such a continuum. Recent human (19,30) data suggest that in some patients the frontal lobes may be the seizure and GSWD generators. These authors suggest that thalamus may be involved in GSWD generation as a part of the network that participates in seizure propagation rather than being the main component of such network. If IGEs patients represent a continuum of the same disorder with thalamic onset then, at least theoretically, they should respond to one and possibly the same AED, especially VPA, the prototypical AED used in IGEs (31). Why do so many patients require AEDs other than VPA or remain poorly controlled despite multiple therapeutic trials (32,33)? This retrospective study tries to shed light on the underlying factors leading to AED resistance.

Relatively little is known about the prevalence and the risk factors associated with drug resistance or intractability in IGE patients. Few studies tried to address this question in selected group of IGEs patients (mainly patients with JME). For example, in a retrospective review of 155 consecutive patients with newly diagnosed JME, 15.5% had persisting seizures despite adequate therapy and lifestyle adjustment (4). Clinical features associated with drug resistance were the presence of psychiatric problems and the combination of 3 seizure types (absence, myoclonic and GTC). Further, in concordance with our findings, family history of epilepsy, age at seizure onset, gender, results of conventional neuroimaging (CT and MRI) were not significantly associated with drug resistance in JME. A study of risk factors associated with VPA resistance in childhood epilepsy found that experiencing generalized seizures and high pre-treatment absence frequency were associated with poor seizure control (11). Another retrospective review of JME patients with intractable epilepsy found that 10/33 patients (30%) were VPA resistant (10) and, as a group, the VPA-resistant patients had a higher frequency of EEG asymmetries, although the asymmetries were not clearly defined. Atypical seizure characteristics, including auras and post-ictal confusion and intellectual deficiency, were also associated with medication resistance. This brings the issue of EEG asymmetries into light. In our study, we performed two separate analyses of EEG data – one based on review of the EEG report and one based on review of the EEG itself. While we do not see any substantial differences in EEG characteristics between JME vs. other IGE patients, there is clear evidence that EEG asymmetries, whether based on review of the EEG report of the EEG itself (initial or all EEG data), are associated

with VPA and/or other AED resistance. This may be related to differences in localization the GSWD generators. If, in fact, IGEs-like epilepsies can be a manifestation of focal lesions, this would explain the presence of focal EEG abnormalities and also the lower response to VPA (34-36). Finally, IGEs as a group of epilepsies are considered to be of primarily genetic origin but specific genetic abnormalities were thus far identified in only a minority of IGE patients (37). While some of the families with identified genetic abnormalities have mendelian or monogenetic abnormalities (38-40) other, complex modes of inheritance (e.g., single nucleotide polymorphisms) were also identified (41). Since the genetic abnormalities and associated with them molecular abnormalities are likely widespread, we would expect these patients to have symmetric EEG abnormalities more frequently than other patients diagnosed with IGEs. Such molecular differences may also underlie differences in VPA response between the patients with genetic vs. other etiologies of their epilepsies but currently such data are not available.

To our knowledge, there have been few large studies that have included patients with multiple IGEs subtypes and their EEG data. In an analysis of 962 pediatric and adult patients with IGEs, Nicolson et al. found that age of onset of less than 5 years or an “atypical” presentation were associated with poor outcome (31). These authors also reviewed EEG data as a part of syndromic classification and did not find any EEG differences between controlled patients and patients with persistent seizures (their EEG data description for analysis was very limited – GSWD, photoparoxysmal response or focal abnormalities). A study by Wolf and Inoue noted asymmetric GSWD were associated with lack of response to medications in patients with absence seizures (9). Another, already mentioned study by and Fernando-Dongas et al., noted that EEG asymmetries were associated with medication resistance in JME patients (10). Finally, Leutmezer et al. noted focal EEG features in 30-35% of the IGEs patients with poorly controlled seizures (20). Our findings of the association between focal EEG abnormalities and poor seizure control are in concordance with these studies. Based on the above, a pattern appears to be emerging – focal EEG abnormalities are associated with increased risk of poor seizure control. So, the question remains whether there is other evidence to support focal, possibly frontal lobe dysfunction in IGE patients and, therefore, to support the theory that that frontal lobes and not the thalamus may be the reason for AED-resistance in atypical IGE patients? Based on the notion that patients with asymmetric EEG findings could have focal onset epilepsy we conducted additional analyses to evaluate the effect of syndrome-appropriate vs. syndrome-inappropriate AED use in these patients as syndrome-inappropriate AEDs were observed previously to lead to poor seizure control (25,26). The lack of this relationship in our data may be related to the fact that these analyses were performed based on the current status of seizure control after AEDs were adjusted by epilepsy-trained physicians who are known to afford patients with epilepsy better seizure control than non-epilepsy trained physicians (18).

The issue of frontal lobe dysfunction in patients with frontal lobe epilepsy and JME was previously examined using neuropsychological testing and PET (4,42-46). These studies found frontal lobe dysfunction in patients with JME to be similar to the abnormalities seen in patients with frontal lobe epilepsy. Furthermore, previously mentioned MRI studies confirmed that up to 40% of patients with JME have structural abnormalities (47-49), but neither these nor other studies have questioned whether the functional and structural abnormalities are more prevalent in patients with VPA-resistant or in VPA-controlled JME. These studies confirmed the autopsy findings from two case series of patients with IGE and/or JME that have shown frontal cortical and subcortical dystopic neurons and microdysgenesis in some of these patients (50,51). Several studies examined the psychiatric co-morbidities and cognitive profiles of patients with IGEs. One study found that patients with JME as a group had more psychiatric disorders, psychosocial problems, and anxiety and mood disorders when compared to matched healthy controls (52), while other studies

showed maladaptive behavioral consequences and overall frontal lobe dysfunction in JME patients (42,53). Such psychiatric problems are more likely to exist in JME patients who are poorly responsive to AEDs (58.3% vs. 19%; $p < 0.001$) (4). Further, symptoms of frontal lobe dysfunction seen in patients with psychiatric conditions, which include depression, apathy, lack of drive, inertia, and irritability, are also seen in patients with epilepsy, especially frontal lobe epilepsy (54,55). Therefore, the available clinical, EEG and neuroimaging evidence appears to point towards the frontal lobes as the sources of GSWD and possibly seizures in patients with poorly controlled IGEs.

Limitations of this study should be noted. First, not all EEGs were reviewed and not all reports were identified. This is related to some patients being older and treated by many physicians prior to their visits to our center. Therefore we cannot exclude the possibility that some EEGs with focal features were missed. Further, EEG interpretation can sometimes be subjective, especially when involving interpretation of subtle spike wave asymmetries. We were surprised at the consistency between the EEG reports and our direct analysis of EEG, thus we believe subtle differences in interpretation did not have a major effect on our results. Second, as in all retrospective studies, selection bias may have led to inclusion of patients who are more likely referred to a tertiary epilepsy center i.e., patients with poorly controlled IGEs. Again, this appears to be unlikely as the proportion of patients with seizures controlled with medications in our study is similar to other reports. Another limitation related to retrospective nature of the study is lack of standardized approach for making the diagnosis and selecting appropriate AEDs – hence, it is possible that some patients were misclassified as IGEs while having other types of epilepsies and/or treated with medications that may not be indicated for patients with IGEs.

In summary, our study showed that in patients with IGEs the prognosis for long-term seizure freedom may depend on initial response to VPA and EEG characteristics. Failure of VPA or the presence of EEG asymmetries may indicate the diagnosis of frontal lobe epilepsy rather than IGEs.

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Table 1

Demographic, clinical, and EEG/MRI characteristics of enrolled patients (N=267; patients with normal EEGs not included). Left side of the table includes comparisons between all patients with JME vs. other IGEs, right side of the table compares seizure-free vs. not seizure-free patients with JME or other IGEs (GTC – generalized tonic-clonic seizure; GSWD – generalized spike and wave discharge; ED – epileptiform discharge)

	Not JME		**JME**		**p-value**	**Not JME**					**JME**				
						Seizure-free		**Not seizure free**		**p-value**	**Seizure free**		**Not seizure free**		**p-value**
Age of onset	17.16	11.30	13.70	5.51	**0.001**	17.80	11.85	14.24	7.90	0.125	13.98	5.62	12.13	4.70	0.216
male	53	32.9	39	36.8		43	32.6	10	34.5		35	38.9	4	25.0	
					0.514					0.831					0.402
female	108	67.1	67	63.2		89	67.4	19	65.5		55	61.1	12	75.0	
GTC	149	92.5	98	92.5	1.000	120	90.9	29	100.0	0.126	82	91.1	16	100.0	0.604
Absence seizures	97	60.2	51	48.1	0.059	75	56.8	22	75.9	0.063	37	41.1	14	87.5	**0.001**
Family history of epilepsy (any type)	72	44.7	54	50.9	0.119	59	44.7	13	44.8	0.990	43	47.8	11	68.8	0.281
GSWD on most recent EEG	92	57.1	74	69.8	**0.040**	70	53.0	22	75.9	**0.037**	59	65.6	15	93.8	0.035
Other abnormalities on most recent EEG	30	18.6	13	12.3	0.178	20	15.2	10	34.5	**0.032**	7	7.8	6	37.5	**0.004**
GSWD on the first EEG	50	78.1	33	80.5	0.811	46	80.7	4	57.1	0.171	32	80.0	1	100.0	1.000
Other abnormalities on the first EEG	10	15.4	5	12.2	0.778	6	10.3	4	57.1	**0.008**	5	12.5	0	0	1.000
Any EEG - other abnormalities	72	44.7	35	33.0	0.074	49	37.1	23	79.3	**0.000**	24	26.7	11	68.8	**0.003**
Any EEG - focal slowing	29	18.0	15	14.2	0.501	19	14.4	10	34.5	**0.016**	8	8.9	7	43.8	**0.002**
Any EEG - focal EDs	47	29.2	28	26.4	0.677	31	23.5	16	55.2	**0.001**	19	21.1	9	56.3	**0.011**
MRI NORMAL	142	88.2	93	87.7	0.931	116	87.9	26	89.7	0.850	78	86.7	15	93.8	0.563
Reviewed - last EEG	129	80.1	75	70.8	0.105	106	80.3	23	79.3	1.000	62	68.9	13	81.3	0.386
Reviewed - GSWD present	69	53.5	47	62.7	0.241	52	49.1	17	73.9	**0.038**	35	56.5	12	92.3	**0.024**
Reviewed - asymmetric EDs	32	24.8	18	24.0	1.000	18	17.0	14	60.9	**0.000**	11	17.7	7	53.8	**0.011**
Reviewed - other focal abnormalities	14	10.9	7	9.3	0.815	8	7.5	6	26.1	**0.019**	4	6.5	3	23.1	0.095
Reviewed - normal last EEG	55	42.6	24	32.0	0.140	50	47.2	5	21.7	**0.035**	23	37.1	1	7.7	**0.050**

	Not JME	JME	p-value	Not JME			JME		
				Seizure-free	Not seizure free	p-value	Seizure free	Not seizure free	p-value