EEG correlates of seizure freedom in genetic generalized epilepsies

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Abstract

Background: We investigated the association between epileptiform EEG abnormalities and the preceding duration of seizure freedom in genetic generalized epilepsies (GGE). **Methods:** We analyzed 24-hour ambulatory EEG recordings of patients with GGE diagnosed and classified according to the International League Against Epilepsy criteria. We quantified epileptiform EEG abnormalities into density scores (total duration of epileptiform discharges per hour) and estimated the preceding seizure-free duration at the time of EEG recording based on the last self-reported seizure. We then employed regression analysis to quantitate the relationship between the duration of seizure freedom and EEG variables. **Results:** We analyzed 6,923 epileptiform discharges from 105 patients with abnormal 24-hour EEGs. In the regression analysis exploring the crude associations, we found significant correlations between 6 EEG variables and the duration of seizure freedom indicating that shorter duration of seizure freedom was associated with higher spike densities and longer paroxysms. These associations were not affected by confounders such as syndrome, age at EEG, age at epilepsy onset, sex, duration of epilepsy, or number of antiepileptic drugs. **Conclusions:** Higher densities and longer durations of epileptiform discharges may be retrospectively associated with a shorter duration of self-reported seizure freedom. Hence, EEG can potentially be used as a biomarker of prognosis in GGE. These findings need to be validated in a prospective study in order to define EEG markers of future seizure freedom. *Neurol Clin Pract* 2017;7:35-44

Prognosis describes the course and outcome of a disease, reflecting the persistent relationship between predictors and outcomes. In epilepsy prognosis studies, the most commonly measured outcomes include seizure freedom and intractability, whereas EEG findings and etiology are among the most frequently studied predictors.¹

The value of EEG in the diagnosis and classification of epilepsy is well-accepted. However, there are conflicting results from studies on the use of EEG as a predictor of prognosis in genetic generalized epilepsy (GGE). Some studies found that certain EEG features predicted seizure remission,²⁻¹¹ whereas others refuted this claim¹²⁻²¹ (see reference 1 for a summary table). Many variables, particularly recording techniques and duration of recording, affect the yield of EEG abnormalities in GGE.²² Therefore, heterogeneity of studies, particularly in methodology, may account for the conflicting results reported on the prognostic value of EEG in GGE.

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We hypothesized that epileptiform EEG abnormalities (predictor) correlate with the preceding duration of self-reported seizure freedom (outcome) in GGE, and conducted the current study to investigate this association. In order to overcome the limitations of previous research, we prospectively planned and performed 24-hour ambulatory EEG recordings according to a standard protocol in a well-characterized cohort of GGE.

METHODS

Case ascertainment

We have previously described the methodologic details of our research.^{23,24} We recruited patients through consecutive referrals from epilepsy clinics at 2 tertiary hospitals in Melbourne, Australia (St. Vincent's Hospital and Monash Medical Centre), with a large proportion of patients from outer metropolitan and rural regions. We prospectively planned ambulatory EEG recordings, whereas clinical data collection was retrospective. We used medical records as well as a validated questionnaire administered by an interviewer²⁵ to obtain details of seizures. The diagnosis and syndromic classification of GGE were established using the International League Against Epilepsy (ILAE) criteria.^{26,27}

We included patients with an unequivocal diagnosis of GGE. An abnormal EEG with generalized epileptiform discharges (ED) on at least one occasion was an inclusion criterion. We excluded patients with epileptogenic structural abnormalities on MRI, coexistent focal and generalized epilepsies, secondary bilateral synchrony, and a single seizure with generalized epileptiform abnormalities on EEG.

We classified patients into childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and generalized epilepsy with generalized tonic-clonic seizures only (GTCSO) according to the ILAE criteria.^{26,27} Patients who were not included in the 4 major syndromes were classified as GGE unspecified (GGEU).

Data acquisition

All patients had 24-hour ambulatory EEGs according to a standard protocol.^{23,24} EEG signals were acquired with 32-channel Compumedics (Melbourne, Australia) Siesta ambulatory EEG system. We did not change the antiepileptic drugs (AED) during the recording. For further details of EEG data acquisition and definitions, the reader is referred to our previous publications.^{23,24}

An investigator (U.S.) interviewed all participants at the time of their 24-hour ambulatory EEG recording and went through their medical records to obtain their demographic and clinical information. The clinical data included seizure types (absence, myoclonic, generalized tonic-clonic) and ages at onset, the date of last seizure, AEDs, previous EEG findings, and neuroimaging findings. The epilepsy duration was calculated based on the date of the first-ever seizure and the date of the ambulatory EEG.

Outcome measure

We selected preceding duration of seizure freedom as the outcome measure for the current study. The seizure-free duration was defined as the interval between the last seizure (any seizure type) and the ambulatory EEG. The date of the last seizure was obtained from medical records and patient recall at the time of ambulatory EEG. When a precise date was not available, we used the best estimate provided by the patient. A validated questionnaire was used to collect this information.²⁵ When there was a discrepancy between medical records and patient recall, the information from the questionnaire was taken as the more reliable data point.

Predictors of prognosis

We used the following EEG parameters as a priori predictors. These variables were chosen based on our clinical impression and previous research.

1. Total spike density: The total duration of all ED, in seconds, in the 24-hour EEG divided by the total length of the EEG recording (in hours).
2. Awake spike density: The total duration of ED (in seconds) captured during wakefulness in the 24-hour EEG divided by the total duration of awake state in the EEG (in hours).
3. Sleep spike density: The total duration of ED (in seconds) captured during sleep in the 24-hour EEG divided by the total duration of sleep in the EEG (in hours). Sleep was defined according to the American Academy of Sleep Medicine criteria and included stages REM and non-REM.²⁸
4. Polyspike and polyspike-wave density: The total duration of polyspike and polyspike-wave activity (in seconds) divided by the total length of the EEG recording (in hours).
5. Total ED count: The total number of ED captured over 24 hours of recording.
6. Mean duration of generalized paroxysms: The mean duration (length in seconds) of all generalized paroxysms captured during the 24-hour recording. Generalized ED were classified into fragments and paroxysms based on the duration. Generalized discharges lasting <2 seconds were classified as generalized fragments, whereas ≥ 2 seconds duration was considered to be paroxysms.²⁴
7. Atypical EEG abnormality state: The presence or absence of any atypical EEG abnormality in the 24-hour EEG recording. Amplitude asymmetry of paroxysms and fragments, focal onset of paroxysms, focal offset of paroxysms, focal discharges, abnormal morphology of paroxysms, and generalized paroxysmal fast activity were defined as atypical EEG abnormalities.²⁴ Over 50% amplitude difference between the 2 hemispheres was considered to be amplitude asymmetry. Atypical morphology was defined as any deviation from the typical spikes followed by the wave. Spikes overriding waves and waves without spikes were the abnormal morphologies identified by us. When a paroxysm had focal lead-in discharges lasting >200 milliseconds, it was defined as focal onset. Focal was defined as electrodes confined to a single region in one hemisphere such as frontal, temporal, parietal, and occipital. Bifrontal onset was not considered to be focal. The reader is referred to Seneviratne et al.²⁴ (2016) for more details.
8. Time to the first ED from awakening: The time (in seconds) from sleep offset to the first ED in the EEG.

Statistical analyses

We employed regression analysis to quantitate the relationship between the duration of seizure freedom and EEG variables. The EEG variables tested were total spike density, awake spike density, sleep spike density, polyspike and polyspike-wave density, mean duration of generalized paroxysms, time to first ED from awakening, atypical abnormality state (yes/no), and 24-hour total ED count.

Variables representing time to event observations present problems in regression models. As outcomes they are rarely, naturally, normally distributed and this distorts hypothesis tests involving the regression coefficients. As predictors, they are often excessively leveraged, especially at their tails, and this leads to further distortions. To address these effects, we log-transformed both outcome and predictor variables and used Shapiro-Wilk test and graphical inspection of the regression residuals to confirm the utility and advantages of these transformations.

In order to explore the influence of potential confounders on the duration of seizure freedom–EEG variables relationship, we admitted several confounders into the final model and monitored changes to crude regression coefficients. The confounders we tested were syndrome, age at EEG, age at epilepsy onset, sex, duration of epilepsy, and number of AEDs at the time of EEG recording. All data analyses were conducted with Stata (version 13.1) statistical software package (StataCorp LP, College Station, TX). *p* Values <0.05 were deemed significant.

Table 1 Clinical and demographic characteristics

	Values
Age, y, mean $\pm$ SD (range)	28.5 $\pm$ 10.7 (13–58)
Sex, n (%)	
Male	35 (33.3)
Female	70 (66.7)
Age at epilepsy onset, y, mean $\pm$ SD	13.3 $\pm$ 5.1
Duration of seizure freedom, d, median	120
Duration of epilepsy, y, median	13
Syndromes, n (%)	
JAE	32 (32.4)
GTCSO	28 (26.7)
JME	28 (26.7)
CAE	15 (14.3)
Drug-naïve cases, n (%)	13 (12.4)
Treatment with 1 AED, n (%)	47 (44.8)
Treatment with 2 AEDs, n (%)	36 (34.3)
Treatment with 3 AEDs, n (%)	9 (8.6)
Most frequently used AEDs, n (%)	
Sodium valproate	67 (72.8)
Lamotrigine	36 (39)
Levetiracetam	20 (21.7)
Abbreviations: AED = antiepileptic drugs; CAE = childhood absence epilepsy; GTCSO = generalized epilepsy with tonic-clonic seizures only; JAE = juvenile absence epilepsy; JME = juvenile myoclonic epilepsy.	

Standard protocol approvals, registrations, and patient consents

This study was approved by the Human Research Ethics Committees of St. Vincent's Hospital and Monash Health. All included patients provided written, informed consent to participate.

RESULTS

A total of 120 patients fulfilled the inclusion criteria and ambulatory EEG recordings demonstrated epileptiform abnormalities in 107. Two patients were classified as GGEU and they were excluded from the analysis as the sample was too small. Therefore, the analysis presented here is based on 105 patients diagnosed with CAE, JAE, JME, and GTCSO. The clinical and demographic characteristics of this cohort are summarized in table 1.

The mean lengths of ambulatory EEG recording and sleep were 23.5 ± 0.9 hours and 8.6 ± 1.4 hours, respectively. We captured a total of 6,923 ED consisting of 1,291 generalized paroxysms, 5,535 generalized fragments, and 97 focal discharges from the 105 ambulatory EEGs. The EEG scores are summarized in table 2.

In the first regression analysis exploring the crude associations, we found a strong relationship between 6 EEG variables and the duration of seizure freedom, indicating that shorter duration of seizure freedom was associated with higher spike densities and longer paroxysms (table 3). Atypical EEG abnormalities and time to first ED after awakening were negatively (inversely) correlated, but did not reach statistical significance.

Using the regression model, we have demonstrated that there are certain EEG markers of seizure freedom.

In the final analysis, none of the confounders had a significant effect on the association between seizure-free duration and the 6 EEG variables.

DISCUSSION

Key findings

Using the regression model, we have demonstrated that there are certain EEG markers of seizure freedom. The final analysis, controlled for confounders, has revealed the spike density as well as ED counts and the mean duration of generalized paroxysm as significant predictors with higher spike densities, higher ED counts, and longer paroxysms associated with shorter durations of seizure freedom. Among spike densities, the association with seizure freedom was particularly robust for polyspike and polyspike-wave density (regression coefficient -0.77). These results suggest that a higher burden of ED is associated with a shorter duration of preceding seizure freedom.

Comparison with previous research

We used 24-hour EEG performed according to a uniform protocol followed by quantification of epileptiform EEG abnormalities to evaluate electrographic markers that may predict prognosis in GGE. Previous studies have demonstrated polyspike activity, generalized spike-wave frequency <3.2 Hz, atypical EEG findings, focal abnormalities, asymmetric discharges, and duration of generalized paroxysm as EEG prognostic variables.¹ However, all the studies were retrospective, using brief routine EEGs with varying recording protocols, and most studies used univariate analysis.¹

There are conflicting conclusions on the prognostic value of EEG in GGE, as summarized in ref. 1. This inconsistency is in contrast to the more robust association between EEG abnormalities and prognosis demonstrated in other types of epilepsies. For example, meta-analyses have demonstrated that abnormal EEG is a predictor of seizure recurrence after the first seizure,²⁹ and after discontinuation of AEDs.³⁰ In another study, in patients who had undergone anterior temporal lobectomy for hippocampal sclerosis, interictal ED in the post-surgery EEGs predicted seizure recurrence.³¹

Table 2 Results of EEG scores

	Mean (SD)	Median (IQR)
Total spike density	4.90 (8.26)	1.39 (0.32-5.16)
Total polyspike and polyspike-wave density	1.89 (4.24)	0 (0-1.21)
Awake spike density	3.74 (7.79)	0.73 (0.03-3.40)
Sleep spike density	6.67 (11.63)	1.75 (0.44-6.49)
Mean generalized paroxysm duration	3.57 (2.24)	2.87 (2.37-3.88)
24-Hour epileptiform discharge count	65.01 (81.69)	29.00 (8.00-80.50)
Time (in seconds) to first epileptiform discharge from awakening	1,280.77 (2,398.86)	551.50 (137.75-1,332.00)
Any atypical epileptiform EEG abnormality present	Yes = 70 (66.7%); No = 35 (33.3%)	

Abbreviation: IQR = interquartile range.

Table 3 Results of the regression analysis exploring crude associations

EEG variable	Regression coefficient	95% CI	p Value
Total SD	−0.44	−0.67 to −0.22	<0.001
Awake SD	−0.42	−0.70 to −0.15	0.003
Sleep SD	−0.45	−0.71 to −0.20	0.001
PS and PSW density	−0.77	−1.28 to −0.27	0.003
Mean GP duration	−0.77	−1.34 to −0.19	0.009
24-Hour total ED count	−0.57	−0.86 to −0.28	<0.001
Time to first ED from awakening	−0.07	−0.21 to 0.06	0.296
Atypical EEG abnormality	−0.80	−1.68 to −0.06	0.070

Abbreviations: CI = confidence interval; ED = epileptiform discharge; GP = generalized paroxysm; PS = polyspike; PSW = polyspike-wave; SD = spike density.

We found the duration of generalized paroxysms to be strongly associated with the preceding seizure-free duration (regression coefficient -0.77). Those with longer paroxysms were more likely to have shorter periods of seizure freedom. In the literature, we found only 2 studies evaluating paroxysm duration as a prognostic predictor. A retrospective study involving children (<15 years) reported that paroxysms of <10 seconds duration was associated with a 2-fold increased risk of generalized tonic-clonic seizures (GTCS).⁶ However, this result cannot be directly compared with our study due to methodologic differences. First, the study of Hedstrom and Olsson⁶ was based on short, routine EEGs. They used the dichotomy whether paroxysms of <10 were present or not on that EEG. However, we have found that the duration of paroxysms varies throughout 24-hour period. It is possible that those who had short (<10 seconds) paroxysm on routine EEG and subsequent GTCS may have had longer paroxysm later, which would have been captured if the recording had continued for 24 hours. Second, only GTCS recurrence was taken into account. Finally, they only used univariate statistical analysis without controlling for confounders.

A more recent study used pretreatment EEG in CAE.³² The EEG was recorded for 1 hour. In each recording, the shortest, the longest, and the median durations of paroxysms were used as variables. The presence or absence of paroxysms of >20 seconds duration was taken as a dichotomous variable. Patients had neuropsychological testing and were prospectively followed up. Patients with at least one paroxysm lasting >20 seconds performed poorly in Conners Continuous Performance Test, though other EEG variables had no significant correlations. Those with shorter paroxysms (<7.5 seconds) recorded a poor response to initial treatment (64% seizure-free at 16- to 20-week follow-up vs 74% in longer paroxysm group). These findings are contradicting. On one hand, longer paroxysms were associated with poor neuropsychological outcome, but on the other hand, shorter paroxysms were associated with poor response to therapy. One explanation for this inconsistency may be less reliable estimates of epileptiform load based on shorter EEG recordings. We suggest that paroxysm duration has more precision as a predictor when the EEG is recorded for at least 24 hours.

We found that a heavy burden of epileptiform activity in the EEG (spike densities and ED counts) was significantly associated with shorter durations of seizure freedom. There are no comparable studies in the literature using quantified EEG. One retrospective study found that polyspike activity in sleep was associated with poor response to AED therapy in CAE and JAE.² We found a strong inverse relationship between polyspike/polyspike-wave density and the duration of seizure freedom, suggesting the burden of polyspike/polyspike-wave activity is an unfavorable prognostic sign.

Several previous studies based on retrospective data analysis reported atypical and focal ED as a poor prognostic factor.^{5,6,9,33} We found that the presence of atypical epileptiform EEG

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abnormalities, including focal discharges, in 24-hour EEG was inversely associated with the duration of seizure freedom. However, this association was not significant.

Pathophysiologic mechanisms

How do we explain the link between the burden of epileptiform activity and the seizure-free duration? Cortical excitability is a potential mechanism. There is growing evidence for increased cortical excitability in epilepsy.³⁴ Transcranial magnetic stimulation (TMS) studies have shown that GGE patients who are refractory to treatment have significantly higher cortical excitability.³⁵ Furthermore, reduced cortical excitability has been shown to predict longer seizure freedom in GGE.³⁶ These studies support the hypothesis that higher cortical excitability is associated with increased risk of seizure recurrence and shorter duration of seizure freedom. How are ED linked to cortical excitability? Cellular and network mechanisms of ED in GGE are complex. At cellular level, ion channels and receptors play a key role in the interplay between excitatory and inhibitory neurons involved in the generation of spike-wave discharges.³⁷ Epileptic neurons are characterized by increased excitability. Paroxysmal depolarization shifts occur intracellularly during seizure discharges.³⁴ When there are excessive and synchronous discharges in a population of epileptic neurons, spike-wave activity is recorded on the scalp EEG.³⁸ Following single-pulse TMS, late ED have been recorded on scalp EEG, suggesting excitability of cortex underneath.³⁹ Hence, one may speculate that a higher quantity of epileptiform activity recorded on scalp EEG indicates increased cortical excitability associated with reduced chances of seizure freedom.

Strengths of the study

Rigorous methodology is the principal strength of our study. The diagnosis and classification of GGE in all patients was strictly based on the ILAE criteria. We planned all ambulatory EEGs prospectively and followed a uniform protocol. All patients had 24-hour recordings, in contrast to previous studies based on shorter versions of EEG.

Finally, we quantified epileptiform EEG abnormalities and used those data to explore EEG markers of seizure freedom. However, this method is time-consuming and needs validation in future studies. Automated EEG quantifying techniques would be useful to improve the efficiency and make it a pragmatic option in routine clinical practice.

Study limitations

We acknowledge some limitations of the study. First, EEG data collection was cross-sectional, but clinical data collection was retrospective. The way we estimated seizure-free duration is a major limitation. In order to estimate the seizure-free duration, information on the last seizure was based on medical records as well as retrospective recall by patients, introducing a recall bias. Those who had recent seizures were more likely to remember the details better and provide more accurate information. History of self-reported seizures, in particular absences and myoclonus, is not precise. Additionally, our cohort had a wide range of seizure-free durations ranging from 1 day to 15 years, with a median of 4 months. Second, the participants were recruited from 2 tertiary hospitals, introducing a selection bias. However, both these centers drew patients from outer metropolitan and rural regions, making our findings more representative. Third, the sample was skewed in several aspects. An adult cohort was studied, hence, CAE was underrepresented. Patients with CAE seen by adult epileptologists may be prognostically different from those who go into remission in teenage years. Consequently, our findings may not be generalized to all CAE patients. Furthermore, the cohort was skewed in sex distribution, with a higher proportion of women. Previous

epidemiologic studies have shown that women are more likely to participate in research than men.⁴⁰ Therefore, the higher proportion of women in the cohort is a reflection of bias in participation and health service uptake rather than a biologically driven phenomenon. Fourth, we evaluated only seizure freedom as an outcome in this study. Studying multiple outcomes such as quality of life and psychosocial status is likely to provide a better understanding of the overall prognosis. Finally, the study was conducted in a prevalent cohort and the majority was on AED therapy at the time of ambulatory EEG recording. A prospective study involving an incident cohort is likely to yield more robust results. However, recruiting participants into an incident cohort in sufficient numbers would be a challenging task and is likely to take many years.

Due to these limitations, in particular the retrospective nature of seizure-free duration data collection, our results reflect EEG correlates of past seizure control. Obtaining reliable data on myoclonic and absence seizures is difficult retrospectively. A well-designed prospective study with more precise estimates of seizure recurrence data is needed to understand the EEG predictors of future seizure freedom.

Implication for clinical practice

The place of EEG in the decision-making process for discontinuation of AED therapy in seizure-free patients is not clearly defined. In a review of 37 studies, an abnormal EEG at the time of AED withdrawal predicted a higher risk of seizure relapse in 21 studies.⁴¹ A systematic review analyzed 15 studies on seizure recurrence and EEG at AED withdrawal. Only 5 studies found significant risk of relapse associated with abnormal EEG on univariate analysis and the results were not confirmed by multivariable analysis.⁴² Even among the studies showing a significant association, there was no consistency in terms of the site, type, and density of EEG abnormalities.^{41,42} The studies analyzed in reviews involved both generalized and focal epilepsy syndromes, mostly in children. We did not evaluate the place of EEG in predicting seizure recurrence upon AED withdrawal in GGE. However, our study found clear EEG signals associated with the duration of seizure freedom. This may be considered indirect evidence that a higher ED burden at the time of AED withdrawal could be a potential predictor of seizure recurrence in GGE. However, the validity of this hypothesis needs to be tested in a prospective trial and our study indicates the variables that should be tested in such a study.

CONCLUSION

Despite some practical limitations, our study shows that EEG has the potential to be used as a biomarker in predicting the prognosis in GGE. It also shows that EEG should be recorded for at least 24 hours to obtain reliable data for prognosis. Longer paroxysms and higher spike densities, probably reflecting increased cortical excitability, are associated with shorter durations of retrospective seizure freedom. Our findings also raise the possibility that 24-hour EEG can potentially be helpful before AED withdrawal in GGE, in order to forecast the risk of seizure recurrence. Finally, we emphasize the need to validate our findings in a prospective study in order to define EEG markers of prognosis in GGE.

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AUTHOR CONTRIBUTIONS

U. Seneviratne: study concept and design, literature search, data collection, data interpretation, drafting and revision of manuscript. R.C. Boston: data analysis and interpretation, critical revision of manuscript. M. J. Cook: study concept and design, data interpretation, critical revision of manuscript. W.J. D'Souza: study concept and design, data interpretation, critical revision of manuscript.

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