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Prolonged epileptic discharges predict seizure recurrence in JME: Insights from prolonged ambulatory EEG

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Abstract

Objective: Markers of seizure recurrence are needed to personalize antiseizure medication (ASM) therapy. In the clinical practice, EEG features are considered to be related to the risk of seizure recurrence for genetic generalized epilepsies (GGE). However, to our knowledge, there are no studies analyzing systematically specific EEG features as indices of ASM efficacy in GGE. In this study, we aimed at identifying EEG indicators of ASM responsiveness in Juvenile Myoclonic Epilepsy (JME), which, among GGE, is characterized by specific electroclinical features.

Methods: We compared the features of prolonged ambulatory EEG (paEEG, 22 h of recording) of JME patients experiencing seizure recurrence within a year ("cases") after EEG recording, with those of patients with sustained seizure freedom for at least 1 year after EEG ("controls"). We included only EEG recordings of patients who had maintained the same ASM regimen (dosage and type) throughout the whole time period from the EEG recording up to the outcome events (which was seizure recurrence for the "cases", or 1-year seizure freedom for "controls"). As predictors, we evaluated the total number, frequency, mean and maximum duration of epileptiform discharges (EDs) and spike density (i.e. total EDs duration/artifact-free EEG duration) recorded during the paEEG. The same indexes were assessed also in standard EEG (stEEG), including activation methods.

Results: Both the maximum length and the mean duration of EDs recorded during paEEG significantly differed between cases and controls; when combined in a binary logistic regression model, the maximum length of EDs emerged as the only valid predictor. A cut-off of EDs duration of 2.68 seconds discriminated between cases and controls with a 100% specificity and a 93% sensitivity. The same indexes collected during stEEG lacked both specificity and sensitivity.

Significance: The occurrence of prolonged EDs in EEG recording might represent an indicator of antiepileptic drug failure in JME patients.

KEYWORDS

electroencephalography, epileptiform discharges, genetic generalized epilepsy, juvenile myoclonic epilepsy, prolonged ambulatory eeg, seizure prediction

Key points

- We analyzed prolonged ambulatory EEG recordings of a group of JME persons looking for EEG markers of seizure recurrence.
- We excluded those recordings which were followed by a change of drug regimen before seizure recurrence or one year of seizure freedom.
- The maximum length of epileptic discharges emerged as the only valid predictor of seizure recurrence in a multivariate statistical analysis.
- A cut-off of epileptic discharge duration of 2.68 s predicted seizure recurrence with a specificity of 100% and a sensitivity of 93%.
- As a comparison, we evaluated also standard EEG, but in those recordings none of the EEG markers analyzed predicted seizure recurrence.

1 | INTRODUCTION

The identification of reliable indicators of seizure recurrence still represents one of the main goals in epilepsy research.[1]

In routine clinical practice, interictal EEG features often guide the clinician's decision to start[2] or discontinue antiseizure medications (ASM).[3] However, clear evidence about the risk of seizure recurrence after detection of epileptiform discharges (EDs) lacks, and the efficacy of ASM is still currently assessed in terms of seizures disappearance rather than EEG normalization. More in detail, while EDs in focal epilepsies are not considered as potential indicators of drug efficacy,[4] the occurrence of EDs in genetic generalized epilepsies (GGE) usually leads epileptologists to modify antiepileptic therapy.[5] However, even for GGE, such a strict correlation has not been formally established thus far[6] and, surprisingly, some authors even suggested that EEG abnormalities may not be valid predictors for seizure recurrence in these syndromes.[7]

Among GGE, Juvenile Myoclonic Epilepsy (JME) is quite common;[8] it is characterized by the occurrence of major (generalized tonic clonic-GTC) and minor (myoclonic) motor seizures, with clinical onset in adolescence and young adulthood, and by a significant impact on key aspects of life such as driving, starting a working career and pregnancy.[9] Among GGE, JME is considered to have a peculiar physiopathology.[10] While most JME patients achieve seizure remission for years with an appropriate ASM regimen,[11] in others some ASM trials can be ineffective, or may even precipitate myoclonic/GTC seizures.[12] Up to date, drug responsiveness is unpredictable in a single patient. Valproic acid (VPA), has been considered the gold standard ASM in JME, as it controls seizures in up to 85% of patients,[13] but its use has been recently significantly limited by advice on its potential teratogenic effect.[14] Thus, newer ASM with a safer profile, despite less predictable efficacy,[15,16] such as Levetiracetam (LEV) and Lamotrigine (LTG), have recently become the first-choice therapy in women of childbearing age.[17] Therefore, disclosing a reliable early EEG index of drug-resistance might be particularly useful in this scenario.

Data obtained in previous studies,[7,11,18] aimed at identifying such potential EEG predictors, were hindered by (1) the intra-/inter-study inhomogeneity of EEG recording lengths, timing, and activation method protocols, (2) the lack of quantitative methods of EEG recordings evaluation and, most importantly, by (3) the fact that EEG recordings are often followed by ASM regimen modification, which can alter the clinical outcome.

The aim of the present study consists in assessing the chance to predict seizure recurrence as well as ASM efficacy in JME by using EEG. To overcome the above-mentioned limitations/difficulties we retrospectively assessed a homogeneous population of patients affected by JME, for which: (1) we considered prolonged ambulatory EEG (paEEG) recordings (22 h of recording), covering the whole sleep-wake cycle, as EDs occurrence frequency can vary significantly during the day[19]; (2) the number and duration of EDs were quantitatively assessed; (3) ASM regimen had not been modified from the time of EEG recording up to the last available follow-up/outcome events.

We identified EDs indexes which may be potentially useful as predictors of drug efficacy.

2 | METHODS

We designed a case-control study to compare recordings of JME patients which experienced seizure relapse within a year after EEG acquisition (“cases”), with recordings of patients experiencing long-lasting seizure freedom (“controls”).

We reviewed standard EEG (stEEG) and paEEG recordings, together with clinical data from 65 JME patients followed-up as outpatients at the Epilepsy Center of the Neurology Unit of Santa Chiara Hospital of Pisa from 2005 to nowadays.

All subjects had a diagnosis of JME according to ILAE criteria,[20] a more recent international consensus statement,[21] and updated ILAE recommendations (www.epilepsydiagnosis.org). Seizure events were defined as GTC seizures, clear myoclonic and clear absence seizures.

We included only EEG recordings of patients who had maintained the same ASM regimen (dosage and type) throughout the whole period of time up to the outcome event, which was seizure recurrence for the "cases" group, or seizure freedom for at least one year for the "controls" group. In line with this, we excluded from the analysis those recordings that were followed by ASM regimen change (dosage, type, or both) within one year after EEG recording, for any reason which was not seizure recurrence.

According to good clinical practice in those patients who experienced seizure recurrence, the ASM regimen was promptly changed. These subjects had been included among "controls" or "cases" if such seizure relapse had occurred more than 1 year or within 1 year after EEG, respectively, only if their ASM had been kept unchanged from the time of EEG up to seizure recurrence. The occurrence of other seizure events following the change to this new drug regimen in patients experiencing seizure relapse was not considered a relevant parameter for the aims of this study, and we chose a single seizure event (i.e. seizure recurrence) as an outcome measure rather than seizure frequency after relapse. The study had been approved by our Institutional Review Board and all patients had given their written consent to have their clinical data analyzed for research purposes.

2.1 | EEG data acquisition

StEEG was represented by an EEG recording lasting 20 min, performed in the morning, usually between 9 and 11 a.m. at our EEG laboratory; stEEG included intermittent photic stimulation at different light frequencies and 3 min of hyperventilation.

PaEEG recording started immediately after stEEG.

StEEG and paEEG recordings were performed using a 32-channel EEG. In both cases, collodium-applied silver cup electrodes were placed according to the 10–20 system. Electrocardiogram, chin electromyogram, and electrooculogram signals were also recorded using additional skin surface electrodes. Sample rate frequency was 250 Hz, electrode impedance was kept below 10 kOhm. For paEEG, data were stored in a compact flash card and downloaded the following morning, after 22 h of recording.

2.2 | Data processing

All EEG recordings were anonymized and reviewed independently by two experienced EEG readers (EB and FT), which were blinded to the clinical data. Using the software Sleep-RT (Micromed, SleepRT™) 30-s epochs were reviewed page-by-page on longitudinal bipolar montage with 0.5–70 Hz bandwidth. Each epoch was scored as wake or sleep, and sleep epochs were sub scored according to the American Academy of Sleep Medicine Manual for Scoring of Sleep and Related Events.[22] Epochs contaminated by large artifacts were rejected and excluded from the analysis.

EDs (generalized spikes, polyspikes, spike-and-waves and polyspike-and-waves) were marked and then further evaluated in a 10-s page, using unipolar montage, with Cz as the reference electrode, to further confirm their feature and to manually assess their duration, employing a measuring tool incorporated in the Sleep RT software.

Inter-rater agreement was checked by Wilcoxon signed-rank test and Spearman correlation analysis. To better visualize the circadian patterns of EDs distribution and individual sleep habits, we plotted for each recording EDs length, and sleep/wake stage on a secondary axis, against the time of day.

2.3 | Statistical analysis

We collected: (1) clinical data; (2) data on EDs: number, duration, time of occurrence; (3) "effective duration of EEG recording" analyzed (i.e. after removal of artifact-rich epochs), and (4) wake/sleep state. These parameters were entered in a custom-made electronic database (MATLAB, R2016B).

The analysis has been performed with custom-made MATLAB scripts, employing the built-in statistical toolbox, and re-checked with SPSS (IBM® SPSS® Statistics,v27). The null hypothesis was rejected for $p < .05$.

2.3.1 | Markers of drug efficacy and possible confounders

First, we performed univariate analysis to test whether demographics and clinical variables or EEG predictors may discriminate between cases and controls. We collected data on age at EEG recording, disease duration, seizure history, ASM tried and failed in history, and ASM at the time of EEG.

As EEG predictors, both for paEEG and stEEG we tested the following: "total number of EDs"; "EDs frequency" (i.e. number of EDs sequences per hour of effective recording); "Spike Density" (i.e. the total duration of EDs per hour of effective recording, as defined in Seneviratne et al.[23]); "Mean duration" and "Max duration" of EDs sequences for each recording. As further parameters, we also considered the absence of any EDs on stEEG and paEEG, the presence of photoparoxysmal response to intermittent light stimulation on stEEG, and the effective duration of paEEG recording (i.e. after removal of epochs contaminated by artifacts).

This analysis was performed using chi-square test or Fisher exact test for categorical variables and *t*-test for continuous data, after checking for normality assumption. Then, all significant predictors were analyzed together with a multivariate

model by a step-wise method based on binary logistic regression. Finally, we performed a receiver operating characteristic (ROC) analysis to extrapolate a cut-off value for the most significant predictors of seizure recurrence.

2.3.2 | Intra-subject modification of EEG predictors of drug efficacy

In a subgroup of patients that shifted from case to control group, after appropriate drug regimen modification, we performed a paired sample test, to test whether the predictors of seizure recurrence identified in the previous analysis changed.

3 | RESULTS

Among all persons from our database who are affected by JME and had undergone at least one paEEG (108 recordings of 39 patients), we included in the analysis 32 recordings (14 cases and 18 controls) from 26 patients. The remaining 76 recordings were excluded because: (1) antiseizure drug regimen had been modified during the time lapse between EEG recordings and seizure recurrence; or (2) ASM regimen had been changed before 1 year of follow up despite seizure freedom; or (3) the follow-up after paEEG under stable ASM regimen had been shorter than 1 year. Standard EEG was recorded immediately before paEEG for 26 recordings of 26 patients (10 cases and 16 controls).

3.1 | Clinical and demographic features

Table 1 displays the demographic and clinical features of the two groups, together with the results of the univariate analysis. All of the subjects included in the study were already under antiseizure medication at the time of paEEG. Age, disease duration, and time from the start of the first ASM regimen calculated at the time of EEG acquisition did not differ between groups.

Regarding the seizure history before EEG recording and the number and type of drug regimens previously tried and failed, these parameters were quite heterogeneous among the patients included, and none of these variables (see paragraph below) differed significantly between cases and controls in the univariate analysis (Table S2). In particular, all subjects in the cases group (14/14) and most of the controls (15/18) had experienced at least one GTC seizure during their clinical history, while approximately one-third of them have experienced absence seizures (cases = 5/14; controls = 6/18); the type and frequency of seizure events in the year preceding EEG recording did not differ between the two groups, and are detailed in Table S2. Concerning the number and type of ASM regimen tried and failed, these were not significantly different between the two groups, even after we divided

TABLE 1 Demographic and clinical features of cases and controls groups

Variables		Cases (n = 14)	Controls (n = 18)	*p* value
Age at paEEG recording (years)		27.7 ± 6.6	26.6 ± 8.0	.67
Disease duration at paEEG recording (years)		12.7 ± 7.9	11.7 ± 10.6	.78
Time from first ASM regimen to paEEG recording (years)		10.7 ± 10.5	9.6 ± 7.0	.72
Drug regimen at the time of EEG recording and outcome event	BDZ	1 (7.1%)	—	—
	VPA	2 (14.3%)	6 (33.3%)	.43
	LEV	2 (14.3%)	6 (33.3%)	.41
	LTG	7 (50%)	3 (16.7%)	.06
	POLY	2 (14.3%)	3 (16.7%)	.62
Days from start of the last drug regimen to paEEG recording		63 ± 45.2	58 ± 55.7	.77
Outcome events	GTCS	10/14 (71%)	—	—
	Myoclonic seizures	4/14 (29%)	—	—
	Absence seizures	0	—	—
Days from paEEG to seizures (cases) or last follow-up (controls)		61.4 ± 73.9	1301.6 ± 675.0	**<.0001**
Days from start of the last drug regimen to seizures (cases) or last follow-up (controls)		125 ± 87.0	1445 ± 906.3	**<.0001**

Results are expressed as mean ±standard deviation for continuous variables and absolute values with relative frequency for categorical variables. Data were compared using *t*-test for continuous variables and Fisher exact test or zeta test for two proportion for categorical variables, as appropriate.

Bold characters indicates statistical significance ($p < .05$).

Abbreviations: ASM, antiseizure medication; BDZ, benzodiazepine; GTC, generalized tonic-clonic; LEV, levetiracetam; LTG, lamotrigine; paEEG, prolonged ambulatory EEG; POLY, polytherapy; VPA, valproic acid.

both cases and control groups in (1) patients who were on their first therapy type, whose dosage was recently adjusted (cases = 3/14; controls = 4/18, $p = 0.96$), (2) women of childbearing potential, shifted from VPA to a new drug regimen (LEV or LTG), even if VPA was effective (cases = 9;controls = 6; $p = .08$), and (3) patients who had been put on a second or third drug regimen after one or multiple therapeutical failures (cases = 2; controls = 8; $p = .07$).

Antiseizure Drug regimen and dosages at the time of EEG were various, with a moderate, but not significant, prevalence of LTG monotherapy in the cases group (Table 1). The time-lapse between the last antiseizure treatment modification and paEEG recording was similar in the two groups (63 ± 45.2 days for the cases group and 58 ± 55.7 days for the control group; $p = 0.77$) (Table 1); none of the patients experienced any seizures during this time window.

Within 1 year from EEG, 10/14 patients of the cases group experienced a GTC seizure, 4/14 had severe myoclonic seizures and none had clear absence seizures; mean time from EEG recording to seizure events was 61,4 ± 71,2 days (minimum 1 day, maximum 224 days); none of the patients belonging to control group had a seizure before drug regimen change, which remained stable for a mean of 1301,6 ± 655,9 days (minimum 474 days, maximum 2674 days); only one patient from the controls' group experienced a seizure during prolonged follow-up (GTC seizure 1345 days after EEG recording).

3.2 | EEG recording evaluation

There were no significant differences between the measurements of all the EEG parameters made by the two raters (see Table S1 at Supporting Information Section); thus, for all of the EEG parameters, we used the mean of the measurements made by the two raters. Before performing the statistical analysis on the EEG predictors of seizure recurrence, we evaluated individual patterns of EDs occurrence and length along the whole paEEG recording, together with sleep periods. Figure 1 displays these plots for two representative subjects respectively from controls and cases group. Graphs for all subjects with an active paEEG are available at Supporting Information Section.

3.3 | EEG predictors of seizure recurrence: univariate analysis

Table 2 summarizes the results of the univariate analysis on candidate EEG markers of seizure recurrence. The presence of any EDs on paEEG ($p = .013$), the mean duration ($p = .001$), and the maximum duration ($p < .0001$) of the EDs recorded during paEEG differed significantly between groups. There was a striking, but not statistically significant, difference in the number and frequency of EDs between the two groups ($p = .051$ and $p = .054$, respectively). Effective paEEG recording duration was comparable in the two groups ($p = .658$). None of the EEG markers recorded by stEEG differed significantly in the two groups. A photo-paroxysmal response occurred only in one stEEG recording from the control group, and in none from the case group.

3.4 | Predictors of seizure recurrence: multivariate and ROC analysis

We performed a binary logistic regression with a stepwise approach on the paEEG markers of seizure recurrence which had been identified in the univariate analysis (Table 3); based

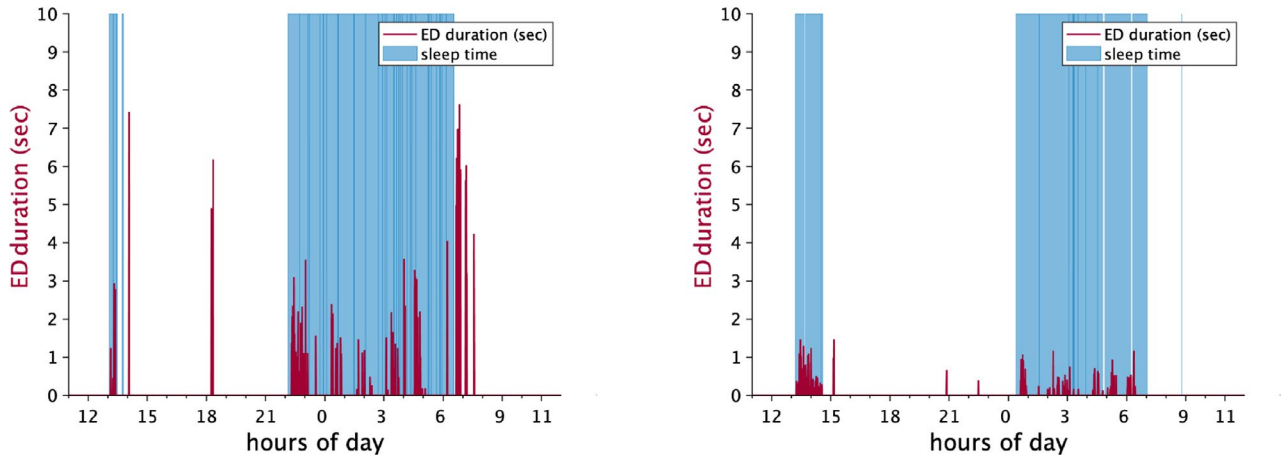

FIGURE 1 Sample datasets from a typical case (left) and control (right) recording. The figure shows Sample datasets from a typical case (left) and control (right) recording. Plots display individual patterns of epileptiform discharges (EDs) occurrence and length during the prolonged ambulatory electroencephalographic recording in two representative subjects (one case, left plot, and one control, right plot). X axis=hours of day, Y axis=EDs duration in seconds. Blue shaded area=sleep periods. Complete datasets from all subjects are available in Figures S1 and S2 of the Supporting Information Section

TABLE 2 Comparison of paEEG and stEEG features between cases and controls groups

Variables		Cases (n = 14)	Controls (n = 18)	*p* value
paEEG	Effective duration of recording (hours, excluding artefacts)	20.28 ± 1.84	20.57 ± 1.69	.658
	Absence of any ED	1 (7.1%)	10 (55.6%)	**.013**
	Number of EDs	328 ± 654	15.40 ± 35.20	.051
	Frequency of EDs (number/h)	16.75 ± 33.99	0.72 ± 1.66	.054
	Mean duration of EDs (seconds)	1.07 ± 0.73	0.24 ± 0.31	**.001**
	Spike Density (s/h)	25.40 ± 66.82	0.44 ± 1.00	.186
	Max duration of EDs (seconds)	4.69 ± 2.37	0.62 ± 0.86	**<.0001**
Variables		**Cases (n = 10)**	**Controls (n = 16)**	***p* value**
stEEG	Absence of any ED	7 (70.0%)	12 (75%)	.078
	Number of EDs	0.80 ± 1.32	0.94 ± 2.20	.654
	Frequency of EDs (number/h)	2.42 ± 3.99	2.75 ± 6.69	.892
	Mean Duration EDs (seconds)	0.40 ± 0.97	0.25 ± 0.45	.594
	Spike Density (seconds/h)	3.80 ± 8.55	2.50 ± 5.93	.650
	Max duration of EDs (seconds)	0.38 ± 0.79	0.54 ± 1.07	.779
	Photoparoxysmal response (stEEG)	0 (0%)	1 (5.6%)	—

Results are expressed as mean ±standard deviation for continuous variables and as absolute value with relative frequency for categorical variables. Data were compared using t-test for continuous variables and Fisher exact test for categorical variables, as appropriate.

Bold black character indicates statistical significance ($p < .05$).

Abbreviations: ED, epileptiform discharges; paEEG, prolonged ambulatory EEG; stEEG, standard EEG.

TABLE 3 Multivariate analysis by stepwise method on paEEG predictors of seizure recurrence

Factors	Regression coefficient	Odd Ratio (95% CI)	*p* value
Max duration of EDs	0.782	2.186 (1.274–3.753)	**.005**
Constant	−2.024	0.132	.006
Number of EDs			.543
Frequency of EDs (number/h)			.524
Mean Duration EDs (s)			.104
Spike Density (s/h)			.642

Data were analysed using binary logistic regression with stepwise method.

Bold black character indicates statistical significance ($p < .05$).

Abbreviations: ED, epileptiform discharges; paEEG, prolonged ambulatory EEG.

on univariate analysis results we did not further analyze anyone of the stEEG predictors. The maximum length of EDs was the only significant factor, with a high concordance between the model and the observed events (Cohen's Kappa=0,811). The ROC analysis individuated a cut-off value of 2,68 seconds, with a sensitivity of 93% and a specificity of 100%.

3.5 | Intra-subject evaluation of predictors of seizure recurrence.

Six patients had been included both in the case and in the control group during their seizure history (i.e. they had undergone a paEEG recording before their seizures were under control, and again once they started the effective drug therapy, which provided at least one-year of seizure freedom). PaEEG did not detect any EDs in five out of six patients. More in detail, of the EEG indices of seizure recurrence considered in the previous analysis, both the maximum duration of the EDs recorded with the paEEG (median cases = 167 s, interquartile range = 50–312 s; median controls = 0 s; Wilcoxon test $p = .028$) and the total number of EDs (median cases = 4.4 s, interquartile range=3.3–6.2 s; median controls=0 s; Wilcoxon test $p = .028$), changed together with group assignment.

4 | DISCUSSION

In this study, we demonstrated that the length of EDs during paEEG (cut-off=2,68 seconds) in JME does predict seizure recurrence with high sensitivity and specificity.

The univariate analysis of demographic and clinical data showed that case and control groups were homogeneous from several points of view; according to the design of our study, they differed only in the outcome experienced after the last EEG recording (see Table 1). Most importantly, we had excluded a priori the potential bias due to variations in ASM regimen, since only subjects in which drug treatment had been maintained stable after the recording up to the outcome event (i.e. seizure recurrence before 1-year follow up, or seizure freedom for at least 1 year) were included. Besides, there

were no differences between the two groups in terms of number of drug regimens previously tried (number and type) and failed (see results and Table S2). Thus, the EEG differences we found between the two groups are unlikely to be related to these confounders.

Concerning the specific drug regimens at the time of EEG recording and of outcome events, these were similar in the two groups, except for LTG, which was slightly, non-significantly, overrepresented in the case group. This is in line with data showing a lower efficacy of LTG compared with VPA[24] and with recent data suggesting a lower efficacy also compared with LEV.[25,26] Some of the patients of the present casistic were women of childbearing potential, which had been shifted from VPA to a new drug regimen (LEV or LTG), even if VPA had been effective (cases = 9; controls = 6; $p = .08$). Based on our data, paEEG recording could be extremely useful in this *scenario* to predict seizure relapse.

In our patients' populations, seizure recurrence in the case group occurred soon after EEG recording (maximum = 224 days), while controls remained seizure-free at prolonged follow-ups (minimum = 474 days). Thus, the two groups are clearly different regarding drug responsiveness.

By univariate analysis, we did not show differences between the two groups concerning any one of the features of the stEEG. Even though the number of stEEG recordings was slightly lower than that of paEEG, we failed to find any clear trend of data among this type of recordings. This could be explained, at least in part, by the low sensitivity of stEEG, which is likely related mainly to the reduced length of recording, but also by its lack of specificity, which is likely due to excessive activation of epileptic abnormalities with hyperpnea and photic stimulation in some patients.[27]

The mere occurrence of EDs on paEEG differed significantly between case and control groups; however, by using only this criterion eight out of 18 controls would be erroneously considered at risk of seizure recurrence, as in these controls a few EDs had been observed.

When applying multivariate analysis to paEEG features, we found that the maximum duration of EDs is strikingly superior to the total number of EDs as a predictor of seizure drug responsiveness. Another main finding of our analysis was that an EDs length of at least 2,68 seconds is a specific and sensitive seizure recurrence predictor, as confirmed by ROC analysis.

These observations are in line with previous data obtained in JME submitted to long-term follow up[18] and in GGE subjects submitted to paEEG recordings,[28] which showed a strong correlation between the length of EDs and clinical outcome measures. More in detail, Arntsen and coll,[18] by pooling EEG recording results obtained during a long follow-up, suggested that the occurrence of prolonged (>3 s) EDs indicates a worse long-term outcome. Unfortunately, these results are difficult to translate into clinical practice, since usually therapeutic decisions are taken based on a single EEG recording. Seneviratne and coll. proposed a different approach,[28] by retrospectively analysing the paEEG of a large court of patients with GGE, including 28 patients with JME. The large number of recordings (n = 108) they used, enabled a multivariate regression analysis on the impact of eight different EEG features on clinical outcome. By this approach, these authors found a moderate-to-strong association for "mean durations of epileptiform discharges" and "spike density" with the duration of seizure freedom preceding EEG recordings. Despite the great interest of such an approach, the main outcome of this study may not have immediate clinical relevance, since these markers were not tested as predictors of seizure recurrence.

Of note, none of the above-mentioned studies answered the need for an index of drug efficacy. Indeed, as far as we know, the potential impact of drug regimen modification between EEG recording and seizure events, representing the clinical outcomes, has never been considered thus far. This is a key point, because the results of the EEG recordings often lead to drug modification in the routine clinical practice, and in the single JME patient seizure control can change dramatically depending on the right choice of ASM.

Conversely, we chose to exclude from the analysis those recordings which were followed by drug modification occurring before the outcome assessment. We chose to use also the "maximum duration" EDs parameter, rather than only the mean duration of EDs. By applying this approach, we showed that finding even just a single ED lasting more than 2,68 seconds on an EEG recording without activation methods, indicates a major risk of seizure recurrence within a year, if drug therapy is not changed, with a specificity of 100%. Moreover, the absence of any ED lasting more than 2,68 seconds in a paEEG (with at least 20 h of artifacts-free recording) would be a valuable index of drug efficacy with a 93% of sensitivity.

We performed a further sub-analysis on the six subjects who, after drug regimen modification, became seizure-free, in order to specifically assess whether the EEG markers of seizure recurrence were subject-specific features, rather than a state (good vs. poor seizure control) feature. We excluded that the EEG parameter was subject-related, as we showed that both the total number and the maximum length of EDs detected decreased significantly in all of these 6 subjects after effective therapy modification, thus predicting seizure control.

As shown by Figure 1 and Figure S1 and S2 of Supporting Information Section, EDs length varies along the sleep-wake cycle, and maximum length EDs can occur at a different time of day depending on the subject analyzed. A more precise description of the temporal pattern of EDs occurrence and their relationship with the sleep-wake cycle has been detailed in GGE patients elsewhere [23,29], and is beyond the aims of the present work.

The main limitations of the present study include its retrospective design and relatively limited sample size.

EEG recordings are routinely used to assess the risk of seizure recurrence, even though, as detailed in the Introduction, clear indications on how to interpret EEG findings, as well as systematic studies on its predictive value, lack. However, prospective studies in JME patients in which, by study design, the investigators could not modify the ASM treatment based on EEG recordings findings, would be difficult to perform, mainly for ethical reasons, and would be hardly accepted by the epilepsy community. Thus, increasing the sample, even by multicentre collaborations, of retrospectively assessed JME patients, may represent the best approach in future studies to further validate our findings.

In conclusion, given the relative rarity of seizure events in JME and the careful selection of the recording we made, we consider our data of relevance. The EEG index we found may be of great help for epileptologists to take decisions in clinical practice, as we provided an index of antiepileptic drug failure in JME patients that can be easily assessed in any Epilepsy Centre, shortly after starting a new ASM in a patient. Lastly, the above-proposed method could contribute to paving the way for the ambitious target of seizure prediction from electrophysiological signals in specific epilepsy syndromes.

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CONFLICTS OF INTEREST

None of the authors has any conflict of interest to disclose.

ETHICAL PUBLICATION STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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