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Prognostic value of EEG asymmetries for development of drug-resistance in drug-naïve patients with genetic generalized epilepsies

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HIGHLIGHTS

- Using visual and innovative quantitative methods, we evaluated the prognostic value of EEG asymmetries for the development of drug-resistance in drug-naïve patients with genetic generalized epilepsies.
- EEG asymmetries were seen in up to 54% of patients with GGE and drug-resistance was identified in 52% of patients after 6 months and in 24% at the end of the follow up period (~4.2 years).
- There was no association between baseline EEG asymmetries of any type and refractoriness to medical therapy, regardless of analytical method applied.

ABSTRACT

Objective: Previous studies based solely on visual EEG analysis reported equivocal results regarding an association of pharmaco-resistance with EEG asymmetries in genetic generalized epilepsies (GGE). We addressed this issue by applying both visual and quantitative methods to the pretreatment EEG of GGE patients.
Methods: Socio-demographic/disease characteristics and response to treatment/discontinuation trial for these patients were recorded at 6 months and at last follow up. The first EEG was retrospectively, blindly, and visually assessed for focal slowing, focal discharges and also quantitatively analyzed for amplitude or latency asymmetries of generalized discharges. Association between these variables and development of drug-resistance was evaluated.
Results: Out of 51 subjects, 40% had some type of EEG asymmetry by visual, 37% by quantitative and 54% by combined analysis. Drug-resistance was identified in 52% of patients after 6 months and in 24% at the end of the follow up period (~4.2 years). 27% of patients underwent a discontinuation trial; 43% unsuccessfully. There was no association between baseline EEG asymmetries of any type and refractoriness to medical therapy, regardless of analytical method used.
Conclusions: In a carefully selected cohort of medication-naïve GGE patients, visual and quantitative asymmetries in the first EEG were not associated with the development of pharmaco-resistance.
Significance: These findings do not provide support for utilization of EEG asymmetries as a prognostic tool in GGE.

1. Introduction

Genetic generalized epilepsy (GGE) (Berg et al., 2010), formerly known as idiopathic generalized epilepsy (IGE), constitutes approximately 20% of epilepsies across all age groups (King et al., 1998) and 33–45% in the pediatric population (Cowan, 2002). Clinically it is characterized by absence seizures, myoclonic seizures and/or generalized tonic–clonic seizures (Proposal for

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revised classification of epilepsies and epileptic syndromes, 1989). It is commonly encountered in genetically predisposed, developmentally normal individuals with no structural brain abnormalities and is typically characterized by the presence of symmetric anteriorly predominant spike-wave (SW) and polyspike-wave complexes on the electroencephalogram (EEG), typically in the context of a normal background (Proposal for revised classification of epilepsies and epileptic syndromes, 1989). EEG asymmetries in the form of focal slowing, focal and/or asymmetric generalized epileptiform discharges are not uncommon, encountered in approximately one-third to two-thirds of phenotypically characterized GGE patients (Aliberti et al., 1994; Leutmezer et al., 2002; Lombroso, 1997).

Although GGE typically responds well to appropriate antiepileptic medications (Kharazmi et al., 2010), approximately one third of patients with GGE have continued seizures despite adequate and appropriate medications (Kwan and Brodie, 2000; Mohanraj and Brodie, 2007). The cause(s) of drug-resistance in GGE remain(s) elusive. Identification of predictors of drug-resistant GGE is a critical step toward designing clinical trials of new therapies. Moreover, if drug-resistance is in part genetically determined, any such predictors would be useful for endophenotyping subjects for genetic studies and pharmaco-genetic initiatives. Finally, patients and clinicians would benefit from early identification of likely drug-resistance by having knowledge available to guide more aggressive early therapy.

Previous studies examined a potential link between EEG asymmetries and pharmaco-resistance and produced mixed results (Nicolson et al., 2004; Szaflarski et al., 2010b), perhaps as the result of variable study populations, loose definitions both for EEG asymmetries and pharmaco-resistance, and most importantly, un-blinded visual analysis of EEG or reliance on written reports without review of the primary data. In addition, some studies may have been confounded by medication effects, as the EEG may be altered by treatment. Here we have examined the relationship between EEG asymmetry and pharmaco-resistance using medication-naïve EEG records from thoroughly phenotyped GGE patients, implementing strict definitions for EEG asymmetries and pharmaco-resistance and foremost, combining blinded visual analysis with quantitative analytical methods.

2. Methods

2.1. Subjects and their assembly

We studied patients with GGE followed at Massachusetts General Hospital from 2003 to 2011 who had available EEG records prior to antiepileptic treatment and who received a minimum of 6 months follow up documentation. The identification of patients was performed by reviewing EEG reports from a searchable EEG database and hospital electronic medical records. Routine EEG studies of up to 1 h duration were obtained using standard departmental protocols with a 32-channel EEG recorder, applying the international 10–20 system for electrode placement and performing intermittent photic stimulation and hyperventilation in the majority of patients. Using the search phrases "generalized spike and/-wave", "generalized polyspike and/-wave", "bilateral spike and/-wave", "bilateral polyspike and/-wave", "spike and/-wave" and "polyspike and/-wave", a database of individuals whose EEGs had abnormalities consistent with IGE were identified as potential GGE subjects. Their diagnoses were validated by chart review. Patients with a GGE phenotype (childhood or juvenile absence seizures, juvenile myoclonic seizures and/or generalized tonic–clonic seizures without aura, developmentally normal, with or without positive family history and with normal clinical examination and neuroimaging) validated by their treating neurologist with expertise in epilepsy were selected. Those who had an EEG record on file with abnormalities prior to the initiation of antiepileptic treatment composed the final study population. In order to ensure that the appropriate patients were selected, a second investigator with expertise in epilepsy reviewed 10% of selected medical records and kappa statistics were used to assess agreement between the 2 reviewers. Any discrepancy was adjudicated by a third investigator.

2.2. Asymmetries and their measurement

The exposure of interest was the presence of asymmetries in the first EEG of untreated patients with GGE. For the visual analysis, the routine EEG records of patients included in the study were evaluated by a board certified electroencephalographer without knowledge of the clinical outcomes to assess for the following parameters: (a) focal slowing, (b) focal epileptiform discharges, or (c) asymmetric generalized spike-wave (SW) discharges. SW discharges were considered asymmetric only if the maximal discharge was lateralized (not along the vertex) and either the peak-to-peak amplitude was 30% greater than the maximal discharge contralaterally or the discharge occurred at least 20 ms earlier compared to the contralateral hemisphere based on visual inspection. An EEG record was considered asymmetric if at least 75% of the generalized discharges were asymmetric or if there were focal epileptiform discharges or focal slowing. Due to the inherently subjective nature of visual inspection, the records were subsequently analyzed quantitatively in MATLAB (The Mathworks, Inc.) using custom code and the freely available EEG analysis tools EEGlab (http://sccn.ucsd.edu/eeglab/) and FieldTrip (http://fieldtrip.fcdonders.nl/). The goal of quantitative analysis was to match the visual analysis approach as closely as possible. First each record was reviewed and epileptiform discharges were marked by hand as follows: epileptiform discharges on any channel(s) that were not within a burst were included; for discharges recurring at 2 Hz or greater only the first epileptiform discharge in the burst was marked; markings were placed to span discharges on all channels (from the earliest visible onset on any channel to the end of the discharge on any channel). The analysis windows included the hand markings and an additional 50 ms before and after, plus additional padding to be at minimum 250 ms. For each window, every channel of EEG data was searched for the maximally negative spike peak with the following criteria: only negative peaks were considered (first derivative = 0 or crossing 0, second derivative > 0), the peak had to be sufficiently "sharp" as defined by a slope of at least 1000 uV/s within 15 ms of the peak, and the peak had to be within the hand marked window. The 1000 uV/s criterion was considered a conservative estimate of sharpness, minimally inclusive of a sharp wave of 200 ms in duration and 100 uV in amplitude. Subsequently the onset and offset of the spikes were determined as follows: the onset had to occur prior to the spike peak and within the analysis window; the offset had to occur after the spike peak and within the analysis window; the onset was considered as the last positive peak prior to the negative spike peak or when the slope of the EEG exceeded −100 uV/s; the offset was considered as the first positive peak after the negative spike peak or when the slope of the EEG exceeded −100 uV/s, The program then displayed all EEG channels with calculated onset, offset, and peak marked for review (with no markings if one of these criteria was absent). Peak spike amplitude was calculated as the maximum of either onset to peak or offset to peak. Latency was calculated for time to onset and time to peak. For each discharge, the channel with the maximum amplitude and minimal latency was determined. If that channel was on the midline, then that spike was characterized as bilateral for amplitude or latency, respectively. If it was off the midline, then the maximum amplitude or minimum latency for

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any spike on the contralateral hemisphere was calculated. If there was a hemispheric asymmetry in which the amplitude was at least 30% greater or the latency difference was at least 20 ms then the spike was considered lateralized. If these criteria were not met, then the spike was not considered lateralized. A record was considered lateralized if both of the following criteria were met: (1) there were at least three counts in one of the lateralization categories (left, right, or bilateral) and, (2) the left or right count was 75% greater than the contralateral count.

2.3. Pharmaco-resistance and its measurement

The outcome of interest was the development of resistance to antiepileptic medications. Resistance was defined as absence of seizure freedom for >6 months at any point of the follow up on 2 or more appropriate antiepileptic medications for GGE, used simultaneously or sequentially, in an appropriate dose. Appropriate medications for GGE were considered to include valproic acid, lamotrigine, levetiracetam, topiramate, zonisamide, ethosuximide (for CAE), felbamate and benzodiazepines (Glauser et al., 2010; Marson et al., 2007). Appropriate dose was defined as the maximum published FDA recommended dose or a recorded therapeutic level based on the pre-defined MGH laboratory normative values. Patients who were treated with other medications or with poor seizure control due to noncompliance or lifestyle factors were deemed "pseudoresistant" and were not included in the analysis. Antiepileptic medication levels were used as a measure of adherence. Data for the 6 months preceding the last available follow up were also tabulated. Finally, the result of a medication discontinuation trial, when attempted within the study period, was noted. In order to avoid misclassification of the outcome, a second investigator with expertise in epilepsy blindly reviewed 10% of subjects and kappa statistics were used to assess agreement between the 2 reviewers. Any discrepancy was adjudicated by a third investigator.

2.4. Confounders and their measurement

Factors that may have independently contributed to the outcome of interest were logged. In particular, information on several socio-demographic and disease characteristics was retrieved from the medical records for the study sample. These included age at diagnosis, gender, GGE type, history of status epilepticus, comorbidities, family history of epilepsy, antiepileptic medications and duration of follow up.

2.5. Analysis

In a univariate analysis, we examined the association of any type of asymmetry (focal slowing, focal epileptiform discharges or asymmetry of generalized epileptiform discharges in amplitude or latency) individually or in combination for visual, quantitative or combined EEG analyses with the development of drug-resistance at 6 months and last follow-up and with discontinuation failure, when this was performed. Risk of drug resistance for each of these conditions was calculated as an odds ratio with confidence intervals. In multivariate analyses a similar association was sought between the exposures (asymmetries in isolation and in combination with visual, quantitative or combined EEG analyses) and the outcomes of interest (drug-resistance at 6 months, last follow up, and failed discontinuation trial) using logistic regression to adjust for potential confounders. Due to the limited number of outcomes of interest, controlling for all measurable potential confounders was not feasible, and therefore adjustment was confined to those deemed to be the most important ones (GGE type and AED type). Analysis was performed using SAS (Cary, NC, USA).

3. Results

51 patients were analyzed. 21 (41%) of them were male. The median age at the time of diagnosis was 8 years old. Approximately half of the patient population suffered from childhood absence epilepsy. No patient had a history of status epilepticus. 31 (61%) were otherwise healthy, while 15 (29%) had mild neuropsychiatric comorbidities (e.g., ADHD, anxiety and depression) and approximately 5 (10%) had some form of somatic comorbidity (e.g., asthma). Family history of epilepsy excluding febrile seizures was encountered in 8 (15%) patients. Concordance between the two medical chart reviewers for GGE adjudication was excellent (kappa: 1). These demographic and disease characteristics data are depicted in Table 1.

The baseline EEG characteristics prior to AED initiation are illustrated in Table 2. Activation with hyperventilation was seen in 33 (75%) patients while photic stimulation was associated with epileptiform activity in 19 (39%) patients. On visual analysis, focal slowing was seen in 11 (22%) patients, in approximately half of whom it was shifting from side to side. Focal epileptiform discharges were noted in 16 (32%) patients, shifting from side to side in approximately half of them. Symmetric generalized IEDs without amplitude or latency asymmetries were identified in 19 (38%) patients, while 13 (26%) had shifting but not clearly lateralized asymmetries and 18 (36%) had lateralized amplitude and/or latency asymmetries in their generalized epileptiform bursts. Altogether, 20 (40%) patients had some type of asymmetry on visual inspection of their EEG, either in the form of focal (unilateral) slowing, focal (unilateral) IEDs or asymmetric (due to consistent unilateral amplitude or latency predominance) generalized bursts. For quantitative analysis, 11 patient EEGs were rejected due to too few analyzable spikes. Of the remaining 40 studies, a consistent latency asymmetry was detected in 7 (18%) patients, while a consistent amplitude asymmetry was detected in 11 (28%) patients. Altogether, 15 (38%) patients had some type of asymmetry on quantitative analysis of their EEG, either in the form of consistent latency or amplitude asymmetry or combination thereof. Despite the similar percentage of asymmetric records detected by the visual and quantitative methods, the agreement between the two methods was poor (Kappa: 0.11). Finally, combining visual with quantitative criteria, 27 (54%) patients were deemed to be asymmetric.

The median follow up period for the study population was 4.2 years. In 23 (45%) valproate was the first medication to be implemented while ethosuximide was selected in 13 (25%) and lamotrigine in 10 (10%). In 51% of cases, no additional medication was used through the end of the follow up period. In those who required a second medication, valproate was the most common, followed by lamotrigine and levetiracetam. When a third medication was required levetiracetam, followed by ethosuximide and

Table 1
Baseline demographic and disease characteristics.

Demographic characteristics	
Age at diagnosis (median, IQR-years)	8 (8)
Gender (male, *n*, %)	21 (41.18)
Disease characteristics	
Type of GGE (n, %)	
1. Childhood absence	25 (49.02)
2. Juvenile myoclonic	8 (15.69)
3. Generalized tonic–clonic only	14 (27.45)
4. Unclassified	4 (7.84)
History of status epilepticus (yes, *n*, %)	0 (0)
Comorbidities (n, %)	
1. None	31 (60.78)
2. Neuropsychiatric	15 (29.41)
3. Somatic	5 (9.80)
Family history of epilepsy (yes, *n*, %)	8 (15.38)

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Table 2
Baseline EEG characteristics.

Activation with hyperventilation (yes, *n*, %)	33 (75)
Activation with photic stimulation (yes, *n*, %)	19 (39.58)
Focal slowing on visual analysis (*n*, %)	
Focal IEDs on visual analysis (*n*, %)	
Asymmetric generalized IEDs on visual analysis (*n*, %)	
1. No	19 (38)
2. Yes	18 (36)
3. Shifting	13 (26)
Any type of asymmetry on visual analysis (yes, *n*, %)	20 (40)
Amplitude asymmetry of generalized IEDs on quantitative analysis (yes, *n*, %)	11 (27.50)
Latency asymmetry of generalized IEDs on quantitative analysis (yes, *n*, %)	7 (17.50)
Any type of asymmetry on quantitative analysis (yes, *n*, %)	15 (37.50)
Any type of asymmetry on either visual or quantitative analysis (yes, *n*, %)	27 (54.00)

Table 3
Treatment characteristics.

Time of follow up (median, IQR-years)	4.2 (3.6)
First medication trial till last follow-up (n, %)	
1. Valproate	23 (45.10)
2. Ethosuximide	13 (25.49)
3. Lamotrigine	10 (19.61)
4. Levetiracetam	4 (7.84)
Second medication trial till last follow-up (n, %)	
1. None needed	26 (50.98)
2. Valproate	7 (13.73)
3. Lamotrigine	5 (9.80)
4. Levetiracetam	5 (9.80)
Third medication trial till last follow-up (n, %)	
1. None needed	39 (76.47)
2. Levetiracetam	5 (9.80)
3. Ethosuximide	3 (3.92)
4. Topiramate	3 (3.92)
Total medication trials at last follow-up (#, n, %)	
1. 1	26 (50.98)
2. 2	13 (25.49)
3. 3	10 (19.61)
4. 4 or more	1 (1.96)
Resistant at 6 months of follow-up (yes, *n*, %)	25 (52.08)
Resistant at last follow-up (yes, *n*, %)	12 (24.49)
Time of discontinuation trial (median, IQR-years)	3 (2)
Medication discontinuation trial (yes, *n*, %)	14 (27.45)
Discontinuation failure (yes, *n*, %)	6 (42.86)

topiramate were the most likely choices. At the last follow-up visit, 26 (51%) of the patients tried a total of one medication, 13 (25%) two, 10 (20%) three and 1 (2%) tried four. By the end of the first 6 months, 25 (52%) patients were uncontrolled. That percentage was reduced to 24% at the end of total follow up period of 4.2 years median duration. An attempt to discontinue AEDs was undertaken in 14 (27%) patients and failed in 6 (43%) of them. Concordance between the two medical chart reviewers for pharmaco-resistance adjudication was excellent (kappa: 1). Table 3 summarizes these treatment characteristics.

In the univariate adjusted analyses (Table 4), the presence of asymmetric features either in the visual analysis, the quantitative analysis or the combined analysis was examined independently as a predictive measure for pharmaco-resistance either at 6 months of follow up, or at the last follow up visit or as a predictor of AED discontinuation failure. In the visual analysis, the presence EEG asymmetry was not associated with any of the three endpoints. That was a consistent finding irrespective of including the shifting asymmetric generalized epileptiform discharges in overall symmetric or asymmetric records. Similarly in the quantitative analysis the presence of consistent latency or amplitude asymmetries or combination thereof were not associated with any of the three endpoints of interest. Finally, there was no statistically significant association or suggestion of increased risk between any asymmetry derived by combining visual and quantitative data and the development of any of the three endpoints.

In the multivariate analysis (Table 5), the presence of asymmetries identified in the visual, quantitative and combined EEG analysis were examined as potential predictors for the development of pharmaco-resistance in the first 6 months or in the last follow up of approximately 4.2 years, adjusting for confounders of epilepsy type (absence vs other) and type of first AED administered (Valproate vs other). Again, there was no statistically significant association between the presence of baseline EEG asymmetries and the development of short or longer term pharmaco-resistance, no matter whether qualitative, quantitative or combined EEG analytical methods were applied. An adjusted analysis for a potential association between any type of EEG asymmetry and AED discontinuation failure was not feasible due to the limited frequency of that endpoint. Fig. 1 illustrates an example of a significantly asymmetric EEG derived from a patient whose epilepsy was controlled immediately with the first medication (panels A, EEG sample, and C, colorized topographic distribution of discharges), and an example of a symmetric EEG that was from a patient whose epilepsy was pharmaco-resistant at all time points (panels B and D).

4. Discussion

In a carefully selected cohort of medication-naïve GGE patients we were unable to show an association between visually and quantitatively detected EEG asymmetries with the development of pharmaco-resistance.

Genetic generalized epilepsy has been traditionally thought to emanate from thalamic generators and subsequently shown to project simultaneously homogeneously to the cortex through reentrant thalamocortical circuitries (Avoli et al., 2001; Gloor, 1968). Accumulating evidence derived both from genetic animal models (Avanzini et al., 1996) and EEG/fMRI human studies (Moeller et al., 2008; Tyvaert et al., 2009) over the years has supported that notion, providing a plausible explanation for the prevailing symmetry seen in the EEG of patients with GGE. However, as has been recognized previously (Aliberti et al., 1994; Leutmezer et al., 2002; Lombroso, 1997) and confirmed here, EEG asymmetries are not uncommon in generalized epilepsy. What this reflects and whether this is clinically relevant remains under question.

The underlying pathophysiological mechanism of asymmetry in generalized epileptic discharges has been the focus of intense investigation. There is mounting evidence for the primary role of the frontal cortex in the generation of SW abnormalities seen in GGE patients. Animal model studies have shown close, bidirectional interactions between cortical and thalamic sites with the cortical focus leading the thalamus (Meeren et al., 2002). Pathological studies have identified an increased number of dysgenetic cortical lesions in patients of patients with GGE compared to non-epileptic brains (Meencke and Janz, 1985). Electrophysiological studies with depth electrodes in patients with generalized

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Table 4
Univariate analysis of EEG asymmetries with drug-resistance at 6 months and last follow-up and with discontinuation failure.

	Drug-resistance at 6 months ($n = 51$)		Drug-resistance at last follow-up ($n = 51$)		Discontinuation failure ($n = 14$)	
	OR	95% CI	OR	95% CI	OR	95% CI
Visual analysis						
Focal slowing (unilateral)	0.43	0.07–2.62	3.66	0.62–21.35	1.5	0.14–15.46
Focal IEDs (unilateral)	0.32	0.05–1.89	2.06	0.41–10.36	3.5	0.23–51.89
Asymmetric generalized IEDs	0.77	0.23–2.52	1.26	0.33–4.79	0.83	0.09–7.67
Any type of asymmetry	0.78	0.24–2.50	1.57	0.42–5.85	1.66	0.19–14.26
Quantitative analysis						
Amplitude asymmetry of generalized IEDs	0.92	0.21–3.96	1.07	0.22–5.21	0.3	0.01–4.90
Latency asymmetry of generalized IEDs	7.84	0.83–73.46	0.40	0.04–3.88	0.5[a]	0.26–0.92[a]
Any type of asymmetry	2.34	0.59–9.20	0.57	0.12–2.68	0.3	0.01–4.90
Combined analysis						
Any type of asymmetry	1.08	0.34–3.40	1.78	0.45–7.02	2	0.22–17.89

[a] RR(95% CI) estimate due to inadequate sample for all cells to estimate OR.

Table 5
Multivariate analysis of EEG asymmetries with drug-resistance at 6 months and last follow-up.

	Drug-resistance at 6 months[a] ($n = 51$)		Drug-resistance at last follow-up[b] ($n = 51$)	
	OR	95% CI	OR	95% CI
Visual analysis (any type of asymmetry)	0.90	0.24–3.30	1.56	0.41–5.86
Quantitative analysis (any type of asymmetry)	2.05	0.46–9.18	0.54	0.11–2.62
Combined analysis (any type of asymmetry)	1.13	0.32–3.90	1.78	0.45–7.02

[a] Adjusted for epilepsy type (absence vs other) and first medication used (valproate vs other).
[b] Adjusted for epilepsy type (absence vs other).

SW abnormalities thought to suffer from GGE failed to suggest thalamic involvement (Niedermeyer et al., 1969). Radiological studies using quantitative MRI techniques have identified significantly larger cortical grey matter volumes and distribution abnormalities in GGE patients than control subjects (Woermann et al., 1998). Recently, multimodal studies using MEG/EEG (Stefan et al., 2009) and EEG/fMRI (Szaflarski et al., 2010a) have provided further evidence in support of a frontal hypothesis. A microstructural cortical explanation would be in accord with the consistency of electrographic asymmetries noted in a previous study (Lombroso, 1997), but would be incongruent with the alternating (Letourneau et al., 2010) and transitory localization of electrographic asymmetries in other studies that examined GGE records of the same patients longitudinally (Hedstrom and Olsson, 1991). The development of a focal, self-sustaining hyperexcitability in low threshold cortical structures subjected to repeated generalized epileptiform activity (Lombroso, 1997) seems to provide a more plausible explanation.

Similarly, the prognostic value of EEG asymmetries has been addressed in previous studies with mixed results. While certain studies failed to show an association between electrographic asymmetries and the development of pharmaco-resistance (Betting et al., 2006; Lancman et al., 1994; Letourneau et al., 2010; Nicolson et al., 2004), others have suggested the opposite (Fernando-Dongas et al., 2000; Leutmezer et al., 2002; Szaflarski et al., 2010b; Wolf and Inoue, 1984). These studies have been limited by variable sample sizes, selection bias of refractory populations, variable and often loosely defined GGE subjects that were typically already under treatment when EEGs were examined, inconsistent definitions of what constitutes EEG asymmetry, EEG interpretations performed un-blinded and visually only, frequent reliance on EEG reports, varying definitions of pharmaco-resistance often without adequately addressing the issue of pseudo-resistance and in an era where newer antiepileptic agents were not available yet, frequently unadjusted or limited statistical analysis and retrospective design.

Here we found no association between EEG asymmetry and the development of pharmaco-resistance, which we feel is not an entirely surprising result. Despite its well accepted utility as an adjunctive tool, routine EEG has commonly proven inadequate to confirm the presence of epilepsy in this population with 45% of patients having a normal first EEG (Betting et al., 2006). Moreover, it may occasionally lead to misclassification. Specifically, studies focusing on JME patients revealed interictal routine EEG asymmetries in more than half of the cases (Letourneau et al., 2010; Lombroso, 1997), interictal continuous video-EEG combined semiologic or electroencephalographic asymmetries in 54% of cases (Usui et al., 2005) and exceptionally, even lateralizing ictal propagations (Usui et al., 2005). These findings can occasionally lead to misclassification of the epilepsy type and clinical deterioration due to inappropriate treatment (Gelisse et al., 2004). Furthermore, EEG normalization is not always linked to clinical quiescence and vice versa (Hedstrom and Olsson, 1991).

The results of our study are strengthened by certain methodological advantages. The study sample was medication-naïve GGE patients, early on in their disease, assembled by using strict inclusion criteria. That is particularly important, since it is known that the EEG may change with pharmacotherapy and/or aging (Panayiotopoulos et al., 1989). Strict definitions for EEG asymmetries and pharmaco-resistance were applied and pseudo-resistance was taken into account by excluding inappropriate AEDs and by incorporating drug levels as means to assess compliance. Visual analysis was performed by a board certified electroencephalographer by directly and blindly reviewing high quality EEG recordings. Quantitative EEG analysis was performed by using an automated methodology, to our knowledge not previously utilized to address this question. That was of paramount importance given the subjectivity in pure visual interpretation of EEG asymmetries, as indicated by the moderate degree of inter-rater agreement in prior studies (Letourneau et al., 2010). The observed poor concordance between visual and quantitative analysis also highlights the subjectivity of visual EEG analysis and emphasizes the utility of quantitative methodology. Multiple checkpoints to reduce bias and ensure correct classification were performed by utilizing a second, independent reviewer to confirm the appropriateness of the study

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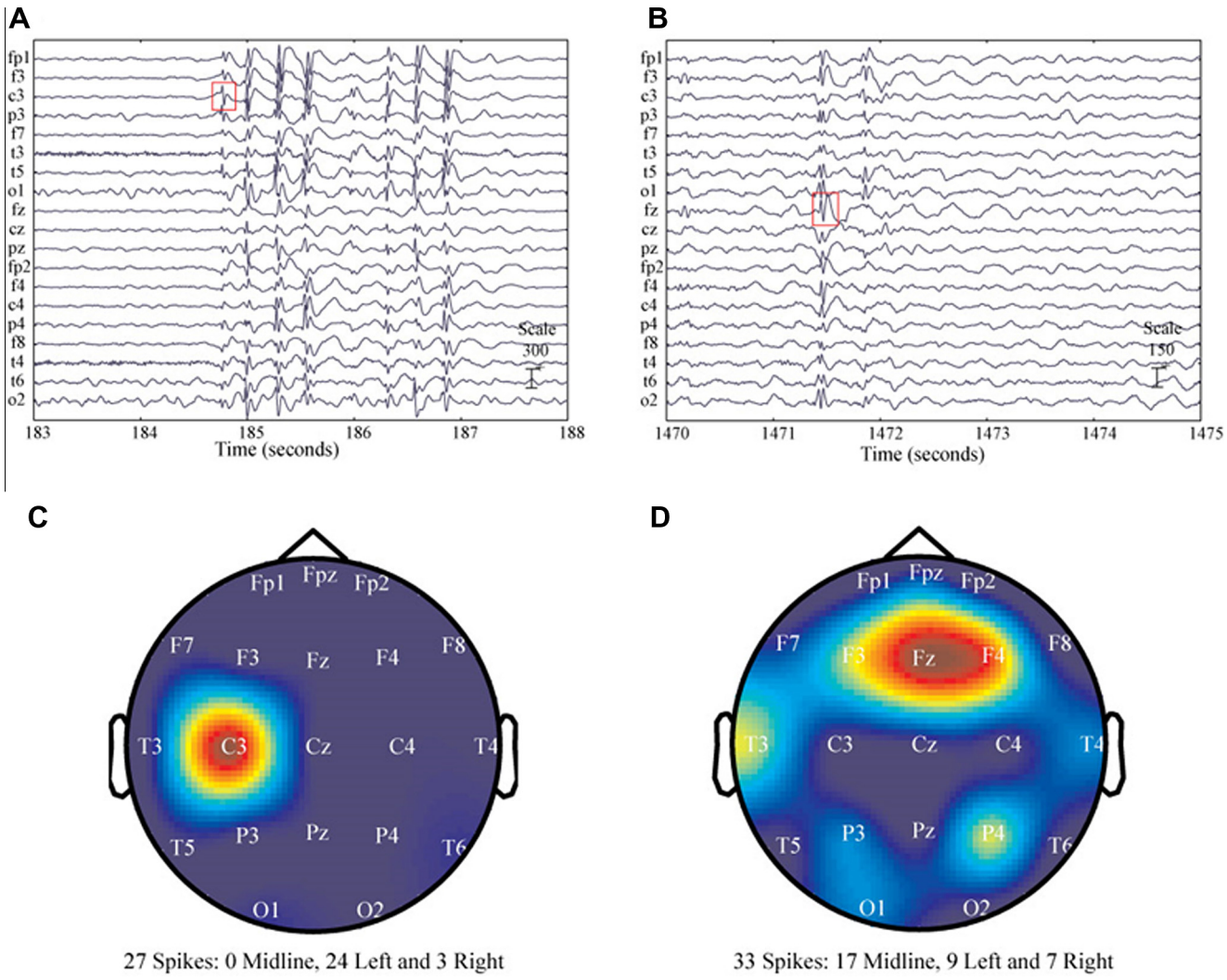

Fig. 1. Example of epileptiform discharge distributions from refractory and controlled GGE patients. Panels A and B show EEG data demonstrating lateralized (A) and symmetric (B) generalized epileptiform discharges in two separate patients. Panels C and D show the overall distribution of spikes as a colorized topographical plot. Panel C demonstrates a strong lateralization of discharges (same patient as panel A), from a patient whose epilepsy was controlled at all time points. Panel D demonstrates symmetric discharges (same patient as panel B), from a patient with refractory epilepsy at all time points. Total number of quantitated discharges are as indicated.

sample and validate the outcome of interest. Finally, statistical analysis was performed independently and in combination for the visual and quantitative analyses, adjusting for the most important measurable confounders including the type of epilepsy and the antiepileptic treatment used. That is significant given the higher number of "atypical" EEG records in certain subtypes (e.g., adult-onset GGE vs absence) (Betting et al., 2006) and the widely acknowledged superiority of valproate in controlling the generalized seizure components of patients with GGE (Marson et al., 2007; Penry et al., 1989).

On the other hand, there are certain limitations to acknowledge. Due to the strict inclusion and exclusion criteria, our study may well have been underpowered to show an existing association. Even in cases where significant positive or negative associations were suggested by large or small odds ratios respectively, the large confidence intervals associated with them repudiated any statistical significance. A larger study sample would have definitely strengthened any potential association, or lack thereof. Having said that, there was no consistency in any calculated trend, in favor of chance variation than potential association. Due to the small study sample we were able to adjust for only the most important potential confounders. That was a more apparent limitation in the last endpoint of medication discontinuation outcome, where the events of interest pertained to <1/3 of the study sample, hampering further adjustments. Further investigation using quantitative methodology and larger samples are needed to address these limitations. The median time of diagnosis was 8 years of age and the median follow up period was 4.3 years. After accounting for the variable follow up period for each subject our results did not change substantially. Albeit representative of the typical population for GGE, it is unclear whether the same conclusions would hold for a younger or older population sample with a more prolonged follow up period. Our study sample was derived from a tertiary referral center, and although it included only newly diagnosed, medication-naïve cases, it is uncertain if it could be generalizable to the community. Finally, despite the methodological precautions, this was a retrospective cohort study, and as such, is inherently limited by the potential of selection and observation biases.

5. Conclusion

In a carefully selected, modestly-sized cohort of medication-naïve GGE patients, we were unable to show an association between visual and quantitative asymmetries in the first EEG with

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the development of pharmaco-resistance. Until further molecular advances allow for better characterization of the underlying mechanisms for pharmaco-resistance, utilization of EEG asymmetries as a prognostic tool in GGE appears dubious.

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