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Quantitative Electroencephalography Findings in Treatment-resistant and Responsive Patients with Idiopathic Generalized Tonic-Clonic Epilepsy

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Abstract

Background: With roughly 50 million people affected in the world, epilepsy is a particularly important disorder of the brain commonly diagnosed based on findings of quantitative electroencephalography (QEEG). The present investigation was aimed to evaluate differences in QEEG readings of drug-resistant and drug-responsive patients with idiopathic generalized epilepsy (IGE) with tonic-clonic seizures in a northwestern Iranian population.

Methods: A total of 60 participants, consisting of 30 drug-resistant and 30 drug-responsive patients with IGE, were enrolled. Data, including demographic information and Z-transformed absolute power values of QEEG in anterior, central and posterior alpha, beta, delta and theta bands were collected. The analysis was conducted using IBM SPSS and a p-value<0.05 was considered as statistically significant.

Results: Of the 60 participants with a mean age of 31.55 ± 10.48, 41 (68.3%) were female and 19 (31.7%) were male. Statistically significant differences were observed in anterior alpha, beta and theta bands, central alpha, beta, delta and theta bands, and posterior beta, delta and theta bands between the two groups, with the absolute power Z-scores of drug-resistant groups being significantly higher than the other (P-values<0.05). Abnormal EEGs were recorded for 16 (53.3%) and 5 (23.8%) patients from the drug-resistant and drug-response groups, respectively, indicating a significant difference (P-value=0.006). Female patients were more likely to have drug-resistant disease than male participants (P-value=0.003).

Conclusions: QEEGs with normal readings indicate a more favorable prognosis, compared with those containing abnormal findings.

Keywords: Quantitative electroencephalography; QEEG; Idiopathic generalized epilepsy; Tonic-clonic seizure; Anti-epileptic drug resistance

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Introduction

Epilepsy is the second highly-discussed brain pathology after stroke, which affects approximately 50 million individuals at the world, and in nearly 30% of cases is not amenable to anti-epileptic drugs (1, 2). The frequent episodes of fit or seizure are the principal cause of physical and social distress in these patients, which severely impacts the quality of life (1, 2). There is no definite cure for the condition, though, in a very few number of cases, certain surgical procedures such as middle temporal lobectomy may be indicated, albeit, the prominent postoperative sequelae (2). Accordingly, lobectomy can only be tried in about 8% of all patients, with a good 25% remaining resistant to the currently available therapeutics (1). Refractory epilepsy has also devastating consequences and 20-40% of newly diagnosed patients will become refractory (3). Furthermore, uncontrolled epilepsy could lead to various consequences in terms of education, occupation, and psychological status (4).

As of now, epilepsy is diagnosed based on specific alterations that can be recorded in an electroencephalogram (EEG), either visually by the physicians or quantitatively by a computer (1, 2). The electric signals of brain reflect the activity of this central organ, are subject to change in time and differ from one individual to another. Among the methods developed for detection and recording of these signals developed thus far, EEG has become a widely used modality thanks to its portability, ease of use and inexpensiveness (5, 6). While the visual or qualitative interpretation of brain waves is widely practiced as the conventional method of diagnosis, quantitative EEG (QEEG) is being increasingly considered a complementary, or even substitutional, approach for clinical diagnosis of epilepsy (1, 2). Compared with other cerebral functional imaging modalities, QEEG is a relatively inexpensive technique, devoid of ionizing rays, that confers good sensitivity in the evaluation of temporal neuronal function, with a diagnostic threshold as precise as milliseconds (7). Brain waves, in this technique, are recorded by means of 19 standardly positioned electrodes, while the patient is resting with their eyes closed. The quantitative analysis of the output EEG is then carried out based on the Fast Fourier Transform (FFT), returning four important variables including absolute power, relative power, coherence and symmetry (8).

To date, several attempts have been made at delivering a comparative analysis of the diagnostic accuracy of QEEG in relation to other techniques. A systematic review on 6 investigations found that QEEG had performed considerably better, in terms of sensitivity, in two studies (9). Also, two clinical investigations on paediatric epilepsy and seizure subtypes suggested that QEEG was a suitable biomarker to be considered in modulation of antiepileptic drugs (AED) (10) and could confer higher sensitivity for distinguishing different subtypes of seizure from one another (11).

The state of consciousness was evaluated in 96 comatose patients and reported that QEEG delivered more reliable estimates of awareness for prognostication of post-anoxic coma (12). Dating back to 2004, a study on 35 patients with idiopathic generalized epilepsy (IGE) was also indicative of the diagnostic value of QEEG in identification of this pathology (13).

As clinical investigations on the application of QEEG for diagnosis of IGE are scarce, particularly in the developing countries of the Middle East region, the present study was designed to address the many issues in the field, that remain unaccounted for, by delivering a comparative analysis of this diagnostic modality on a population of IGE patients in Northwest of Iran.

Materials and Methods

Study design

The present investigation was an observational study of 60 patients with idiopathic epilepsy with generalized tonic-clonic seizure manifestation who had been receiving anti-epileptic medication before being enrolled.

The overall design of the study and population size was determined based on the investigations led by Clemens (13) and Ouyang et al. (10). Briefly, this is a observational study which evaluates quantitative EEG parameters in IGE, comparing drug-resistant patients with good responders. According to approved criteria for quantitative EEG investigations, all EEG recordings were made during the morning hours by trained staff using the same equipment in the same semi-isolated room. The definition of abnormal EEG was based on the International League Against Epilepsy (ILAE) criteria and determined by two expert neurologists (14). A convenient sampling was used for inclusion of participants. We used a set of inclusion and exclusion criteria for the enrolment of potentially eligible participants. Our inclusion criteria were as follow:

1. There was a past medical history of IGE with tonic-clonic seizures based on patient claims
2. Positive drug history of anti-epileptic agents
3. Patient consent for participation

Those participants who had other types of epileptic disorders at the same time or had epilepsy secondary to focal or systemic diseases such as brain tumours and encephalopathy were excluded.

The present study was conducted after it was approved by the Committee of Ethics in Biomedical Research of Tabriz University of Medical Sciences, Tabriz, Iran. Personal data collected from patients were kept confidential. Participants were not made subject to any experimental therapeutic interventions. All methods were performed in accordance with the national guidelines and regulations. Informed consent was obtained from all patients in the study. The study was approved by the regional ethics committee (Ethics Code: IR.TBZMED.REC.1398.788). All methods were performed in accordance with the national guidelines and regulations.

Data collection

The subjects were divided into two groups, namely, properly controlled/drug-responsive and poorly controlled/drug-resistant, each containing 30 participants. The clinical criteria for being considered as drug-resistant or poorly controlled was

Table 1. Demographic information of patients in the two groups being studied.

Variable		Group		P-value
		Drug-responsive	Drug-resistant	
Sex (number (percent))	Female	19 (39.0%)	25 (61.0%)	0.025
	Male	14 (73.7%)	5 (26.3%)	
Age (mean ± SD)		25.90 ± 8.08	37.20 ± 9.61	0

Abbreviations: SD: standard deviation

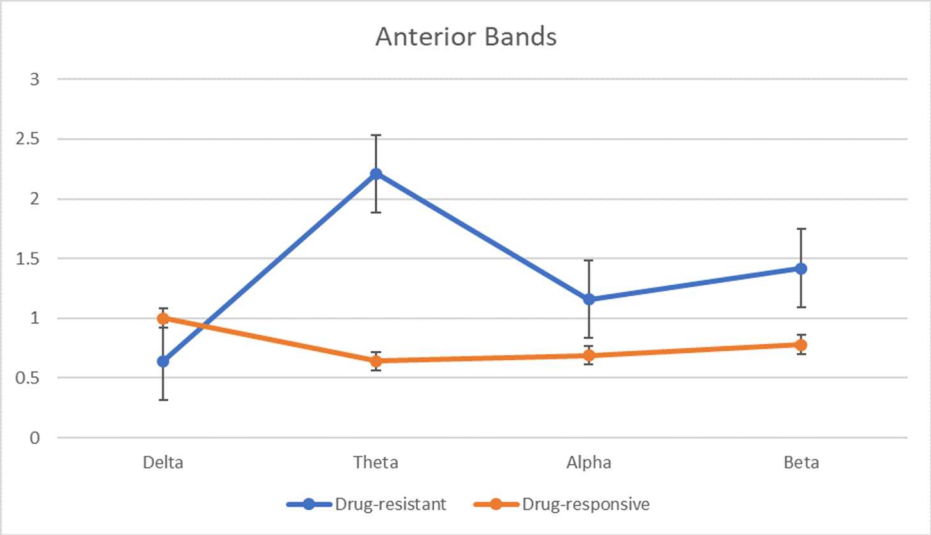

Figure 1. Comparative diagram of anterior delta, theta, alpha and beta bands between drug-resistant and drug-responsive groups.

the occurrence of at least one episode of seizure within 30 days from the study. Participants in both groups were then studied with QEEG, which provided us with absolute power Z scores for three bands, namely, anterior, central and posterior, each corresponding to four waves, including alpha, beta, delta and theta. Demographic information, including the frequency of seizures, drug history and the age of disease onset, were collected before being analysed between the two groups.

Statistical analysis

We used IBM SPSS version 21.0 software for conduction of statistical analysis. Quantitative data were presented in mean ± standard deviation (SD). Normal distribution of data was determined using the Kolmogorov–Smirnov test. Correlational analysis between qualitative variables was performed using Chi-squared and Fisher's exact tests. Quantitative data were analysed between the groups using independent sample t-test for those with normal distribution and Mann-Whitney U test for those with non-normal distribution. The Bonferroni test was used to control type 1 error rate due to using multiple comparisons. A P-value<0.05 was considered as statistically significant.

Results

We studied 60 patients with a mean age of 31.55 ± 10.48, divided equally into drug-responsive and drug-resistant groups, of whom 41 (68.3%) were female, and the remaining 19 (31.7%) were male.

Statistical analyses revealed a significant association between resistance to treatment and patient sex, as shown in Table 1. Female participants were more resistant to treatment, i.e., they were more likely to have poorly controlled disease (P-value=0.025). There was significant difference between the groups in terms of mean age (P-value<0.001). Drug resistance was found to be significantly associated with age, based on the results of independent sample t-test.

As shown in Figure 1, we also detected a considerable difference in the anterior alpha, beta and theta bands between the two groups, as participants who were resistant to treatment exhibited higher frequencies in the three band, which was more significant in the theta band (P-value≤ 0.005). Similar to the anterior bands, the central alpha, beta and theta bands were also found to be of higher frequencies in the drug-resistant groups, who also demonstrated significantly different delta bands as read by the central electrodes (P-value<0.05) (Figure 2). In the case of posterior electrodes those with poorly controlled disease had markedly higher beta, delta and theta bands (P-value<0.05), the latter of which showed a more pronounced difference (Figure 3 and Table 2).

Out of the 30 participants in drug-resistant group, 16 (53.3%) patients returned abnormal QEEG. On the contrary, only 23.5% (n=5) of patients with properly controlled disease were found to exhibit aberrancies in their QEEG, a difference which was deemed statistically significant (P-value=0.006). While there was not meaningful association between QEEG abnormality and age, we did find a correlation between abnormal QEEG and sex (P-value=0.003), the former of which was more prevalence among male patients (Table 3).

Discussion

In the present study, we enrolled 60 participants divided in equal numbers into two groups, namely, drug-resistant and drug-responsive. We aimed to evaluate differences in QEEG readings of drug-resistant and drug-responsive patients with IGE with tonic-clonic seizures.

Based on the literature, an EEG taken immediately after seizure, known as postictal EEG, may show abnormal findings in 2% to 86% of cases (15). As such, we observed abnormal findings in the EEGs recorded for 38.55% of our patients, which was in line with the 2014 study led by Hemmati et al. on 111 patients, that reported abnormal findings in 36.7% of patients (16). Similarly, Jeong et al. demonstrated a prevalence of 31% for abnormal EEGs in their population of 131 epileptic

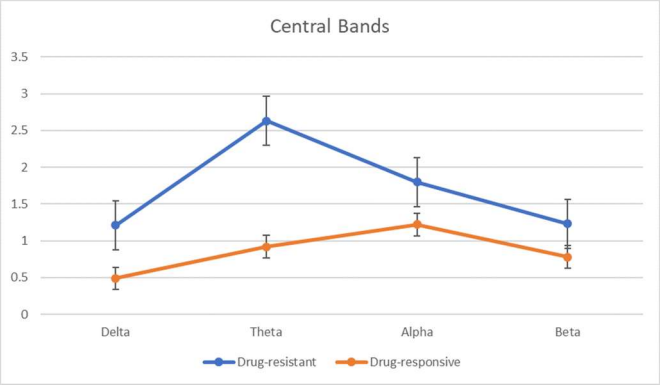

Figure 2. Comparative diagram of central delta, theta, alpha and beta bands between drug-resistant and drug-responsive groups.

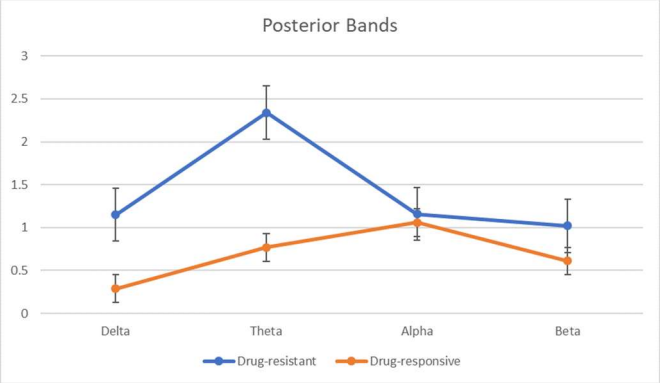

Figure 3. Comparative diagram of posterior delta, theta, alpha and beta bands between drug-resistant and drug-responsive groups.

children, with higher occurrence in those affected by complex febrile seizures that commonly comprised sharp waves, followed by slow waves (17). Karimzadeh et al. conducted an EEG study on 36 children with febrile seizure within 48 hours and 2 weeks from the occurrence of seizure, noting similar distribution of sharp and slow waves in terms of prevalence. Though, they did not report a significant difference between EEGs taken at different times, as the prevalence of abnormal EEGs among those taken at 2 and 14 days following seizure was 80.6% and 69.4%, respectively (18). The apparent disparity in the findings of this particular study with those of ours could have emanated from differences in the age and number of participants. Hemmati et al. observed more extensive changes, although not significant, in the EEG of participants of smaller age (16).

In the present investigation the mean ages of subjects were also similar between subjects with abnormal and normal EEGs. Nevertheless, the drug-resistant group did exhibit a statistically significant difference in their age, compared with the control or drug-responsive group.

Our experimental population (n= 60) consisted of 41 (68.3%) female and 19 (31.7%) male patients, indicating an overall higher prevalence of epilepsy among women. Likewise, Picot et al., in 2008, reported that women in France were more commonly affected by epileptic disorders than men (19).

We noted significant differences in the frequencies of alpha, beta and theta (anterior band), alpha, beta, delta and theta (central band), and beta, delta and theta (posterior band) waves between drug-resistant and drug-responsive groups. A significant difference was also discovered in the prevalence rates of abnormal EEGs between the two groups, that were 53.3% and 23.8%, respectively. Consistently, Clemens, in 2004, found a significant correlation between the abnormality of EEG and complicity of IGE (13). In 2008, Santiago-Rodríguez et al. identified abnormal Z-transformed absolute power scores in anteroposterior (AP) delta bands in frontotemporal and occipital leads, and AP alpha and beta bands in frontoparietal leads of patients with juvenile myoclonic epilepsy (JME) (20). Cekirge et al. confirmed presence of aberrancy in alpha, beta, delta and theta bands of epileptic patients of Turkish descent in 2017 (21). Most recently, in 2021, Chacón et al. came across higher beta, delta and theta, and lower alpha frequencies in their control subjects, i.e., patients with epileptic encephalopathy who had not been receiving cannabidiol Epidiolex (22).

In the present investigation, we noticed a significant association between sex and resistance to therapy, as male patients were more likely to exhibit drug-resistance. Likewise, abnormal EEG was found to be correlated with sex, since men more often displayed aberrancies in their EEG. Few studies have sought to delve into the relationship between EEG aberrancy and sex, because it is a difficult subject matter to investigate. However, some have stipulated that this difference might be due to different effects of sex or gonadal hormones on EEG, in view of the fact that male patients were shown to have lower serum levels of testosterone (23), which is thought to reduced EEG synchronization and prevent hyper-synchronization in normal concentrations (24). This is one of the basic principles underlying administration of levetiracetam in the treatment of epilepsy, as it effectively abrogates hyper-synchronization (25).

In 2000, García-Marín and González-Feria suggested that the routinely performed EEG, rather than QEEG, was not a suitable method for patient follow-up. They also proposed deep or intracranial placement of electrodes as a candidate method for monitoring of neuronal activity in temporal lobe epileptic disorders (26). Ebner and Hoppe, in 1995, reported preoperative interictal and ictal EEG findings of 24 patients with mesial temporal sclerosis (MTS), highlighting the occurrence of spike waves in the contralateral temporal lobe in 50% of cases, along with an ictal EEG seizure pattern comprising rhythmical activity in the delta, theta, or alpha range (27). In their investigation on temporal lobe epilepsy (TLE), Ebersole and Pacia concluded that EEG might be of great clinical value at discerning seizures of temporal neocortical origin from those of hippocampal origin (28). Another work with greater resemblance to the present study, by O'Brien et al., found that patients with TLE secondary to MTS were not different from patients with neocortical lesion-induced TLE in terms of EEG waves (29), while Watanabe et al. suggested that temporal lobe spikes recorded in EEG might be the result of mesial temporal spikes propagating to neocortex (30). Regardless, Raghavendra et al. still recognize EEG as the most important diagnostic tool for non-invasive detection of TLE (31).

Table 2. Z-transformed absolute power values recorded for alpha, beta, delta and theta bands by anterior, central and posterior electrodes.

Electrode	Band	Group (mean ± SD)		P-value
		Drug-responsive	Drug-resistant	
Anterior	Delta	1.00 ± 1.05	0.64 ± 1.19	0.218
	Theta	0.64 ± 1.19	2.21 ± 1.18	0
	Alpha	0.69 ± 1.10	1.16 ± 1.02	0.005
	Beta	0.78 ± 0.81	1.42 ± 0.77	0.003
Central	Delta	0.49 ± 1.05	1.21 ± 1.40	0.029
	Theta	0.92 ± 1.50	2.63 ± 1.21	0
	Alpha	1.22 ± 1.18	1.80 ± 1.00	0.046
	Beta	0.78 ± 0.81	1.23 ± 0.65	0.005
Posterior	Delta	0.29 ± 1.21	1.15 ± 1.05	0.005
	Theta	0.77 ± 1.77	2.34 ± 0.84	0
	Alpha	1.06 ± 1.36	1.16 ± 0.68	0.722
	Beta	0.61 ± 0.79	1.02 ± 0.57	0.026

Abbreviations: SD: standard deviation

Table 3. Distribution of abnormal QEEG and its association with age and sex.

Variable		QEEG		P-value
		Normal	Abnormal	
Group	Responsive	25 (76.2%)	5 (23.8%)	0.006
	Resistant	14 (46.7%)	16 (53.3%)	
Sex	Female	32 (78.0%)	9 (22.0%)	0.003
	Male	7 (36.8%)	12 (63.2%)	
Age (mean ± SD)		30.85 ± 10.54	31.92 ± 10.57	0.711

Abbreviations: SD: standard deviation; QEEG: Quantitative electroencephalography.

We acknowledge that our study has some limitations which should be taken into account in interpretation of the findings. In this regard, the current investigation is limited in its scope and participants, and several confounding factor such as mood disorders, underlying medical conditions and duration of treatment might have been left unaddressed (14). There were significant differences between the groups in terms of age and sex, while we did not conduct regression model to adjust the different findings for other characteristics of the sample. Therefore, the findings could arguably be attributed to low sample size and disproportionate gender or age representation in the study. We did not consider treatment with valproate as a separate item in this study, since in some cases it can define the refractoriness of epilepsy in IGE. Moreover, the history of IGE and response to the treatments are based on the patient's claim which should be considered in the interpretation of the results.

Conclusions

Patterns revealed by QEEG could be used for determining prognosis or following-up patients, for whom a QEEG would indicate a favourable prognosis. Further studies are warranted to extend our knowledge regarding applicability of QEEG in clinical management of epileptic disorders with regards to their high prevalence.

Declarations

Ethical considerations

The present study was conducted after it was approved by the Committee of Ethics in Biomedical Research of Tabriz University of Medical Sciences, Tabriz, Iran. Personal data collected from patients were kept confidential. Participants were not made subject to any experimental therapeutic interventions. All methods were performed in accordance with the national guidelines and regulations. Informed consent was obtained from all patients in the study. The study was approved by the regional ethics committee (Ethics Code: IR.TBZMED.REC.1398.788). All methods were performed in accordance with the national guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due for they are personal data but are available from the corresponding author on reasonable request.

Competing interests
The authors declared no potential conflict of interest.

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Authors' contributions
S.S. and S.M.N. conceptualized and designed the study; S.S. and S.M.N. implemented the study and collected the data; S.M.N., G.C., and S.A.N. wrote the first draft of the paper and critically revised the manuscript. All the authors reviewed and approved the final draft of the manuscript.

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