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Assessment of the response to antiepileptic drugs in epileptic patients with structural lesion(s) on neuroimaging

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Abstract

Background: Focal epilepsy is the most common form of epilepsy in adults. Advances in brain imaging allowed better identification of different structural lesions underlying focal epilepsy. However, the response to antiepileptic drugs in lesional epilepsy is heterogeneous and difficult to anticipate. This study aimed to evaluate the response to antiepileptic drugs (AED) in patients with lesional epilepsy and to identify the predictors for poor seizure control.

Methods: One hundred and sixty-five patients with lesional epilepsy were included; the clinical diagnosis of epilepsy and seizure classification was based on the revised criteria of the International League Against Epilepsy (ILAE). Patients were subjected to full clinical assessment, MRI brain imaging epilepsy protocol, and EEG monitoring. All subjects were followed in the epilepsy clinic for at least 6 months.

Results: 75.8% of patients with lesional epilepsy showed poor response to antiepileptic medications. Cerebromalatic lesions related to brain trauma was the most frequently encountered (21.8%). Malformations of cortical development were significantly associated with poor response to AED ($p = 0.040$). Polytherapy and the combined use of 1st- and 2nd-generation AED were higher in the poor response group. Logistic regression analysis revealed that younger age at seizure onset and abnormal EEG findings was 0.965 times and 2.5 times more associated with poor seizure control, respectively.

Conclusion: This study revealed that patients with lesional epilepsy who develop seizures in their early life, who suffer from malformations of cortical development, or who show abnormal EEG findings are more suspected to show poor response to AED.

Keywords: Lesional epilepsy, MRI brain, Malformation of cortical development, Abnormal EEG, Antiepileptic drugs

Introduction

One of the key challenges facing physicians treating patients with epilepsy is to predict the response to the administered antiepileptic drugs (AED) and promptly identify drug-resistant epilepsy. This serves both for patient counseling and for early referral of patients to non-pharmacologic treatments such as epilepsy surgery and/or neurostimulation [1].

Subjects with symptomatic epilepsy are more likely to develop refractory seizures [2]. Advances in brain imaging have allowed better identification of the structural abnormalities underlying localization-related epilepsy with the majority of the published data concerned with surgical outcome in patients with partial onset seizures while only a few studied factors related to the response to AED therapy [3].

Previous studies reported that the cause of focal epilepsy can influence the response to AED. However, these studies include those who were idiopathic or cryptogenic

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epilepsy patients. In fact, studies that include only patients with lesional epilepsy are very scarce [4].

In this study, we aimed to assess the demographic and clinical variables along with the EEG findings and MRI features in patients with lesional epilepsy and compare the results of patients with good versus poor response to AED in order to identify the predictive factors related to medication response.

Methods

This descriptive and analytic study was conducted on epileptic patients from the epilepsy clinic related to a third referral medical institute during the period from August 2018 to February 2019. Patients were diagnosed with epilepsy according to the 2014 ILEA definition of epilepsy [5], and the seizures were classified based on the recent ILAE 2017 operational classification of seizure types [6]. Subjects who were diagnosed with lesional epilepsy and fulfilled the inclusion criteria were consecutively recruited in the study; all underwent thorough history taking; general and neurological examination with special emphasis on age of seizure onset, seizure type and duration, history of febrile seizures, and/or status epilepticus; and positive family history for epilepsy. The EEG results and drug history for AED were documented, including the type, number, and duration, and followed to verify that the patients were receiving appropriately chosen and well-tolerated antiepileptic drug for at least 6 months. We excluded patient with a history suggestive of psychogenic non-epileptic seizures and those with poor history reporting, with acute symptomatic seizures, with non-compliant to their AED, that had structural lesions unlikely to be causally related to their epilepsy, or who underwent epilepsy surgery.

All patients included were scheduled to do EEG according to the International 10-20 electrode placement system; a cap was used for each recording with an ear lobe electrode as a reference. The high-frequency filter was 70 Hz, the time constant 0.3 s, and the paper speed 30 mm/s with EB Neuro Galileo NT machine (EBNeuro, Firenze, Italy, serial number DAUNL7HQ4NUSFG; model Mizar B8351037899; version 3.61). Provocations were done by means of hyperventilation for 3 min and intermittent photic stimulation with increasing frequency from 5 to 25 Hz. The EEG was visualized for interictal changes suggestive of an epileptic disturbance and was then labeled as “*abnormal*”. Epileptiform activity is defined as abnormal paroxysmal activity consisting, at least in part, of spikes or sharp waves. A spike is defined arbitrarily as a potential having a sharp outline and duration of 20 to 70 ms, whereas a sharp wave has a duration between 70 and 200 ms [7].

All patients underwent a dedicated MRI epilepsy protocol on Philips Interna 1.5 T, Philips Achieva 1.5 T,

and GE Signa 0.2 T systems, which included T2-weighted and FLAIR coronal oblique plane perpendicular to the long axis of hippocampus, T1-weighted inversion recovery coronal oblique, and magnetization prepared rapid gradient echo and contrast-enhanced MRI if required.

Findings were reviewed blindly by an expert neuroradiologist, and structural lesions on MRI were categorized into 9 categories: cerebromalacic lesions, atrophic lesions, cystic lesions, cerebral infarction, vascular malformations, tumors, tuberous sclerosis complex, malformations of cortical development, and hippocampal sclerosis.

In the current study, all patients included were followed for at least 6 months; if the patient reported a decrease in seizure frequency to less than three times the longest pretreatment inter-seizure interval [8] or has less than one seizure per month [9] whichever is longer after an adequate trial of AED, he is labeled with good response “GR”.

Patients who underwent adequate trials (used two tolerated and appropriately chosen AED whether sequential or simultaneous) [8] however their seizure frequency did not decrease to the aforementioned criterion, were labeled with poor response “PR”.

First-generation antiepileptic drugs used in our study are phenytoin, carbamazepine, valproic acid, phenobarbital, ethosuximide, and clonazepam. While second-generation antiepileptics included levetiracetam, lamotrigine, topiramate, zonisamide, and oxcarbazepine.

Written informed consent was obtained from all participants involved in this investigation prior to the conduct of any study-related activities.

Statistical analysis

Data was entered on the computer using “Microsoft Office Excel Software” program (2010) for Windows. Data was then transferred to the Statistical Package of Social Science Software program, version 23 (IBM SPSS Statistics for Windows, version 23.0. Armonk, NY; IBM Corp.) to be statistically analyzed.

Data are presented using range, mean, standard deviation, median and interquartile range for quantitative variables, and frequency and percentage for qualitative ones. Comparison between groups was conducted using Chi square test for qualitative variables and Mann-Whitney test [10] (due to data skewness) for quantitative ones. Multivariate logistic regression model was performed to explore predictors of uncontrolled fits [11]. *P* values less than 0.05 were considered statistically significant. Figures were used to illustrate some information.

Results

We identified 165 patients with the diagnosis of lesional epilepsy receiving regular antiepileptic medications; 40

patients (24.2%) were included in the good response group (GR), while 125 patients (75.8%) were categorized as having poor response to AED (PR). Only 27 (16.36%) patients were under 18 years (of those, 3 (11.1%) were GR, while 24 (88.8%) were PR); the rest of the demographics and clinical findings are presented in Table 1.

A total of 127 electroencephalography results were analyzed (38 were unavailable as some patients did not attend their scheduled EEG test or refused to repeat EEG that was previously done elsewhere). No significant

difference was found between both groups regarding the EEG findings.

The characteristics of MRI lesions are presented in Table 2. Regarding the etiology, posttraumatic lesions were the most frequently encountered followed by post-infectious cerebromalatic lesions, while malformations of cortical development were the lesion associated with poor response to antiepileptic medications.

The percent of other different etiologies are listed in Fig. 1.

Table 1 Comparison of the demographic features, clinical findings, EEG results, and AED(s) used

| | | Total (n = 165) | Controlled (< 1 seizure per month), n = 40 | Uncontrolled (≥ 1 seizure per month), n = 125 | P value | |
|-------------------------------|--------------------|--------------------|--|---|-----------|--------|
| Sex | Male | 99 (60%) | 25 (62.5%) | 74 (59.2%) | 0.711 | |
| | Female | 66 (40%) | 15 (37.5%) | 51 (40.8%) | | |
| Age | Range, mean ± SD | 3–68, 29.9 ± 12.6 | 2–62, 34.7 ± 12.5 | 0.3–50, 28.4 ± 12.4 | 0.005* | |
| | Median | 28 (20–37) | 35 (27–40) | 27 (19–36) | | |
| Age of onset | Mean ± SD | 16.1 ± 13.6 | 22.7 ± 15.7 | 14 ± 12.1 | 0.001* | |
| | Median | 13 (5–24) | 22.5 (8–34.5) | 11 (4–20) | | |
| Duration of epilepsy | Mean ± SD | 13.9 ± 9.9 | 12 ± 9.5 | 14.5 ± 10 | 0.152 | |
| | Median | 13 (5.7–20.5) | 11.5 (3–18) | 13 (6–21) | | |
| Family history | Yes | 22 (13.3%) | 2 (9.1%) | 20 (90.9%) | 0.075 | |
| | No | 143 (86.7%) | 38 (26.6%) | 105 (73.4%) | | |
| History of status epilepticus | Yes | 22 (13.3%) | 8 (36.4%) | 14 (63.6%) | 0.154 | |
| | No | 143 (86.7%) | 32 (22.4%) | 111 (77.6%) | | |
| History of febrile seizures | Yes | 12 (7.3%) | 4 (33.3%) | 8 (66.7%) | 0.487 | |
| | No | 153 (92.7%) | 36 (23.5%) | 117 (76.5%) | | |
| Mentality | Normal | 139 (84.2%) | 36 (25.9%) | 103 (74.1%) | 0.251 | |
| | Abnormal | 26 (15.8%) | 4 (15.4%) | 22 (84.6%) | | |
| Type of seizure | Generalized | Motor | 33 (20%) | 9 (35%) | 24 (65%) | 0.413 |
| | | Non-motor | 33 (20%) | 9 (35%) | 24 (65%) | |
| | Focal | Motor | 120 (72.7%) | 30 (25%) | 90 (75%) | |
| | | Non-motor | 8 (4.8%) | 1 (12.5%) | 7 (87.5%) | |
| | Aware | 90 (54.5%) | 20 (22.2%) | 70 (77.8%) | 0.417 | |
| | Impaired awareness | 38 (23%) | 11 (28.9%) | 27 (71.1%) | | |
| | To BTC | 99 (60%) | 28 (28.3%) | 71 (71.7%) | | 0.047* |
| | Not to BTC | 29 (17.6%) | 3 (10.3%) | 26 (89.7%) | | |
| EEG | Normal | 53 (32.1%) | 14 (25.9%) | 40 (74.1%) | 0.160 | |
| | Abnormal | 74 (44.9%) | 11 (15.7%) | 59 (84.3%) | | |
| No. of antiepileptic drugs | 1 | 32 (19.4%) | 20 (50%) | 12 (9.6%) | < 0.001* | |
| | 2 | 87 (52.7%) | 17 (42.5%) | 70 (56%) | 0.137 | |
| | 3 or more | 46 (27.9%) | 3 (7.5%) | 43 (34.4%) | 0.001* | |
| Type of antiepileptic | 1st generation | 57 (34.5%) | 24 (60%) | 33 (26.4%) | < 0.001* | |
| | 2nd generation | 12 (7.3%) | 5 (12.5%) | 7 (5.6%) | 0.165 | |
| | 1st + 2nd | 96 (58.2%) | 11 (27.5%) | 85 (68%) | < 0.001* | |

SD standard deviation, EEG electroencephalography, BTC bilateral tonic-clonic

*P value < 0.05 is significant, and P value < 0.01 is highly significant

Table 2 Comparison of MRI findings between controlled and poorly controlled patients

| | | Total (n = 165) | Controlled (< 1 seizure per month), n = 40 | Uncontrolled (≥ 1 seizure per month), n = 125 | P value |
|----------------------------|------------------------|--------------------|--|---|---------|
| Type of lesion | Cerebromalatic lesion | 53 (32.1%) | 17 (32.1%) | 36 (67.9%) | 0.106 |
| | Atrophic lesion | 21 (12.7%) | 3 (14.3%) | 18 (85.7%) | 0.254 |
| | Cystic lesion | 19 (11.5%) | 5 (26.3%) | 14 (73.7%) | 0.782 |
| | Cerebral infarction | 6 (3.6%) | 2 (33.3%) | 4 (66.7%) | 0.633 |
| | Vascular malformation | 12 (7.3%) | 6 (50%) | 6 (50%) | 0.072 |
| | Tumors | 15 (9.1%) | 2 (13.3%) | 13 (86.7%) | 0.527 |
| | TSC | 16 (9.7%) | 3 (18.8%) | 13 (81.3%) | 0.763 |
| | MCD | 12 (7.3%) | 0 (0%) | 12 (100%) | 0.040* |
| | Hippocampal sclerosis | 11 (6.7%) | 2 (18.2%) | 9 (81.8%) | 0.627 |
| Hemisphere involved | Right | 56 (33.9%) | 15 (26.8%) | 41 (73.2%) | 0.585 |
| | Left | 78 (47.3%) | 19 (24.4%) | 59 (75.6%) | 0.974 |
| | Bilateral | 31 (18.8%) | 6 (19.4%) | 25 (80.6%) | 0.481 |
| Site (lobe) | Frontal | 40 (24.2%) | 11 (27.5%) | 29 (72.5%) | 0.581 |
| | Temporal | 56 (33.9%) | 15 (26.8%) | 41 (73.2%) | 0.585 |
| | Parieto-occipital | 33 (20%) | 7 (21.2%) | 26 (78.8%) | 0.650 |
| | Hemiatrophy | 17 (10.3%) | 3 (17.6%) | 14 (82.4%) | 0.765 |
| Topographical distribution | Cortical | 32 (19.4%) | 5 (15.6%) | 27 (84.4%) | 0.205 |
| | Subcortical | 27 (16.4%) | 8 (29.6%) | 19 (70.4%) | 0.475 |
| | Cortical + subcortical | 89 (53.9%) | 24 (27%) | 65 (73%) | 0.377 |
| | Subependymal | 10 (6.1%) | 3 (30%) | 7 (70%) | 0.706 |
| | Periventricular | 7 (4.2%) | 0 (0%) | 7 (100%) | 0.197 |
| Number of lesions | Single | 132 (80%) | 35 (26.5%) | 97 (73.5%) | 0.173 |
| | Multiple | 33 (20%) | 5 (15.2%) | 28 (84.8%) | |

MCD malformations of cortical development, TSC tuberous sclerosis complex

*P value < 0.05 is significant, and P value < 0.01 is highly significant

Logistic regression analysis was done to detect the independent predictor for poor response to AED among patients with lesional epilepsy and the only independent predictors were the early age of onset of seizures and the presence of abnormal EEG (Table 3).

Discussion

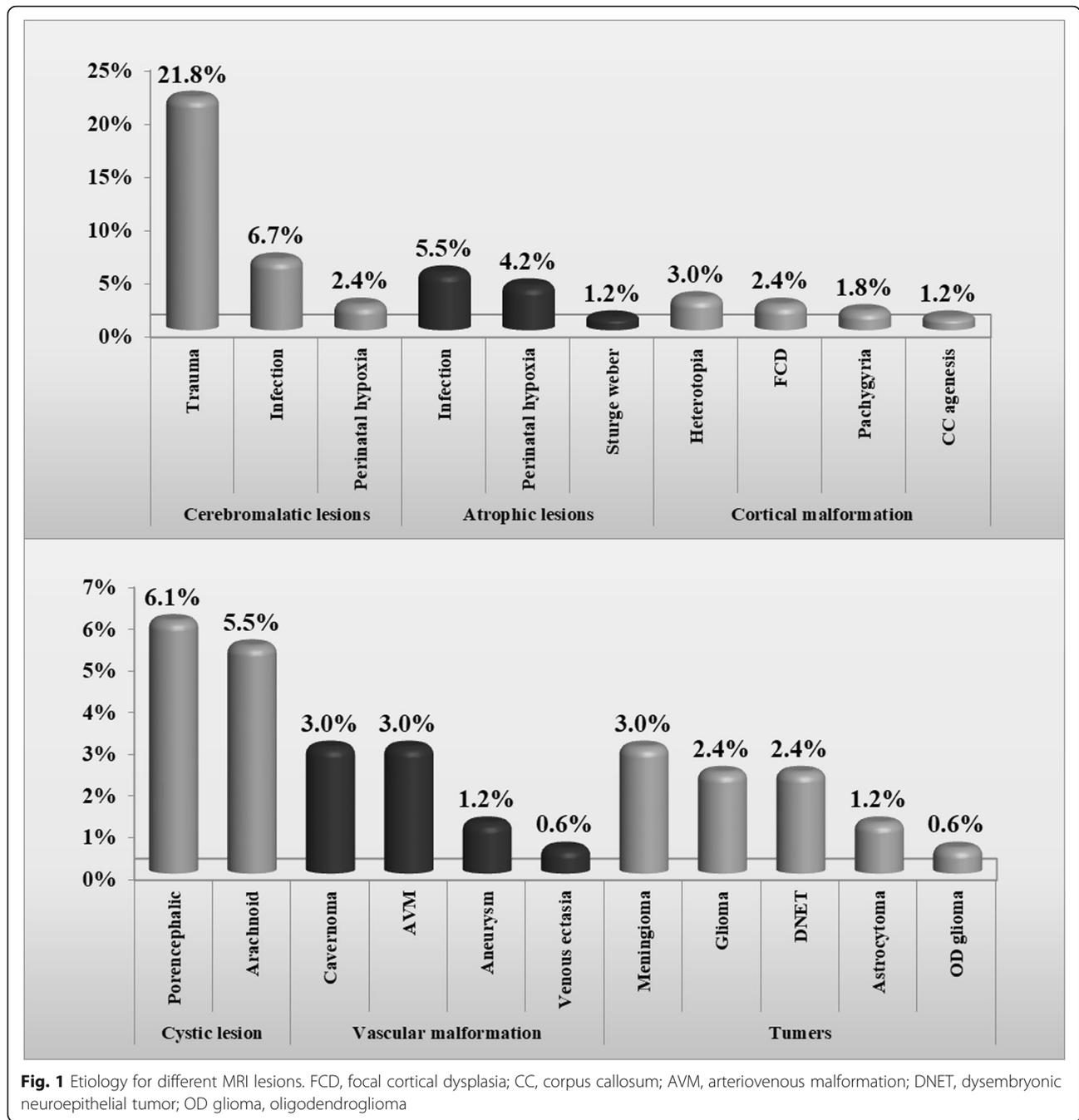
In this study, we found that 24.2% of patients with lesional epilepsy showed good response to antiepileptic medications. Such results are close to those reported by Semah et al. [12] (35% of patients with symptomatic epilepsy were well controlled (> 1 year seizure free)) but are much lower than Mohanraj and Brodie [13] and Stephen et al. [3] who found that about 50% of such patients showed good response to AED. This might be explained by the fact that both of these later studies were performed in a primary referral seizure service facility where MRI was done only when localization-related epilepsy was suspected and both of them included cryptogenic epilepsy patients (non-lesional MRI), while in tertiary epilepsy centers, where this study is conducted,

patients are subjected to sophisticated imaging evaluation and higher prevalence of severe cases is expected.

The male patients in our cohort were found to have a higher rate of lesional epilepsy than females, such observation was also documented by Christensen et al. [14] reflecting gender differences in risk of structural damage to the brain and subsequent seizure development.

In this study, a younger age at seizure onset was significantly associated with poor response to AED. Also logistic regression analysis revealed that the age at seizure onset was independent predictors for poor response to AED. This goes in agreement with several studies [15, 12] which proposed that patients with early seizure onset are more prone to potential adaptive functional reorganization in areas distant to the site of lesion rendering them more refractory to treatment [16]. These findings further emphasize the need for early aggressive treatment and seizure control in infants and young children.

Our study is keeping with the results of most other studies, which failed to find a link between the duration



of epilepsy and outcome [17–19] but contradicts others [1, 4, 20] who have found that long duration of epilepsy was associated with poor seizure control. This might be explained by the fact that these studies, unlike our study, included a higher number of hippocampal sclerosis which is known to be a progressive disease; thus, longer duration will be associated with progressive neuronal loss and less seizure control [21]. Also, several studies reported that the high number of seizures rather than

the duration of epilepsy leads to drug resistance by target hypothesis [22–24].

We also noticed that patients with positive family history of seizures are nearly significantly poorly controlled on antiepileptic medication. This goes in agreement with a study done by Hitiris et al. [25] who found that family history is one of the predictors of pharmaco-resistance. Several explanations are suggested; first, some lesions that are known to be more resistant to AED may be the

Table 3 Multivariate logistic regression model to explore the predictors of poorly controlled seizures ($R^2 = 0.189$)

| Independent predictors | OR | 95% CI for OR | P value |
|-------------------------|-------|---------------|---------|
| Age of onset | 0.965 | 0.937–0.993 | 0.016* |
| Family history | 3.577 | 0.721–17.741 | 0.119 |
| History of status | 0.422 | 0.141–1.264 | 0.123 |
| Abnormal EEG | 2.505 | 1.077–5.825 | 0.033* |
| Multiplicity of lesions | 0.971 | 0.307–3.078 | 0.961 |
| Bilateral tonic-clonic | 0.557 | 0.240–1.293 | 0.173 |

R^2 coefficient of determination, OR odds ratio, CI confidence interval
*P value < 0.05 is significant, and P value < 0.01 is highly significant

result of familial disorders such as cortical dysplasia, tuberous sclerosis, or hippocampal sclerosis [3]; secondly, upregulation of several genes could be related to the epileptogenic mechanisms of several acquired conditions such as hypoxia, trauma, infections, or metabolic unbalances [26, 27]; and lastly, certain genes may be linked directly or indirectly to being resistant to antiepileptic drugs [28, 29].

In the current study, focal onset followed by bilateral tonic-clonic seizures was significantly associated with poor response to epilepsy medications; a similar study [30] reported that the response to AED in patients with lesional epilepsy was best for those with generalized tonic-clonic convulsions, worst for complex partial seizures, and intermediate for secondary generalization. These previous findings support the fact that kindling might be related to the frequency of secondary generalization where, in kindling models, development of a primary site leads progressively to secondarily generalized convulsions. In addition, subsequent kindling of a secondary site results in rapid kindling from that site, presumably because of its facilitated access to the primary kindled network [31].

Of the structural lesions in MRI, cerebromalatic lesion related to traumatic brain injury was the most frequently encountered followed by post-infectious causes. In view that road traffic accident is the commonest cause of brain trauma [32, 33] in our region and when relating this to our results, we may emphasize the importance of developing national preventive programs to reduce the incidence of such injuries, thus preventing a major cause of lesional epilepsy.

Also, patients with malformations of cortical development were significantly less likely to respond to antiepileptic medications (100% poorly controlled) than other types. This finding is consistent with Palmiini et al. [34] and Semah et al. [12] and might be attributed to the fact that malformation of cortical development might have extension of epileptic network beyond the visible lesion in MRI rendering it more resistant to antiepileptic

medications than other causes of lesional epilepsy such as cerebromalatic lesions and/or cerebral infarction [4].

On the contrary, others [3, 13] found that patients with malformation of cortical development have a more favorable prognosis; however, the median age at seizure onset in both studies (21 and 33 years, respectively) was older than that of our study (13 years), and since we found that younger age at seizure onset is significantly associated with poor seizure control, this might explain the higher percentage of poorly controlled patients in our cohort.

Despite the fact that some lobes are epileptogenic than others, our study found that the site, side, and number of lesions in MRI was not related to the degree of response to antiepileptic medication.

When evaluating the number and type of AED used, we found that more patients in the PR compared to GR group were on polytherapy; this goes in agreement with studies that found that polytherapy is a significant predictor of refractory epilepsy [35] and treatment with lower number of AED is a favorable predictor of seizure control [36]. We also found that 60% of the GR patients used first-generation antiepileptic drugs, while 68% of the PR patients used either second generation alone or both first- and second-generation AED. Such results imply that the efficacy of new antiepileptics is not superior to that of the old ones in control of epilepsy as reported by many [5].

Finally, logistic regression analysis found that in addition to younger age of onset, patients with abnormal EEG findings are 2.5 times more liable to have poor response to AED compared to patients with normal EEG. This goes in agreement with several studies [37–39] and Uva et al. who suggested that there is a predictive or causal relation between EEG changes and ictogenesis as interictal spikes might reach a critical temporal density and lead to seizures [40]. Although many studies found abnormal EEG findings to be significant predictors of poor epilepsy control, there are no prospective studies evaluating the predictive power of interictal EEG following brain injury [41]. Such studies would help guide care before the development of epilepsy [42].

Our population sample was composed of patients recruited all from the same setting related to tertiary referring center which may render our sample less heterogeneous and with more severe symptoms than the spectrum of patients in the general population. The sample size was relatively small and the number of patients in both groups was unequal; however, it was based on the recruitment capacity during the period of the study and the study design, where consecutive patients fulfilling the criteria were included. Serum drug level was not done for the patients to verify their compliance; we depended on patient's self-reporting measures;

moreover, many patients were using new AED with unavailable tests of their serum levels. We do recommend a further prospective multicenter study that will include a higher number of patients with equal number of participants in both groups who would be followed for at least 1 year which will allow better generalization of the results.

Conclusion

Poor response to drug treatment in lesional epilepsy was found to be related to multiple factors which include anomalies in the brain during its early maturation, the nature of the underlying pathology, and presence of detectable electrophysiological abnormalities.

Abbreviations

AED: Antiepileptic drugs; AVM: Arteriovenous malformation; BTC: Bilateral tonic-clonic; CC: Corpus callosum; CI: Confidence interval; DNET: Dysembryonic neuroepithelial tumor; EEG: Electroencephalography; FCD: Focal cortical dysplasia; GR: Good response; ILAE: International League Against Epilepsy; MCD: Malformations of cortical development; MRI: Magnetic resonance imaging; OD: Oligodendroglioma; OR: Odds ratio; PR: Poor response; TSC: Tuberous sclerosis complex

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Authors' contributions

All authors contributed to the research idea. LN contributed to the data collection. MA, RS, and LN analyzed and interpreted the data. Further, LN and RS completed the first draft of the article. MA revised it critically for important intellectual content, and all authors approved the final version to be published.

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Availability of data and materials

All datasets generated and analyzed during the current study are not publicly available but are available by reasonable request from the corresponding author.

Ethics approval and consent to participate

All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments; committee's reference number is not applicable. Written informed consent was obtained from all participants involved in this investigation prior to the conduct of any study-related activities. The study was ethically approved by research committee and reviewed by the Neurology Department, Faculty of Medicine Cairo University Board, date of approval 11 August 2018.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests (financial and non-financial).

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