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ORIGINAL COMMUNICATION

Long-term follow-up of a large cohort with focal epilepsy of unknown cause: deciphering their clinical and prognostic characteristics

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Abstract

Background and purpose Focal epilepsy of unknown cause (FEUC) is an under-investigated topic despite its remarkable frequency. We aimed to report the long-term follow-up findings along with the drug-response, 5 year remission rates and diagnostic changes to give an insight about the heterogeneous characteristics of FEUC.

Methods Demographic, clinical, neurophysiological and imaging data of 196 patients diagnosed as FEUC according to ILAE criteria, with a minimum 5-year follow-up were evaluated in a tertiary epilepsy center. The drug resistance, 5 years of remission and relapse rates were investigated and the subgroups were compared statistically.

Results The rate of drug resistance was 21.8% and status epilepticus ($p < 0.001$), abnormal neurological examination ($p = 0.020$), seizure onset before 10 years ($p = 0.004$) and a high initial seizure frequency ($p = 0.006$) were significant predictors of drug resistance. The rates of terminal 5-year remission, 5-year remission ever and relapse were 39.9%, 44.26% and 24.04%, respectively. There were 13 patients (6.6%) with a changed final diagnosis. Drug resistance ($p = 0.004$), pathological EEG ($p = 0.034$) and status epilepticus ($p = 0.021$) were negative variables for achieving remission. The lobar localization of seizures was not a predictor of remission or relapse. Onset after 10 years of age had a higher probability of achieving a 5-year remission according to Kaplan–Meier curves ($p < 0.001$).

Conclusions Focal epilepsy of unknown cause has a benign electroclinical subgroup with favorable long-term course, lower drug resistance and higher 5 years of terminal remission and remission ever rates, when appropriately treated. Our findings might be valuable in terms of counseling and management of patients with FEUC at the first referral to epilepsy clinics.

Keywords Focal epilepsy with unknown cause · Prognosis · Cryptogenic epilepsy · Long-term follow-up · MRI-negative epilepsy · Focal epilepsy

Introduction

Focal epilepsy of unknown cause (FEUC) or with its former name cryptogenic focal epilepsy is an under-investigated topic despite its remarkable frequency and importance for the patients who will face anxiety about their prognosis labeled as "unknown". There are only a handful of papers reporting prognosis of these patients. FEUC is a term that refers to localization-related epilepsy with an unknown, still uncovered etiology [1, 2]. The cause is presumed to be symptomatic but no observable abnormality can be detected on magnetic resonance imaging (MRI) and also by other diagnostic investigations including genetic, metabolic and autoimmune reasons. About 40% of adult-onset epilepsies are diagnosed as FEUC, thus they constitute an important subgroup among all types of epilepsies [1, 2]. Data about the etiology and prognosis of FEUC accumulate with time

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and the number of patients diminishes with the improvement of imaging techniques and diagnostic tools like genetic and autoimmune studies [3–9]. However, there is a lack of studies about the long-term clinical course, prognostic markers and final diagnosis of FEUC patients.

In this study, we aimed to report the long-term prognosis, drug-response, 5-year remission rates, and diagnostic changes during the follow-up in patients diagnosed with FEUC in an established epilepsy center. Our second aim was to distinguish some characteristics of FEUC shared among subgroups like age at onset, antiepileptic drug resistance etc., to give an insight about the heterogeneous nature of FEUC and to highlight the importance of correct diagnosis to apply appropriate management plan.

Methods

Patient selection

A total of 196 patients aged between 16–75 years, regularly followed-up in our epilepsy center, diagnosed as FEUC according to the criteria of International League Against Epilepsy (ILAE) were included to the study [10]. Other inclusion criteria involved at least one normal 1.5 or 3 T MRI performed with a specific epilepsy protocol and a minimum of one EEG recorded in our laboratories, available for re-evaluation. Exclusion criteria comprised noncompliance of the patient, short follow-up time (less than 5 years), absence of appropriate neuroimaging and other necessary biochemical, metabolic, serological and immunological laboratory investigations. When a clinical suspicion is considered, we additionally performed lumbar puncture analysis and excluded patients with diagnostic cerebrospinal fluid results for a given etiology. We also excluded those patients diagnosed with psychogenic non-epileptic seizures at the beginning of our study.

Patients with FEUC were classified into subgroups according to the electroclinical lobar localization, from which the seizures originated as follows; temporal, frontal, parieto-occipital, multifocal and unknown origin of FEUC. Temporal lobe epilepsy with unknown cause (TLE-UC) is further subdivided into lateral and mesial subtypes. The traditional lobar localization of the patients was defined upon the concordant semiology of the seizures, ictal EEG and interictal EEG data and PET findings, respectively [11] (Fig. 1).

The local ethics committee has approved the retrospective study protocol.

Clinical and EEG data collection

We collected the following data from the medical records: the demographic characteristics such as age, sex, age of onset, age at diagnosis, duration of epilepsy, habits of alcohol and illicit drug use, history of complicated birth, head injury; febrile seizure and status epilepticus, neurological and psychiatric comorbid diseases, other comorbid systematic diseases (thyroid disease, autoimmune diseases, etc.), family history of epilepsy, parental consanguinity.

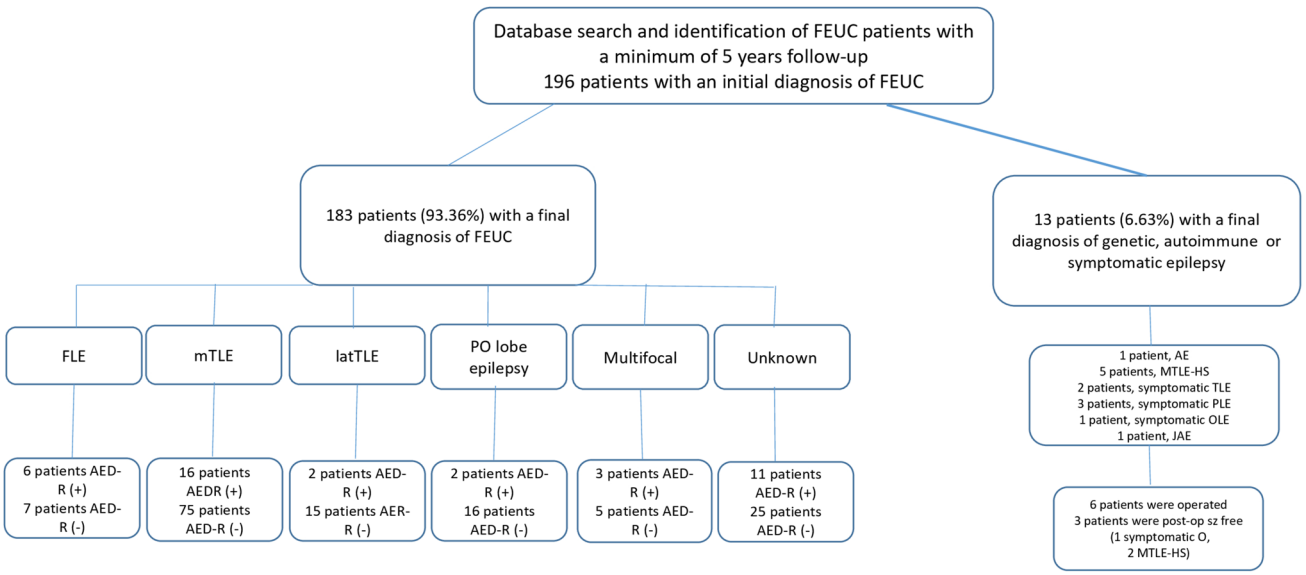

Fig. 1 Flow chart of the study. *AE* autoimmune epilepsy (diagnosed with anti-neuronal antibodies), *TLE* temporal lobe epilepsy, *PLE* parietal lobe epilepsy, *OLE* occipital lobe epilepsy, *FEUC* focal epilepsy of unknown cause, *F* frontal, *T* temporal, *PO* parieto-occipital, *P* parietal, *JAE* juvenile absence epilepsy, *AED-R* antiepileptic drug resistance, *MTLE-HS* mesial temporal lobe epilepsy with hippocampal sclerosis, *Sz* seizure

The initial EEG and all other follow-up EEGs were reviewed by two experienced clinical neurophysiologists (BB and NB). EEGs were recorded with scalp electrodes placed according to the International 10–20 system with bipolar and reference montages. Standard activating procedures were performed in all participants. We also reviewed video-EEG data in these patients if available. The standard definitions for EEG activities were used [12].

Other investigated clinical data included seizure types, ictal semiology, types of aura, initial antiepileptic therapy regimen, current antiepileptic therapy, initial type of seizures, initial frequency of seizures, current frequency of seizures, 5-year remission, relapses and, antiepileptic drug resistance and final diagnosis of the patient. Aura was defined as an ictal phenomenon preceding an observable seizure; when isolated, it may represent a focal sensory aware seizure as well [13]. Drug-resistant epilepsy was defined as using two properly chosen and well-tolerated antiepileptic drugs at adequate doses according to suitable antiepileptic drug schedules and achieving seizure-freedom [14]. Remission was defined as being seizure-free for any type of seizure for a minimum of 5 years with or without antiepileptic medication during the course of epilepsy [15]. Relapse was defined as having seizures after a minimum 5 years of seizure-freedom.

We also performed serological, immunological and genetic tests to explore a possible symptomatic etiology and excluded those patients with auto-antibody positivity or genetic mutations at the end of the follow-up period. Additionally, we investigated the patients who underwent epilepsy surgery and recorded the type of surgery, neuropathological diagnosis, post-op EEG examinations and outcome of the surgery according to the Engel classification [16].

Neuroimaging data

We excluded the patients without any MRI after 2009 because 1.5 T MRI was not available in our institution before this date.

MRI studies were performed with a 1.5-T scanner (Magnetom Siemens Symphony, Erlangen, Germany) with thin coronal in addition to sagittal and axial planes including T1, T2, and fluid-attenuated inversion recovery (FLAIR) images to visualize mesial temporal regions optimally. We proceed with investigation of mesial temporal lobe structures with the following series: T2 W paracoronal series [repetition time (TR): 4900, echo time (TE): 104, field-of-view (FOV): 230, matrix: 256 × 512, flip angle: 150°, slice thickness: 3 mm, recording time: 4.31 min], paracoronal FLAIR (TR: 8080, TE: 111, TI: 2500, FOV: 230, matrix: 179 × 256, flip angle: 150°, slice thickness: 3 mm, recording time: 4.31 min) and paracoronal multiplanar reconstruction (TR: 1900, TE: 3.3, FOV: 250, matrix: 179 × 256, flip angle: 15°, slice thickness: 3 mm, recording time: 5.42 min) series. Images taken at conditions in compliance with 1.5 T MRI epilepsy protocol and were reviewed by an experienced neuroradiologist [7, 17]. Most of the patients also underwent 3 T MRI to clarify the etiology of seizures, according to clinical needs.

We also collected positron emission tomography (PET) and single photon emission computerized tomography (SPECT) data from the medical files of included patients, when available. These investigations were reviewed by a nuclear medicine specialist who was blind to clinical features.

Statistical analysis

Descriptive statistics were applied for the clinical and demographic features. The findings of FEUC patients with and without drug resistance were compared with χ^2 test, Fisher's exact test and *t* test, where appropriate. The potential risk factors for predicting drug resistance which showed a significant association ($p < 0.05$) in univariate analysis were investigated by binary logistic regression analysis as well. We additionally performed ROC analysis to determine a cutoff value for age of seizure onset using ROC analysis method and chose 10 years as a cutoff value ($p = 0.01$, sensitivity 80%, specificity 58%). As the main outcome measure was long-term seizure remission (> 5 years), time to seizure remission in relation with age of seizure onset was analyzed by the Kaplan–Meier method to illustrate the likelihood of remission. To the purpose of performing Kaplan–Meier analysis we divided age of seizure onset as < 10 years and ≥ 10 years of age, as the age of onset before 10 years was one of the significant factors for having drug resistance in our statistical analysis. The log-rank test was performed to compare survival between patient subgroups. IBM SPSS Statistics V.22 was used and the level of significance was set at $p < 0.05$.

Results

Clinical and laboratory properties

There were 107 (58.5%) female and 76 (41.5%) male patients in the cohort with FEUC, after exclusion of 13 patients with a final changed diagnosis. The mean follow-up duration was 18.98 ± 11.18 years.

The mean age, age of onset, age of diagnosis and disease duration of the included patients were 39.12 ± 13.26, 18.86 ± 13.10, 20.30 ± 13.19 and 20.25 ± 11.21 years, respectively. The mean number of EEG examinations of the

patients were 5.74 and the mean number of MRIs applied was 2.01 ± 1.07.

The initial seizure type was focal to bilateral tonic–clonic (fTC) in 124 patients (67.8%), focal seizure with impaired awareness (FSIA) in 48 patients (26.2%) and focal onset aware seizures (FoAS) in 11 patients (6.0%). Initial seizure frequency was ≥ 1/month in 80 patients (56.3%) and < 1/month in 103 patients (43.7%).

The initial EEG examinations were normal in 73 patients (39.9%) and pathological (including epileptiform (*n*: 61, 55.45%) and nonepileptiform (*n*: 49, 44.55%) discharges in 110 patients (60.1%). During the long-term follow-up, only 18 patients' interictal EEG examinations persisted to be normal (9.8%) whereas 129 patients (70.5%) developed epileptiform discharges (sharp waves, spikes, polyspikes) and 36 patients (19.7%) had focal nonspecific findings (slow wave activity) in their EEG examinations. Moreover, 40 patients (21.85%) had generalized EEG discharges (epileptiform (*n*: 18) or nonspecific generalized (*n*: 22) additionally.

At the end of the 5 years of follow-up period, 23 patients with FEUC (12.6% of the cohort) had non-epileptic psychogenic seizures in addition to their proven epileptic seizures.

Patients with a change in the final diagnosis

After inclusion with the FEUC diagnosis and a minimum of 5 years follow-up in our center, there were 13 patients (6.6%) with a changed final diagnosis at the end of the follow-up period. Their latter diagnoses and the basis of the new diagnoses were as follows:

- Eleven patients with previously undetected symptomatic focal epilepsy (a) 5 with hippocampal sclerosis [In 3 of them hippocampal sclerosis was not detected in the initial 1.5 T MRI but diagnosed with 3 T MRI, the remaining two were diagnosed with post-operative neuro-pathological analysis, only], (b) 6 with other structural lesions (1 temporal cortical dysplasia diagnosed with the help of MR-spectroscopy, 1 small post-traumatic left parietal encephalomalacia; 1 left temporal uncal cavernoma and 2 with lesions of unknown etiology detected with 3 T MRI not seen in 1.5 T and the last patient with type 1A occipital cortical dysplasia diagnosed with post-operative pathology, only).
- One patient with autoimmune epilepsy diagnosed with immunological analysis with *N*-methyl-D-aspartate receptor (NMDA-R) auto-antibody positivity,
- One patient with genetic epilepsy (diagnosed as juvenile absence epilepsy with video-EEG recordings of absence seizures after many years).

Four of these patients were operated and three of them (one patient with cortical dysplasia type-1 and 2 patients who had temporal neuronal gliosis in sector CA4) were post-op seizure-free, whereas another one did not improve and had post-op Engel 4 grade (neuropathological reports of CA1 and partial CA2 gliosis).

In the end of the follow-up these 13 patients were excluded from further analysis due to their changed final diagnoses (see flow chart in Fig. 1).

Antiepileptic drug responses

The majority of the patients were under monotherapy (*n* = 98, 53.6%) at the beginning of the follow-up period and the seizures were under control with a single antiepileptic drug. During the follow-up period; 16 patients (8.7%) became drug-free, 51 patients were under carbamazepine (27.86%), 14 patients (7.65%) under oxcarbazepine, 13 patients (7.1%) under levetiracetam, 9 patients (4.91%) under lamotrigine and 5 patients (2.73%) were under valproic acid monotherapy and remaining 40.9% of the patients were receiving polytherapy.

Of these 183 patients with FEUC, 40 patients (21.8%) had drug resistance. The lobar distribution of patients with FEUC according to drug resistance is shown in Fig. 1. The demographic and clinical properties of FEUC patients with and without drug resistance are summarized in Table 1, comparatively.

A binary logistic regression analysis was performed and a model was developed including the following significant clinical features; status epilepticus, having a pathological EEG, abnormal neurological examination, high initial seizure frequency and seizure onset < 10 years of age. Having a status epilepticus history ($p < 0.001$), abnormal neurological examination ($p = 0.020$), seizure onset before 10 years of age ($p = 0.004$) and a high initial seizure frequency (more than one seizure per month) ($p = 0.006$) were found statistically significant between patients with and without drug resistance, as shown in Table 2.

Five-year remission and relapse rates

During the follow-up, 73 (39.9%) of the 183 patients had a terminal 5-year remission, 11 (15.06%) of these patients were drug-free whereas 49 (67.12%) were under monotherapy. Eighty-one patients (44.26%) had a 5-year remission ever and 44 patients (24.04%) had experienced one or more relapses during the follow-up.

The statistical analysis of clinical and demographic factors which could be related with 5-year terminal remission showed that; antiepileptic drug resistance ($p = 0.004$), presence of at least one pathological EEG ($p = 0.034$) and a history of status epilepticus ($p = 0.021$) were significantly higher in patients with FEUC without a 5-year remission.

Table 1 Patients with focal epilepsy of unknown cause with regard to drug resistance

Demographic and clinical properties	Antiepileptic drug resistance (+) ($n=40$)	Antiepileptic drug resistance (−) ($n=143$)
Age (mean ± SD)	35.13 ± 11.71	40.24 ± 13.50
Gender (M/F) (%)	(14/26) (35/65)	(62/81) (43.3/56.6)
Age of seizure onset (mean ± SD)	14.33 ± 13.33	20.13 ± 12.80*[b]
Disease duration (mean ± SD)	20.78 ± 10.20	20.10 ± 11.51
Family history of epilepsy (*n*) (%)	13 (32.5)	47 (32.9)
Abnormal neurological examination	11(27.5)	19 (13.3)**
Presence of aura (*n*) (%)	31 (77.5)	120 (83.9)
Febrile seizure history (*n*) (%)	7 (17.5)	33 (23.1)
High seizure onset frequency[a] (*n*) (%)	27 (67.5)	53 (37.1)*
Initial seizure type as fTC (*n*) (%)	100 (69.9)	24 (60)
Abnormal initial EEG (*n*) (%)	30 (75)	80 (55.9)***
Pathological EEG (*n*) (%)	38 (95)	96 (67.1)[¥]
History of status epilepticus (*n*) (%)	10 (25)	2 (1.4)[¥¥]
Additional psychogenic seizures (*n*) (%)	9 (22.5)	13 (9.09)
Remission (≥ 5 years) (*n*) (%)	8 (20)	32 (45.4)[€]
Presence of relapses (*n*) (%)	10 (25)	30 (60.8)[€€]

AED-R (+) antiepileptic drug-resistant subgroup, *AED-R (−)* antiepileptic drug non-resistant subgroup, *EEG* electroencephalography, *F* female, *fTC* focal to bilateral tonic clonic, *M* male, *n* number, *SD* standard deviation, % percentage

*$p=0.001$, **$p=0.032$, ***$p=0.03$, [¥] $p<0.001$, [¥¥] $p<0.001$, [€] $p=0.04$, [€€] $p<0.001$

[a]High seizure onset frequency is identified as more than 1 seizure per month

[b]Mann–Whitney *U* test

Table 2 Logistic regression analysis of patients with antiepileptic drug resistance based on clinical variables

	B	SE	Wald	*df*	Sig[a]	Exp (*B*)	95% CI for exp (*B*)	
							Lower	Upper
Seizure onset < 10 years of age	1.270	0.444	8.183	1	0.004	3.561	1.492	8.500
High initial seizure frequency[b]	1.177	0.430	7.498	1	0.006	3.245	1.397	7.534
Status epilepticus	−2.674	0.823	10.560	1	0.001	0.069	0.014	0.346
Pathological EEG	−1.407	1.070	1.729	1	0.189	0.245	0.0380	1.995
Abnormal neurological examination	−1.150	0.494	5.414	1	0.020	0.317	0.120	0.834
Constant	1.168	0.940	1.542	1	0.214	3.214		

Variables entered as seizure onset < 10 years of age, initial seizure frequency, status epilepticus, pathological EEG, abnormal neurological examination

The model summary showed a −2 log likelihood ratio of 140.883 and using this model 78.1% of the patients could be classified correctly with a cutoff value of 0.5

EEG electroencephalography, *CI* confidence interval, *B* beta regression coefficient, *SE* standard error, *df* degrees of freedom, *Exp(B)* exponential B

[a]Statistically significant *p* values < 0.05

[b]High initial seizure frequency is defined as more than one seizure per month

The cumulative rate of achieving a 5-year terminal remission related with the age of seizure onset was analyzed by Kaplan–Meier curve, comparing seizure onset before (early onset) and after (late onset) 10 years of age. Patients with seizures starting after 10 years of age had a higher probability of achieving a 5-year remission compared to the patients with seizure onset before 10 years of age (log rank test significance, $p<0.001$) (Fig. 2).

Analysis of the lobar distribution for the patients with 5 years of terminal remission, 5-year remission ever and relapses are given in Fig. 3. The remission and relapse

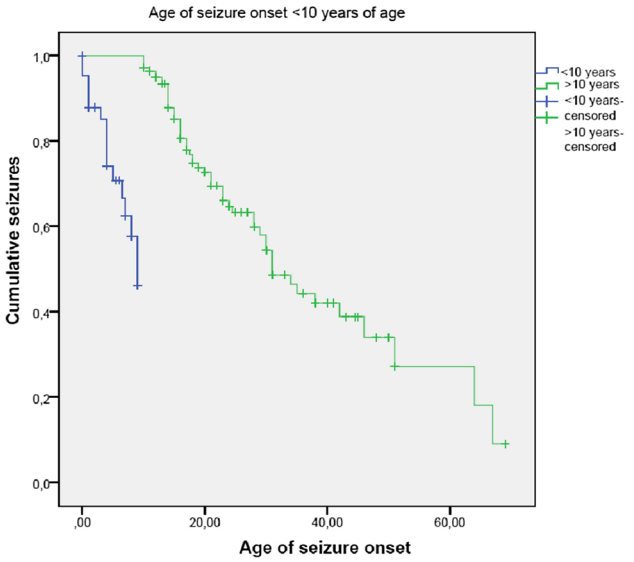

Fig. 2 Cumulative time-dependent analysis of achieving 5-year remission related to the age of seizure onset (seizure onset before and after 10 years of age) by Kaplan–Meier analysis

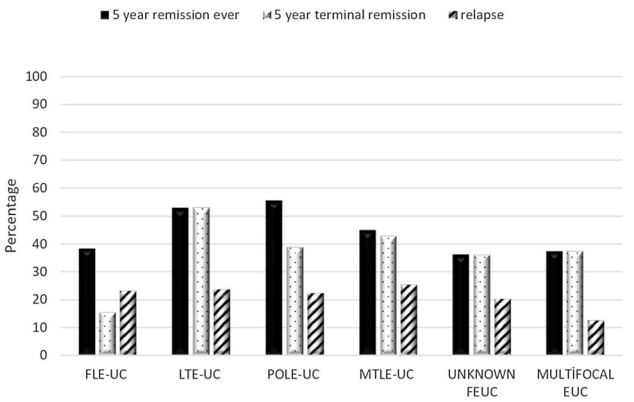

Fig. 3 Lobar distribution of the patients with FEUC with 5 years of terminal remission, 5-year remission ever and relapses. *EUC* epilepsy of unknown cause, *FEUC* focal epilepsy of unknown cause, *FLE-UC* frontal lobe epilepsy of unknown cause, *LTLE-UC* lateral temporal lobe epilepsy of unknown cause, *MTLE-UC* mesial temporal lobe epilepsy of unknown cause, *POLE-UC* parietal lobe epilepsy of unknown cause

rates were found to be similarly distributed among the lobar origin of seizures, statistically.

Amongst the 183 patients which constituted our main study cohort, two patients only were eligible for epilepsy surgery; one was post-op seizure-free whereas the other patient had post-op Engel 3; they both had neuro-pathology reports as undefined.

Discussion

The present long-term study of a large cohort with FEUC highlighted that this under-investigated group showed a relatively low rate of drug resistance (21.8%). The drug resistance in FEUC was predicted by a history of status epilepticus, abnormal neurological examination, early age of seizure onset and a high initial seizure frequency like in other epileptic populations. Moreover, we demonstrated that even in a tertiary epilepsy center, a considerable number of patients (6.6%) with a prior diagnosis of FEUC might switch to a different diagnosis during long-term follow-up which emphasizes the significance of continuing diagnostic investigations in establishing the cause of epilepsy in these patients [10]. Hence, it is crucial to reevaluate these patients with new diagnostic tools such as improved neuroimaging, video-EEG monitoring, genetic, serologic and immunologic methods; epilepsy surgery specimen may also change the final diagnosis in most of the cases [18–21].

Considering that our center is a reference center for epilepsy, it is important to note that the rate of drug resistance in our FEUC patients at the end of the long-term follow-up was lower than expected when compared to the general epilepsy population (between 30 and 40%) [22–26]. The etiology of epilepsy was known to be associated with the risk of drug resistance in many studies despite the diversities in the classification criteria creating controversial results [27]. In a study classifying focal epilepsy into symptomatic and "probably symptomatic" (mostly defining patients with FEUC) groups, 57.8% versus 39.2% of the patients had drug resistance. Thus the "probably symptomatic" group showed lower drug resistance rates with a more favorable course in this study with shorter follow-up than ours [28]. In a retrospective study, 94 (40%) out of 234 patients with lesional symptomatic epilepsy were reported as drug-resistant and majority of these patients had hippocampal sclerosis as the causative lesion for their seizures [29]. Kwan et al. reported, on the other hand, similarly higher drug resistance rates in both symptomatic (43%) and cryptogenic (FEUC) (39%) epilepsies than generalized epilepsies (26%) in their prospective study including a sample of 525 patients [25]. A plausible explanation for this higher drug resistance rates in FEUC might be that their study design did not allow some diagnostic investigations by epileptologists and lack of some new methods such as genetic, advanced neuroimaging and immunologic investigations at the time of the study. Remarkably, symptomatic epilepsies and FEUC were reported to have higher chance of developing drug resistance than idiopathic generalized epilepsies as previous studies have shown [30–32]. Our results strikingly

demonstrate that drug resistance in some patients with FEUC is even closer to the drug resistance rates in idiopathic/genetic epilepsies which implies a more favorable outcome and benign course even in a series from a tertiary epilepsy center.

Determinants of antiepileptic drug response

Early identification of the predictive factors for developing drug resistance is crucial to foresee long-term outcome and potential treatment options in FEUC [33]. The identified risk factors have a lot of discrepancies across the studies due to the variable definitions of drug resistance and lack of consistency between study cohorts. Although the predictors of drug resistance have been previously investigated in genetic and symptomatic epilepsies and some significant factors like the lobar origin of seizures along with some specific etiologies such as hippocampal sclerosis and cortical developmental disorders have been reported, there are no studies focused exclusively on patients with FEUC with long-term follow-up [28, 34–36].

We disclosed that early seizure onset, higher initial seizure frequency, a history of status epilepticus, abnormal neurological examination and having a minimum of one pathological EEG associated with drug resistance in univariate analysis, in line with the previously reported studies [22, 37, 38]. Furthermore, multivariant analysis confirmed that, status epilepticus history, abnormal neurological examination findings, seizure onset before 10 years of age and a high initial seizure frequency (more than one per month) were the most significant predictors of drug resistance in our cohort with FEUC.

Early age at epilepsy onset has been described as one of the risk factors for drug resistance in many of the previous reports, consistently [34, 39–45]. In a sample of 605 children with epilepsy (25.79% idiopathic epilepsy, 28.43% FEUC), an association between the age of seizure onset and prognosis was suggested in patients with FEUC, as earlier seizure onset being related with a more unfavorable prognosis [42]. Likewise, higher initial seizure frequency, abnormal neurological examination, status epilepticus history are other reported predictors of drug resistance reported by the previous studies with shorter follow-up [28, 46]. As all these factors were found to be significant mostly in symptomatic focal epilepsies, it was tempting to speculate that the predictive value of these factors, might point out to the presence of an underlying symptomatic etiology which could not be uncovered yet in our patient group with drug resistance with current technologies.

On the other hand, the role of EEG findings in predicting the outcome of epilepsy is still vague [47, 48]. According to some reports, pathological EEG findings like epileptiform discharges or focal slowing (nonspecific findings) were found to be related with the risk of developing drug resistance [49, 50]. Although majority of our patients with drug resistance had pathological EEG findings, it was not established as one of the significant predictors of drug resistance in the final regression analysis.

Determinants of long-term seizure remission and outcome

It is of great importance to foresee the probability of achieving seizure freedom in FEUC patients as these patients will continue to live with the burden of having an elusive diagnosis as "unknown". Having a drug resistance is widely accepted to be related with a poor prognosis, and an important negative predictor for entering remission regardless of the etiological diagnosis of epilepsy [51, 52]. The results of our study confirmed the role of drug resistance as an important negative variable for achieving a terminal long-term remission as expected, besides other clinical and demographic factors such as; presence of at least one pathological EEG and a history of status epilepticus. Both of the last two variables may reflect the presence of an underlying severe brain dysfunction with more extensive involvement of hyperexcitable epileptogenic networks which might negatively affect the long-term remission chance and create an unfavorable outcome in some patients with FEUC [15, 31, 48, 53–55].

In a large Italian prognostic study reporting the long-term prognosis of epilepsy and identifying the prognostic factors in 1006 newly diagnosed children and adults with different etiologies; factors related with a 5 years of remission were reported as having one or two seizures at diagnosis, having a generalized epilepsy, no additional psychiatric diseases and being treated with one or two antiepileptic medications [56]. Our results reporting the role of drug resistance and the related factors such as high initial seizure frequency are line with the results of this study.

In further analysis by Kaplan–Meier method, age of seizure onset after 10 years was demonstrated to be a strong predictive factor for entering a terminal long-term remission in our sample. Aguglia et al., reported older age of onset as an independent prognostic predictor of seizure freedom in their cohort including non-lesional and hippocampal sclerosis-related temporal lobe epilepsy and suggested a positive relationship with older age of seizure onset and higher remission rates [57]. In another population-based study in children, younger age of onset was found to be related with higher drug resistance and a worse outcome where the unknown etiology of epilepsy was associated with less drug-resistance rates [58]. Our results in adult population with long-term data are in harmony with these studies.

The 5-year terminal remission rates (39.9%) and 5 years of remission ever rates (44.26%) in our FEUC group were

encouraging when compared to previously reported rates in other focal epilepsy groups [4]. It is worth to emphasize that 15.06% of these patients were even drug-free and a notable rate of patients were only under monotherapy (67.12%). In the study of Kwan and Brodie, a rate of 45% with terminal remission was reported in cryptogenic focal epilepsies but the definition of remission was limited to 1 year of seizure-freedom [25]. Gasparini et al., reported that a quarter of their patients with cryptogenic focal epilepsy entered a 5 year of terminal remission regardless of age of onset [5]. Another important finding in our study was that one fourth of these patients, experienced one or more relapses during the course. Unlike other focal epilepsies with lower relapse rates [59, 60], the magnitude of our relapse rate is surprising and resembles the higher relapse rates in idiopathic/genetic epilepsies suggesting the possibility of an underlying genetic etiology [15]. Berg et al., showed that children with FEUC had a repeating relapse and remission cycle and higher relapse rates [61].

In a large prognostic study including a variety of different etiologies; the most common prognostic pattern was reported as relapsing remitting course with a high relapse rate of 52.5% where the relapse rate was reported as 49.2% in patients with an unknown etiology [56]. However, in another study, a pattern of relapse and remission could not be demonstrated in majority of the patients with FEUC and the relapse rates were reported as 10% with higher first remission rates at the final follow-up [4] The discrepancies between these studies might be the result of a clinical heterogeneity within FEUC where patients with higher remission and relapse rates with a benign course are related with a possibly genetic etiology whereas the others might be related with a rather uncovered symptomatic etiology [4].

Interestingly, the lobar origin of seizures was not demonstrated to be a predictor of remission or relapse in our group. We observed statistically similar terminal remission, remission ever and relapse rates between different lobar origins of seizures. This observation is in line with other prognostic studies [46, 62]. A plausible explanation for this observation might be a shared genetic pathophysiology which resembles the complex genetic mechanisms underlying familial epilepsies, where the different members of the same family might have seizures originating from different cortical regions [63]. We believe complex genetic mechanisms might, in the future, explain the similar prognostic rates in terms of remission and relapse among different lobar localizations in our sample with FEUC. Therefore, the integration of genetic testing into everyday clinical practice might be valuable for diagnostic research to uncover etiology of FEUC and to give proper prognostic information to the patients in a near future [64].

Strengths and limitations

Our study has some strengths; it is a study focusing on an ignored topic with long-term follow-up of minimum 5 years in the inclusion step, based on a large sample of compliant patients with FEUC in an established tertiary epilepsy center. In addition, all patients are well investigated and followed-up with regular visits in our center by experienced epileptologists. There are also some limitations of our study; first, this study was performed in a tertiary referral center which might create a selection bias. In spite of this limitation, the drug resistance and remission rates of our FEUC sample were favorable implying that our results are less likely to be negatively affected from this selection bias and giving hope for some patients with FEUC. Second, because of the retrospective nature of our study, there might be some missing data involving the pre follow-up period of our patients which might affect our results.

Conclusion

Our study emphasized that the initial diagnosis of FEUC always needs further diagnostic evaluation such as genetic testing, immunological studies, advanced imaging which might illuminate the underlying hidden etiology in at least 6.6% of patients even in a tertiary center. We conclude that when appropriately treated, FEUC has a benign subgroup with favorable course, lower drug resistance and higher 5 years of terminal remission and remission ever rates comparing to other focal epilepsies. In this regard, we believe that our data might be valuable in terms of patient counseling, treatment decisions, and management in patients with FEUC at the first referral to epilepsy clinics. Clinicians must be aware of the related factors regarding drug resistance and long-term remission in FEUC and enlighten the patients at the pretreatment phase to give an insight to their epilepsy and diminish the anxiety of having an unclarified diagnosis. Further well-designed prospective researches are needed in this aspect to confirm our results.

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Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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