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Factors predicting uncontrolled seizures in epilepsy with auditory features

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ABSTRACT

Purpose: To analyse the factors predicting uncontrolled seizures in epilepsy with auditory features (EAF).
Methods: We analysed individual data from EAF patients who were previously reported. Two authors independently reviewed the titles and abstracts identified and extracted data from each eligible study using a standardized form. The outcome measure was uncontrolled seizures. The odds ratio (OR) and 95% confidence interval (CI) were used.
Results: A total of 27 studies including 181 patients with familial and sporadic EAF met our inclusion criteria. None of the clinical factors appeared to affect seizure outcomes significantly except that treatment with carbamazepine was a protective factor against uncontrolled seizures (OR = 0.399, 95% CI: 0.195–0.820, p = 0.012), and polytherapy was associated with uncontrolled seizures. Treatment with carbamazepine was also a protective factor against uncontrolled seizures for families with LGI1 mutations (OR = 0.248, 95% CI: 0.085–0.724, p = 0.011). Carbamazepine might have a better efficacy in patients with frequent seizures (p = 0.041). Low-dose carbamazepine might completely control seizures in some EAF patients, although other effective doses of antiepileptic drugs might not. Patients without carbamazepine treatment were more likely to use new antiepileptic drugs, which might be due to the higher rate of uncontrolled seizures.
Conclusions: Carbamazepine treatment is a protective factor against uncontrolled seizures for EAF. However, this evidence is not strong enough to state that carbamazepine is the first choice drug for EAF.

1. Introduction

Epilepsy with auditory features (EAF) is a heterogeneous clinico-molecular syndrome, with or without bilateral tonic-clonic seizures, featured by seizures with auditory symptoms suggesting lateral temporal-lobe origin [1,2]. The aetiology underlying EAF is considered to be associated with specific genes because autosomal-dominant EAF has been reported extensively, and mutations mainly in the leucine-rich glioma-inactivated protein 1 (LGI1) gene were detected [3,4]. About 50% of autosomal-dominant EAF families and < 2% of sporadic cases have LGI1 gene mutations [5]. EAF has been proposed as a benign epilepsy syndrome with good seizure outcome. However, a recent study showed a less favourable outcome than previous studies, with only 34% of the EAF patients realizing five seizure-free years [1]. Treatment of EAF still seems to be difficult.

Identification of the predicting factors of uncontrolled seizures is the first step to improve the outcomes of EAF. However, EAF is a relatively rare epilepsy syndrome. It is difficult to conduct a study with a large sample to identify predicting factors because of its low prevalence. Therefore, the current study used meta-analytic methods to pool available data to investigate predicting factors of uncontrolled seizures in EAF. We expected that this meta-analysis would indicate one or more risk factors that could provide an intervention point to decrease the uncontrolled seizure rate.

2. Materials and methods

2.1. Literature-search strategy

A literature search was performed without restriction of publication year, regions or publication types within MEDLINE and Embase, using the following search terms: “auditory features”, “leucine-rich glioma inactivated”, “LGI1”, “chromosome 10q”, “reelin”, “MICAL-1”, “ADAM22”, “ADAM23”, “autosomal dominant epilepsy with auditory features”, “autosomal dominant lateral temporal epilepsy”, “epitempin”, “seizur*” and “epilep*”. The last retrieval was performed on 20 September 2018. Additional studies were added from the references of identified publications. The protocol of this study was based on the Cochrane review method (www.cochrane-handbook.org).

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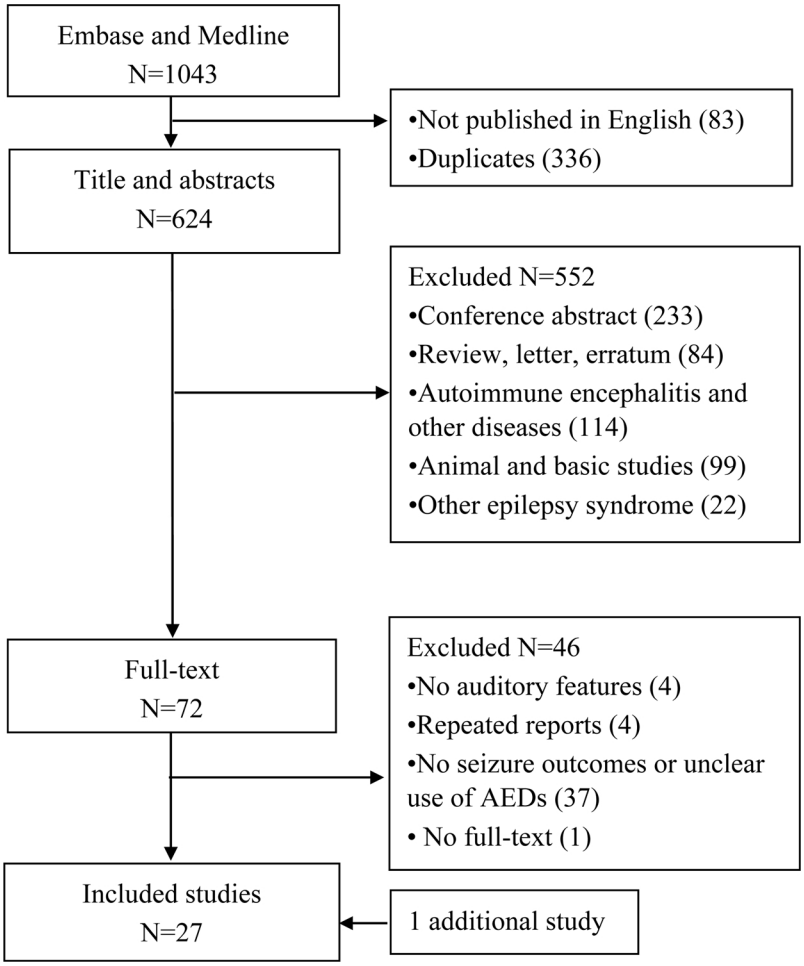

Fig. 1. The flow chart.

2.2. Inclusion and exclusion criteria

Studies were included if they (1) were published in English and the full text could be obtained, (2) included familial or sporadic EAF patients with and without a mutation and (3) reported whether treatments were accepted. Studies were excluded if they (1) were meeting abstracts, reviews, letters and erratum, (2) focused on autoimmune encephalitis and other diseases, (3) were animal and basic studies, (4) were unclear about the use of antiepileptic drugs (AEDs), (5) did not document seizure outcomes and (6) repeated data. If there was any disagreement about article selection, they would be resolved through discussion among all the authors.

2.3. Diagnosis criteria and outcomes measure

The diagnosis criteria of EAF were the occurrence of at least two lifetime seizures preceded by auditory or aphasic aura and a negative family history for epilepsy in first- and second-degree relatives (sporadic cases) [6] and a positive family history for EAF, with or without auditory aura (familial cases). Auditory auras were classified as seizures. If patients had a history of only febrile seizures but not epilepsy, they were excluded. We chose uncontrolled seizures as an outcome measure. Uncontrolled seizures was defined by ongoing seizures, with or without AEDs treatment, which was indicated by authors in the included articles. If authors indicated that a patient was seizure-free, this patient would not be classified into groups with uncontrolled seizure even though the duration of seizure freedom was not addressed.

2.4. Data extraction

Data were collected in Microsoft® Excel®. Data about repeatedly reported families were recorded once. Two authors (Lin Zhang and Xi Zhu) searched and screened the titles, abstracts and full-text articles independently. The same two reviewers independently extracted relevant information from each eligible study, using a standardised form. The first author, date of publication and country, gender, age, symptoms of seizures, onset age of seizures, ethnicity, family ID, number of affected participants in family, abnormal gene and chromosome, generation, type of seizure (only focal seizures, with or without bilateral tonic-clonic seizures and convulsive seizures), frequency at seizure onset or until onset of treatment, previous and current AEDs, seizure outcomes (uncontrolled seizures or not), neuroimaging results and interictal electroencephalogram (EEG) patterns were recorded according to the included studies. If patients with different AEDs and with uncontrolled seizures were seizure free on one or more certain AEDs in the past was also recorded.

2.5. Standard protocol approvals, registrations, and patient consents

This work was performed based on published studies, so no approvals, registrations or informed consent were required.

2.6. Statistical analysis

Considering that the use of AEDs is an important factor in seizure outcomes, patients were not included in the analysis if (1) they used

AEDs irregularly or they were not compliant, (2) whether AEDs were used was unclear and (3) the number of used AEDs was unclear.

All analyses were based on the individual data from familial and sporadic EAF patients. Continuous variables were presented as mean ± standard deviation (SD). The two-tailed, unpaired *t*-test was used to compare continuous variables. Categorical variables were compared using the χ^2 test or Fisher's exact test. Logistic regression analyses were used to estimate adjusted odds ratios (OR) and 95% confidence interval (CI). In logistic regression analyses, factors were mainly selected according to a p-value < 0.10 in univariate analysis, and patients with missing data were excluded. $P < 0.05$ was determined to be statistically significant. Statistics were performed using SPSS (version 20.0).

3. Results

3.1. Study identification and selection

The selection process is shown in Fig. 1. After removing duplicates, 624 titles and abstracts were screened. Full-text screenings were performed on 72 articles. Forty-six articles were removed, and the reasons are shown in Fig. 1. A total of 27 studies, including 204 patients with familial or sporadic EAF, met our inclusion criteria [3,4,6–30]. However, 23 patients were excluded because of unclear or irregular use of AEDs. Finally, 181 patients were included in the analysis. The characteristics of the included studies are presented in Table 1. All included families or sporadic cases had at least one difference in the following items: ethnicity, mutations, medical institutions and pedigree. No families or sporadic cases were duplicated. There were 29 patients with different AEDs and with uncontrolled seizures. Twenty-five of those patients used a combination drug regimen according to the authors' statements. Authors did not indicate that any of the patients with different AEDs and uncontrolled seizures were seizure free on certain AEDs in the past.

3.2. Univariate analysis and logistic regression analysis

The clinical features of the included population and univariate analysis with comparison of the clinical features between uncontrolled seizures and seizure remission (SR) groups are listed in Table 2. Some factors (generation of patients, multiple AEDs, treatment without carbamazepine (CBZ), and only treatment with new AEDs) tended to be associated with uncontrolled seizures. In logistic regression analysis, none of the clinical factors appeared to affect seizure outcomes significantly except that treatment with CBZ was a protective factor against uncontrolled seizures (adjusted OR = 0.399, 95% CI: 0.195–0.820, p = 0.012, see Table 3), and polytherapy was associated with uncontrolled seizures (adjusted OR = 4.111, 95% CI: 1.928–8.763, $p < 0.001$).

3.3. Comparison between groups with and without CBZ for predicting factors of uncontrolled seizures

In the past, CBZ was the first choice in focal epilepsy. Therefore, a bias toward carbamazepine might exist. To verify this question, we compared baseline characteristics of predicting factors, which were chosen from Table 2, between groups with and without CBZ treatment.

Table 1
Characteristics of the included studies.

Ref	Studies	Ethnicity	No. of patients	Included family	Gene	Repeated statements
[3]	Brodtkorb 2002	Norwegian	12	One family	10q22-q24	None
[4]	Fertig 2003	Italian-American	3	One family	T→G transversion at position 953 in LGI1	None
[6]	Magini 2014	Italian?	35	Sporadic; family was excluded	No LGI1 del	None
[7]	Pisano 2005	Italian?	5	One family	T→G transversion at position 461 in LGI1 exon 5	None
[8]	Chabrol 2007	Nepalese, Portuguese, French, Australian	18	Family NEP1, POR1, FRA1-6, and AUS1-10	No mutations in LGI1	None
[9]	Klein 2016	Israel	10	One family	LGI1 exon 6 c.641 T > C	New family
[10]	Dazzoa 2015	Italian	6	Family A Family B 1 sporadic case	LGI1 exon 2 del LGI1 exon 8 c.1118 T > C LGI1 exon 8 c.856 T > C	New family
[11]	Diani 2008	Italian?	15	Family CT, GR, PR, and PL	No mutations in LGI1	Family ZN, I-3, I-4, I-5
[12]	Poza 1999	Basque	11	One family	10q	None
[13]	Bisulli 2014	Brazilian	4	One family	19q13.11–q13.31	None
[14]	Michelucci 2000	Italian?	3	One family	10q24	None
[15]	Ikeda 2000	Japanese	3	Family U	LGI1 1421 G > A	Ref.15
[16]	Michelucci 2007	Italian	1	1 sporadic case	LGI1 exon 4 c.406C > T	None
[17]	Bonaventura 2009	Italian?	3	One family	LGI1 exon 4 c.367 G > A	None
[18]	Cendes 2006	Brazilian?	4	One family	NA	None
[19]	Striano 2011	Italian?	2	One family	LGI1 exon 8 c.1219C > T	None
[20]	Berghuis 2013	Dutch	5	One family	LGI1 intron 5 c.431 + 1 G > A	None
[21]	Fanciulli 2012	Italian?	5	One family	LGI1 exon 4 del	None
[22]	Bonaventura 2011	Italian?	8	Family A Family B Family C Family D	LGI1 exon 4 c.365 T > C LGI1exon 6 c.535 T > C LGI1exon 8 c.1075 A > G LGI1 exon 4 c.406C > T	None
[23]	Kawamata 2010	Japanese	2	Family O	LGI1 exon 8 1418C > T	Family U
[24]	Dazzoa 2018	Italian	2	Family 24 and DL	MICAL	Family 23
[25]	Lee 2014	Korean	8	One family	LGI1 exon 1 c.137 G > T	New family
[26]	Striano 2008	Italian?	5	One family	LGI1 exon 4 c.365 T > A	None
[27]	de Bellescize 2009	French?	5	One family	LGI1 exon 4 c.377 379delACA	None
[28]	Sadleir 2013	New Zealand and Australian	9	Family A Family B Family C	LGI1 exon 2 c.245 T > C LGI1 exon 6 c.673 G > T LGI1 exon 5 c.432- 2_4 36del	None
[29]	Chabrol 2007	Algerian	6	Family A Family B	LGI1 exons 3 and 4 c.431 + 1 G > A LGI1 exon 7 c.695 T > C	None
[30]	Barba 2008	Italian	1	1 sporadic case	No mutations in LGI1	None

Table 2
Univariate analysis with comparison of the clinical features between uncontrolled seizures groups and the SR groups.

Variables	Uncontrolled seizures n = 76	SR n = 104	P	Uncontrolled seizures n = 51 [a]	SR n = 62 [a]	P
Age	41.2 ± 16.9	41.2 ± 19.5 (2 NA)	0.990	37.6 ± 15.5	36.8 ± 15.6	0.775
Onset age of seizure	17.1 ± 9.9 (3 NA)	17.3 ± 10.4 (5 NA)	0.909	17.7 ± 9.4	17.7 ± 8.9	1.000
Publication year	2009.8 ± 4.8	2009.4 ± 5.2	0.563	2010.2 ± 4.9	2010.0 ± 5.4	0.883
Gender, male	36	57	0.366	22	33	0.346
Sporadic cases	20	17	0.135	19	17	0.313
Number of affected patients in family			0.265			0.228
1-9	36	64		18	32	
> 9	20	23		14	13	
Generation of patients			0.185			0.074
1	1	5		0	3	
2	14	20		4	9	
3	31	34		19	14	
4	9	25		8	19	
5	1	4		1	1	
LGI1 mutation			0.279			1.000
Yes	42	56		28	33	
No	34	48		23	29	
NA	0	4				
Seizure types			0.532			0.458
Only focal seizures	15	16		11	9	
Bilateral tonic-clonic seizures or convulsive seizures	59	87		40	53	
NA	2	1				
CT/MRI/SPECT/PET			0.895			1.000
Normal	51	66		48	59	
Abnormal	3	5		3	3	
NA	22	33				
Interictal EEG			0.182			0.258
Epileptiform	29	39		19	30	
Slow waves or normal	36	39		32	32	
NA	11	26				
Number of used AEDs			< 0.001			0.010
0	12	15		8	6	
1	35	74		22	44	
> or = 2	29	15		21	12	
Treatment with CBZ	22	50	0.013	13	32	0.015
Treatment with PHT	12	12	0.506	7	6	0.562
Treatment with PB	19	21	0.472	9	9	0.797
Treatment with VPA	14	13	0.296	10	11	0.813
Only treatment with new AEDs [b]	12	6	0.042	10	6	0.177

SR: seizure remission. NA: not available. CT: computed tomography. MRI: magnetic resonance imaging. SPECT: single photon emission computed tomography. PET: positron emission tomography. EEG: electroencephalogram. AEDs: antiepileptic drugs. CBZ: carbamazepine. PHT: phenytoin. PB: phenobarbital. VPA: valproic acid.
[a] All variables are completed.
[b] New AEDs: topiramate, lamotrigine, oxcarbazepine, zonisamide, gabapentin, and levetiracetam.

Table 3
Logistic regression analysis for uncontrolled seizure predictors.

Characteristics	Odds ratio	95% confidence interval		P value
		Lower	Upper	
Age	1.005	0.987	1.024	0.582
Male	0.741	0.389	1.410	0.361
Generation of patients	1.200	0.947	1.520	0.132
Treatment with carbamazepine	0.399	0.195	0.820	0.012
Only treatment with new AEDs	1.513	0.488	4.687	0.473
Number of used AEDs > 1	4.111	1.928	8.763	< 0.001

AEDs: antiepileptic drugs.

There were no significant differences for most factors, except that patients with CBZ treatment were younger than those without CBZ treatment (Table 1). The possible reason was that phenobarbital (PB) and phenytoin (PHT) were used earlier than CBZ. Patients without CBZ treatment were also more likely to use new AEDs, which may be due to the higher rate of uncontrolled seizures. In EAF patients who were treated with traditional AEDs, the first drugs were not only CBZ (< 54/61) but also valproic acid (VPA), PB or PHT (> 58/65). The first drugs in seven patients could not be identified. There was no strong bias toward carbamazepine (p = 1.000).

3.4. CBZ for EAF patients with frequent seizures

The clinical features of EAF patients with frequent seizures are presented in Table 4. Fourteen EAF patients were treated with CBZ and 13 EAF patients were treated with other traditional AEDs or oxcarbazepine (OXC). CBZ might have a better efficacy than other traditional AEDs for frequent seizures (p = 0.041). In addition, two patients with monthly seizures became seizure-free when VPA was changed to CBZ [15]. Another two patients were also free from seizures when PB and PHT were changed to CBZ [27].

3.5. Doses of CBZ and SR

The doses of 10 EAF patients treated with CBZ alone were described, and one of them still had seizures. Five of them used CBZ 400 mg/day, below the 50% WHO defined daily dose (DDD), and none of these five individuals had seizures. The doses of 27 EAF patients treated with other AEDs were described. Only one of them used a dose below the

Table 4
Efficacy of antiepileptic drugs on frequent seizures.

Ref	Sex	Age, year	Frequency at seizure onset or until onset of treatment	Interictal EEG	AEDs	Uncontrolled seizure
[13]	Female	50	Weekly	NA	CBZ	No
[13]	Female	22	Daily	Epileptiform	PB CBZ	No
[15]	Female	19	Monthly	Epileptiform	VPA 600 mg/day to CBZ 500 mg/day	No
[15]	Male	24	Monthly	Epileptiform	VPA 1000 mg/day to CBZ 500 mg/day	No
[20]	Male	52	Daily	Epileptiform	CBZ 600 mg/day	No
[24]	Female	20	Weekly	Epileptiform	CBZ	No
[24]	Female	54	Monthly	Epileptiform	CBZ 400 mg/day	No
[26]	Female	28	Monthly	Epileptiform	CBZ 400 mg/day	No
[27]	Male	14	Monthly	Epileptiform	CBZ 400 mg/day	No
[11]	Female	36	Monthly	Epileptiform	PB CBZ	Yes
[11]	Male	27	Monthly	Epileptiform	CBZ	Yes
[17]	Female	67	Monthly	NA	PHT VPA PB CBZ TPM LEV ZSN	Yes
[20]	Male	56	Weekly	Epileptiform	CBZ 600 mg/day	Yes
[23]	Female	27	Daily	Normal	ZNS CNZ CBZ	Yes
	Male	7	Daily	Epileptiform	CBZ	Yes
[7]	Male	59	Monthly	Epileptiform	PHT PB	No
[10]	Male	23	Frequent	Normal	VPA 800 mg/day	No
[14]	Female	32	Monthly	NA	PB 50 mg/day	No
[29]	Male	64	Frequent	Normal	PHT 100 mg/day PB 10 mg/day CZP 2mg	No
[11]	Female	52	Monthly	Epileptiform	PB LEV	Yes
[11]	Female	23	Monthly	Epileptiform	PB TPM	Yes
[13]	Male	45	Daily	NA	PB PHT	Yes
[16]	Female	36	Frequent	Normal	PB 100 mg/day	Yes
[22]	Female	24	Monthly	Epileptiform	VPA TPM to OXC	Yes
[21]	Male	64	Monthly	Normal	PB 50 mg/day PHT 300 mg/day	Yes
[21]	Male	47	Monthly	Normal	PB 75 mg/day	Yes
[21]	Male	42	Monthly	Epileptiform	OXC 600 mg/day	Yes
[21]	Male	35	Monthly	Epileptiform	VPA 1000 mg/day	Yes

EEG: electroencephalogram. AEDs: antiepileptic drugs. NA: not available. CBZ: carbamazepine. PB: phenobarbital. PHT: phenytoin. VPA: valproic acid. TPM: topiramate. LEV: levetiracetam. ZSN: zonisamide. CZP: clonazepam. OXC: oxcarbazepine.

50% DDD, but this patient was treated with three AEDs. However, 16 of 27 patients did not achieve SR. Therefore, low-dose CBZ might completely control seizures in some EAF patients, although other effective doses of AEDs might not.

3.6. Predicting factors of uncontrolled seizures in LGI1-associated epilepsy

We performed a comparison of the clinical features and a logistic regression analysis for families with LGI1 mutations (Tables 2 and 3) to predict uncontrolled seizures. Some factors (generation of patient, multiple AEDs and treatment without CBZ) tended to be associated with uncontrolled seizures. In the logistic regression analysis, none of the clinical factors appeared to affect seizure outcomes significantly, except that treatment with CBZ was a protective factor against uncontrolled seizures (adjusted OR = 0.248, 95% CI: 0.085–0.724, p = 0.011, see Tables 3), and polytherapy was associated with uncontrolled seizures (adjusted OR = 4.097, 95% CI: 1.492–11.255, p = 0.006).

4. Discussion

In the present study, the focus was on the prognostic factors for uncontrolled seizures in EAF. The main findings of the study were as follows: (1) Most factors, such as gender, age, LGI1 mutation and interictal EEG patterns, did not appear to affect seizure outcomes significantly. (2) EAF patients with uncontrolled seizures used more new AEDs. (3) EAF patients with uncontrolled seizures were more likely to be treated without CBZ. (4) CBZ might be more effective than other traditional AEDs for EAF patients with frequent seizures. (5) Low-dose CBZ might completely control seizures in some EAF patients.

AEDs are the most common forms of treatment for EAF. The current literature provides little valuable evidence for choice of AEDs for patients with EAF. We noticed that VPA with the trough blood level of 62–70 mg/L could not control the focal seizures in patients with familial EAF. However, the patients were free from seizures when VPA was changed to CBZ 500 mg/day [15]. CBZ completely suppressed seizures in seven of 11 patients with sporadic EAF, whereas only six of 21 patients had SR from using other AEDs [6]. CBZ also had a higher rate of SR in familial focal epilepsy with markers on 10q than VPA did [12,31]. In this study, we also found that seizures were not more likely to be controlled if patients were not treated with CBZ. In addition, CBZ might be more effective than other traditional AEDs for EAF patients with frequent seizures. Low-dose CBZ might completely control seizures in partial EAF patients, although other effective-dose AEDs might not. Therefore, it was reasonable to assume that CBZ provided better control of seizures than VPA, PHT or PB for EAF. For new AEDs, there was not enough data to draw the conclusion that CBZ was superior. Patients who were also treated with new AEDs were more likely to have uncontrolled seizures, this was presumably because their physicians might prescribe new AEDs if traditional AEDs failed.

There are some possible explanations for the significant advantages of CBZ in efficacy. About 50% of EAF cases are induced by LGI1 dysfunction, which is different from other seizures because of differing pathophysiologic processes. LGI1, as a secretory protein binding to ADAM22/23, regulates intrinsic excitability by postsynaptic density protein-95 (PSD-95) and Kv1 channels [32,33]. Low expression of PSD-95 greatly decreases AMPA receptor-mediated synaptic transmission in wild-type neurons [34]. Reduced AMPA receptor function on inhibitory thalamic neurons causes disinhibition of the thalamocortical network and contributes to seizures [32]. CBZ can significantly increase PSD-95 levels in a cytotoxicity model [35]. Therefore, CBZ may recover the abnormal intrinsic excitability induced by the loss of LGI1 function. On the other hand, LGI1 regulates neuronal excitability by setting the density of Kv1 channels. Abnormal Kv1 expression results in disinhibition of glutamate release, which is considered the basis of abnormal

neuronal excitability [33]. CBZ, as a sodium channel blocker, can reduce this effect via various mechanisms, such as inhibiting Na^+ channel-mediated glutamate release but not necessarily the Kv1 expression [36–38]. Therefore, CBZ may have the capacity to inhibit abnormal neuronal excitability in LGI1-associated epilepsy.

A few patients with sound-induced seizures in EAF families were reported [8,16,27]. Some researchers also thought that auditory auras and seizures sometimes triggered by noises or voices, although a specific percentage was not provided [39,40]. This was why they tried to prove that auditory stimuli induce seizures at a lower threshold in LGI1 knockout mice, which reflected the human pathology of sound-triggered seizures in some EAF patients [40]. Previous studies provided evidence that chronic CBZ therapy had a suppressive effect on the auditory pathways through the central and peripheral structures of the auditory system [41–43]. It is well known that the auditory pathway ends at the cortex of the temporal lobe. Therefore, CBZ might counteract the effect of the lowered seizure threshold and suppress the initiation process of auditory-triggered seizures in EAF patients with sound-induced seizures. However, most patients with EAF do not have sound-induced seizures. The discussion above may not reflect most situations. The mechanisms as to how CBZ may influence outcome in EAF patients merits further study.

This study has clinical significance. More than 15 AEDs can be used for adults and children with focal seizures. However, focal epilepsy is a heterogeneous disease because of different aetiologies such as genetic, structural, metabolic, autoimmune, and infectious causes. People who suffer from focal seizures with different causes respond quite differently to the same drug. Therefore, precision medicine for focal seizures with different causes is necessary, and EAF is not an exception. The most important significance of our study is that it may provide a more accurate choice for EAF. In addition, EAF patients with high seizure frequency at onset had a lower SR rate than those with low seizure frequency at onset [1]. CBZ may have a better efficacy than other AEDs against frequent seizures. More interesting, seizures can be completely controlled in some patients even if the doses of CBZ are below the 50% DDD; therefore, dose-dependent side effects and treatment costs are less than with other AEDs. After performing more studies with large samples, CBZ may be the first choice for EAF patients.

The present study has several limitations. First, no ideal data collection could be performed. For example, we only searched for English literature in two electronic databases. Second, a statistical analysis had to be performed by relying only on the included studies. However, this might result in less-accurate results because of selective reports and incomplete data. Third, the number of studies and patients included was insufficient for part of the results. Fourth, 4 patients with different AEDs and with uncontrolled seizures might not use a combination drug regimen. It was unclear if any of them were seizure free on certain AEDs, and these might have been stopped. However, we thought that the results were unlikely to be affected by a few patients. These results should be interpreted carefully. A random controlled trial with a large sample is needed for further study.

5. Conclusion

Our study supports the hypothesis that CBZ treatment is a protective factor against uncontrolled seizures for EAF. Our study was based only on the individual patient data from published literature, which limited the reliability of results. Random controlled trials with large samples are required to verify this finding. Further studies of the mechanisms underlying the therapeutic efficacy of CBZ may be helpful in revealing molecular pathways and the discovery of new treatments for EAF.

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Ethical publication statement

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

Conflict of interest

All authors reports no disclosures.

References

[1] Bisulli F, Menghi V, Vignatelli L, Licchetta L, Zenesini C, et al. Epilepsy with auditory features: long-term outcome and predictors of terminal remission. Epilepsia 2018;59:834–43.
[2] Pippucci T, Licchetta L, Baldassari S, Palombo F, Menghi V, et al. Epilepsy with auditory features A heterogeneous clinico-molecular disease. Neurol Genet 2015:1.
[3] Brodtkorb E, Gu W, Nakken KO, Fischer C, Steinlein OK. Familial temporal lobe epilepsy with aphasic seizures and linkage to chromosome 10q22-q24. Epilepsia 2002;43:228–35.
[4] Fertig E, Lincoln A, Martinuzzi A, Mattson RH, Hisama FM. Novel LGI1 mutation in a family with autosomal dominant partial epilepsy with auditory features. Neurology 2003;60:1687–90.
[5] Ottman R, Winawer MR, Kalachikov S, Barker-Cummings C, Gilliam TC, et al. LGI1 mutations in autosomal dominant partial epilepsy with auditory features. Neurology 2004;62:1120–6.
[6] Magini P, Bisulli F, Baldassari S, Stipa C, Naldi I, et al. LGI1 microdeletions are not a frequent cause of partial epilepsy with auditory features (PEAF). Epilepsy Res 2014;108:972–7.
[7] Pisano T, Marini C, Brovedani P, Brizzolara D, Pruna D, et al. Abnormal phonologic processing in familial lateral temporal lobe epilepsy due to a new LGI1 mutation. Epilepsia 2005;46:118–23.
[8] Chabrol E, Gourfinkel-An I, Scheffer IE, Picard F, Couarch P, et al. Absence of mutations in the LGI1 receptor ADAM22 gene in autosomal dominant lateral temporal epilepsy. Epilepsy Res 2007;76:41–8.
[9] Klein KM, Pendziwiat M, Cohen R, Appenzeller S, de Kovel CG, et al. Autosomal dominant epilepsy with auditory features: a new LGI1 family including a phenocopy with cortical dysplasia. J Neurol 2016;263:11–6.
[10] Dazzo E, Santulli L, Posar A, Fattouch J, Conti S, et al. Autosomal dominant lateral temporal epilepsy (ADLTE): novel structural and single-nucleotide LGI1 mutations in families with predominant visual auras. Epilepsy Res 2015;110:132–8.
[11] Diani E, Di Bonaventura C, Mecarelli O, Gambardella A, Elia M, et al. Autosomal dominant lateral temporal epilepsy: absence of mutations in ADAM22 and Kv1 channel genes encoding LGI1-associated proteins. Epilepsy Res 2008;80:1–8.
[12] Poza JJ, Saenz A, Martinez-Gil A, Cheron N, Cobo AM, et al. Autosomal dominant lateral temporal epilepsy: clinical and genetic study of a large Basque pedigree linked to chromosome 10q. Ann Neurol 1999;45:182–8.
[13] Bisulli F, Naldi I, Baldassari S, Magini P, Licchetta L, et al. Autosomal dominant partial epilepsy with auditory features: a new locus on chromosome 19q13.11-q13.31. Epilepsia 2014;55:841–8.
[14] Michelucci R, Passarelli D, Pitzalis S, Dal Corso G, Tassinari CA, Nobile C. Autosomal dominant partial epilepsy with auditory features: description of a new family. Epilepsia 2000;41:967–70.
[15] Ikeda A, Kunieda T, Miyamoto S, Fukuyama H, Shibasaki H. Autosomal dominant temporal lobe epilepsy in a Japanese family. J Neurol Sci 2000;176:162–5.
[16] Michelucci R, Mecarelli O, Bovo G, Bisulli F, Testoni S, et al. A de novo LGI1 mutation causing idiopathic partial epilepsy with telephone-induced seizures. Neurology 2007;68:2150–1.
[17] Di Bonaventura C, Carni M, Diani E, Fattouch J, Vaudano EA, et al. Drug resistant ADLTE and recurrent partial status epilepticus with dysphasic features in a family with a novel LGI1mutation: electroclinical, genetic, and EEG/fMRI findings. Epilepsia 2009;50:2481–6.
[18] Cendes F, Kobayashi E, Lopes-Cendes I. Familial temporal lobe epilepsy with auditory features. CNS Spectr 2006;11:60–1.
[19] Striano P, Busolin G, Santulli L, Leonardi E, Coppola A, et al. Familial temporal lobe epilepsy with psychic auras associated with a novel LGI1 mutation. Neurology 2011;76:1173–6.
[20] Berghuis B, Brilstra EH, Lindhout D, Baulac S, de Haan GJ, van Kempen M. Hyperactive behavior in a family with autosomal dominant lateral temporal lobe epilepsy caused by a mutation in the LGI1/epitempin gene. Epilepsy Behav 2013;28:41–6.
[21] Fanciulli M, Santulli L, Errichiello L, Barozzi C, Tomasi L, et al. LGI1 microdeletion in autosomal dominant lateral temporal epilepsy. Neurology 2012;78:1299–303.
[22] Di Bonaventura C, Operto FF, Busolin G, Egeo G, D'Aniello A, et al. Low penetrance and effect on protein secretion of LGI1 mutations causing autosomal dominant lateral temporal epilepsy. Epilepsia 2011;52:1258–64.
[23] Kawamata J, Ikeda A, Fujita Y, Usui K, Shimohama S, Takahashi R. Mutations in LGI1 gene in Japanese families with autosomal dominant lateral temporal lobe epilepsy: the first report from Asian families. Epilepsia 2010;51:690–3.
[24] Dazzo E, Rehberg K, Michelucci R, Passarelli D, Boniver C, et al. Mutations in MICAL-1cause autosomal-dominant lateral temporal epilepsy. Ann Neurol 2018;83:483–93.

[25] Lee MK, Kim SW, Lee JH, Cho YJ, Kim DE, et al. A newly discovered LGI1 mutation in Korean family with autosomal dominant lateral temporal lobe epilepsy. Seizure 2014;23:69–73.
[26] Striano P, de Falco A, Diani E, Bovo G, Furlan S, et al. A novel loss-of-function LGI1 mutation linked to autosomal dominant lateral temporal epilepsy. Arch Neurol 2008;65:939–42.
[27] de Bellescize J, Boutry N, Chabrol E, Andre-Obadia N, Arzimanoglou A, et al. A novel three base-pair LGI1 deletion leading to loss of function in a family with autosomal dominant lateral temporal epilepsy and migraine-like episodes. Epilepsy Res 2009;85:118–22.
[28] Sadleir LG, Agher D, Chabrol E, Elkouby L, Leguern E, et al. Seizure semiology in autosomal dominant epilepsy with auditory features, due to novel LGI1 mutations. Epilepsy Res 2013;107:311–7.
[29] Chabrol E, Popescu C, Gourfinkel-An I, Trouillard O, Depienne C, et al. Two novel epilepsy-linked mutations leading to a loss of function of LGI1. Arch Neurol 2007;64:217–22.
[30] Barba C, Guerrini R. Unpleasant auditory illusions and related avoidance behaviour in a child. Epileptic Disord 2008;10:35–8.
[31] Picard F, Baulac S, Kahane P, Hirsch E, Sebastianelli R, et al. Dominant partial epilepsies. A clinical, electrophysiological and genetic study of 19 European families. Brain 2000;123(Pt 6):1247–62.
[32] Fukata Y, Yokoi N, Miyazaki Y, Fukata M. The LGI1-ADAM22 protein complex in synaptic transmission and synaptic disorders. Neurosci Res 2017;116:39–45.
[33] Seagar M, Russier M, Caillard O, Maulet Y, Fronzaroli-Molinieres L, et al. LGI1 tunes intrinsic excitability by regulating the density of axonal Kv1 channels. Proc Natl Acad Sci U S A 2017;114:7719–24.
[34] Lovero KL, Fukata Y, Granger AJ, Fukata M, Nicoll RA. The LGI1-ADAM22 protein complex directs synapse maturation through regulation of PSD-95 function. Proc Natl Acad Sci U S A 2015;112:E4129–37.
[35] Park SW, Lee JG, Seo MK, Cho HY, Lee CH, et al. Effects of mood-stabilizing drugs on dendritic outgrowth and synaptic protein levels in primary hippocampal neurons. Bipolar Disord 2015;17:278–90.
[36] Sitges M, Chiu LM, Guarneros A, Nekrassov V. Effects of carbamazepine, phenytoin, lamotrigine, oxcarbazepine, topiramate and vinpocetine on Na+ channel-mediated release of [3H]glutamate in hippocampal nerve endings. Neuropharmacology 2007;52:598–605.
[37] Sitges M, Chiu LM, Nekrassov V. Single and combined effects of carbamazepine and vinpocetine on depolarization-induced changes in Na+, Ca2+ and glutamate release in hippocampal isolated nerve endings. Neurochem Int 2006;49:55–61.
[38] Waldmeier PC, Baumann PA, Wicki P, Feldtrauer JJ, Stierlin C, Schmutz M. Similar potency of carbamazepine, oxcarbazepine, and lamotrigine in inhibiting the release of glutamate and other neurotransmitters. Neurology 1995;45:1907–13.
[39] Michelucci R, Pasini E, Nobile C. Lateral temporal lobe epilepsies: clinical and genetic features. Epilepsia 2009;50(Suppl. 5):52–4.
[40] Chabrol E, Navarro V, Provenzano G, Cohen I, Dinocourt C, et al. Electroclinical characterization of epileptic seizures in leucine-rich, glioma-inactivated 1-deficient mice. Brain 2010;133:2749–62.
[41] Yuksel A, Senocak D, Sozuer D, Keskin G, Dirican A, et al. Effects of carbamazepine and valproate on brainstem auditory evoked potentials in epileptic children. Childs Nerv Syst 1995;11:474–7.
[42] Mervaala E, Keranen T, Tiihonen P, Riekkinen P. The effects of carbamazepine and sodium valproate on SEPs and BAEPs. Electroencephalogr Clin Neurophysiol 1987;68:475–8.
[43] Hamed SA. The auditory and vestibular toxicities induced by antiepileptic drugs. Expert Opin Drug Saf 2017;16:1281–94.