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Tonic-clonic seizures in idiopathic generalized epilepsies: Prevalence, risk factors, and outcome

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Purpose: We investigated the prevalence of generalized tonic-clonic seizures (GTCSs) in patients with idiopathic generalized epilepsy (IGE) and the risk factors associated with them. We also studied the seizure outcome in patients with IGEs.

Methods: In this retrospective study, all patients with a diagnosis of IGE were recruited at the epilepsy clinic at Shiraz University of Medical Sciences, from 2008 through 2019. Age, gender, age at seizure onset, seizure type(s), EEG findings, and seizure outcome of all patients were registered.

Results: A total of 601 patients with IGE were studied; 516 patients (86%) had GTCSs. The ROC curve showed that reporting GTCSs was significantly associated with the time since the start of the disease (P = .0001; area under the curve = 0.71 [95% CI: 0.66-0.76]; a cutoff point of 4 years [sensitivity = 61% and specificity = 76%]). Age at onset was 3.3 years later in patients with GTCSs compared with that in patients without GTCSs. Generalized spike-wave complexes during interictal EEG recording were more frequently observed among patients without GTCSs. Generalized tonic-clonic seizures were significantly associated with experiencing seizure-related injuries. Valproate reduced the risk of experiencing GTCSs significantly (OR: 0.58; 95% CI: 0.34-0.99; P = .04).

Conclusion: Generalized tonic-clonic seizures do not affect the seizure outcome in patients with IGEs per se, but how we manage them significantly affects the seizure outcome in these patients. Failure to prescribe valproate for women with IGE, particularly when another first-line treatment has failed, may not be in a patient's best interests.

KEYWORDS
epilepsy, idiopathic, seizure, tonic-clonic, valproate

1 | INTRODUCTION

Idiopathic (genetic) generalized epilepsies (IGEs) are common epilepsy syndromes with generalized seizures (ie, generalized tonic-clonic, absence, and/or myoclonic seizures), that are diagnosed by strict clinical and electroencephalographic (EEG) criteria.[1-3] Idiopathic generalized tonic-clonic seizure (GTCS) is the most common seizure type among patients with IGE syndromes.[1] Generalized tonic-clonic seizures are also the most important of all seizure types in patients with epilepsy; GTCSs are associated with the highest risk of seizure-related injuries[4] and also with a significant risk for premature deaths in patients with epilepsy.[5,6]

In the current study of GTCSs in patients with IGEs, we aimed to investigate the prevalence of GTCS in various syndromes of IGE. In addition, we investigated the risk factors associated with having GTCSs in patients with IGE. Finally, we studied their outcome and

the potential factors associated with a favorable seizure outcome in patients with IGE-GTCS.

2 | METHODS AND MATERIAL

In this retrospective study, all patients with a clinical diagnosis of IGE were recruited at the outpatient epilepsy clinic at Shiraz University of Medical Sciences, from 2008 until 2019. The diagnosis of various IGE syndromes was made by the epileptologist and based on the clinical grounds (including a detailed clinical history of all seizure types) and EEG findings (Ref.[2,3]). There were no exclusion criteria and no age limits. All patients had to be under the care of the epileptologist at our institution.

We studied the demographic, clinical, and interictal EEG findings of all patients. Age, gender, age at seizure onset, seizure type(s), family history of epilepsy, seizure-related injuries, interictal EEG findings (the most informative EEG, when they had multiple EEGs), and seizure outcome (at least 1 year of seizure-free state [of all seizure types] or not, in their last visit) of all patients were registered routinely.

Demographic variables and relevant clinical and EEG variables were summarized descriptively to characterize the study population. First, we studied the demographic, clinical, and electrographic factors associated with GTCSs in the whole cohort of patients with IGE. Then, we selected the patients with GTCSs, who had at least 1 year of follow-up at our clinic and investigated the demographic, clinical, and electrographic factors that might have association with their final seizure outcome (of at least 1 year of seizure-free state) in their last follow-up visit. For the statistical analyses, we performed univariate analyses using Pearson chi-square, Fisher's exact, and *t* test, as appropriate. Then, the variables that were significant ($P < .05$) in univariate analyses were assessed in a logistic regression analysis model at each step of the study (see above). Odds ratio (OR) and 95% confidence interval (CI) were calculated. The receiver operating characteristic curve (ROC curve) was also used to investigate the relationship between the time since the start of the disease in the patients (before their first visit) and the occurrence of GTCS. A *P* value <.05 was considered significant. This study was conducted with the approval by Shiraz University of Medical Sciences Institutional Review Board.

3 | RESULTS

During the study period, 601 patients with IGE were registered at our epilepsy clinic; 361 patients (60%) were females, and 240 people (40%) were males. Five hundred and sixteen patients (86%) had GTCSs, and 85 patients (14%) had never experienced a GTCS anytime during their disease (from the start of their disease to their first visit at our clinic). The mean time before we made the syndromic diagnosis at our clinic (disease duration before the diagnosis) for the whole cohort was 8 years (range: 0-44 years). Only 86 patients (14%) came to our attention with less than a year since the start of their disease; of these, 65 patients (76%) already had GTCSs. The rate of having GTCSs in patients with a year or more since the start of their disease was 449/512 (88%) (three patients did not have the data on this); the *P* value was significant in the comparison between these two groups ($P = .006$). The ROC curve showed that reporting GTCSs was significantly associated with the time since the start of the disease in the patients ($P = .0001$; area under the curve = 0.72 [95% CI: 0.66-0.76]; a cutoff point of 4 years [sensitivity = 61% and specificity = 76%]). In other words, some patients may develop GTCSs with the passage of time. Table 1 shows the prevalence of GTCSs in various syndromes of IGE. Table 2 shows the demographic, clinical, and electrographic factors associated with GTCSs in the whole cohort of patients with IGE. Age at onset of disease was 3.3 years later in patients with GTCSs compared with that in patients without GTCSs. Generalized spike-wave complexes during interictal EEG recording were more frequently observed among patients without GTCSs. Finally, having GTCSs were significantly associated with experiencing seizure-related injuries. We then analyzed these three variables in a binary logistic regression model. The model that was generated by regression analysis was significant ($P = .0001$) and could predict the possibility of having an association with GTCSs in 86.1% of the patients. Within this model, age at onset (OR: 1.04; 95% CI: 1.00-1.08; $P = .03$), generalized spike waves during interictal EEG recording (OR: 0.5; 95% CI: 0.26-0.96; $P = .03$), and seizure-related injuries (OR: 59.22; 95% CI: 8.13-431.30; $P = .0001$) were significantly associated with having GTCSs.

TABLE 1 Prevalence of generalized tonic-clonic seizures (GTCSs) in various syndromes of idiopathic generalized epilepsy (IGE)

IGE syndrome	Number of patients with GTCS (%)
GTC-only	91 of 91 (100)
Juvenile myoclonic epilepsy (JME)	246 out of 266 (92)
Juvenile absence epilepsy (JAE)	87 out of 111 (78)
Childhood absence epilepsy (CAE)	48 out of 82 (59)
Other syndromes[a]	44 out of 51 (86)
Total	516 out of 601 (86)

[a]Other syndromes: Jeavons, phantom absences, epilepsy with myoclonic absences, myoclonic epilepsy of infancy, and febrile seizure plus.

We then selected the patients with at least 1 year of follow-up at our clinic (N = 357; 117 patients had less than a year of follow-up, and 127 people had no follow-up at our center [some patients were referred for certification of the diagnosis, but were under the follow-up by other physicians]). The mean (±standard deviation) period for their follow-up at our clinic was 4.7 (±2.9) years (range: 1-10 years). Three hundred and six patients (86%) had GTCSs and 51 patients (14%) did not. Having GTCSs did not have an association with the final seizure outcome of at least 1 year of seizure-free state (of all seizure types) (166 patients of those with and 25 people of

TABLE 2 Factors associated with generalized tonic-clonic seizures (GTCSs) in idiopathic generalized epilepsies (IGEs) in univariate analysis

Factor	Patients with GTCS (N = 516)	Patients without GTCS (N = 85)	*P* value
Sex ratio (Female: Male)	305:211	56:29	.2
Age at onset, years (mean ± standard deviation)	12.8 ± 6.9	9.5 ± 5.7	.0001
Family history of epilepsy	215 (42%)	29 (34%)	.2
Generalized spike waves in EEG	375 (73%)	70 (82%)	.04
Polyspikes in EEG	287 (56%)	46 (54%)	.9
Photosensitivity in EEG	54 (10%)	4 (5%)	.1
Seizure-related injuries	232 (45%)	2 (2%)	.0001

TABLE 3 Factors associated with seizure-free state in idiopathic generalized epilepsies (IGEs) with generalized tonic-clonic seizures (GTCSs) in univariate analysis

Factor	Patients with a seizure-free state (N = 166)	Patients without seizure freedom (N = 140)	*P* value
Sex ratio (Female: Male)	93:73	95:45	.04
Age at onset, years (mean ± standard deviation)	12.2 ± 5.9	13.2 ± 7.4	.2
Time to diagnosis at our clinic, years (mean ± standard deviation)	7.6 ± 8.5	9.3 ± 7.4	.06
GTCS frequency per year (mean ± standard deviation)	1 ± 2.7	4.1 ± 27.7	.1
Having absence seizures	68 (41%)	78 (56%)	.01
Having myoclonic seizures	86 (52%)	95 (68%)	.005
Generalized spike waves in EEG	125 (75%)	106 (76%)	.8
Polyspikes in EEG	91 (55%)	90 (64%)	.08
Photosensitivity in EEG	13 (8%)	20 (14%)	.09
Syndromic diagnosis (JME/GTC-only/JAE/CAE/Others)[a]	75/38/26/12/15	75/15/22/17/11	.04
Valproate in the drug regimen	115 (69%)	78 (56%)	.01

Abbreviations: CAE, Childhood absence epilepsy; GTC-only, Generalized tonic-clonic only; JAE, Juvenile absence epilepsy; JME, Juvenile myoclonic epilepsy.

[a]Other syndromes: Jeavons, phantom absences, epilepsy with myoclonic absences, myoclonic epilepsy of infancy, and febrile seizure plus.

those without GTCSs were seizure-free in their last follow-up visit; *P* = .5).

Finally, since the likelihood of detecting GTCS depends on time, we selected the patients who already had GTCSs (before their first visit at our center), who also had at least 1 year of follow-up at our clinic (N = 306). We investigated the demographic, clinical, and electrographic factors that might have association with their final seizure outcome (of at least 1 year of seizure-free state) in their last follow-up visit, in univariate analysis (Table 3). Sex, having absences or myoclonic seizures, their syndromic diagnosis, and receiving valproate (either in mono- or in a polytherapy regimen) had significant associations with GTCSs in univariate analyses. We then analyzed these significant variables in a binary logistic regression model. The model that was generated by regression analysis was significant (*P* = .005) and could predict the possibility of achieving a seizure-free state in 61.4% of the patients. Within this model, only receiving valproate

retained its significance, showing a protective effect against having a bad outcome of having seizures (OR: 0.58; 95% CI: 0.34-0.99; P = .04). All other variables lost their significance. Among patients, who were taking valproate, 167 (87%) individuals were on monotherapy regimens, and 26 (13%) people were on polytherapy. Among patients, who were not receiving valproate, 101 (89%) people were on monotherapy regimens. Table 4 shows a comparison of the seizure freedom rates between different drugs used as monotherapy, using a chi-squared test. Patients, who were receiving valproate monotherapy, more often achieved a seizure-free state compared with those who were on monotherapy with other AEDs.

4 | DISCUSSION

In this large cohort of patients, we observed that IGE-GTCS is the most common seizure type among patients with IGE syndromes. This is consistent with that in previous studies.[1,7] In our study, 86% of the patients reported experiencing GTCSs at some time during their disease; this rate was 73% in an Irish study.[7] In the current study, we showed that the chance of experiencing GTCSs is a function of the duration of disease in patients with IGEs; therefore, the observed difference between our study and that Irish study could be due to the different durations of disease between the study populations. In addition, we observed that some patients may develop new seizure types with time. These two observations imply that IGEs might evolve clinically, with the development of new seizure types with the passage of time. It has previously been documented that some syndromes of IGE may evolve to others (eg, CAE to JME or GTC-only).[8,9] Therefore, it is necessary to obtain a detailed history on all possible seizure types during every follow-up visit of patients with epilepsy, and in particular in all patients with IGEs. This may have important clinical implications for an appropriate adjustment of the treatment strategy according to any new scenarios.

Secondly, we observed that GTCSs have a striking association with seizure-related injuries in patients with IGE (with an odds ratio of 59). In a previous study,[4] we observed that severe injuries were three times more frequent among patients having tonic-clonic seizures compared to healthy controls. No patient reported having severe injuries due to myoclonic or absence seizures. Mild injuries were 10 times more frequent among those with tonic-clonic seizures compared to healthy controls.[4] In the current study, we did not investigate the details of seizure-related injuries, but our current observation corroborates that previous study. In addition and even more importantly, tonic-clonic seizures have been associated with premature death in patients with epilepsy.[6] For example, sudden unexpected death in epilepsy (SUDEP) commonly occurs during sleep and it preferentially affects young adults with drug-resistant epilepsy (especially, those with tonic-clonic seizures).[6] Interestingly, it has been shown that bringing the tonic-clonic seizures under control may save lives in patients with epilepsy.[5] Therefore, in order to reduce the risk of seizure-related injuries and also decrease the chance of premature death in patients with IGE, it is important to try hard and bring their GTCSs under control.

We had two subtle, but intriguing observations with regard to the factors associated with GTCSs in patients with IGE; age at onset of disease was 3.3 years later in patients with GTCSs compared with that in patients without GTCSs (OR = 1.04) and generalized spike-wave complexes during interictal EEG recording were more frequently observed among patients without GTCSs (OR = 0.5). These two observations may simply reflect what we already know based on the current (Table 1) and many previous studies; patients with CAE, who more often have generalized spike waves in their EEGs and have an earlier age at onset, less often have GTCSs compared with that in patients with JAE or JME.[10-12] However, since both of these variables retained their significance in the logistic regression analysis model independently, this observation deserves further attention in future studies.

Finally and most importantly, we observed that GTCSs do not affect the seizure outcome in patients with IGEs per se, but how we manage them significantly affects the prognosis and seizure outcome of these patients. Valproate either in monotherapy or in polytherapy regimens is the most effective antiepileptic drug (AED) to bring GTCSs under the control in patients with IGE; this is consistent with previous studies.[13,14] Current recommendations on the treatment of young women with IGE wisely advise against the use of valproate as the first-line AED.[15] However, we should bear in mind that these guidelines only recommend caution regarding teratogenic risks of valproate in women of child-bearing potential, but do not advocate absolute avoidance. Failure to prescribe valproate for patients with IGE, particularly when another first-line AED treatment (eg, lamotrigine or levetiracetam) has failed, may not be in a young woman's best interests. Indiscriminate avoidance of valproate in women needs to be recognized as a misinterpretation of the current epilepsy guidelines, as it may harm young patients.[16] Although the use of valproate demands careful consideration, there remains a strong case to always discuss this medication with the patients and their families. Patients must be allowed to make their own informed decisions about the most effective and safest epilepsy treatments.[16] We strongly believe that the position taken by some drug companies and regulatory agencies on valproate use in women (ie, "Valproate is forbidden during pregnancy and should no longer be prescribed to girls, teenagers and

TABLE 4 Seizure-free rates and drugs the patients were receiving in monotherapy regimens[a]

Antiepileptic drug	Seizure-free rate
Valproate	103 out of 167 (62%)
Lamotrigine	30 out of 71 (42%)
Levetiracetam[b]	5 out of 14 (36%)
Other drugs	8 out of 16 (50%)

[a]Valproate monotherapy was more effective than other monotherapy regimens in bringing the seizures under the control (P = .03).

[b]Levetiracetam is not covered by most insurance policies and people have to pay the cost out of their pocket.

women of child-bearing age unless exceptional circumstances"[17,18]) is very irrational and may cause harm to the patients.

Our study has some limitations. This was a clinic-based series and may not represent the full spectrum of patients with IGE as the mildest disease varieties may not be referred to a busy university clinic (selection bias). In addition, data were collected retrospectively and recall bias is also a consideration. However, we can conclude that GTCS is the most common seizure type among patients with IGE syndromes and the chance of experiencing GTCSs is a function of the duration of the disease in these patients. Therefore, it is necessary to obtain a detailed clinical history on all possible seizure types during every follow-up visit of patients with IGE. In addition, GTCSs have a striking association with seizure-related injuries in patients with IGE, and in order to reduce the risk of seizure-related harms, it is important to bring GTCSs under control. Interestingly, GTCSs do not affect the seizure outcome in patients with IGEs per se, but how we manage them significantly affects the seizure outcome in patients with IGE. Failure to prescribe valproate for women with IGE, particularly when another first-line AED treatment has failed, may not be in a patient's best interests.

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CONFLICT OF INTEREST

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AUHTORS'CONTRIBUTIONS

Ali A. Asadi-Pooya, MD: Study design, data collection, statistical analysis, manuscript preparation. Maryam Homayoun, MD, Data collection, manuscript preparation.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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