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Egypt J Neurol Psychiatry Neurosurg (2023) 59:4
https://doi.org/10.1186/s41983-022-00604-4

The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

RESEARCH

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Genetic generalized epilepsy: factors associated with drug resistance polytherapy

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Abstract

Background Different studies investigating generalized genetic epilepsy (GGE) have shown that achieving 5 years of remission, early seizure remission, and needing antiseizure medication (ASM) monotherapy may predict favorable long-term outcomes.

Results This is a retrospective analytical cohort study. Records of patients with GGE diagnoses at a large epilepsy center in Cairo served as the data source. 630 patients (297 male patients (47.1%) and 333 female (52.9%)) were included, their median onset age was 13 years. The follow-up period of this study was at least 4 years. 418 patients (66.1%) were early remitters, 160 patients (25.4%) were late remitters, and 52 patients (8.3%) were intractable. In addition, 367 patients (58.3%) needed a single ASM to achieve a maximum remission period (monotherapy group), while 263 patients (41.7%) needed ASM polytherapy. Stepwise regression analysis revealed that absence seizures, clusters of seizures, seizure frequency before treatment, and dose of sodium valproate (VPA) until the first remission were independent predictors for polytherapy. Moreover, absence seizures, seizure frequency before treatment, VPA dose, and catamenial seizures in females were independent predictors of intractability.

Conclusion The majority of GGE have a favorable outcome, some clinical features could predict the need for polytherapy and failure of remission on treatment.

Keywords Genetic generalized epilepsy, Predictors, Intractability, Polytherapy, Long-term outcome

Background

Genetic generalized epilepsy (GGE) includes distinct clinical syndromes, according to the International League Against Epilepsy (ILAE): epilepsy with generalized tonic–clonic seizures alone, juvenile myoclonic epilepsy (JME), childhood absence epilepsy (CAE), and juvenile absence epilepsy (JAE) [1]. Despite GGE being typically associated with a positive prognosis, there is a large variance in remission rate [2]. In clinical practice, drug resistance and the need for polytherapy pose a significant problem in patients with GGE [3, 4].

Actually, few long-term outcome studies on GGE have been conducted. In addition, relatively few studies have examined the determinants of continued insufficient seizure control from epilepsy diagnosis till the end of follow-up [5].

On this background, we sought to analyze seizure outcomes throughout a long-term (4-year) follow-up of a cohort of GGE patients who had been followed from diagnosis in a large epilepsy center. We studied the predictors of polytherapy and persistent treatment resistance among different outcome measures.

Methods

In this retrospective cohort analysis, we analyzed the records of 630 patients diagnosed with GGE by a single expert epileptologist between 1994 and 2017 and followed them for at least four years at a single specialized epilepsy center. The diagnosis was determined by a

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comprehensive clinical evaluation and a conventional interictal electroencephalography (EEG) measurement.

The subjects were recruited based on the following criteria: (a) patients diagnosed and categorized as having genetic generalized epilepsy following ILAE classification (1981 and 1989); (b) both sexes and all age groups; (c) a minimum follow-up duration of 4 years; and (d) complete clinical records are available.

We retrospectively assessed the clinical, demographic, and interictal EEG findings and the previous and current drug regimen. The studied predictors of epilepsy prognosis included the onset age, family history of epilepsy, catamenial seizures, history of febrile seizures, nocturnal seizures, seizure type and frequency, history of status epilepticus or non-convulsive status epilepticus, epilepsy syndrome, temporal patterns of seizures, history of clusters of seizures, EEG findings, early response to treatment with an antiseizure medications (ASMs), response to valproate (VPA) and its dose, and the number of ASMs used to achieve maximum remission.

The follow-up period of this study was at least 4 years, and the intervals between follow-up visits were about 2–3 months for patients with relapse and about 12 months for patients in remission. The follow-up visit was done by patient attendance or telephone call. The duration of follow-up was estimated from the diagnosis date to the final follow-up visit date, while disease duration was calculated from the onset to the last follow-up visit. Therapy and seizure control compliance were evaluated at each medication regimen follow-up visit.

Remission, the most prevalent active principle investigated independently in this analysis, was defined as two or more years of full seizure control following epilepsy diagnosis. Early remission was defined as two or more years of seizure remission that began promptly or within the first two years following an epilepsy diagnosis. In contrast, late remission was defined as 2 years or more of full seizure control attained at least 24 months following the diagnosis of epilepsy. Terminal remission was defined as remission for at least 2 years before the final follow-up visit. Relapse refers to the recurrence of a seizure after at least 2 years of seizure remission. No remission (intractable) was defined as not achieving full seizure control for at least 2 years. The maximum remission time was defined as the longest period of seizure freedom attained during the course of the illness. All categories were applied to patients who had received acceptable ASMs therapy at the recommended daily dosage [6–8].

The SPSS software version 28 (IBM Corporation, Armonk, New York, USA) was used for data analysis. The Mann–Whitney test (non-parametric) was used to compare quantitative variables. The Chi-square test was used for comparing categorical data. The Spearman correlation coefficient was used to compute correlations between quantitative variables. Logistic regression was used to identify independent factors of late remission and polytherapy. P-value < 0.05 was regarded significant.

Results

630 patients with GGE were identified. 367 patients (58.3%) were newly diagnosed and started treatment at our center, and 263 (41.7%) were previously diagnosed and started treatment at another center.

Among the studied group, 333 patients (52.9%) were females. The median age at the onset and diagnosis was 13 and 14 years, respectively. Regarding the number of seizure types, 168 patients (26.7%) experienced a single seizure type, 386 patients (61.3%) had two seizure types, while 76 patients (12.1%) had 3 seizure types. The median seizure frequency (GTCs) before treatment was one year, with a range of 0–36 GTCs per year.

The most common syndrome was JME (49.8%), while the least represented syndrome was myoclonic absence epilepsy (1.1%), JAE represented 24.9% (157 patients), GTCs was found in 95 patients (15.5%), CAE was diagnosed in 38 patients (6%), and MAS was detected in 19 patients (3%), moreover, 22 patients (3.5%) had a history of remitted absence epilepsy during childhood as a predictor of poor outcomes. The rest of clinical characteristics are described in Table 1.

Regarding EEG, 52 patients (8.3%) had focal features in EEG, and patients (2.4%) had paroxysmal photo response in EEG. In addition, 122 patients (19.4%) had active EEGs represented by generalized discharges > 3 s.

418 patients (66.3%) achieved early remission, 160 patients (25.4%) achieved late remission, and 52 patients (8.3%) did not achieve 2 years of seizure freedom throughout the disease course (intractable).

52 patients (8.3%) failed to reach at least 2 years without any seizures; 30 of them (57.7%) were females, 2 (3.8%) had febrile seizures previously, and 6 (11.5%) had a history of epilepsy in their families. The median age for patients with intractable epilepsy onset was 12 years (range: 2–26 years); most of them (53.8%) were diagnosed as JME, 14 (26.9%) were diagnosed as JAE, 5 (9.6%) diagnosed as CAE, GTCs was diagnosed in 4 patients and only one patient diagnosed as myoclonic astatic seizures (MAS). The majority (43 patients, 82.7%) had multiple seizure types, 8 of the females (26.7%) had history of catamenial seizures (perimenstrual). nocturnal seizures were detected in 11 patients (21.2%), moreover, 13 patients (25%) had seizures induced by sleep deprivation. Besides, the median frequency of GTCs before treatment was 2/year with a range of 0–36 GTC seizures in a year, history of clusters of seizures was found in 9 patients (17.3%), status epilepticus and non-convulsive status epilepticus

Table 1 Clinical data of the study population

	Count	%
Nocturnal seizures		
Yes	100	15.9%
No	530	84.1%
Febrile convulsions		
Yes	36	5.7%
No	594	94.3%
Family history of epilepsy		
Yes	80	12.7%
No	550	87.3%
Absence		
Yes	260	41.3%
No	370	58.7%
Myoclonic jerks		
Yes	368	58.4%
No	262	41.6%
GTCs		
Yes	540	85.7%
No	90	14.3%
NCSE		
Yes	17	2.7%
No	613	97.3%
Status epilepticus		
Yes	5	0.8%
No	625	99.2%
Focal semiology		
Yes	35	5.6%
No	595	94.4%
Catamenial seizures (female)		
Yes	18	2.9%
No	612	97.1%
Clusters		
Yes	60	9.5%
No	570	90.5%
Psychiatric comorbidities		
Yes	62	9.8%
No	568	90.2%
Sleep-deprived GTCs		
Yes	153	24.3%
No	477	75.7%

GTCs generalized tonic clinic seizures, *NCSE* non-convulsive status epilepticus

(NCSE) was reported in 1 (1.9%) and 5 (9.6%) patients, respectively. Referring to EEG, 2 patients (3.8%) had focal features in EEG, 11 patients (21.1%) had an active EEG, and none had a paroxysmal photo response.

The logistic regression analysis was performed to identify independent determinants of intractability and showed that the presence of absence seizures, seizure frequency before treatment, catamenial seizures in females and mean dose of VPA were significant independent predictors of intractability in patients with GGE. Table 2 depicts the results of logistic regression.

Table 2 Regression analysis of predictors of intractability

Intractable	*P* value	OR	95% CI	
			Lower	Upper
Age at onset	0.451	0.975	0.914	1.041
Nocturnal seizures	0.805	1.106	0.495	2.472
Number of seizure types	0.361	1.301	0.739	2.291
Seizure frequency (GTC) before treatment (number in year)	< 0.001	1.113	1.057	1.171
Absence seizures	0.005	0.409	0.209	0.796
H\O CAE	0.339	0.346	0.039	3.051
Catamenial seizures (female)	< 0.001	8.085	2.786	23.464
Clusters	0.143	1.915	0.803	4.566
Valproate dose till first remission	< 0.001	1.0029	1.0020	1.0039
EEG focal features	0.197	0.376	0.085	1.664

GTCs generalized tonic clinic seizures, *CAE* childhood absence epilepsy, *EEG* electroencephalography, *OR* odds ratio, *CI* confidence interval

The most commonly used drug was VPA (90.5%); 128 patients (20.3%) experienced side effects from VPA. The median dose of VPA to achieve the first remission was 750 mg/day, with a range of 0–2000 mg/day. 328 patients (52.1%) were on a single AED at the last visit, 235 patients (37.3%) were on 2 or more ASMs at the last visit, and 67 (10.6%) patients were off medication.

386 patients (61.3%) achieved the first remission period using a single ASM, while 244 patients (38.7%) needed more than a single ASM to accomplish the first remission. 367 patients (58.3%) required a single ASM to achieve a maximum remission period (monotherapy group), while 263 patients (41.7%) failed to reach a maximum remission period in a single ASM (polytherapy group).

Patients treated with polytherapy had a higher age at onset, a higher age at diagnosis. Besides, they achieved a maximum remission period at older age, had a higher seizure frequency before treatment, a greater number of seizure types, and were diagnosed more with JAE and myoclonic absence. Patients in the monotherapy group are more likely to achieve 5 years of remission and more liable to drug withdrawal than the polytherapy group, as shown in Tables 3 and 4.

The multivariable logistic regression analysis demonstrated significant independent predictors of polytherapy in patients with GGE, including nocturnal seizures, absence seizures, cluster of seizures, catamenial seizures in females, higher seizure frequency before treatment, higher VPA dose till achievement of first remission, and

Table 3 Comparison between monotherapy and polytherapy

	Monotherapy		**Polytherapy**		***P* value**
	Count	**%**	**Count**	**%**	
Gender					
Male	169	46.0%	128	48.7%	0.516
Female	198	54.0%	135	51.3%	
Febrile convulsions					
Yes	23	6.3%	13	4.9%	0.48
No	344	93.7%	250	95.1%	
Family history					
Yes	48	13.1%	32	12.2%	0.735
No	319	86.9%	231	87.8%	
Syndrome					
CAE	19	5.2%	19	7.2%	0.2
JAE	82	22.3%	75	28.5%	0.02
JME	193	52.6%	121	46.0%	0.1
GTCs only	64	17.4%	31	11.8%	0.06
MAS	7	1.9%	12	4.6%	0.1
Myoclonic absence	2	0.5%	5	1.9%	0.02
No. of seizure types					
1	109	29.7%	59	22.4%	< 0.001
2	233	63.5%	153	58.2%	
3	25	6.8%	51	19.4%	
Absence seizure					
Yes	120	32.7%	140	53.2%	< 0.001
No	247	67.3%	123	46.8%	
Myoclonic seizure					
Yes	214	58.3%	154	58.6%	0.951
No	153	41.7%	109	41.4%	
GTCs					
Yes	316	86.1%	224	85.2%	0.742
No	51	13.9%	39	14.8%	
Nocturnal seizures					
Yes	39	10.6%	61	23.2%	< 0.001
No	328	89.4%	202	76.8%	
Clusters					
Yes	23	6.3%	37	14.1%	0.001
No	344	93.7%	226	85.9%	
Catamenial seizures (females)					
Yes	4	2.0%	14	10.4%	0.002
No	194	98.0%	121	89.6%	
H\O CAE					
Yes	8	2.2%	14	5.3%	0.034
No	359	97.8%	249	94.7%	
NCSE					
Yes	6	1.6%	11	4.2%	0.052
No	361	98.4%	252	95.8%	
Status epilepticus					
Yes	2	0.5%	3	1.1%	0.654
No	365	99.5%	260	98.9%	
Focal semiology					

Table 3 (continued)

	Monotherapy		Polytherapy		*P* value
	Count	%	Count	%	
Yes	16	4.4%	19	7.2%	0.122
No	351	95.6%	244	92.8%	
Psychiatric comorbidities					
Yes	35	9.5%	27	10.3%	0.762
No	332	90.5%	236	89.7%	
Sleep deprivation-induced seizures					
Yes	81	22.1%	72	27.4%	0.126
No	286	77.9%	191	72.6%	
EEG focal features					
Yes	21	5.7%	31	11.8%	0.006
No	346	94.3%	232	88.2%	
Active EEGs					
Yes	56	15.3%	66	25.1%	0.002
No	311	84.7%	197	74.9%	
Photoparoxysmal response					
Yes	10	2.7%	5	1.9%	0.504
No	357	97.3%	258	98.1%	
OFF medication last visit					
Yes	51	13.9%	18	6.8%	0.005
No	316	86.1%	245	93.2%	
Achievement of at least 5 years remission on AEDs					
Yes	251	76.8%	121	52.8%	< 0.001
No	76	33.2%	108	47.1%	
Achievement of at least 5 years remission off AEDs					
Yes	45	13.8%	10	4.4%	0.001
No	282	86.2%	219	95.6%	

CAE childhood absence epilepsy, *JAE* juvenile absence epilepsy, *JME* juvenile myoclonic epilepsy, *GTCs* generalized tonic clonic seizures, *MAS* myoclonic astatic seizures, *EEG* electroencephalography, *AED* antiepileptic drug, *NCSE* non-convulsive statue epilepticus

EEG focal discharges. The results of multivariable logistic regression analysis are illustrated in Table 5.

There was a highly significant negative correlation between the number of ASMs needed till the achievement of the maximum remission period and the maximum remission period ($r = -0.366$) ($p < 0.001$), denoting that the more ASMs needed, the shorter the maximum remission period and poorer prognosis (Fig. 1).

Discussion

Patients fulfilling the criteria for GGE according to the ILAE 1989 classification were enrolled in this study. Interestingly, the vast majority of the patients had a favorable outcome, 66.3% of them achieved early remission, and the remission rate at 5 years was almost 70%. Given the overall satisfactory result of GGE provided by the literature, the emphasis of the research is to analyze the clinical course over time in order to determine the factors of the requirement for polytherapy and drug resistance among these patients.

367 patients (58.3%) needed a single ASM to achieve a maximum remission period (monotherapy group), while 263 patients (41.7%) failed to achieve a maximum remission period on a single ASM (polytherapy group). From 630 patients studied in this group, 52 (8.3%) did not reach 2 years of seizure freedom throughout the disease course. Older age at onset and delayed diagnosis were statistically found in polytherapy group. However, there was an insignificant difference regarding gender, family history of epilepsy, or febrile seizure between the groups treated with multiple drugs and those who needed a single drug. No significance was also detected concerning drug resistance. These findings agree to some extent with Gomez-Ibañez and colleagues, who stated that family history of epilepsy, sex, and delayed diagnosis were not associated with significant drug resistance [9].

Table 4 Comparison between monotherapy and polytherapy

	Monotherapy					Polytherapy					*P* value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Age at onset	13.87	5.98	14.00	2.00	50.00	12.71	5.49	12.00	1.00	30.00	0.013
Age of diagnosis	14.77	6.45	14.00	2.00	50.00	13.27	6.67	13.00	1.00	60.00	0.001
Interval between onset and diagnosis	0.89	2.25	0.00	0.00	16.00	0.60	3.14	0.00	0.00	35.00	< 0.001
Age of first remission (R1)	15.46	6.69	15.00	2.00	52.00	16.90	9.36	16.00	1.00	62.00	0.151
Age of maximum remission (Rmax)	18.17	8.39	17.00	2.00	52.00	20.90	11.51	20.00	1.00	62.00	0.011
Seizure frequency (GTC) before treatment (number/ year)	1.42	2.16	1.00	0.00	24.00	3.21	5.62	1.00	0.00	36.00	< 0.001
Maximum remission period	6.69	3.91	5.00	2.00	30.00	4.45	3.43	4.00	0.00	17.00	< 0.001
VPA_dose_R1	635.56	353.91	600.00	250	1500.00	912.74	382.86	1000.00	250	2000.00	< 0.001

GTCs generalized tonic clonic seizures, *VPA* valproate, *R1* first remission, *Rmax* maximum remission, *SD* standard deviation

Table 5 Regression analysis of polytherapy

Polytherapy	*P* value	OR	95% C.I	
			Lower	Upper
Nocturnal seizures	0.007	2.013	1.209	3.351
Number of seizure types	0.917	0.983	0.705	1.369
Absence seizure	< 0.001	2.455	1.583	3.806
Cluster of seizures	0.029	2.072	1.080	3.976
H\O CAE	0.182	1.991	0.724	5.475
Seizure frequency (GTC) before treatment (number in year)	< 0.001	1.134	1.054	1.220
Dose of sodium valproate till first remission	< 0.001	1.002	1.002	1.003
Age at onset	0.061	0.964	0.929	1.002
EEG focal features	0.017	2.216	1.151	4.264
Active EEGs	0.275	1.297	0.813	2.071
Catamenial seizures (female)	0.043	3.511	1.041	11.835

CAE childhood absence epilepsy, *GTCs* generalized tonic clonic seizures, *EEG* electroencephalogram, *OR* odds ratio, *CI* confidence interval

Our study noticed a greater number of seizures was associated with poor outcomes. Higher seizure frequency before treatment was an independent predictor of polytherapy (OR 1.134, 95% CI; 1.054–1.220) and drug resistance (OR 1.113, 95% CI; 1.057–1.171). Powell and colleagues also concluded that higher seizure frequency before treatment predicted a reduced probability of seizure remission [10].

Absence seizure was statistically significant for poor outcome in our study (independent predictor for intractability and polytherapy). A recent study by Irelli and his colleagues found similar results [2]. They studied 177 IGE patients and found that early remission group had a significant lower incidence of absence seizure. Miro and colleagues studied 54 IGE patients and noted the seizures in JAE tended to be more resistant to treatment, higher doses of VPA or polytherapy are usually needed in these patients [11]. This conclusion agrees with our finding that absence seizure predicts poor outcome.

Patients with clusters of seizures had poor outcome in the present study. Sillanpää and Schmidt also stated that patients with cluster of seizures are more liable for drug-resistant epilepsy [12]. Nocturnal seizures were statistically significant for an unfavorable outcome in our study, similarly, a large epilepsy center in Cairo had concluded that sleep convulsive seizure was an independent predictor of lack of 5 years remission in patients with genetic generalized epilepsy [13].

When referring to catamenial seizures, we found that women with catamenial seizures had an eightfold increased risk for intractability (OR 8.085, 95% CI 2.786–23.464). The presence of catamenial seizures in females was an independent predictor of intractability. A recent study by Kamitaki and colleagues revealed almost similar

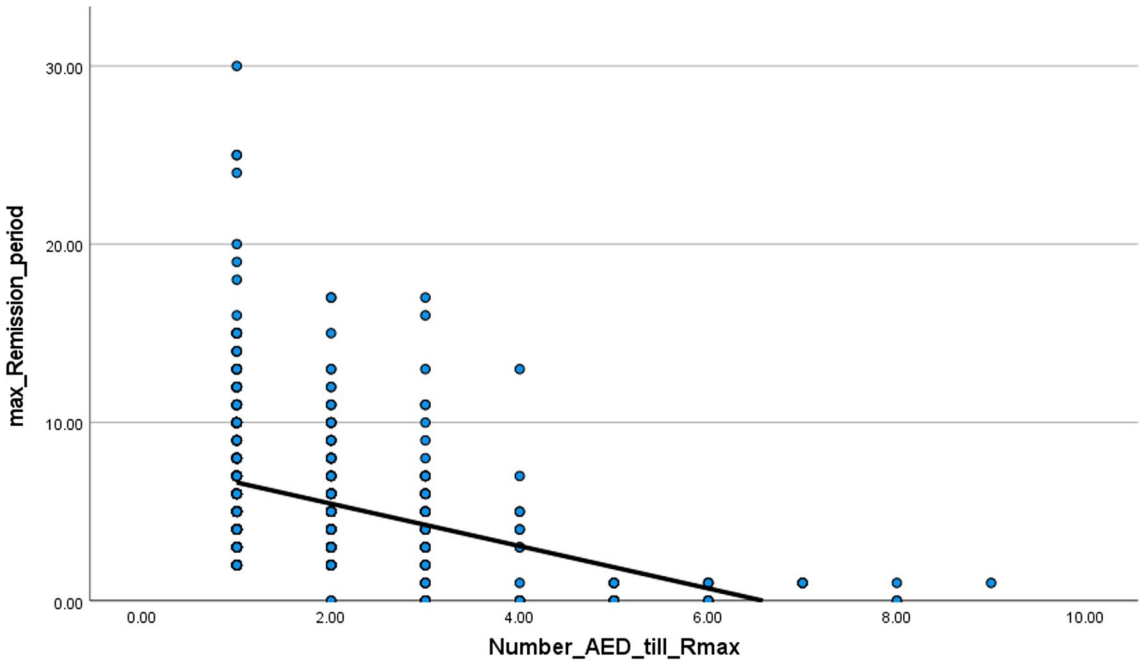

Fig. 1 Correlation between number of AEDs till achievement of maximum remission period and maximum remission period

results [14]. They identified 118 drug-responsive controls and drug-resistant cases with IGE and concluded that female catamenial seizures were an independent predictor of poor outcomes.

The EEG in GGE usually shows the classical findings of Generalized spike wave discharges which often appear fragmented during sleep and can have focal features. However, persistent focal epileptiform activity of focal slowing should not be seen in GGE [15]. A photoparoxysmal response in the form of spike wave complexes with intermittent photic stimulation can be detected in patients with GGE [15]. EEG activity is defined as runs of generalized discharges more than 3 s [16].

Focal EEG features and active EEG were significantly associated with polytherapy Gelisse and colleagues concluded that there was no prognostic impact of focal features in EEG in patients with IGE [17]. In prospective research, EEG characteristics did not influence the outcome [18]. Persistent EEG abnormalities after ASMs withdrawal were independent predictors of seizure relapse, according to other studies [19, 20].

The dose of VPA needed to achieve the first remission significantly differed between the monotherapy and polytherapy groups ($p < 0.001$). According to the multivariable analysis, VPA resistance was substantially related to the requirement for multiple drugs to accomplish the first remission (OR: 1.002, 95% CI = 1.002–1.003). This finding matches the study by Gesche and his colleagues, who concluded with almost similar results. They studied 137 adult GGE patients, 33 patients fulfilled the criteria for drug-resistant epilepsy. In addition, VPA resistance was the most significant predictive indicator for refractory seizures [21].

The fundamental limitation of our research is that the data were obtained retrospectively, making it hard to create a predetermined standard classification of our prognostic criteria. All participants, however, had detailed clinical and EEG recordings, and patients were reevaluated at the end of the long-term follow-up, with the clinical course documented. The assignment of the first ASM in newly diagnosed patients was not randomized, preventing us from making conclusions on the comparative effectiveness of drugs administered at the time of diagnosis.

Conclusions

The majority of GGE have a favorable outcome. Absence seizures, clusters of seizures, seizure frequency before treatment, and dose of sodium valproate until the first remission were independent predictors for polytherapy. Moreover, absence seizures, seizure frequency before treatment, VPA dose, and catamenial seizures in females were independent predictors of intractability.

Abbreviations

ASM	Antiseizure medication
CAE	Childhood absence epilepsy
CI	Confidence interval
EEG	Electroencephalography
GGE	Genetic generalized epilepsy
GTC	Generalized tonic clonic
IBM	International Business Machines
IGE	Idiopathic generalized epilepsy
ILAE	International League Against Epilepsy
JAE	Juvenile absence epilepsy
JME	Juvenile myoclonic epilepsy
MAS	Myoclonic astatic seizures
NCSE	Non-convulsive statue epilepticus
OR	Odds ratio
SSPS	Statistical Package for the Social Sciences
USA	United States of America
VLP	Valproate

Acknowledgements
The authors acknowledge subjects for their participation and cooperation in this study.

Author contributions
HH, NE and HA contributed to the conception, design, drafting, and revising of the manuscript. MA contributed to data acquisition. MA and HA contributed to data analysis and interpretation. All authors read and approved the final manuscript.

Funding
No funding was received for this research.

Availability of data and materials
The data used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Permission from Neurology department, Cairo University ethical committee was obtained on April 2019.

Consent for publication
Not applicable.

Competing interests
The authors have no conflict of interests to disclose.

Received: 21 October 2022 Accepted: 28 December 2022
Published online: 10 January 2023

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