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Female preponderance in genetic generalized epilepsies

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ABSTRACT

Introduction: Epilepsy is more prevalent in men but Genetic Generalized Epilepsies (GGE) seem to be more common in women. A predominant maternal inheritance has been previously described in GGE. Our objective was to determine sex and inheritance patterns in a GGE population compared to mesial temporal lobe epilepsy with hippocampal sclerosis (MTLEHS).

Methods: We performed a prospective observational study including adult GGE and MTLEHS patients followed up at a tertiary epilepsy center from January 2016 to December 2019. Patients' familial history was obtained by a detailed questionnaire. Clinical and demographic data was retrieved from clinical notes.

Results: A cohort of 641 patients, 403 with GGE and 238 with MTLEHS, was analyzed. GGE was more common in women than MTLEHS (58.8% vs 44.5%, OR=1.63, $p = 0.004$). Compared to MTLEHS patients, more GGE patients had familial history of epilepsy (45.4% vs 25.2%; $p<0.001$). The GGE group had a higher percentage of female relatives with epilepsy (55% vs 37%; $p = 0.006$). The prevalence of maternal inheritance was not different between GGE and MTLEHS groups (62.9% vs 57.7%; $p = 0.596$). Photosensitivity was more common in females than in males (44.7% vs 34.3%, $p = 0.036$).

Conclusion: There is a female preponderance in GGE when compared to MTLEHS, as both GGE patients and their affected relatives are more frequently women. The prevalence of maternal inheritance was not higher in GGE than in MTLEHS.

1. Introduction

Epilepsy is a common neurological disorder affecting 45.9 million individuals worldwide[1]. Sex is usually not considered a susceptibility factor for epilepsy, but differences in epilepsy incidence and prevalence between men and women have been reported[2-6]. It is slightly more prevalent in men (329.3 per 100.000 population) than in women (318.9 per 100.00 population)[1]. Men with epilepsy have higher disability-adjusted life-years rates (201.2 per 100.000 population) and higher mortality rates (2.09 per 100,000) than women (163.6 per 100,000 population and 1.4 per 100,000, respectively)[1]. This male preponderance remains across the lifespan and increases in people aged older than 75 years[1]. This difference between sex prevalence could be partially explained by higher frequency of epilepsy risk factors in males, such as traumatic brain injury[7] and vascular brain disease[8,9]. However, the influence of sex in epilepsy manifestation needs to be clarified, and studies looking for sex differences in the prevalence of specific epileptic syndromes are lacking[4,10].

Genetic Generalized Epilepsies (GGEs) are a group of epilepsy syndromes that encompass Childhood Absence Epilepsy (CAE), Juvenile Absence Epilepsy (JAE), Juvenile Myoclonic Epilepsy (JME) and Generalized Tonic-Clonic Seizures Alone (GTCSA)[11], and represent 20 to 50% of all epilepsies[1,4,12,13]. These were previously called Idiopathic Generalized Epilepsies, but that term was replaced for GGE in the recent classification of epilepsies proposed by the International League Against Epilepsy (ILAE)[11] due to the preponderant role of genetic

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factors involved in its etiology[14]. Accordingly, relatives of patients with GGE have a 8.3-fold increased risk of developing GGE compared with the general population, while relatives of patients with focal epilepsy have a 2.5-fold increase[12]. However, despite a high familial aggregation, very few cases of GGE are explained by simple Mendelian inheritance and most have a genetically complex pattern of inheritance with modest penetrance[15].

Not in accordance with epilepsy in general, the incidence and prevalence of GGE is slightly higher in women than in men[4,16-19]. A maternal preponderance was also previously described in GGE, meaning that offspring have a higher risk of having epilepsy if their mother had epilepsy rather than their father[10,12,17,20,21]. Therefore, it is not known if maternal inheritance has clinical implications for offspring or if it is the female sex that carries a higher susceptibility risk for epilepsy.

The primary objective of this study was to compare the prevalence of female sex in GGE patients with a control group consisting in Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis (MTLEHS) patients, a focal epilepsy. MTLEHS is a structural syndrome regarded as an acquired epilepsy within which the contribution of genetic factors is scarce, although genetic susceptibility was described[22] and familial forms are very rare[23,24]. The secondary objectives were to determine maternal inheritance prevalence in both groups and to compare other demographic and clinical data.

2. Methods

Adult patients with previous diagnosis of GGE and MTLEHS followed up at the Epilepsy/Neurology outpatient clinic of Hospital de Santo António, Centro Hospitalar Universitário do Porto, in the North of Portugal, were consecutively included from January 2016 to December 2019. Alone or with the help of their relatives, patients were invited to fill in a questionnaire where they should discriminate all their relatives with epilepsy or febrile seizures, their sex and degree of kinship. Patients were consecutively included and none refused to complete the questionnaire. Patients' demographic and clinical data (sex, age, age at seizure onset, report of photosensitivity [only in GGE patients], past history of febrile seizures and report of focal or generalized seizures in the last year) were retrieved from clinical data. A patient with persistent seizures in the last year despite having tried at least two appropriate anti-seizure medications (ASMs) was considered to have refractory epilepsy[25].

Epilepsy syndromes were reviewed from clinical notes and were classified according to the International Classification of Epilepsies and Epileptic Syndromes criteria by combining seizure types, age at onset and electroencephalogram (EEG) patterns[11] in JAE, JME and GTCSA. CAE was not considered because the study was performed in patients from an adult epilepsy clinic. All GGE patients had at least one interictal EEG with generalized paroxysmal discharges, and a normal cerebral tomography and/or brain magnetic resonance imaging (MRI). MTLEHS diagnosis was based on clinical data, electrophysiological studies (interictal and/or ictal EEG and/or video-EEG monitoring) and brain MRI (minimum 1.5 Tesla) according to the ILAE criteria[26]. Patients with bilateral MTLEHS were also included.

Relatives were accounted for until the third degree of kinship. If a patient had only a fourth degree relative with epilepsy, his family history was considered negative. A maternal inheritance was considered if the relatives with epilepsy were the mother of patient, siblings of mother, parents of mother, grandparents of mother, direct uncles or aunts of mother, nieces or nephews of mother or if the patient was female and had affected children or affected grandchildren. A mixed inheritance was considered if the patient had affected relatives in both the mother's and father's family. An undetermined inheritance was considered if the patient had only siblings affected.

Levene's test was used to study homogeneity of variances and Kolmolgorov-Smirnov was used to inspect normality of continuous variables. Student *t*-test was used to compare means across two or more groups. Mean and standard deviation are reported except when stated otherwise. Chi-square test was applied to analyze the relationship between two categorical variables. Logistic regressions were performed to analyze the influence of sex and other covariates specified in tables 2 to 5. Results were deemed significant if 2-sided p-value was inferior to 0.05. All statistics were performed using IBM Statistical Package for Social Sciences (SPSS) Statistics 23.

The study was approved by the Ethics Committee of Centro Hospitalar Universitário do Porto and all patients gave their written informed consent according to the Declaration of Helsinki.

3. Results

3.1. General characterization

Demographic, clinical and inheritance data is detailed on table 1. We inquired a total of 641 patients, 403 with GGE and 238 with MTLEHS. Mean age was 35.6 ± 14.0 and 50.6 ± 14.5 years and mean age of seizure onset was 12.7 ± 7.2 and 14.5 ± 11.4 years in GGE and MTLEHS patients, respectively (table 1). When analyzing GGE syndromes, 89 patients (22.1%) had JAE (67.4% female), 204 (50.6%) had JME (58.3% female), and 110 (27.3%) had GTCSA (52.7% female). Photosensitivity was reported in 163 (40.4%), history of febrile seizures in 64 (15.9%), and refractory epilepsy in 113 (28.0%) patients (table 1).

As expected, the MTLEHS group had a higher prevalence of refractory epilepsy (75.6% vs 28.0%; $p<0.001$) and febrile seizures (52.9% vs 15.9%, $p<0.001$) than the GGE group (table 2). Female sex was significantly more common in the GGE group than in the MTLEHS group (58.8% vs 44.5%, OR=1.63, $p = 0.004$) (table 2). Sex was not significantly different among GGE subgroups ($p = 0.110$, not shown).

Table 1
Demographic, clinical and inheritance data by epilepsy type.

	GGE (n = 403)	MTLEHS (n = 238)
Female sex	237 (58.8%)	106 (44.5%)
Age, years (mean ± SD)	35.6 ± 14.0	50.6 ± 14.5
Age of onset, years (mean ± SD)	12.7 ± 7.2	14.5 ± 11.4
Refractory epilepsy	113 (28.0%)	180 (75.6%)
Febrile seizures	64 (15.9%)	126 (52.9%)
Photosensitivity	163 (40.4%)	Non-applicable
GGE syndromes		
– JAE	89 (22.1%)	Non-applicable
– JME	204 (50.6%)	Non-applicable
– GTCSA	110 (27.3%)	Non-applicable
Patients with positive family history	183 (45.4%)	– 1.64 ± 0.93
– Paternal inheritance	– 56 (30.6%)	– 21 (35.0%)
– Maternal inheritance	– 95 (51.9%)	– 28 (46.7%)
– Mixed/undetermined inheritance	– 32 (17.5%)	– 11 (18.3%)
– Maternal inheritance excluding mixed/undetermined inheritance	– 95 (62.9%)	– 28 (57.1%)
– Patients with first-degree relatives with epilepsy	– 95 (62.9%)	– 20 (33.3%)
– Number of affected relatives (mean ± SD)	– 1.64 ± 0.93	– 1.55 ± 0.75
– Number of affected female relatives (mean ± SD)	– 0.84 ± 0.73	– 0.53 ± 0.62
– Proportion of affected relatives who are female (mean ± SD)	– 0.55 ± 0.44	– 0.37 ± 0.44
Number of relatives with epilepsy (total)	301	93

GGE, Genetic Generalized Epilepsies; GTCSA, Generalized Tonic-Clonic Seizures Alone; MTLEHS, Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis; JAE, Juvenile Absence Epilepsy; JME, Juvenile Myoclonic Epilepsy; SD, standard deviation.

Table 2
Clinical characteristics by epilepsy type.

	GGE (n = 403)	MTLEHS (n = 238)	OR	95% CI	p-value
Female sex	237 (58.8%)	106 (44.5%)	1.63	1.17 – 2.27	0.004
Age of onset, years (mean ± SD)	12.7 ± 7.2	14.5 ± 11.4	0.98	0.97 – 1.00	0.073
Refractory epilepsy	113 (28.0%)	180 (75.6%)	8.40	5.61 – 12.60	<0.001
Febrile seizures	64 (15.9%)	126 (52.9%)	6.21	4.07 – 9.50	<0.001
Positive family history of epilepsy	183 (45.4%)	60 (25.2%)	2.30	1.61 – 3.28	<0.001

CI, confidence interval; OR: odds ratio; SD, standard deviation.

3.2. Family history and inheritance

We inquired the whole group about relatives with history of epilepsy. Among GGE patients, 183 (45.4%) had a positive family history of epilepsy, and the number of relatives with epilepsy was 301, resulting in a total of 704 people with epilepsy (table 1). Compared to MTLEHS, a significantly higher proportion of patients with GGE had a positive family history of epilepsy (45.4% vs 25.2%, OR=2.30, p<0.001) (table 2). Percentage of family history was not significantly different between JAE, JME and GTCSA (p = 0.524, not shown). Patients with MTLEHS had 93 relatives with epilepsy, resulting in a total of 331 people with epilepsy.

Our population had a globally high prevalence of maternal inheritance. When excluding mixed or undetermined inheritances, maternal inheritance was observed in 62.9% of GGE and in 57.7% of MTLEHS patients, but this difference was not statistically significant (p = 0.471, not shown). When taking mixed or undetermined inheritances into account, maternal inheritance was observed in 51.9% of GGE and in 46.7% of MTLEHS patients (p = 0.471, table 3). However, the GGE group had a significantly higher prevalence of female patients than the MTLEHS group (65.0% vs 48.3%, OR=1.85, p = 0.045), and also a higher prevalence of first degree relatives with epilepsy (51.4% vs 40.0%; p = 0.038) (table 3).

Analyzing only the GGE group, a positive familial history did not predict any clinical characteristic, namely female sex (p = 0.220), age of seizure onset (p = 0.588), refractory epilepsy (p = 0.467), history of febrile seizures (p = 0.940) or photosensitivity (p = 0.219) (table 4). In GGE patients with a positive family history of epilepsy, the pattern of inheritance was also not related to sex (p = 0.335), age of seizure onset (p = 0.859), refractory epilepsy (p = 0.449), history of febrile seizures (p = 0.793) or photosensitivity (p = 0.171) (table 5).

Table 3
Clinical and inheritance characteristics by epilepsy type in patients with a positive familial history of epilepsy.

	GGE (n = 183)	MTLEHS (n = 60)	OR	95% CI	p-value
Female sex	119 (65.0%)	29 (48.3%)	1.85	1.01 – 3.40	0.045
Age of onset, years (mean ± SD)	11.9 ± 7.2	13.6 ± 9.1	0.98	0.94 – 1.01	0.139
Presence of 1st degree relatives	94 (51.4%)	24 (40.0%)	2.06	1.04 – 4.06	0.038
Paternal inheritance	56 (30.6%)	21 (35.0%)	1	–	–
Maternal inheritance	95 (51.9%)	28 (46.7%)	1.28	0.51 – 3.23	0.596
Mixed/undetermined inheritance	32 (17.5%)	11 (18.3%)	1.78	0.72 – 4.35	0.210

CI, confidence interval; GGE, Genetic Generalized Epilepsies; MTLEHS, Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis; OR: odds ratio; SD, standard deviation.

Table 4
Clinical characteristics by presence of family history of epilepsy in patients with Genetic Generalized Epilepsies.

	Positive family history (n = 183)	Negative family history (n = 220)	OR	95% CI	p-value
Female sex	119 (65.0%)	118 (53.6%)	1.49	0.79 – 2.80	0.220
Age of onset, years (mean ± SD)	11.9 ± 7.2	13.4 ± 7.1	0.99	0.95 – 1.03	0.588
Refractory epilepsy	59 (32.3%)	54 (24.5%)	0.79	0.42 – 1.49	0.467
Febrile seizures	34 (18.6%)	30 (13.6%)	0.97	0.45 – 2.09	0.940
Photosensitivity	75 (41.0%)	88 (40.0%)	0.67	0.37 – 1.26	0.219

CI, confidence interval; OR: odds ratio; SD, standard deviation.

Table 5
Clinical characteristics by pattern of inheritance in patients with Genetic Generalized Epilepsies and a positive familial history of epilepsy.

	Maternal (n = 95)	Paternal (n = 56)	OR	95% CI	p-value
Female sex	58 (61.1%)	(67.9%)	0.70	0.35 – 1.44	0.335
Age of onset, years (mean ± SD)	12.1 ± 7.5	12.1 ± 7.1	1.01	0.96 – 1.06	0.859
Refractory epilepsy	33 (34.7%)	16 (28.5%)	0.76	0.37 – 1.56	0.449
Febrile seizures	18 (18.9%)	11 (19.6%)	1.12	0.47 – 2.70	0.793
Photosensitivity	42 (44.2%)	19 (33.9%)	0.61	0.30 – 1.24	0.171

CI, confidence interval; OR: odds ratio; SD, standard deviation.

The mean number of relatives with epilepsy per patient was 1.62 ± 0.89 and was not different between GGE and MTLEHS groups (1.64 ± 0.93 *vs* 1.55 ± 0.75, p = 0.773) (table 1). GGE patients had a higher mean proportion of affected relatives who were women when compared with MTLEHS patients (0.55 ± 0.44 *vs* 0.37 ± 0.44; p = 0.006). This was also true when patients with maternal inheritance were excluded (mean 0.47 ± 0.44 in GGE patients vs 0.27 ± 0.42 in MTLEHS patients; p = 0.024) (not shown). The detailed number of relatives with epilepsy can be found in table 6.

3.3. Photosensitivity

In our cohort, 40.4% of GGE patients had photosensitivity. It was more common in female than in male patients (44.7% vs 34.3%; p = 0.036) and, as expected, more common in JME patients than in JAE or GTCSA patients (51.5%, 29.3%, 28.3% respectively, p<0.001) (not shown). No differences were observed in photosensitivity frequency comparing patients with and without family history (41.0% vs 40.0%). Also, photosensitivity was not affected by the mode of inheritance (44.2% in maternal inheritance vs 37.5% in non-maternal inheritance patients; p = 0.356) (not shown).

4. Discussion

In our study we demonstrated that there is a female preponderance in GGE patients (58.8% were women), whereas in the MTLEHS group sex differences were more balanced (44.5% were women). Several studies have addressed sex differences in epilepsy with contradictory results. Some authors found no sex-based differences in epilepsy prevalence[27,28], whilst the majority defend that in general epilepsy seems to be slightly more prevalent in males[1,29-31]. Although information

Table 6
Detailed number of relatives with epilepsy.

	GGE (n = 403)	MTLEHS (n = 238)
Number of relatives with epilepsy	301	93
Number of 1st degree relatives with epilepsy	112 (37.2%)	25 (26.9%)
– Number of fathers with epilepsy	– 19 (17.0%)	– 4 (16%)
– Number of mothers with epilepsy	– 24 (21.4%)	– 4 (16%)
– Number of brothers with epilepsy	– 24 (21.4%)	– 9 (36%)
– Number of sisters with epilepsy	– 35 (31.2%)	– 4 (16%)
– Number of sons with epilepsy	– 5 (4.5%)	– 4 (16%)
– Number of daughters with epilepsy	– 6 (5.4%)	– 0 (0%)
Number of 2nd degree relatives with epilepsy	99 (32.9%)	29 (31.2%)
– Number of paternal uncles with epilepsy	– 14 (14.1%)	– 5 (17.2%)
– Number of paternal aunts with epilepsy	– 9 (9.1%)	– 4 (13.8%)
– Number of paternal grandfathers with epilepsy	– 2 (2%)	– 2 (6.9%)
– Number of paternal grandmothers with epilepsy	– 6 (6.1%)	– 0 (0%)
– Number of maternal uncles with epilepsy	– 23 (23.2%)	– 8 (27.6%)
– Number of maternal aunts with epilepsy	– 20 (20.2%)	– 5 (17.3%)
– Number of maternal grandfathers with epilepsy	– 20 (20.2%)	– 2 (6.9%)
– Number of maternal grandmothers with epilepsy	– 19 (19.2%)	– 3 (10.3%)
Number of 3rd degree relatives with epilepsy	90 (29.9%)	39 (41.9%)

GGE, Genetic Generalized Epilepsies; MTLEHS, Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis.

on the mechanisms underlying these observations is scarce, it is thought that individual life experiences and intrinsic biological sex differences may be important. One possible explanation is that the most common risk factors for epilepsy, such as traumatic brain injury and stroke, are more prevalent in men[7-9]. On the contrary, GGE and its syndromes seem to be more common in women[4,16,18,19], but this association remains unexplained. In our study we observed that GGE patients were not only more commonly female, but also had a higher percentage of relatives with epilepsy who were women, when compared to MTLEHS patients, and this result was still true after accounting for the effect on sex of maternal inheritance. This implies that women express epilepsy more easily than men in genetically susceptible families.

There are numerous possible mechanisms that might explain this female sex preponderance, and they probably compete together. Genetic, epigenetic and environmental factors may act in the prenatal period, modulating brain development and increasing the risk of neurodevelopment disorders such as epilepsy, and leading to a higher expression of GGE in females. As GGE have a genetic etiology, it can be argued that genetic and epigenetic factors that are involved in sexual dimorphisms in brain morphology connectivity may partially explain these differences. For instance, women have a generally thicker cortex and higher gray matter volumes in the frontal cortex than men, a structural difference that also characterizes JME[32,33]. Subcortical structures such as *substantia nigra pars reticulata* and *locus coeruleus*, which are known to be especially involved in generalized seizures, are also anatomically and functionally different depending on sex and age [33-35]. Furthermore significant sex-specific DNA methylation differences in brain development were observed between genders in human fetal brain samples, and the X-chromosome was associated with higher methylation levels than the Y-chromosome[36,37]. Early hormonal exposure may also confer a sex-specific risk for GGE. Steroid hormones are involved in maturation of several brain structures, such as hypothalamus and hippocampus[38] and in perinatal synaptic development, influencing differently the expression of neurotransmitters[29]. They also modulate neural excitability, as they are generally considered to have a pro-convulsive effect throughout life[39]. Studies in gonadectomized epilepsy models show that the role of sex hormones in brain architecture establishment early in life may be more important than its plasma levels in adulthood[40]. All these female-related factors are therefore important to brain maturation and connectivity and may trigger epilepsy manifestation in genetic susceptible individuals at a specific early age.

We failed to prove a maternal preponderance in GGE when compared to MTLEHS, which is in accordance with a recent population-based study conducted by Ellis[41]. This is a matter of ongoing debate, as several studies found a maternal inheritance predominance in GGE and also in focal epilepsies[10,12,17,21]. In this study, we could not find a different prevalence of maternal inheritance between GGE and MTLEHS probably because maternal inheritance is associated with epilepsy as a whole and not with specific epileptic syndromes. Nevertheless, independently of the existence of a maternal pattern of inheritance, women seem to develop GGE more commonly than men.

Photosensitivity is described in GGE patients and is known to be less common in GTCSA or JAE than in JME, where it may occur in 30 to 75% of the patients[42,43]. In our cohort it was clinically present in 40.4% of GGE patients and in 51.5% of JME patients. Photosensitivity is believed to have an autosomal dominant inheritance but we did not find a higher prevalence of family history in patients with photosensitivity compared to patients without it. Photosensitivity was more common in female patients and also in JME than in JAE or GTCSA, as expected.

A strength of our study is that it was a prospective work performed in a genetic homogeneous population in the North of Portugal and we studied two very well-defined epileptic syndromes that avoided clinical and genetic heterogeneity.

Our study carries some limitations. It was conducted in a single tertiary epilepsy center, and the results may be more difficult to extrapolate to other populations. Another limitation is that there was a significant difference in the sample size of the studied groups. However, it is unlikely that these aspects have influence in the distribution of sex or inheritance. Information was obtained through a questionnaire answered by the patients, therefore it is possible that some relatives who were considered to have epilepsy do not have it in fact and, on the opposite, some relatives that have epilepsy may have not disclosed it. This is especially relevant for MTLEHS patients, who were older and had more refractory epilepsy than GGE patients, which could be associated with more difficulties in remembering details about family history of epilepsy. We tried to minimize this effect by asking the patient's companion in the consultation (generally a family member) to help fulfilling the questionnaire.

5. Conclusion

Different from epilepsy as a whole, where the prevalence is slightly higher in male, there is a female sex preponderance in GGE. Both GGE patients and their affected relatives are more frequently women, implying a higher expression of GGE in the female sex. A high prevalence of maternal inheritance was found in GGE and MTLEHS groups, but it was not significantly different between them. In line with previous works, photosensitivity was more prevalent in women. Sex must be considered a susceptibility factor for GGE and photosensitivity, but further studies are needed to clarify the role of sex in epilepsy manifestation.

Declaration of Competing Interest

None.

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