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Sex-based electroclinical differences and prognostic factors in epilepsy with eyelid myoclonia

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Abstract

Although a striking female preponderance has been consistently reported in epilepsy with eyelid myoclonia (EEM), no study has specifically explored the variability of clinical presentation according to sex in this syndrome. Here, we aimed to investigate sex-specific electroclinical differences and prognostic determinants in EEM. Data from 267 EEM patients were retrospectively analyzed by the EEM study group, and a dedicated multivariable logistic regression analysis was developed separately for each sex. We found that females with EEM showed a significantly higher rate of persistence of photosensitivity and eye closure sensitivity at the last visit, along with a higher prevalence of migraine with aura, whereas males with EEM presented a higher rate of borderline intellectual functioning/intellectual disability. In female patients, multivariable logistic regression analysis revealed age at epilepsy onset, eyelid myoclonia status epilepticus, psychiatric comorbidities and catamenial seizures as significant predictors of drug resistance. In male patients, a history of febrile seizures was the only predictor of drug resistance. Hence, our study reveals sex-specific differences both in terms of electroclinical features and prognostic factors. Our findings support the importance of a sex-based personalized approach in epilepsy care and research, especially in genetic generalized epilepsies.

Introduction

Epilepsy with eyelid myoclonia (EEM), previously known as Jeavons syndrome, is a generalized genetic epilepsy (GGE) syndrome characterized by the classical triad of prominent eyelid myoclonia (EM), photosensitivity (PS) and eye closure sensitivity (ECS).[1] The clinical description of EEM has been expanded during the past years and distinct EEM sub-phenotypes have been identified, characterized by different age at onset, electroclinical features and neuropsychiatric profiles.[2,3]

A striking female preponderance has been described along the entire EEM continuum, with a female to male ratio ranging from 2:1 to 4:1, and has been considered a disease hallmark in this heterogenous epilepsy syndrome.[4] In spite of this prominent female predominance, no study has investigated the sex differences in terms of both electroclinical features and prognostic factors in EEM. Conversely, previous studies in juvenile myoclonic epilepsy (JME) highlighted relevant differences in clinical presentation according to sex, with female patients displaying higher rates of absence seizures, PS and reflex seizures.[5] The importance of a sex-stratified approach in GGE was further supported by recent results highlighting the prognostic impact of catamenial seizures in JME and other GGE syndromes.[5-7] Moreover, the recent limitations introduced by worldwide regulatory agencies for the use of valproate (VPA) in female patients of childbearing potential, and the consequent differences in antiseizure medication (ASM) exposure, once again highlighted the prognostic relevance of sex across different GGE syndromes.[8,9]

In this study, by the ongoing EEM study group, we aimed to explore the occurrence of electroclinical differences according to sex and investigate the possible existence of sex-specific prognostic determinants in EEM.

Methods:

Study participants and data collection

Through the ongoing EEM study group, we collected the clinical data of 313 individuals followed for at least 24 months from 1983 to 2020, recruited retrospectively from 20 sites across 9 countries. Institutional/regional ethics committees approved this study and signed consent was obtained from all participants or their parents/caregivers.

Patients were enrolled according to the following criteria, previously described elsewhere:[4] 1) EM with or without absences; 2) history of PS and/or ECS; 3) EEG generalized spike-wave discharges (SWDs) and/or polyspike-wave discharges (PWDs); 4) normal neuroimaging (when available). Patients with sporadic myoclonia in body regions other than the eyelids were included, provided that EM represented the predominant seizure type. To avoid the enrollment of patients with a definite developmental or epileptic encephalopathy, individuals with cognitive deficits other than borderline intellectual functioning and mild intellectual disability (ID) were excluded.

Clinical, EEG and outcome assessment

Clinical charts were thoroughly examined to gather demographic information, family history of epilepsy in 1st and 2nd degree relatives, history of febrile seizures (FS), psychiatric comorbidities, history of migraine with or without aura, age at epilepsy onset, seizure types experienced (including EM status epilepticus), history of self-induced seizures, and catamenial worsening of seizures. We also examined drug regimen changes, treatment adherence and response to ASMs. For every patient, we recorded the presence of borderline intellectual functioning and/or mild ID, as determined by the Wechsler Intelligence Scale for children or adults, depending on the age at

standardized investigation. Standard EEGs were analyzed to identify SWDs and PWDs with their corresponding frequencies, ECS and/or PS, and focal epileptiform abnormalities.

The primary outcome was the occurrence of drug resistance at the last follow-up visit, as defined by the International League Against Epilepsy (ILAE).[10] The recurrence of epileptic seizures as a probable consequence of poor adherence to treatment and/or attempts at ASM tapering/withdrawal was considered as "pseudo-resistance" and did not contribute to the outcome definition.

Statistical analysis

Descriptive statistic methods and data visualization were used to assess data distribution. Comparisons of demographic and electroclinical variables between males and females were performed with independent sample t-test and the Mann-Whitney U test in cases of normal and non-normal distribution, respectively. Comparisons across proportions were performed with Fisher's exact test. To investigate the sex-specific factors associated with drug resistance, a dedicated multivariable logistic regression model was developed separately for each sex (M1 model for females, M2 model for males). All variables showing a p value < 0.2 at univariable analysis were included in the multivariable model, whereas follow-up duration was retained in both models as a potential confounder.

Results

Demographic and electroclinical differences according to sex

A total of 267 patients (195 females) were included in the present study.[4] Female and male EEM patients did not differ in terms of age at epilepsy onset, follow-up duration, and age at the last follow-up visit (Table 1). Female patients showed a significant higher rate of ECS ($p=0.02$) and PS persistence ($p<0.001$) at the last visit, combined with a higher rate of a history of migraine ($p=0.047$), whereas male patients showed a higher rate of intellectual disability/borderline intellectual functioning ($p=0.025$) (Table 1).

The two groups did not differ in terms of the number of ASMs used during follow-up (p=0.4). VPA use at the last visit was significantly more frequent in males compared to females (p<0.001), whereas levetiracetam (LEV) was significantly more used in the latter group (p=0.048). No significant differences between females and males were found in the use of other ASMs. See table 1 for a detailed comparison of demographic and clinical characteristics, including ASM use, between females and males (Table 1).

Sex-specific determinants of drug resistance

Drug resistance at the last follow-up visit did not significantly differ according to sex, although was found to be slightly higher in females [88/195 (45.1%) vs 27/72 (37.5%), p=0.3)].

In female patients, the M1 model revealed that age at epilepsy onset, catamenial seizures, psychiatric comorbidities and eyelid myoclonia status epilepticus were significantly associated with drug-resistance, whereas a borderline statistical significance was found for self-induced seizures (area under the curve -AUC- of the multivariable model = 0.71). In male patients, the M2 model showed that a personal history of febrile seizures (FS) was the only factor associated with drug resistance (AUC = 0.62). See Table 2 for odds ratios and confidence intervals of both multivariable models (Table 2).

Discussion

In this study we highlighted the existence of electroclinical differences between female and male EEM patients and we identified sex-specific determinants of drug resistance.

When focusing on electroclinical differences, female EEM patients showed a higher prevalence of several EEG markers of occipital cortex hyperexcitability, namely ECS and PS persistence at the last visit.[11,12] Similarly, female patients in our cohort also displayed a higher rate of migraine with/without aura, a condition in which the primary role of occipital cortex excitability has been repeatedly demonstrated.[13] Based on these observations, we might hypothesize a sexual dimorphism

in occipital cortex excitability, which may also account for the striking female preponderance observed in this epilepsy syndrome.[11] A similar sex-based difference in cortical excitability has been observed in other GGE syndromes characterized by female preponderance. In particular, a higher excitability of the motor cortex was found in female patients with JME using transcranial magnetic stimulation.[14] The specific role of genetic, epigenetic and hormonal factors in determining these differences should be further investigated.

In this study, we also found a higher rate of cognitive abnormalities (when considering together intellectual disability and borderline intellectual functioning) in male patients compared with females, suggesting a possible contribution of X-linked variants on cognitive functioning in EEM.[15] When considering ASM treatment, we documented systematic differences in ASM exposure between females and males, showing a significantly higher use of LEV in the former group and a higher use of VPA in the latter, as observed in other GGE syndromes.[16]

In the present study, prognostic factors previously identified in EEM (namely eyelid myoclonia status epilepticus, age at epilepsy onset and psychiatric comorbidities),[3,4,17] could be confirmed in females only. Conversely, FS, which appeared as a strong predictor of a reduced chance of sustained remission in EEM,[2] was found to be associated with the outcome only in the male sex. Based on this observation, we might hypothesize that physiological sex differences could confer distinct protection against early-life neurological insults, such as FS, as suggested in preclinical studies.[18] However, the impact of genetic variants predisposing to both drug resistance and FS cannot be excluded.

Moreover, we highlighted for the first time the impact of catamenial seizures on seizure outcome in EEM, similarly to what has been increasingly observed in other GGE syndromes, particularly in JME.[5-7]

Finally, when comparing the discriminative ability of the logistic regression models, we found a better AUC in females compared to male patients, suggesting that other unmeasured variables could play a role in the development of drug resistance in male EEM patients.

The retrospective design of our study represents the most important limitation in the interpretation of our findings, whereas the large sample size and the multicenter design with 18 epilepsy centers may support their generalizability. Moreover, the lower use of VPA in females may partially explain some of the electroclinical differences observed, especially regarding the significant higher rate of PS and migraine, considering the well-known role of this ASM in the treatment of these conditions.[8,9]

In conclusion, our study confirms the relevance of a sex-personalized approach in epilepsy care and research and paves the way for future studies exploring the underlying pathophysiological and biological significance of the observed sex-specific differences. A clinical and research approach based on sex could be of paramount importance in the context of GGE, considering the striking differences in terms of sex distribution observed in some syndromes and the prognostic relevance of sex-based factors (i.e., catamenial seizures).

Table 1. Comparison of demographic and clinical characteristics according to sex

	Females (195 patients)	Males (72 patients)	p value
Age at epilepsy onset, years, median (IQR)	7 (5-10)	8 (5-10)	1
Follow-up duration, years, median (IQR)	14 (9-24)	14 (7.2-23.8)	0.8
Age at the last follow-up visit, median (IQR)	22 (17-31)	21 (17-31.7)	0.4
Family history of epilepsy in 1st or 2nd degree relatives, n (%)	57 (29.2)	26 (36.1)	0.3
Personal history of febrile seizures, n (%)	22 (11.2)	8 (11.1)	1
Borderline intellectual functioning and or mild intellectual disability, n (%)	51 (26.2)	29 (40.3)	0.025*
Migraine with or without aura, n (%)	32 (16.4)	5 (6.9)	0.047*
Psychiatric comorbidities, n (%)	44 (22.6)	18 (25)	0.7
Seizure types experienced during history			
Generalized tonic-clonic seizures, n (%)	133 (68.2)	49 (68.1)	1
Myoclonia in body districts other than eyelid, n (%)	45 (23.1)	13 (18.1)	0.4
Eyelid myoclonia status epilepticus, n (%)	26 (13.5)	9 (12.7)	0.8
Provoking factors			
Self-induced seizures, n (%)	35 (17.9)	13 (18.1)	1
Catamenial worsening of seizures, n (%)	23 (11.8)	0	
ECS at any time during follow-up, n (%)	156 (80)	51 (70.8)	0.13
PS at any time during follow-up, n (%)	66 (91.7)	66 (91.8)	1
ECS persistence at the last visit, n (%)	82 (48.8)	19 (30.2)	0.02*
PS persistence at the last visit, n (%)	109 (60.2)	19 (31.1)	<0.001*
EEG features			
Polyspike-wave discharges, n (%)	140 (71.8)	52 (72.2)	0.9
Focal spikes, n (%)	38 (19.5)	16 (22.2)	0.6
ASM treatment			
ASM tried during history, median (IQR)	2 (2-4)	3 (2-4)	0.4
Valproate use at the last visit, n (%)	92 (47.2)	54 (75)	<0.001*
Levetiracetam use at the last visit, n (%)	77 (39.5)	19 (26.4)	0.048*

Abbreviations : ASM = antiseizure medication ; ECS = eye closure sensitivity ; EEM = Epilepsy with eyelid myoclonia ; EO = early onset ; IO = intermediate onset ; LO = late-onset ; PS = photosensitivity. Note : The asterisks indicate statistically significant variables ($p<0.05$).

Table 2. Prognostic factors for drug resistance based on sex according to two distinct multivariable logistic regression models

Multivariable model developed for female patients (M1)			
Predictor	OR	95% CI	p value
Age at epilepsy onset	0.88	0.81-0.97	0.008*
Follow-up duration	0.98	0.96-1.10	0.2
Psychiatric comorbidities	2.33	1.1-4.94	0.03*
Eyelid myoclonia status epilepticus	2.78	1.12-6.94	0.03*
History of self-induced seizures	2.29	0.99-5.31	0.053
Catamenial worsening of seizures	2.67	1.02-7.04	0.047*
Multivariable model developed for male patients (M2)			
Predictor	OR	95% CI	p value
Follow-up duration	1.01	0.97-1.04	0.8
History of self-induced seizures	2.31	0.63-8.51	0.2
History of febrile seizures	6.19	1.12-34.26	0.04*

Abbreviations : CI = confidence interval ; OR = odd ratio. Note : The asterisks indicate statistically significant variables ($p<0.05$).

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.

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Data availability statement: Anonymized data can be made available upon reasonable request.

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