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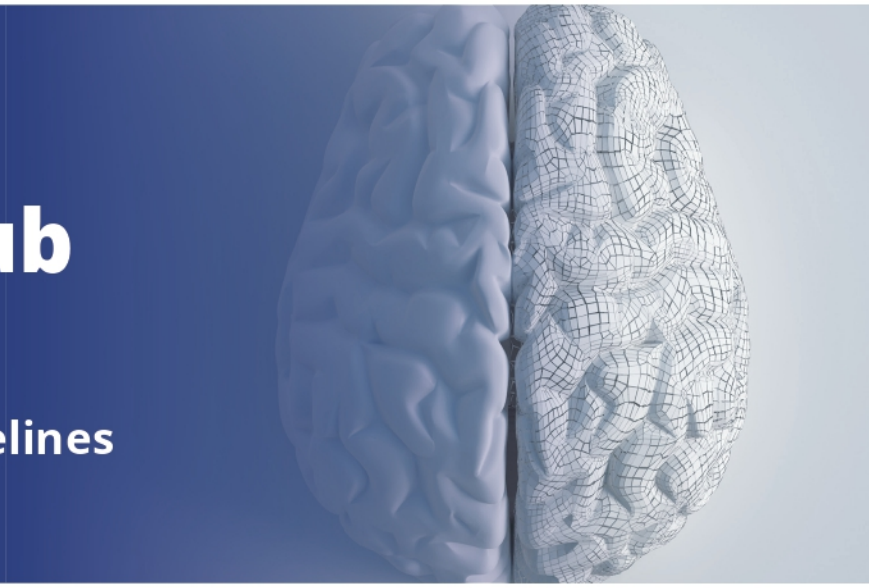

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The spectrum of epilepsy with eyelid myoclonia: delineation of disease subtypes from a large multicenter study

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Abstract

Objective: Epilepsy with eyelid myoclonia (EEM) has been associated with marked clinical heterogeneity. Early epilepsy onset has been recently linked to lower chances of achieving sustained remission and to a less favorable neuropsychiatric outcome. However, much work is still needed to better delineate this epilepsy syndrome.

Methods: In this multicenter retrospective cohort study, we included 267 EEM patients from 9 countries. Data about electroclinical and demographic features, intellectual functioning, migraine with or without aura, family history of epilepsy and epilepsy syndromes in relatives were collected in each patient. The impact of age at epilepsy onset (AEO) on EEM clinical features was investigated, along with the distinctive clinical characteristics of patients showing sporadic myoclonia over body regions other than eyelids (body-MYO).

Results: Kernel density estimation revealed a trimodal distribution of AEO and Fisher-Jenks optimization disclosed three EEM subgroups: early-onset (EO-EEM), intermediate-onset (IO-EEM) and late-onset subgroup (LO-EEM). EO-EEM was associated with the highest rate of intellectual disability, antiseizure medication refractoriness and psychiatric comorbidities and with the lowest rate of family history of epilepsy. LO-EEM was associated with the highest proportion of body-MYO and generalized tonic-clonic seizures (GTCS), whereas IO-EEM had the lowest observed rate of additional findings. A family history of EEM was significantly more frequent in IO-EEM and LO-EEM compared with EO-EEM. In the subset of patients with body-MYO (58/267), we observed a significantly higher rate of migraine and GTCS but no relevant differences in other electroclinical features and seizure outcome.

Significance: Based on AEO, we identified consistent EEM subtypes characterized by distinct electroclinical and familial features. Our observations shed new light on the spectrum

of clinical features of this generalized epilepsy syndrome and may help clinicians towards a more accurate classification and prognostic profiling of EEM patients.

Introduction

The definition of epilepsy with eyelid myoclonia (EEM), previously known as eyelid myoclonia with absences (EMA) or Jeavons Syndrome, has always been considered a conundrum, especially regarding its recognition as a specific epilepsy syndrome to be set apart from juvenile myoclonic epilepsy (JME) and other idiopathic/genetic photosensitive epilepsies.[1] Eye closure sensitivity (ECS), photosensitivity (PS) and eyelid myoclonia (EM) represent the core electroclinical features of EEM and can also be found in other epilepsy syndromes.[2,3] Nonetheless, growing evidence from EEG, functional magnetic resonance imaging and genetic studies favor the concept of EEM as an epilepsy syndrome distinct from other idiopathic generalized epilepsies (IGEs) and genetic generalized epilepsies (GGEs).[4-6] The International League Against Epilepsy (ILAE) has recently proposed a new classification for GGE, viewed as a complex spectrum of syndromes, encompassing IGEs (namely childhood absence epilepsy, juvenile absence epilepsies, JME and generalized tonic-clonic seizures alone) - which represent a distinct group, and other generalized syndromes, including EEM.[7]

However, much work is yet to be done to better outline the limits of EEM and characterize the electroclinical features of people with this condition. Several EEM electroclinical features, including both seizure types (i.e., EM) and activating conditions (namely PS and ECS), greatly overlap with other IGEs and photosensitive idiopathic/genetic epilepsies, including JME, perioral myoclonia with absences and idiopathic photosensitive occipital lobe epilepsy.[8,9] Due to previous case reports showing some clinical overlap between EEM and JME, with patients described to evolve from one condition to the other,[10] several authors preferred, on the one hand, to consider body-MYO (however rare) as an exclusion criterion for EEM,[8] and, on the other, to exclude patients with prominent EM and only sporadic body-MYO from JME cohorts.[11] Furthermore, after the first clinical description by Jeavons,[12] marked clinical heterogeneity has been reported in the context of EEM itself, beyond body-MYO.[1] A variable proportion of subjects can develop self-induced seizures and EM status epilepticus during follow-up, and a variable degree of intellectual disability (ID) has been reported in different cohorts.[13,14] Although the underlying genetic background is likely to play a major role in this clinical heterogeneity, other contributors still need to be explored.

The age of onset has always been considered an important factor in defining homogenous disease subtypes in several neuropsychiatric disorders, with relevant clinical, familial and biological differences.[15-17] In the context of EEM, the age at epilepsy onset (AEO) has been typically described during mid-childhood, although seizures may begin from early infancy to late adolescence.[18-19] In a previous paper by our study group, we highlighted the prognostic relevance of AEO, with earlier onset patients showing a lower chance of achieving sustained remission at long-term follow-up.[20]

Here, we first aimed to explore through statistical modeling the distribution of AEO in EEM patients, to identify distinct disease subgroups according to AEO. Second, we aimed to determine if EEM patients with sporadic body-MYO represent a distinct entity within the

EEM spectrum, by comparing the electroclinical characteristics of EEM patients with and without sporadic body-MYO.

Methods:

Study participants

Through the ongoing EMA study group, we collected the clinical data of 313 individuals followed from 1983 to 2020 recruited retrospectively from 20 sites across 9 countries. Institutional/regional ethics committees gave approval for this study and informed consent was obtained from all participants or their parents/caregivers.

Patients were enrolled according to the following criteria: 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 also included, as long as EM represented the predominant seizure type. Patients with predominant myoclonia in cranial regions other than eyelids were excluded, to avoid including patients with perioral/periorbital myoclonia with absences. Individuals with cognitive deficits other than borderline intellectual functioning and mild ID were excluded to avoid the enrollment of patients with a definite developmental/epileptic encephalopathy. Patients with a follow-up period (from the first antiseizure medication -ASM- prescription to the last visit) shorter than 24 months were also excluded, to allow a better prognostic characterization of the study participants. The clinical data of each patient were reviewed by ECI, CDB and PS to confirm the diagnosis of EEM according to the inclusion and exclusion criteria, as previously specified.

Clinical and EEG assessment

All medical charts and EEGs were reviewed to obtain demographic and electroclinical data, as previously described.[20] The occurrence of migraine with or without aura was also noted in each patient. The presence of borderline intellectual functioning and/or mild ID, as established by the Wechsler Intelligence Scale for children or adults, depending on the age at standardized investigation, was recorded for each patient. In addition, we created an extended pedigree for each participant reporting a family history of epilepsy, including the number of first- and second-degree relatives with epilepsy, and their specific epilepsy syndrome, based on patients' or relatives' interview, where applicable.

The presence of PS and/or ECS was defined as the occurrence of brief SWD/PWDs appearing within 1-3 seconds and lasting 1-4 seconds after eye closure. These should be clearly distinguishable from fixation-off sensitivity, defined as the occurrence of occipital or generalized epileptiform discharges induced by elimination of central vision and fixation. PS and/or ECS were mainly assessed by reviewing EEG recordings, provided that at least one EEG was available for each patient. However, to avoid an underreporting of ECS/PS in those patients who first presented to the outpatient clinic after remission of these epilepsy traits, we also took into account their occurrence based on clinical grounds alone.

For each patient the occurrence of 2-year remission from all seizure types during history, as well as the number and type of ASMs tried over time was evaluated. According to the definition by Kamitaki and colleagues, the failure of at least two adequately prescribed ASMs during history was regarded as ASM refractoriness, whereas patients with "rare breakthrough seizures due to missed doses of medication and occasional nondisabling myoclonic seizures if these did not necessitate a change in management" were considered ASM-responsive.[21] The following ASMs were considered as adequately prescribed in the treatment of EEM: valproate, lamotrigine, ethosuximide, zonisamide, topiramate, levetiracetam, phenobarbital, primidone, clonazepam, clobazam and perampanel. Finally, seizure recurrence after ASM

withdrawal was investigated in patients with ≥ 12-month follow-up after ASM discontinuation.

Statistical analysis

Data were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) according to their normal or non-normal distribution, respectively. As regards AEO, the Kernel Density Estimation (KDE) was used to investigate its distributional pattern and assess the possible occurrence of multimodality.[22] Subsequently, the Fisher-Jenks algorithm was used to identify the optimal cut-offs to split the data and outline the underlying AEO-dependent clusters. Fisher-Jenks algorithm represents a class interval analysis that naturally integrates the KDE multimodal analysis. This algorithm improves the minimum distance analysis performed through K-Means, especially for unidimensional data.[23] The identified AEO-related subgroups were compared by the Kruskal-Wallis or one-way ANOVA test in case of continuous variables and by the Fisher-Exact test in case of nominal variables. Finally, comparisons of the electroclinical characteristics between patients with or without body-MYO were performed by the Fisher Exact Test in case of nominal variables, whereas the Mann-Whitney U test and the unpaired-T test were used to compare continuous variables in case of their non-normal or normal distribution, respectively. Values of $p<0.05$ were considered statistically significant. Analyses were performed and figures were generated using R 3.5.1 (R Project for Statistical Computing, Vienna, Austria).

Results

Demographic Data

Of the 313 EEM patients initially recruited, 267 were included according to the study methods. Reasons for exclusion were unconfirmed diagnosis of EEM in 35 cases and inadequate follow-up duration in 11.

The median AEO across the entire cohort was 7 years (IQR 5-10). When considering the specific seizure types, the median age at onset was 7 years (IQR 5-10) for EM, 12 years (IQR 10-15) for GTCS, and 14 years (IQR 8-17) for body-MYO (Figure 1).

Kernel density estimation revealed a trimodal distribution of AEO across the entire cohort (Figure 2), and Fisher-Jenks algorithm defined 6.5 years and 10.5 years as the best cut-offs for splitting the data into three AEO-dependent subgroups (Figure 2), namely: early-onset EEM (EO-EEM), including 118 patients (44.2%) with a mean AEO of 4.3 years (standard deviation -SD-) ± 1.54, intermediate-onset EEM (IO-EEM), including 87 patients (32.6%) with AEO of 8.5 years (SD ± 1.07), and late-onset EEM (LO-EEM), including 62 patients (23.2%) with AEO of 13.1 years (SD ± 1.76).

Clinical characteristics

The AEO subgroups did not differ in terms of sex distribution, follow-up duration, personal history of febrile seizures, self-induced seizures and EM status epilepticus. EO-EEM showed a higher rate of mild ID (p=0.002) and psychiatric comorbidities (p=0.009), whereas IO-EEM had the highest rates of family history of epilepsy in 1st- and 2nd-degree relatives (p=0.01). Finally, LO-EEM was associated with a higher rate of GTCS (p=0.006) and more frequently experienced body-MYO (p=0.03). A family history of EEM was more frequent in IO-EEM and LO-EEM compared with EO-EEM (p=0.02). As to EEG findings, the only significant difference between the groups lay in the proportion with persistent PS at the last follow-up, which was higher in EO-EEM (p=0.04). The detailed clinical characteristics of the three AEO subgroups are illustrated in Table 1 (Table 1).

When focusing on body-MYO, we found that 58 individuals (21.7%) experienced them at some point during the disease course, but in only one case were they the presenting seizure type. In patients with body-MYO (from now on referred to as 'body-MYO+' patients), the

age at onset of both EM and GTCS was significantly higher compared with the other study participants (Figure 3). In addition, a family history of both EEM (8.6% vs 4.8%, p=0.3) and JME (5.2% vs 1.9%, p=0.2) was slightly more common in body-MYO+ patients, whereas the proportion of participants with epilepsy in 1st- and 2nd-degree relatives did not vary with the presence of body-MYO.

Body-MYO+ patients were more likely to develop GTCS during follow-up (p=0.002) and report migraine with/without aura compared with the other study participants (p<0.001). Other clinical characteristics, including history of borderline intellectual functioning or mild ID, febrile seizures, psychiatric comorbidities, EM status epilepticus and self-induced seizures did not differ according to the presence of body-MYO (Table 2).

Finally, a similar proportion of patients with and without body-MYO had ECS and PS both at disease onset and at the last follow-up, and the rate of focal EEG findings was also comparable between these two subgroups (Table 2). Conversely, bursts of PWDs were recorded in a lower proportion of body-MYO+ patients compared with the remaining cohort (59.3% vs 73.9%, p=0.036).

ASM treatment and seizure outcome

The three AEO-subgroups did not differ in terms of ASMs used at first and last medical observation, except for lamotrigine, which was significantly more frequently used as first-line monotherapy in LO-EEM (Supplementary figure, S1). ASM withdrawal was more frequently attempted in IO-EEM compared with the two other subgroups (EO-EEM 33.1% vs IO-EEM 44.8% vs LO-EEM 25.8%, p=0.046), whereas seizure recurrence after withdrawal did not differ significantly between AEO-subgroups (EO-EEM 73.7% vs IO-EEM 74.4% vs LO-EEM 73.3%, p=1).

ASM refractoriness was found to be significantly more frequent in EO-EEM compared with IO-EEM and LO-EEM [EO-EEM: 75/118 (63.6%) vs IO-EEM: 41/87 (47.1%) vs LO-EEM: 31/62 (50%), p=0.04], and a trend towards statistical significance was also observed for higher rates of polytherapy regimen (≥ 2 ASMs) at the last follow-up visit in the same subgroup [EO-EEM: 60/118 (50.8%) vs IO-EEM: 30/87 (34.5%) vs LO-EEM: 27/62 (43.5%), p=0.06]. Two-year remission during history appeared slightly more common – though not significantly - among individuals who were older at epilepsy onset [EO-EEM: 68/118 (57.6%) vs IO-EEM: 55/87 (63.2%) vs LO-EEM: 35/62 (72.6%), p=0.1].

When focusing on body-MYO, the only significant difference in ASM trials lay in the use of ethosuximide at the last follow-up visit, which was less common among body-MYO+ patients compared with the rest of the cohort (1.9% vs 16%, p=0.005). ASM refractoriness, 2-year remission during history and recurrence after ASM withdrawal did not differ according to the presence of body-MYO during follow-up (see Table 2).

Genetic data

A total of 24/267 (9%) patients in the study cohort underwent whole exome sequencing. Among them, 6 patients harboured pathogenic variants in CHD2, two patients in NEXMIF and one in SCN8A.

Discussion

Clinical characteristics and family history of epilepsy according to AEO

In this study, we highlighted the existence of remarkable electro-clinical differences among EEM patients according to AEO. Through statistical modeling on the largest cohort of EEM patients so far reported, we demonstrated that AEO displays a trimodal distribution, thus revealing three different EEM subtypes. Indeed, in several medical conditions age at onset

has been previously identified as an important factor in defining homogenous disease clusters, with crucial genetic, clinical and prognostic implications.[15-17,24]

The largest group identified was EO-EEM, which was characterized by the highest rates of ID, psychiatric comorbidities and ASM refractoriness. Further than confirming previous findings as to the negative impact of early age at onset in this epilepsy syndrome, both in terms of neuropsychiatric profile and seizure outcome,[14,20] we identified for the first time a significant correlation between AEO and family history of epilepsy. Indeed, EO-EEM patients showed the lowest rate of family history of epilepsy compared with the other subgroups, suggesting a likely more prominent role of *de novo* mutations in this EEM subtype, as hypothesized for other epilepsies and neurodevelopmental disorders.[25,26] Conversely, the higher frequency of positive family history of EEM found in both IO-EEM and LO-EEM suggests a stronger influence of inherited genetic burden in these two subtypes.

LO-EEM was the smallest group, including patients with epilepsy onset during adolescence. Adolescent-onset EEM had the highest rates of body-MYO and GTCS over the course of the disease, suggesting that these patients may lay at the farthest end of the EEM spectrum, at the border of IGE, as hypothesized in the latest classification framework proposed by ILAE.[27] Finally, IO-EEM could be considered in all respects as the "pure" EEM sub-phenotype, characterized by electro-clinical findings consistent with the original description by Jeavons.[12]

A striking female preponderance, as well as high rates of PS, ECS, febrile seizures, EM status epilepticus and self-induced seizures, were found in all AEO-dependent subgroups, thus emerging as consistent hallmarks along the entire EEM continuum.[28]

Is EEM with sporadic myoclonia in other body regions a distinct clinical entity?

EEM associated with sporadic body-MYO has been classically considered as an intermediate phenotype between EEM and JME. In the present study we provided an extensive electro-clinical characterization of patients with body-MYO, revealing striking electroclinical differences between them and previously reported JME cohorts.[29-31] First, febrile seizures appeared more frequent in our body-MYO+ patients (as well as in the whole study population) compared with well-defined cohorts of JME and other IGEs, reinforcing the hypothesis of a shared genetic background between EEM and generalized epilepsies with febrile seizures plus.[32] Second, body-MYO+ patients showed strikingly higher rates of PS, ECS, borderline intellectual functioning and ID compared with JME, as well as higher rates of EM status epilepticus and self-induced seizures.[29-31]

Conversely, we did not observe remarkable familial, electroclinical and prognostic differences between body-MYO+ and body-MYO- participants. Overall, our data suggest that body-MYO+ patients should be set apart from JME since they suit well the complex continuum of EEM.

Nevertheless, a few phenotypic traits beyond the AEO mentioned above differed between body-MYO+ patients and the rest of our cohort. In particular, the significantly lower rate of PWDs, along with the higher proportion of patients showing GTCS in the body-MYO+ subgroup, suggests a peculiar pathophysiological background in these patients. In line with this hypothesis, we also found a significant association between migraine with/without aura and a history of body-MYO, as recently observed in a large cohort of idiopathic/genetic epilepsies as well.[33]

EEM as a spectrum disorder

In a previous paper by our study group,[20] we outlined two distinct EEM sub-phenotypes which differed to a great extent in terms of electroclinical features and long-term outcome:

namely, the "EEM-plus" subgroup, with lower AEO, high rates of ID and ASM refractoriness, and the "EEM-only" subgroup, showing a more favorable prognostic profile. In the present study, after expanding the initial cohort by including patients with body-MYO, we confirmed the existence of remarkably different AEO-dependent sub-phenotypes. Interestingly, the EO-EEM cluster greatly overlaps with the previously described "EEM-plus" subgroup, with respect to its neuropsychiatric profile and seizure outcome, and shares clinical features with developmental and epileptic encephalopathies (DEEs). Conversely, IO-EEM is akin to the above-mentioned "EEM-only", considering its "pure" phenotype and the favorable response to ASMs. In addition, in this study we could identify a third subgroup, i.e., LO-EEM, more closely resembling the clinical and family features of JME, in spite of its distinct traits.

Overall, our data suggest that EEM should be considered as a spectrum disorder, encompassing a wide range of disease subtypes characterized by a variable combination of different ages at epilepsy onset, family history of epilepsy, seizure types, response to treatment, neuropsychiatric profiles, and neurological comorbidities. Our findings showed, once again, the thin line - and overlapping borders – existing between and within different clinical entities in the context of generalized epilepsies.[34-36]

Limitations and conclusions

The main limitation of our study arises from the lack of systematic genetic testing, which could have helped us interpret our findings, especially regarding the identified EEM subtypes. In addition, our retrospective study design entails several potential confounders, especially recall and inclusion biases, with the potential enrollment of some patients with EEM look-alike syndromes (e.g., perioral myoclonia with absences, Sunflower syndrome, JME and childhood absence epilepsy evolving to JME). In addition, the long follow-up of the

study along with its retrospective nature prevented us from collecting more detailed information regarding seizure recurrence after ASM withdrawal (e.g., number and type of ASMs, age, and duration of seizure freedom at the time of withdrawal, etc.), which may have helped us in the interpretation of data about seizure recurrence. Furthermore, we decided to exclude patients with moderate/severe ID, to avoid including patients with clear-cut DE/DEE, who could have biased our analyses regarding the age at epilepsy onset; however, the exclusion of these patients may have prevented us from defining the entire spectrum of EEM subphenotypes.

Finally, the epilepsy syndrome of the participants' relatives was identified mainly through patients' interviews, possibly determining some classification errors. Conversely, the large sample size and the multicenter design represent the main strengths of our study.

In conclusion, through an innovative statistical approach, we identified homogenous EEM subtypes according to AEO, characterized by distinct electroclinical and familial features. Our observations shed new light on the spectrum of clinical features of this generalized epilepsy syndrome and may help clinicians towards a more accurate classification and prognostic profiling of EEM patients.

Key points

-Epilepsy with eyelid myoclonia (EEM) has been recently recognized as a distinct genetic generalized epilepsy syndrome by the ILAE.

-Based on age at epilepsy onset (AEO), we identified consistent EEM subtypes characterized by distinct electroclinical and familial features.

-EEM patients showing sporadic myoclonia over body regions other than the eyelids suit well the EEM spectrum and should be distinguished from juvenile myoclonic epilepsy

-Our results pave the way to genetic studies on EEM and help clinicians towards a more accurate classification of EEM patients.

Figure captions and legends

Fig. 1 Age at onset of each seizure type

Body-MYO = myoclonia involving body districts other than eyelids; EM = eyelid myoclonia; GTCS = generalized tonic-clonic seizures;

Fig. 2 Distribution according to age at epilepsy onset and underlying clusters

PANEL A: Kernel density estimation revealing three underlying modes according to age at epilepsy onset; PANEL B: Fisher-Jenks algorithm showing the optimal cut-off for patient classification into three distinct clusters (early, intermediate, late) according to age at epilepsy onset.

Fig. 3 Age at onset of different seizure types in patients with sporadic myoclonia over body regions other than eyelids (body-MYO+) compared to the remaining cohort (body-MYO-)

EM = eyelid myoclonia; GTCS = generalized tonic-clonic seizures.

Table 1. Clinical characteristics according to age at onset subgroup

	EO-EEM (118 pts)	IO-EEM (87 pts)	LO-EEM (62 pts)	p value
Sex, female (%)	89 (75.4)	61 (70.1)	45 (72.6)	0.7
Age at epilepsy onset, years, median (IQR)	5 (3-6)	9 (7-9)	13 (11.7-14)	<0.001*
Follow-up duration, years, median (IQR)	16 (11-24)	13 (8-24)	13 (6.8-22)	0.28
Age at the last follow-up visit, median (IQR)	21 (14-29)	22 (17-32)	24 (18-34)	0.01*
Family history of epilepsy in 1st or 2nd degree relatives, n (%)	27 (22.9)	37 (42.5)	19 (30.6)	0.01*
Family history of EEM, n (%)	2 (1.7)	9 (10.3)	5 (8.1)	0.02*
Family history of febrile seizures, n (%)	12 (10.2)	8 (9.2)	3 (4.8)	0.5
History of febrile seizures in 1st and 2nd degree relatives, n (%)	16 (13.7)	8 (9.2)	6 (9.7)	0.5
Borderline intellectual functioning, n (%)	26 (22)	13 (14.9)	8 (12.9)	0.2
Mild intellectual disability, n (%)	24 (20.3)	6 (6.9)	3 (4.8)	0.002*
Migraine with/without aura, n (%)	13 (11)	10 (11.5)	14 (22.6)	0.08
Psychiatric comorbidities, n (%)	37 (31.6)	13 (13.1)	14 (22.6)	0.009*
Mood disorders, n (%)	14 (11.9)	5 (5.7)	9 (14.5)	0.2
Behavioral disorders, n (%)	20 (16.9)	6 (6.9)	5 (8.1)	0.052
Psychotic disorder, n (%)	3 (2.5)	1 (1.1)	0	0.4
Seizure types				
Generalized tonic-clonic seizures, n (%)	70 (59.3)	61 (70.1)	51 (82.3)	0.006*
Myoclonia in body districts other than eyelids, n (%)	20 (16.9)	17 (19.5)	21 (33.9)	0.03*
Eyelid myoclonia status epilepticus, n (%)	16 (13.5)	10 (11.6)	9 (14.5)	0.8
Self-induced seizures, n (%)	23 (19.5)	15 (17.2)	10 (16.1)	0.8
Catamenial worsening of seizures, n (%)	10 (11.2)	6 (9.8)	7 (15.6)	0.6
EEG features				
ECS at any time during follow-up, n (%)	89 (75.4)	68 (78.2)	50 (80.6)	0.7
PS at any time during follow-up, n (%)	110 (93.2)	80 (92)	55 (88.7)	0.6
ECS at the last follow-up visit, n (%)	44 (45.4)	35 (40.2)	22 (35.5)	0.8
PS at the last follow-up visit, n (%)	62 (52.5)	42 (48.3)	22 (35.5)	0.04*
Polyspike-wave discharges, n (%)	93 (78.8)	61 (70.9)	44 (73.3)	0.4
Focal spikes, n (%)	17 (17.2)	15 (20.5)	9 (20.5)	0.8
Seizure outcome				
ASM refractoriness, n (%)	75 (63.6)	41 (47.1)	31 (50)	0.04*
≥ 2 ASMs used at the last visit, n (%)	60 (50.8)	30 (34.5)	27 (43.5)	0.06
2-year remission during history, n (%)	68 (57.6)	55 (63.2)	35 (72.6)	0.1

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. Comparison of clinical and EEG characteristics according to the presence or not of sporadic myoclonia over body regions other than eyelids

	Body-MYO (58 pts)	No-Body-MYO (209 pts)	p value
Sex, female (%)	45 (77.6)	150 (71.8)	0.4
Age at epilepsy onset, years, median (IQR)	8.5 (6-13)	7 (5-10)	0.02*
Follow-up duration, years, median (IQR)	15.5 (10.7-26)	14 (8-23)	0.1
Age at the last follow-up visit, median (IQR)	24 (18-33)	21 (16-30)	0.04*
Family history of epilepsy in 1st or 2nd degree relatives, n (%)	19 (32.8)	64 (30.6)	0.7
Family history of EEM, n (%)	5 (8.6)	11 (5.3)	0.4
Family history of JME, n (%)	3 (5.2)	4 (1.9)	0.2
History of febrile seizures in 1st or 2nd degree relatives, n (%)	8 (13.8)	15 (7.2)	0.1
Personal history of febrile seizures, n (%)	7 (12.3)	23 (11)	0.8
Borderline intellectual functioning, n (%)			
Mild intellectual disability, n (%)	11 (19)	22 (10.5)	0.08
Migraine with or without aura, n (%)	16 (27.6)	21 (10)	<0.001*
Psychiatric comorbidities, n (%)	13 (22.8)	49 (23.8)	0.9
Mood disorders, n (%)	8 (13.8)	21 (10)	0.5
Behavioral disorders, n (%)	5 (8.6)	24 (11.5)	0.6
Psychotic disorder, n (%)	0	4 (1.9)	0.6
Seizure types			
Generalized tonic-clonic seizures, n (%)	49 (84.5)	133 (63.6)	0.002*
Eyelid myoclonia status epilepticus, n (%)	7 (12.1)	28 (13.7)	0.8
Self-induced seizures, n (%)	10 (17.2)	38 (18.2)	0.9
Catamenial worsening of seizures, n (%)	7 (15.6)	16 (10.7)	0.4
EEG features			
ECS at any time during follow-up, n (%)	46 (79.3)	161 (77)	0.7
PS at any time during follow-up, n (%)	55 (94.8)	190 (90.9)	0.4
ECS at the last follow-up visit, n (%)	21 (36.2)	80 (38.3)	0.9
PS at the last follow-up visit, n (%)	27 (46.5)	99 (47.4)	1
Polyspike-wave discharges, n (%)	36 (62.1)	156 (75.7)	0.04*
Focal spikes, n (%)	15 (25.9)	39 (18.7)	0.2
Seizure outcome			
ASM refractoriness, n (%)	34 (58.6)	113 (54.1)	0.6
2-year remission during history, n (%)	38 (65.5)	130 (62.2)	0.7
ASM withdrawal attempt, n (%)	21 (36.2)	73 (34.9)	0.9
Seizure recurrence after ASM withdrawal, n (%)	17 (77.3)	54 (75)	0.8

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 ($p<0.05$).

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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Appendix: Coinvestigators EMA study group			
Name	Location	Role	Contribution
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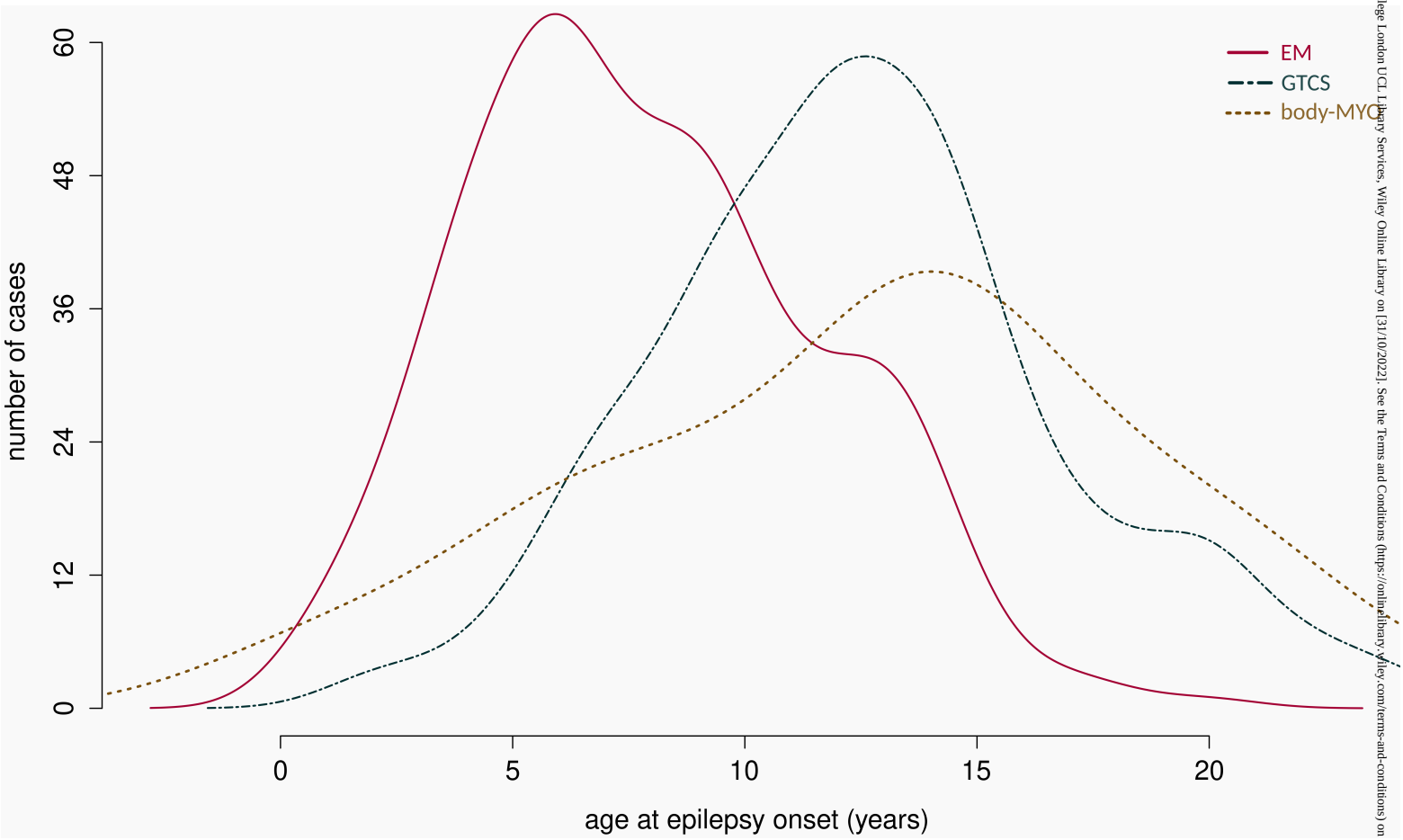

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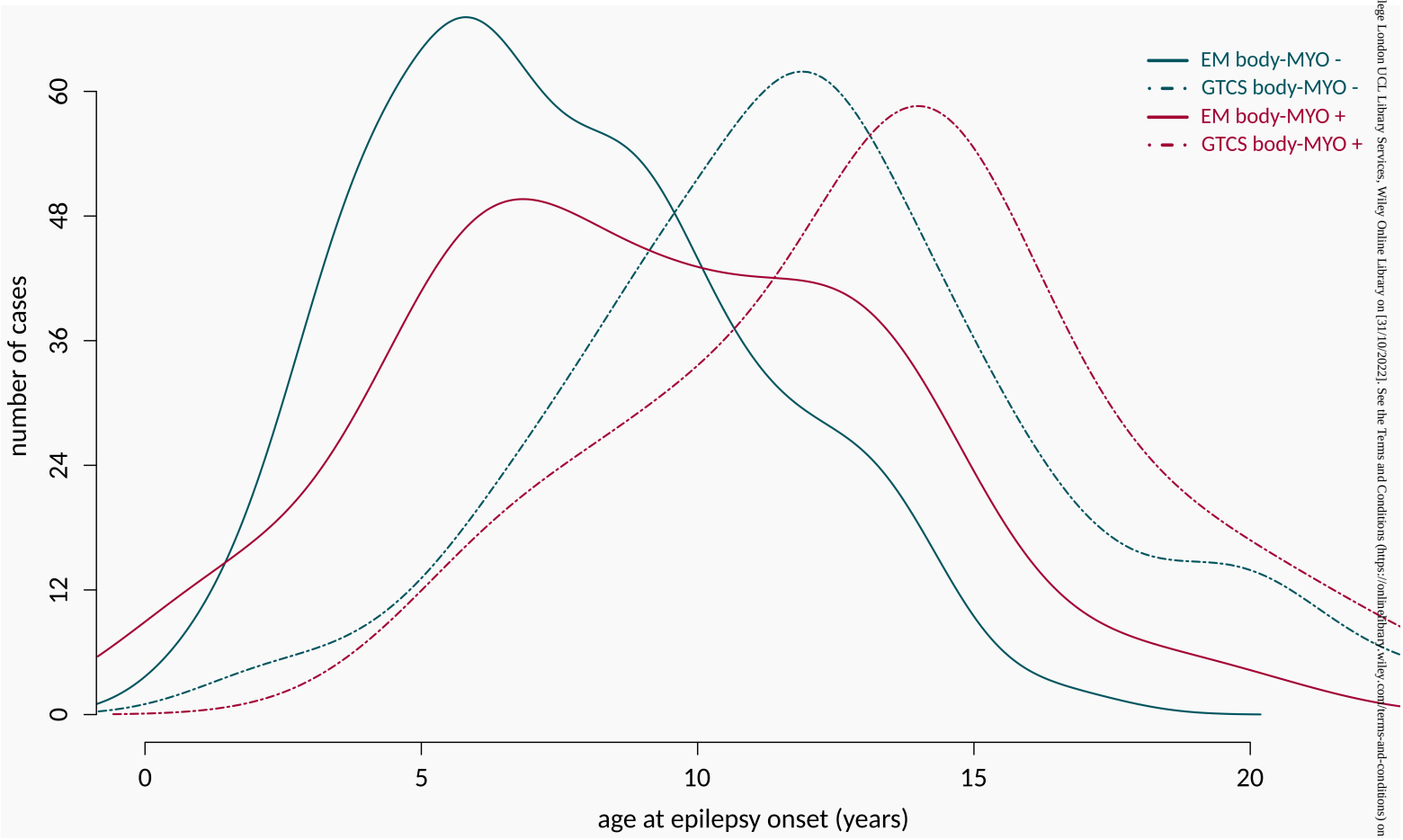

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