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

Emanuele Cerulli Irelli, MD,[1], Enrico Cocchi, MD,[2] Georgia Ramantani, MD, PhD,[3] Antonella Riva, MD,[4] Roberto H Caraballo, MD,[5] Alessandra Morano, MD, PhD[1] Loretta Giuliano, MD,[6] Tülay Yilmaz, MD,[7] Eleni Panagiotakaki, MD, PhD,[8] Francesca F Operto, MD,[9] Beatriz Gonzalez Giraldez, MD,[10] Simona Balestrini, MD, PhD,[11] Katri Silvennoinen, MD[12] Sara Casciato, MD, PhD,[13] Marion Comajuan, MD,[8] Francesco Fortunato, MD,[14] Anna T Giallonardo, MD,[1] MD, Rimma Gamirova, MD, PhD[15] Antonietta Coppola, MD, PhD,[16] Giancarlo Di Gennaro, MD, PhD,[13] Angelo Labate, MD, PhD,[14] Vito Sofia, MD,[6] Gerhard J Kluger, MD,[17] Antonio Gambardella, MD, PhD,[14] Dorothée Kasteleijn-Nolst Trenité, MD, PhD,[18] Betul Baykan, MD,[7] Sanjay M Sisodiya, MD, PhD,[12] Alexis Arzimanoglou, MD, PhD,[8] Pasquale Striano, MD, PhD,[4] Carlo Di Bonaventura, MD, PhD,[1*] on behalf of the EMA study group

1 Department of Human Neurosciences, Sapienza, University of Rome, Rome, Italy
2 Department of Precision Medicine and Genomics, Department of Medicine, Columbia University, New York
3 Department of Neuropediatrics, University Children's Hospital Zurich, Zurich, Switzerland
4 Pediatric Neurology and Muscular Diseases Unit, IRCCS Istituto “Giannina Gaslini", Genoa, Italy; Department of Neurosciences Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genoa, Genoa, Italy
5 Department of Neurology, Hospital de Pediatría "Prof. Dr. Juan P Garrahan", Buenos Aires, Argentina
6 Department of Medical and Surgical Sciences and Advanced Technologies "G.F. Ingrassia", Section of Neurosciences, University of Catania, Catania, Italy
7 Departments of Neurology and Clinical Neurophysiology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey
8 Department of Paediatric Clinical Epileptology, Sleep Disorders and Functional Neurology, University Hospitals of Lyon (HCL), Member of the ERN EpiCARE, Lyon, France
9 Child and Adolescent Neuropsychiatry Unit, Department of Medicine, Surgery and Dentistry, University of Salerno, Salerno, Italy
10 Epilepsy Unit, Neurology Service, Hospital Universitario and IIS Fundación Jiménez Díaz and CIBERER, Madrid, Spain.
11 Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, London, UK and Chalfont Centre for Epilepsy, Bucks, UK; Neuroscience Department, Meyer Children's Hospital-University of Florence, Florence, Italy
12 Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, London, UK and Chalfont Centre for Epilepsy, Bucks, UK
13 IRCCS NEUROMED, Pozzilli, Isernia, Italy.
14 Institute of Neurology, University Magna Graecia, Catanzaro, Italy
15 Kazan Federal University, Russia
16 Department of Neuroscience, Reproductive and Odontostomatological Sciences, Federico II University, Naples, Italy

17 Clinic for Neuropediatrics and Neurorehabilitation, Epilepsy Center for Children and Adolescents, Schoen Clinic Vogtareuth, Vogtareuth, Germany; PMU Salzburg, Salzburg, Austria
18 Department of Neurosurgery and Epilepsy, University Medical Center, Utrecht University, Utrecht, The Netherlands
* Corresponding author

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AUTHOR FOR CORRESPONDENCE:
Carlo Di Bonaventura
Department of Human Neurosciences
“Sapienza” University of Rome
Viale dell’Università, 30
00185 Rome, Italy
Phone: +390649914726
Fax: +390649914722
E-mail: c_dibonaventura@yahoo.it

Abstract

Background: Eyelid myoclonia with absences (EMA) 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 define this generalized epilepsy syndrome.

Methods: In this multicenter retrospective cohort study, we included 267 EMA patients from 9 countries. The impact of age at epilepsy onset (AEO) on EMA 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 EMA subgroups: early-onset (EO-EMA), intermediate-onset (IO-EMA) and late-onset subgroup (LO-EMA). EO-EMA 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-EMA was associated with the highest proportion of body-MYO and generalized tonic-clonic seizures (GTCS), whereas IO-EMA had the lowest observed rate of additional findings. A family history of EMA was significantly more frequent in IO-EMA and LO-EMA compared with EO-EMA. 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 terms of other electroclinical features and seizure outcome.

Conclusion: Based on AEO, we identified consistent EMA subtypes characterized by distinct electroclinical and familial features. Our observations highlight EMA as a model genetic generalized epilepsy syndrome, encompassing a spectrum of disease subtypes ranging from idiopathic generalized epilepsy to developmental/epileptic encephalopathy.

Introduction

The definition of eyelid myoclonia with absences (EMA) has always been considered a conundrum, especially regarding its recognition as a specific epilepsy syndrome to be set apart from juvenile myoclonic epilepsy (JME).[1] Eye closure sensitivity (ECS), photosensitivity (PS) and eyelid myoclonia (EM) represent the core electroclinical features of EMA and can also be found in JME patients.[2,3] Nonetheless, growing evidence from EEG, functional magnetic resonance imaging and genetic studies favor the concept of EMA as an epilepsy syndrome distinct from JME and other idiopathic generalized epilepsies (IGEs).[4-6] The International League Against Epilepsy (ILAE) has recently proposed a new classification for genetic generalized epilepsy (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 EMA.[7]

However, much work is yet to be done to better outline the limits of EMA and characterize the electroclinical features of people with this condition. Indeed, various sets of diagnostic criteria have been used for EMA over time, particularly heterogeneous in regard to the presence of myoclonia in body regions other than the eyelids (body-MYO).[8,9] Due to previous case reports showing some clinical overlap between EMA 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 EMA,[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 EMA 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 as 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 EMA, 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 EMA patients, in order to identify distinct disease subgroups according to AEO. Second, we aimed to determine if EMA patients with sporadic body-MYO represent a distinct entity within the EMA spectrum, by comparing the electroclinical characteristics of EMA patients with and without sporadic body-MYO.

Methods:

Study participants

Through the ongoing EMA study group, we collected the clinical data of 313 individuals 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. Individuals with cognitive deficits other than borderline intellectual functioning (BIF) 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.

Clinical and EEG assessment

All the medical charts were reviewed in order to obtain demographic and clinical data, as previously described elsewhere.[20] The presence of BIF and/or mild ID, as established by at least one standardized neuropsychological test, was recorded for each patient. In addition, for each participant reporting a family history of epilepsy an extended pedigree was reconstructed, including the number of first- and second-degree relatives with epilepsy; whenever possible, their specific epilepsy syndrome was defined based on either patients' or relatives' interview.

Standard EEGs were also reviewed in order to detect: SWDs and PWDs with their relative frequency; ECS and/or PS; focal epileptiform abnormalities.

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 recurrence of seizures after ASM withdrawal was also 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 EMA patients initially recruited, 267 were included according to the study methods. Reasons for exclusion were unconfirmed diagnosis of EMA in 35 cases and inadequate follow-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 showed 6.5 years and 10.5 years to be the best cut-offs to split the data into three AEO-dependent subgroups (Figure 2), namely: early-onset EMA (EO-EMA), including 118 patients (44.2%) with a mean AEO of 4.29 years (standard deviation -SD-) ± 1.54, intermediate-onset EMA (IO-EMA), including 87 patients (32.6%) with AEO of 8.46 years (SD ± 1.07), and late-onset EMA (LO-EMA), 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, family history of epilepsy, personal history of febrile seizures (FS), self-induced seizures and EM status epilepticus. EO-EMA showed a higher rate of mild ID (p=0.002) and psychiatric comorbidities (p=0.009), whereas IO-EMA had the highest rates of family history of epilepsy in 1st- and 2nd-degree relatives (p=0.01). Finally, LO-EMA was associated with a higher rate of GTCS (p=0.006) and more frequently experienced body-MYO (p=0.03). A family history of EMA was more frequent in IO-EMA and LO-EMA compared with EO-EMA (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-EMA (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 (hereinafter 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 EMA (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 BIF or mild ID, FS, 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 (see Table 2). Conversely, bursts of PWDs were recorded in a lower proportion of body-MYO+ patients when 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-EMA (Supplementary Figure 1). ASM withdrawal was more frequently attempted in IO-EMA compared with the two other subgroups (EO-EMA 33.1% vs IO-EMA 44.8% vs LO-EMA 25.8%, p=0.046), whereas seizure recurrence after withdrawal did not differ significantly between AEO-subgroups (EO-EMA 73.7% vs IO-EMA 74.4% vs LO-EMA 73.3%, p=1).

ASM refractoriness was found to be significantly more frequent in EO-EMA compared with IO-EMA and LO-EMA [EO-EMA: 75/118 (63.6%) vs IO-EMA: 41/87 (47.1%) vs LO-EMA: 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-EMA: 60/118 (50.8%) vs IO-EMA: 30/87 (34.5%) vs LO-EMA: 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-EMA: 68/118 (57.6%) vs IO-EMA: 55/87 (63.2%) vs LO-EMA: 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).

Discussion

Clinical characteristics and family history of epilepsy according to AEO

In this study, we highlighted the existence of remarkable electro-clinical differences among EMA patients according to AEO. Through statistical modeling on the largest cohort of EMA patients so far reported, we demonstrated that AEO displays a trimodal distribution, thus revealing three different EMA 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-EMA, 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-EMA 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 EMA subtype, as hypothesized for other epilepsies and neurodevelopmental disorders.[25,26] Conversely, the higher frequency of positive

family history of EMA found in both IO-EMA and LO-EMA suggests a stronger influence of inherited genetic burden in these two subtypes.

LO-EMA was the smallest group, including patients with epilepsy onset during adolescence. Adolescent-onset EMA 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 EMA spectrum, at the border of IGE, as hypothesized in the latest classification framework proposed by ILAE.[27] Finally, IO-EMA could be considered in all respects as the "pure" EMA 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, FS, EM status epilepticus and self-induced seizures, were found in all AEO-dependent subgroups, thus emerging as consistent hallmarks along the entire EMA continuum.[28]

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

EMA associated with sporadic body-MYO has been classically considered as an intermediate phenotype between EMA 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, FS 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 EMA and generalized epilepsies with FS plus.[32] Second, body-MYO+ patients showed strikingly higher rates of PS, ECS, BIF 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 properly belong to the complex continuum of EMA.

Nevertheless, a few phenotypic traits beyond the above-mentioned AEO 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]

EMA as a disease model of genetic generalized epilepsy

In the previous paper by our study group,[20] we outlined two distinct EMA sub-phenotypes which differed to a great extent in terms of electroclinical features and long-term outcome: namely, the "EMA-plus" subgroup, with lower AEO, high rates of ID and ASM refractoriness, and the "EMA-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-EMA cluster greatly overlaps with the previously described "EMA-plus" subgroup, with respect to its neuropsychiatric profile and seizure outcome, and shares clinical features with developmental and epileptic encephalopathies (DEEs). Conversely, IO-EMA is akin to the above-mentioned "EMA-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-EMA, more closely resembling the clinical and family features of JME, in spite of its distinct traits.

Overall, our data suggest that EMA should be considered as a spectrum disorder, which encompasses a continuum of disease subtypes ranging from IGE to DEE. Our observations are in line with the latest classification proposal by the ILAE,[7,27] which recognizes EMA as one of the GGE syndromes. In fact, EMA could be considered with good reason the 'model' GGE, located

halfway between typical IGEs and epileptic/developmental encephalopathies, and showing, once again, the thin line - and overlapping borders – existing between 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 a systematic genetic testing, which could have helped us interpret our findings, especially regarding the identified EMA subtypes. In addition, our retrospective study design entails several potential confounders, especially recall and inclusion biases. 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 EMA subtypes according to AEO, characterized by distinct electroclinical and familial features. These novel insights may help clinicians towards a more accurate classification and prognostic profiling of EMA patients. Finally, our observations suggest that EMA may be considered a model disease in the context of generalized epilepsies.

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-EMA (118 pts)	IO-EMA (87 pts)	LO-EMA (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 (10.7-24.2)	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 EMA, 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

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

Appendix: Coinvestigators EMA study group			
Name	Location	Role	Contribution
Giacomo Fisco, MD	Sapienza, University of Rome, Rome, Italy	Site investigator	Data acquisition
Stefano Meletti, md	University of Modena and Reggio Emilia, Modena, Italy	Site investigator	Data acquisition
Natalia Liukshina, MD	MIDEAL Medical Clinic, Russia	Site investigator	Data acquisition
Tatiana Tomenko, MD	European medical center UMMC-Health, Russia	Site investigator	Data acquisition
Giuseppe Gobbi, MD	IRCCS, Istituto delle Scienze Neurologiche di Bologna, Bologna, Italia	Site investigator	Data acquisition
Daniela Buti, MD	Meyer Hospital, Firenze, Italy	Site investigator	Data acquisition
Susanna Casellato, MD	University Hospital of Sassari, Sassari, Italy	Site investigator	Data acquisition
Salvatore Striano, MD, PhD	Federico II University, 80131 Naples, Italy	Site investigator	Data acquisition
Tullio Messana, MD	IRCCS, Istituto delle Scienze Neurologiche di Bologna, Bologna, Italia	Site investigator	Data acquisition
Lucio Giordano, MD	ASST Spedali Civili of Brescia, Brescia, Italy	Site investigator	Data acquisition
Edoardo Ferlazzo, MD, PhD	Magna Græcia University of Catanzaro, Catanzaro, Italy.	Site investigator	Data acquisition
Aglaia Vignoli, MD	University of Milan, Italy	Site investigator	Data acquisition
Maurizio Viri, MD	AOU Maggiore della Carità Novara, Novara, Italy	Site investigator	Data acquisition
Irene Bagnasco, MD	Marini Hospital, Torino, Italy	Site investigator	Data acquisition
Nerses Bebek, MD, PhD	Istanbul University	Site investigator	Data acquisition
Gunes Altıokka-Uzun, MD	Istanbul University	Site investigator	Data acquisition

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References

1. Striano S, Capovilla G, Sofia V, et al. Eyelid myoclonia with absences (Jeavons syndrome): a well-defined idiopathic generalized epilepsy syndrome or a spectrum of photosensitive conditions?. Epilepsia 2009;50 Suppl 5:15-19. doi:10.1111/j.1528-1167.2009.02114.x

2. Giannakodimos S, Panayiotopoulos CP. Eyelid myoclonia with absences in adults: a clinical and video-EEG study. Epilepsia 1996;37:36-44. doi:10.1111/j.1528-1157.1996.tb00509.x

3. Tekin Güveli B, Baykan B, Dörtcan N, et al. Eye closure sensitivity in juvenile myoclonic epilepsy and its effect on prognosis. Seizure 2013;22:867-871. doi:10.1016/j.seizure.2013.07.008

4. Mayo S, Gómez-Manjón I, Fernández-Martínez FJ, et al. Candidate Genes for Eyelid Myoclonia with Absences, Review of the Literature. Int J Mol Sci 2021;22:5609. Published 2021 May 25. doi:10.3390/ijms22115609

5. Vaudano AE, Ruggieri A, Tondelli M, et al. The visual system in eyelid myoclonia with absences. Ann Neurol 2014;76:412-427. doi:10.1002/ana.24236

6. Adachi M, Inoue T, Tsuneishi S, et al. Eyelid myoclonia with absences in monozygotic twins. Pediatr Int 2005;47:343-347. doi:10.1111/j.1442-200x.2005.02065.x

7. Specchio N, Wirrell EC, Scheffer IE, et al. International League Against Epilepsy classification and definition of epilepsy syndromes with onset in childhood: Position paper by the ILAE Task Force on Nosology and Definitions [published online ahead of print, 2022 May 3]. Epilepsia 2022;10.1111/epi.17241.

8. Striano S, Striano P, Nocerino C, et al. Eyelid myoclonia with absences: an overlooked epileptic syndrome?. Neurophysiol Clin 2002;32:287-296. doi:10.1016/s0987-7053(02)00343-x

9. Giuliano L, Fatuzzo D, Mainieri G, et al. Eyelid myoclonia with absences: Electroclinical features and prognostic factors. Epilepsia 2019;60:1104-1113. doi:10.1111/epi.15157

10. Destina Yalçin A, Forta H, Kiliç E. Overlap cases of eyelid myoclonia with absences and juvenile myoclonic epilepsy. Seizure 2006;15:359-365. doi:10.1016/j.seizure.2006.02.006

11. Martínez-Juárez IE, Alonso ME, Medina MT, et al. Juvenile myoclonic epilepsy subsyndromes: family studies and long-term follow-up. Brain 2006;129:1269-1280. doi:10.1093/brain/awl048

12. Jeavons PM, Clark JE, Maheshwari MC. Treatment of generalized epilepsies of childhood and adolescence with sodium valproate ("epilim"). Dev Med Child Neurol 1977;19:9-25. doi:10.1111/j.1469-8749.1977.tb08015.x

13. Darby CE, de Korte RA, Binnie CD, et al. The self-induction of epileptic seizures by eye closure. Epilepsia 1980;21:31-41. doi:10.1111/j.1528-1157.1980.tb04042.x

14. Caraballo RH, Fontana E, Darra F, et al. A study of 63 cases with eyelid myoclonia with or without absences: type of seizure or an epileptic syndrome? Seizure. 2009;18:440-445. doi:10.1016/j.seizure.2009.04.004

15. Bellivier F, Golmard JL, Henry C, et al. Admixture analysis of age at onset in bipolar I affective disorder. Arch Gen Psychiatry 2001;58:510-512. doi:10.1001/archpsyc.58.5.510

16. Naj AC, Jun G, Reitz C, et al. Effects of multiple genetic loci on age at onset in late-onset Alzheimer disease: a genome-wide association study [published correction appears in JAMA Neurol. 2014 Nov;71(11):1457]. JAMA Neurol 2014;71:1394-1404. doi:10.1001/jamaneurol.2014.1491

17. Nicolson A, Chadwick DW, Smith DF. A comparison of adult onset and "classical" idiopathic generalised epilepsy. J Neurol Neurosurg Psychiatry 2004;75:72-74.

18. Appleton RE, Panayiotopoulos CP, Acomb BA, et al. Eyelid myoclonia with typical absences: an epilepsy syndrome. J Neurol Neurosurg Psychiatry 1993;56:1312-1316. doi:10.1136/jnnp.56.12.1312

19. Smith SJM. Eyelid myoclonia with absences in adults: comparison with other absence seizures. In: Duncan JS,Panayiotopoulos CP, eds. Eyelid myoclonia with absences. London: John Libbey, 1996.

20. Cerulli Irelli E, Cocchi E, Ramantani G, et al. Electroclinical Features and Long-term Seizure Outcome in Patients With Eyelid Myoclonia With Absences. Neurology 2022;98:e1865-e1876. doi:10.1212/WNL.0000000000200165

21) Kamitaki BK, Janmohamed M, Kandula P, et al. Clinical and EEG factors associated with antiseizure medication resistance in idiopathic generalized epilepsy Epilepsia. 2022;63:150-161. doi:10.1111/epi.17104

22) Silverman BW. Using Kernel Density Estimates to Investigate Multimodality. Journal of the Royal Statistical Society: Series B (Methodological) 1981;43:97-99. doi:10.1111/j.2517-6161.1981.tb01155.x

23) Khan F. An initial seed selection algorithm for k-means clustering of georeferenced data to improve replicability of cluster assignments for mapping application. Applied Soft Computing 2012;12:3698-3700. doi:10.1016/j.asoc.2012.07.021

24. Marini C, King MA, Archer JS, et al. Idiopathic generalised epilepsy of adult onset: clinical syndromes and genetics. J Neurol Neurosurg Psychiatry 2003;74:192-196. doi:10.1136/jnnp.74.2.192

25. Epi4K Consortium; Epilepsy Phenome/Genome Project, Allen AS, et al. De novo mutations in epileptic encephalopathies. Nature 2013;501:217-221.

26. Hamdan FF, Srour M, Capo-Chichi JM, et al. De novo mutations in moderate or severe intellectual disability. PLoS Genet 2014;10:e1004772.

27. Hirsch E, French J, Scheffer IE, et al. ILAE definition of the Idiopathic Generalized Epilepsy Syndromes: Position statement by the ILAE Task Force on Nosology and Definitions [published online ahead of print, 2022 May 3]. Epilepsia 2022;10.1111/epi.17236. doi:10.1111/epi.17236

28. Covanis A. Jeavons syndrome – updated review. J Epileptol 2015;23:113-123. doi:10.1515/joepi-2015-0033

29. Baykan B, Wolf P. Juvenile myoclonic epilepsy as a spectrum disorder: A focused review. Seizure 2017;49:36-41. doi:10.1016/j.seizure.2017.05.011

30. Cerulli Irelli E, Morano A, Orlando B, et al. Seizure outcome trajectories in a well-defined cohort of newly diagnosed juvenile myoclonic epilepsy patients. Acta Neurol Scand 2022;145:314-321. doi:10.1111/ane.13556

31. Kasteleijn-Nolst Trenité DG, Schmitz B, Janz D, et al. Consensus on diagnosis and management of JME: From founder's observations to current trends. Epilepsy Behav 2013;28 Suppl 1:S87-S90. doi:10.1016/j.yebeh.2012.11.051

32. Sadleir LG, Vears D, Regan B, et al. Family studies of individuals with eyelid myoclonia with absences. Epilepsia 2012;53:2141-2148. doi:10.1111/j.1528-1167.2012.03692.x

33. Atalar AÇ, Türk BG, Ekizoglu E, et al. Headache in idiopathic/genetic epilepsy: Cluster analysis in a large cohort. Epilepsia 2022;63:1516-1529. doi:10.1111/epi.17205

34. Johannesen K, Marini C, Pfeffer S, et al. Phenotypic spectrum of GABRA1: From generalized epilepsies to severe epileptic encephalopathies. Neurology 2016;87:1140-1151. doi:10.1212/WNL.0000000000003087

35. Cerulli Irelli E, Barone FA, Mari L, et al. Generalized Fast Discharges Along the Genetic Generalized Epilepsy Spectrum: Clinical and Prognostic Significance. Front Neurol 2022;13:844674. Published 2022 Mar 10. doi:10.3389/fneur.2022.844674

36. Berkovic SF, Andermann F, Andermann E, et al. Concepts of absence epilepsies: discrete syndromes or biological continuum?. Neurology 1987;37:993-1000. doi:10.1212/wnl.37.6.993