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Electroclinical Features and Long-term Seizure Outcome in Patients With Eyelid Myoclonia With Absences

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Abstract

Background and objectives: Eyelid myoclonia with absences (EMA) is a generalized epilepsy syndrome whose prognosis and clinical characteristics are still partially undefined. We investigated electroclinical endophenotypes and long-term seizure outcome in a large cohort of EMA patients.

Methods: In this multicenter retrospective study, 172 EMA patients with ≥5 years of follow-up were recruited. Prognostic patterns and sustained terminal remission (STR) were the main outcome measures, and prognostic factors were investigated. Moreover, a two-step cluster analysis was used to investigate the presence of distinct EMA endophenotypes.

Results: Median age at epilepsy onset was 7 years (interquartile range (IQR) 5-10) and median follow-up duration was 14 years (IQR 8.25-23.75). Sixty-six patients (38.4%) displayed a non-remission pattern, whereas remission and relapse patterns were encountered in 56 (32.6%) and 50 (29.1%) subjects. Early epilepsy onset, history of febrile seizures (FS) and eyelid myoclonia (EM) status epilepticus significantly predicted a non-remission pattern according to multivariable multinomial logistic regression analysis. STR was achieved by 68 (39.5%) patients with a mean latency of 14.05 years (standard deviation ± 12.47). Early epilepsy onset, psychiatric comorbidities, and a history of FS and generalized tonic-clonic seizures (GTCS) were associated with a lower probability of achieving STR according to a Cox regression proportional hazards model. Antiseizure medication (ASM) withdrawal was attempted in 62/172 patients, and seizures relapsed in 74.2% of them. Cluster analysis revealed two distinct clusters with 86 patients each. Cluster 1, which we defined as “EMA-plus”, was characterized by an earlier age at epilepsy onset, a higher rate of intellectual disability, EM status epilepticus, self-induced seizures, FS, and poor ASM response, whereas Cluster 2, the “EMA-only” cluster, was characterized by a higher rate of seizure remission and a more favorable neuropsychiatric outcome.

Discussion: Early epilepsy onset was the most relevant prognostic factor for poor treatment response. A long latency between epilepsy onset and ASM response was observed, suggesting the impact of age-related brain changes in EMA remission. Finally, our cluster analysis showed a clear-cut distinction of EMA patients into an EMA-plus insidious subphenotype and an EMA-only benign cluster that strongly differed in terms of remission rates and cognitive outcomes.

Introduction

In 1977, Jeavons originally described an epileptic condition characterized by marked photosensitivity (PS), eye closure sensitivity (ECS), and absences associated with eyelid myoclonia (EM).[1] Following this first report, several authors have expanded the electroclinical description of Jeavons syndrome, also known as eyelid myoclonia with absences (EMA).[2-4] Nevertheless, EMA has not been recognized by the International League Against Epilepsy (ILAE) as a distinct epilepsy syndrome[5] since the features described above may be found across a range of different epilepsy syndromes, including genetic generalized epilepsies (GGE), focal genetic photosensitive epilepsies, structural epilepsies, and genetic epileptic encephalopathies.[6-10] Conversely, many authors have recognized EMA as a unique nosological entity due to its specific electroclinical features and genetic studies reinforcing the differences between EMA and other GGE syndromes.[11-15]

Due to these discrepancies, heterogenous diagnostic criteria have been used across different studies to describe the electroclinical features and prognostic characteristics of EMA.[11,16] In particular, the inclusion of patients showing myoclonia in body regions other than the eyelids by many authors may have led to the inclusion of juvenile myoclonic epilepsy (JME) patients, who share several clinical features with EMA patients, including ECS, PS, and EM.[16,17] Moreover, the majority of existing studies focusing on EMA have been conducted in small patient cohorts, leading to uncertainties regarding the true prognostic trajectories of these patients and their predictive factors. Even with strict diagnostic criteria, significant clinical heterogeneity could be observed across EMA patients.[18] Indeed, the age at onset may vary from early infancy to early adolescence, and the presence and degree of intellectual disability (ID) vary across EMA patients.[19,20] Capovilla et al. described a homogenous group of EMA patients showing antiseizure medication (ASM)

refractoriness, high rates of EM status epilepticus, and ID, suggesting the existence of distinct subphenotypes within the EMA spectrum.[21] Nevertheless, the existence of distinct EMA subgroups has not yet been investigated by modern statistical clustering approaches as applied to other neurological diseases.

The main objective of this multicenter study was to investigate seizure outcome and prognostic factors in a large cohort of well-defined EMA patients during a long-term follow-up. In addition, we used a cluster analysis approach to define different EMA subphenotypes corresponding to distinct prognostic trajectories.

Methods

Study participants, setting, and eligibility criteria

The study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines as a retrospective multicenter cohort study. Data from patients followed from 1983 to 2020 at 14 different pediatric and adult specialized epilepsy outpatient clinics, most of them members of the EpiCARE European Reference Network for Rare and Complex Epilepsies, were retrospectively reviewed.

Patients were enrolled according to the following inclusion criteria: 1) history of 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) absence of spontaneous or provoked myoclonia in body parts other than the eyelids; 5) normal neuroimaging (when available) and neurological examination; 6) follow-up for at least 5 years. We excluded patients with: 1) cognitive deficits other than borderline intellectual functioning and mild ID; and 2) myoclonic jerks in body parts other than the eyelids in order to avoid including patients with JME.

Clinical data collection and EEG assessment

Clinical charts were thoroughly reviewed for demographic data, family history of epilepsy, history of febrile seizures (FS), age at epilepsy onset, seizure types throughout the epilepsy course, occurrence of EM status epilepticus and self-induced seizures, drug regimen changes, MRI findings (when available), psychiatric comorbidities, and follow-up duration. Follow-up information on seizure type(s), frequency, and treatment adherence was reviewed for each visit. The presence of borderline intellectual functioning and/or mild ID, as established by at least one standardized neuropsychological test, was noted for each patient.

Standard EEGs were reviewed to assess the following features: 1) background activity; 2) presence and characteristics of ECS and PS; 3) SWD and PWD occurrence and frequency; 4) presence of focal epileptiform abnormalities, defined as focal discharges confined to a single lobe; 5) asymmetry of SWDs or PWDs both in onset and amplitude; and 6) presence of focal slow waves.

Clinical outcomes

Different seizure outcome measures were assessed during follow-up in each patient. The primary endpoint was the occurrence of sustained terminal remission (STR), defined as a period of at least 4 consecutive years of freedom from all seizures at the last follow-up visit. The time from the first ASM trial to STR was also obtained for each patient, corresponding to the time period from the first ASM trial to the last seizure before STR started. The occurrence of a 2-year remission from all seizure types during clinical history was also considered. Patients who did not achieve at least a 2-year remission during their history were considered to show a non-remission pattern. When at least a 2-year remission was achieved, two distinct patterns of seizure control, namely a relapse and remission pattern, were distinguished according to the occurrence or absence of subsequent seizure relapses during follow-up. The time period to the first 2-year remission from the patient's history was also calculated for each patient to investigate the latency from first ASM prescription to initial medication response. Finally, the occurrence of a 2-year remission from generalized tonic-clonic seizures (GTCS) at the last follow-up visit was evaluated.

Finally, we noted the number of ASM trials during the disease course and the number of ASMs at the last follow-up visit. The recurrence of seizures after ASM withdrawal was also investigated, considering only patients with a follow-up of at least 12 months after ASM discontinuation.

Cluster analysis

The two-step cluster analysis (TSCA) approach was used to investigate the presence of distinct EMA endophenotypes and identify the electroclinical features characterizing these endophenotypes. TSCA is a hybrid cluster approach that performs group clusterization through a double-step procedure. It first separates groups using a distance measure and then chooses the optimal subgroup model through a probabilistic approach. This approach provides several advantages over more traditional clustering techniques since it permits the use of both categorical continuous variables, the handling of outliers, and the selection of the number of clusters based on statistical measurements rather than arbitrary choice, and is highly reliable and reproducible.[22,23] The following variables were used to perform TSCA: 1) the presence of mild ID and/or borderline intellectual functioning; 2) a family history of epilepsy in 1st and/or 2nd degree relatives; 3) early-onset EMA (as defined below); 4) a history of GTCS; 5) a history of EM status epilepticus; and 6) prognostic patterns (i.e., remission, relapse, and non-remission), as defined above.

Statistical analysis

Each variable distribution was graphically analyzed in order to select the appropriate statistical tests and ensure the highest possible reliability of identified results. Among all variables, distribution analysis of age at epilepsy onset showed a multi-modal normal distribution that was extensively investigated through kernel-density estimation to identify thresholds of underlying distributions, and the Fisher-Jenks algorithm was used to exactly split the data based on the best threshold. Early-onset EMA was therefore defined as EMA with age of seizure onset ≤ 8 years. Categorical variables

were compared through Fisher's exact test, while continuous variables were compared using Wilcoxon-Mann-Whitney test due to their non-normal distribution. Group tests were two-sided, with $p < 0.05$ considered statistically significant.

Kaplan-Meier estimates were performed in order to calculate the cumulative time-dependent probability of entering STR during follow-up. The time of entry into the analysis was the date of epilepsy diagnosis, and the time of the endpoint was the date of STR onset or the date of the last follow-up visit (depending on which occurred first), truncated at 40 years of follow-up. Cox proportional hazards model was used to investigate the association between STR occurrence and possible predictors based on previous studies. Results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

Multivariable multinomial logistic regression analysis was used to assess the relation between prognostic patterns (dependent variables) and their possible clinical predictors using the remission pattern as a reference. Results were presented as odds ratios (ORs) with 95% CIs. Finally, a linear regression model was used to assess the relation between the number of ASMs at the last follow-up visit (dependent variable) and its possible clinical predictors.

Data availability

De-identified data are available upon reasonable request.

Standard protocol approvals, registrations, and patient consent

The study was approved by the local ethics committee (5970, 286/2020).

Results

General clinical features of the study cohort

After identifying 301 potential EMA patients, 172 subjects (123 female, 71.5%) were included according to study criteria (supplementary Fig. 1, S1). The median age at epilepsy onset was 7 years

(IQR 5-10) and the median follow-up duration was 14 years (IQR 8.3-23.8). Descriptive statistics of the cohort with main clinical and demographic data are summarized in Table 1.

Electroclinical characteristics

EM with or without absences was the seizure type at epilepsy onset in 131 patients (76.2%), whereas GTCS was reported as the presenting seizure type in 41 (23.8%). All patients fulfilled the criteria of either PS or ECS. A history of either PS or ECS was found in 156 (90.7%) and 134 patients (77.9%), respectively, and a history of both PS and ECS was observed in 117 (68%) patients. During follow-up, 120 (69.8%) patients experienced GTCS at least once, and 22 (12.8%) had a history of EM status epilepticus. The occurrence of self-induced seizures during history was found in 17 patients (9.9%), whereas a clear-cut catamenial worsening of EM and/or GTCS was reported in 15/123 (12.2%) female patients.

All but 6 patients showed spontaneous SWD/PWD during at least one standard EEG, whereas generalized discharges were only provoked by intermittent photic stimulation and/or eye closure in these 6 patients. SWDs were recorded in 144 (83.7%) subjects while PWDs were recorded in 131 (76.2%). SWD/PWD frequency was ≥ 4 Hz in 110 (64%) patients. Focal spike and/or sharp waves were reported in 36 subjects (20.9%), and asymmetric/asynchronous generalized discharges were found in 10 (5.8%).

ASM treatment

The most common first-line ASM was valproate (VPA) in 108/172 patients (62.8%), followed by levetiracetam (LEV) in 19 subjects (11%), ethosuximide (ESM) in 16 (9.3%), and lamotrigine in 8 (4.6%). During follow-up, the median number of prescribed ASMs was 3 (IQR 2-4). At the last follow-up visit, all but 16 patients were on ASMs. The median number of ASMs used at last follow-up was 1 (IQR 1-2, range 1-5) and 78/172 patients (45.3%) were on a polytherapy regimen (≥2 ASMs). The most used ASM at the last follow-up visit was VPA in 95/172 patients (55.2%),

followed by LEV in 58 (33.7%) and LTG in 36 (20.9%). Among those on a bitherapy regimen (63 patients), the most frequently observed combination was VPA + LEV (13/63), which was associated with the highest 2-year remission rate (61.5% vs. 36%, p=0.1) (supplementary Fig. 2, S2). ASMs used at the last follow-up visit and the respective 2-year remission rate are given in supplementary Fig. 2, S2.

Seizure outcome and prognostic factors

During follow-up, 106/172 (61.6%) patients achieved at least a 2-year remission from all seizure types and the mean time from epilepsy onset to the first 2-year remission was 10.45 years (SD ± 10.89). Therefore, 66/172 (38.4%) subjects displayed a non-remission pattern, whereas 56 (32.6%) and 50 (29.1%) patients showed a remission and relapse pattern of seizure control, respectively. Multivariable multinomial logistic regression analysis showed that a longer follow-up duration (OR=1.04, 95% CI =1.01-1.08, p=0.02), a history of GTCS (OR=3.15, 95% CI =1.05-9.43, p=0.04), and a family history of epilepsy (OR=3.11, 95% CI=1.22-7.94, p=0.02) were associated with a relapse pattern of seizure control, whereas early epilepsy onset (OR=4.88, 95% CI=1.82-12.98, p=0.002), EM status epilepticus (OR=5.05, 95% CI=1.24-20.8, p=0.02), and a history of FS (OR=9.01, 95% CI=1.67-47.61, p=0.01) significantly predicted the non-remission pattern (see Table 2 for detailed multivariable multinomial logistic regression results).

STR was achieved in 68 (39.5%) patients, and mean time from epilepsy onset to STR was 14.05 years (SD ± 12.47). Early epilepsy onset (HR=0.41, 95% CI=0.24-0.70, p<0.001), a history of GTCS (HR=0.47, 95% CI=0.27-0.82, p=0.008), psychiatric comorbidities (HR 0.34, 95% CI=0.16-0.71), and a history of FS (HR=0.18, 95% CI=0.05-0.76) were significantly associated with a lower chance of entering STR according to the Cox proportional hazards model. Results of the Cox proportional hazards model are reported in Table 3 and the cumulative probability curves of significant prognostic factors are illustrated in Fig. 1. At the last follow-up visit, 88/120 (73.3%) patients had achieved a 2-year freedom from GTCS.

ASM withdrawal was attempted in 62/172 (36%) patients: seizure freedom at least 1 year after ASM discontinuation was observed in 16/62 patients (25.8%). Among those who displayed seizure relapse after at least 1 year of ASM withdrawal (46/62, 74.2%), GTCS relapse was observed in 28 patients (28/35, 80%) with a previous history of GTCS. Patients with seizure relapse after ASM withdrawal had significantly higher rates of GTCS during their history (36/47 vs. 5/16, p=0.002), whereas no significant differences were found according to other variables.

When considering the number of ASMs at the last follow-up visit as a dependent variable, early epilepsy onset ($\beta = 0.20$, p=0.009) and a history of GTCS ($\beta = 0.17$, p=0.02) were significantly associated with the use of higher numbers of ASMs at the last follow-up visit according to a multiple linear regression model (F=4.5, p<0.001) (Supplementary Table 1).

Cluster analysis: identification of clinical EMA subtypes

TSCA revealed two distinct clusters (86 patients per group) of EMA patients, with similar follow-up duration. The two clusters, hereinafter referred to as "EMA-only" (Cluster 1) and "EMA-plus" (Cluster 2) significantly differed in terms of age at epilepsy onset and cognitive abnormalities, with the latter showing a younger age at epilepsy onset and a higher percentage of ID/borderline intellectual functioning (16.3% vs. 47.7%, p<0.001). In addition, EMA-plus patients were characterized by a higher proportion of FS (5.8% vs. 16.3%, p=0.049), self-induced seizures (4.6% vs. 15.1%, p=0.03), and EM status epilepticus (4.6% vs. 20.9%, p=0.002).

When considering seizure outcome, EMA-plus patients showed a significantly higher rate of non-remission pattern (76.7% vs. 0, p<0.001), a similar rate of relapse pattern (Cluster 1: 31.4% vs. Cluster 2: 23.3%, p=0.3), and a significantly lower rate of remission pattern (0 vs. 68.6%, p<0.001) compared with EMA-only patients.

The two clusters did not significantly differ in terms of sex, family history of epilepsy in 1st or 2nd degree relatives, GTCS history, or psychiatric comorbidities. The electroclinical differences

between the two clusters are illustrated in Fig. 2, whereas all statistics and p values related to comparisons between clusters are reported in Table 4.

Discussion

In this multicenter study, we evaluated the electroclinical characteristics and determined the prognostic factors for distinct epilepsy evolution patterns in a cohort of 172 EMA patients with a long-term follow-up. More than one third of our patients displayed a non-remission pattern, whereas remission and relapse patterns were found at almost equal rates in the remaining subjects.

Only 39.5% of our population achieved STR, with a median latency of 14.05 years. A similarly long delay was also observed when considering the interval from epilepsy onset to the initial medication response (time from onset to first 2-year remission = 10.45 years), suggesting a key role of age-related brain changes, as previously hypothesized for other photosensitive epilepsies.[24-26] Among the investigated prognostic factors, early epilepsy onset was the most powerful predictor in our study and was significantly associated with both failure to reach STR and a no-remission pattern of seizure control. Our observation is in line with previous findings in a much smaller subgroup (9 patients) published by Caraballo et al., who found treatment refractoriness in all patients with early-onset EMA.[27] A previous history of FS was also significantly associated with both not converting to STR and with a non-remission pattern. The negative impact of FS on long-term seizure outcome was also recently highlighted in a GGE cohort and was attributed to genetic factors that may predispose patients to both FS and ASM refractoriness.[28,29] In accordance with this hypothesis, a family study conducted by Sadleir et al. revealed that generalized epilepsy with FS-plus was common among relatives of EMA patients, suggesting shared genetic determinants between these two syndromes.[14] Furthermore, a history of GTCS and psychiatric comorbidities significantly predicted failure to achieve STR, in line with previous observations across different epilepsy syndromes.[30-32] Finally, a previous history of EM status epilepticus was associated with a

5-fold increased risk of not experiencing remission throughout the course of EMA. This latter observation, together with the prognostic impact of an earlier age at epilepsy onset and a history of FS, may reflect shared underlying genetic components, as supported by the results of our cluster analysis.

In this study, we confirmed the existence of a subgroup of EMA patients with an insidious phenotype, referred to as "EMA-plus", and another more benign subgroup, referred to as "EMA-only". Subgroups of EMA patients characterized by a higher rate of moderate ID, status epilepticus, and ASM resistance have been previously described in small cohorts,[21,27] but these observations have not yet been corroborated in larger cohorts with modern statistical approaches. The two EMA patient subgroups, as delineated here, differ to a great extent in terms of both their electroclinical features and long-term seizure outcomes. EMA-plus patients were younger at epilepsy onset and had higher rates of cognitive disturbances, EM status epilepticus, FS, and self-induction when compared with EMA-only patients. In addition, EMA-plus patients showed higher rates of poor response to ASMs, whereas EMA-only patients showed a favorable long-term seizure outcome, with two thirds of patients achieving a remission pattern of seizure control.

EMA has generally been recognized as an epilepsy syndrome with a high rate of ASM refractoriness regardless of the electroclinical characteristics of affected patients.[33,34] Based on cluster analysis, we have made a clear-cut distinction between EMA patient subtypes, with EMA-plus patients having a poor response to ASM and, thus, a less favorable long-term seizure outcome than EMA-only patients. Further studies will clarify if the differences between EMA subtypes may be attributed to the underlying genetic substrate, with EMA-plus patients possibly harboring mutations in genes related to EMA and EMA-like phenotypes, such as *SYNGAP1*, *KIA02022*, and *CHD2*, which have been established as the most consistent genetic contributors in this setting.[35-38]

In this study, for the first time we also explored ASM withdrawal in EMA patients. One third of EMA patients in our cohort discontinued ASMs during follow-up, in line with previous studies in

JME patients,[39] and one fourth of these patients remained seizure-free after ASM discontinuation. A previous history of GTCS emerged as the only predictor of seizure recurrence in our study, suggesting caution when withdrawing ASMs in these patients.

Finally, we documented an EMA onset peak during mid-childhood, as well as a female preponderance (2.51:1) and high rates of family history of epilepsy, thus providing solid evidence in support of previous findings from much smaller cohorts.[2,11,27,34,40]

The main limitations of our study are due to its retrospective design and the lack of systematic genetic testing in all patients, which may have contributed to the interpretation of our findings about prognostic factors and subphenotypes. However, the multicenter design, the large number of patients as compared to previous cohorts, the long-term follow-up, and the strict diagnostic criteria used to define EMA support the generalizability of our results. In addition, we adopted strict criteria to define EMA in order to avoid the inclusion of other myoclonic syndromes, such as JME, especially in later-onset patients.[17] We thus chose to exclude patients with a history of myoclonic seizures involving body regions other than the eyelids, although their classification still represents a controversial topic.

In conclusion, our study reveals the clinical variables predicting the occurrence of sustained remission in EMA patients. In particular, early age at epilepsy onset appeared to be the most relevant predictor of poor seizure outcome. Moreover, using a large database with long-term follow-up data, we outlined the distinct prognostic patterns of this rare epilepsy syndrome. Finally, we identified two distinct EMA subphenotypes with strong implications in terms of seizure control and cognitive outcome.

Figure captions and legends

Fig. 1 Prognostic factors of sustained terminal remission during follow-up

Follow-up was truncated at 40 years and censored patients are indicated by crosses.

Fig. 2 Electroclinical characteristics of clusters

Radar plot showing the electroclinical differences between clusters. Intercluster proportions are represented in the graph to maximize the differences between the two clusters. Abbreviations: ECS = eye closure sensitivity; EM = eyelid myoclonia; PS = photosensitivity

Fig. 3 Probability of entering sustained terminal remission during follow-up depending on the cluster

Follow-up was truncated at 40 years and censored patients are indicated by crosses.

Table 1. Demographic and clinical characteristics	
Age, years, median (IQR)	22 (17-32)
Sex, female, n (%)	123 (71.5)
Age at epilepsy onset (IQR)	7 (5-10)
Follow-up duration, years, median (IQR)	14 (8.25-23.75)
History of FS, n, %	19 (11)
Family history of epilepsy in a 1st degree relative, n (%)	35 (20.3)
Family history of epilepsy in a 2nd degree relative, n (%)	21 (12.2)
Family history of epilepsy in a 3rd degree relative, n (%)	13 (7.6)
Family history of FS in a 1st or 2nd degree relative, n (%)	6 (3.5)
Psychiatric comorbidities, n (%)	45 (26.2)
Borderline IF or mild ID, n (%)	55 (32)
Abbreviations: ID = intellectual disability ; FS = febrile seizures ; IF = intellectual functioning; IQR = interquartile range; SD = standard deviation	

Table 2. Predictors of relapse and no-remission patterns, as determined by multivariable multinomial logistic regression

	Relapse			No remission		
Predictor	OR	95% CI	p value	OR	95% CI	p value
Male sex	0.5	0.17-1.41	0.2	0.68	0.26-1.79	0.4
Early-onset epilepsy	2.42	0.91-6.41	0.08	4.88	1.82-12.98	0.002*
Follow-up duration	1.04	1.01-1.08	0.02	0.98	0.94-1.02	0.3
Febrile seizures	3.6	0.55-23.25	0.2	9.01	1.67-47.61	0.01*
Family history of epilepsy in a 1st or 2nd degree relative	3.11	1.22-7.94	0.02*	1.29	0.51-3.27	0.6
Borderline IF or mild ID	2.05	0.73-5.78	0.2	1.06	0.39-2.87	0.9
Psychiatric comorbidities	1.73	0.58-5.18	0.3	2.28	0.81-6.41	0.1
Eyelid myoclonic status epilepticus	1.86	0.37-9.43	0.5	5.05	1.24-20.8	0.02*
Self-induced seizures	0.72	0.11-4.48	0.7	2.39	0.55-10.41	0.2
History of GTCS	3.15	1.05-9.43	0.04*	2.19	0.85-5.61	0.1
History of both ECS and PS	1.71	0.64-4.57	0.3	1.65	0.64-4.22	0.3
EEG focal abnormalities	1.83	0.69-4.85	0.2	1.68	0.63-4.08	0.3

Note: Data are presented as odds ratios (ORs) along with 95% confidence intervals (CIs). The asterisks indicate statistically significant variables ($p<0.05$). Abbreviations: ECS = eye closure sensitivity; GTCS = generalized tonic-clonic seizures; ID = intellectual disability; IF = intellectual functioning; PS = photosensitivity

Table 3. Prognostic factors for sustained terminal remission according to multivariable Cox proportional hazards model

Predictors	HR	95% CI	p value
Female sex	0.81	0.46-1.44	0.5
Early onset of epilepsy	0.41	0.24-0.7	<0.001*
History of FS	0.17	0.05-0.76	0.02*
Family history of epilepsy in a 1st or 2nd degree relative	0.72	0.42-1.21	0.2
Borderline IF or mild ID	0.95	0.53-1.72	0.9
Psychiatric comorbidities	0.34	0.16-0.71	0.004*
Eyelid myoclonic status epilepticus	0.54	0.22-1.28	0.2
Self-induced seizures	0.71	0.25-2.04	0.5
GTCS during history	0.47	0.27-0.82	0.008*
History of both PS and ECS	1.15	0.65-2.02	0.6
EEG focal abnormalities	0.97	0.56-1.68	0.9

Note: Data are presented as hazard ratios (HRs) along with 95% confidence intervals (CIs). The asterisks indicate statistically significant variables ($p < .05$). Abbreviations: ECS = eye closure sensitivity; EM = eyelid myoclonia; FS = febrile seizures; GTCS = generalized tonic-clonic seizures; ID = intellectual disability; IF = intellectual functioning; PS = photosensitivity; STR = sustained terminal remission

Table 4. Patient clinical characteristics stratified according to cluster

Variable	Cluster 1 (86 pts)	Cluster 2 (86 pts)	p value
Sex, female, n (%)	62 (72.1)	61 (70.9)	1
Early epilepsy onset, n (%)	39 (45.3)	70 (81.4)	<0.001*
Age of epilepsy onset, years, median (IQR)	9 (6-10.7)	6 (4-8)	<0.001*
Follow-up duration, years, median (IQR)	15 (8-25.7)	14 (9.2-21)	0.46
History of FS, n, %	5 (5.8)	14 (16.3)	0.049*
Family history of epilepsy in a 1st or 2nd degree relative, n (%)	30 (34.9)	27 (31.4)	0.7
Psychiatric comorbidities, n (%)	18 (20.9)	27 (31.4)	0.16
Borderline IF or mild ID, n (%)	14 (16.3)	41 (47.7)	<0.001*
Eyelid myoclonic status epilepticus, n (%)	4 (4.6)	18 (20.9)	0.002*
Self-induced seizures, n (%)	4 (4.6)	13 (15.1)	0.03*
History of GTCS, n (%)	61 (70.9)	59 (68.6)	0.87
History of both PS and ECS, n (%)	51 (59.3)	66 (76.7)	0.02*
Focal EEG abnormalities	27 (31.4)	30 (34.9)	0.75
Remission pattern, n (%)	59 (68.6)	0	<0.001*
Relapsing pattern, n (%)	27 (31.4)	20 (23.3)	0.3
No remission pattern, n (%)	0	66 (76.7)	<0.001*

Abbreviations: ECS = eye closure sensitivity; EM = eyelid myoclonia; FS = febrile seizures; ID = intellectual disability; IF = intellectual functioning; IQR = interquartile range; PS = photosensitivity. Note: the asterisks indicate statistically significant variables ($p<0.05$)

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