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Epilepsia®

FULL-LENGTH ORIGINAL RESEARCH

Headache in idiopathic/genetic epilepsy: Cluster analysis in a large cohort

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Abstract

Objective: The link between headache and epilepsy is more prominent in patients with idiopathic/genetic epilepsy (I/GE). We aimed to investigate the prevalence of headache and to cluster patients with regard to their headache and epilepsy features.

Methods: Patients aged 6–40 years, with a definite diagnosis of I/GE, were consecutively enrolled. The patients were interviewed using standardized epilepsy and headache questionnaires, and their headache characteristics were investigated by experts in headache. Demographic and clinical variables were analyzed, and patients were clustered according to their epilepsy and headache characteristics using an unsupervised K-means algorithm.

Results: Among 809 patients, 508 (62.8%) reported having any type of headache; 87.4% had interictal headache, and 41.2% had migraine. Cluster analysis revealed two distinct groups for both adults and children/adolescents. In adults, subjects having a family history of headache, ≥5 headache attacks, duration of headache ≥24 months, headaches lasting ≥1 h, and visual analog scale scores > 5 were grouped in one cluster, and subjects with juvenile myoclonic epilepsy (JME), myoclonic seizures, and generalized tonic–clonic seizures (GTCS) were clustered in this group (Cluster 1). Self-limited epilepsy with centrotemporal spikes and epilepsy with GTCS alone were clustered in Cluster 2 with the opposite characteristics. For children/adolescents, the same features as in adult Cluster 1 were clustered in a separate group, except for the presence of JME syndrome and GTCS alone as a seizure type. Focal seizures were clustered in another group with the opposite characteristics. In the entire group, the model revealed an additional cluster, including patients with the syndrome of GTCS alone (50.51%), with ≥5 attacks, headache lasting >4 h, and throbbing headache; 65.66% of patients had a family history of headache in this third cluster ($n = 99$).

Significance: Patients with I/GE can be clustered into distinct groups according to headache features along with seizures. Our findings may help in management and planning for future studies.

KEYWORDS
cluster analysis, genetic epilepsy, headache, headache phenotypes, idiopathic epilepsy, myoclonic seizures

1 | INTRODUCTION

Epilepsy and headache are both common, paroxysmal, and disabling neurologic disorders that affect individuals worldwide, with a prevalence of .5%–1% for epilepsy and 46% for headache in the general population.[1-2] Although the epidemiology of headache in epilepsy has been studied over the past decades, data are still diverse due to discrepancies between the available studies and the lack of eligible research on larger populations by experts.[3] Headache and epileptic seizures can coexist either in a temporal relationship (peri-ictal headache [PIH]) or independently (interictal headache [IIH]) in an individual, leading to an increased burden of epilepsy.[4]

Headache prevalence in people with epilepsy (PWE) was estimated as between 7% and 57% across different studies, and the majority of these headaches were reported as migraine (14%–24%), followed by tension-type headache (TTH; 5.1%–19.9%).[1,5,6] Recent epidemiologic and clinical reports mostly focused on the link between migraine and epilepsy, because they are both prototypic examples of paroxysmal brain disorders and possibly share common pathophysiologic mechanisms.[1] A growing body of evidence suggests that these are not separate entities but probably different reflections of altered neuronal network excitability.[7–9]

Hypersynchronous cortical activity in epilepsy and cortical spreading depression (CSD) in migraine are two different consequences of this altered mechanism, highlighting the role of common pathophysiologic pathways.[1,10] Several etiopathologic triggers including genetic and environmental factors may lead to this altered neuronal network excitability as a common final pathway and result in either migraine or epilepsy in an individual.[11–13]

Despite previous research emphasizing high rates of this comorbidity, headache is still an underrecognized and overlooked symptom in PWE. Patients may ignore headaches in addition to their seizures and choose not to mention them to their neurologists/epileptologists if not questioned specifically.[4,14,15]

It is of utmost importance to increase the awareness of physicians for this headache comorbidity and the clinical characteristics of headaches, because undertreated headache is a significant burden with a negative impact on patients' quality of life. Questioning headache symptoms and their specific features as a routine part of the clinical interview is essential for planning an appropriate medical treatment regimen for PWE.

To the best of our knowledge, currently, there are no multicenter studies focused exclusively on headache characteristics in a large cohort of patients with idiopathic/genetic epilepsy (I/GE) including both adults and children. Although the link between headache and epilepsy is suggested to be more prominent in patients with genetic forms of epilepsy,[10,16] there are only a handful of studies focusing on this comorbidity with some selected subgroups such as juvenile myoclonic epilepsy (JME) and focal idiopathic/genetic childhood epilepsy syndromes.[17–20] Another reason to study these syndromes is that both headache and I/GE may share common genetic susceptibility.[21]

Our main goal was to investigate the prevalence of headache in I/GE and to cluster patients with regard to their headache features, to give insight to physicians about the correct management of patients with I/GE with headache. Our second goal was to increase the awareness of headache comorbidity in general practitioners/neurologists to avoid underrecognition of a potentially treatable condition in these patients.

Key Points

- Idiopathic/genetic epilepsy had a high prevalence of headache (62.8%)
- Migraine was very frequent (47.2%) in patients with juvenile myoclonic epilepsy
- Milder headaches were related to focal seizures in children with idiopathic epilepsies
- Cluster analysis can detect different clusters in idiopathic epilepsies with headache

2 | MATERIALS AND METHODS

2.1 | Patient selection criteria

A nationwide study was organized by six experts after two meetings and email connections and conducted between April 2019 and December 2020 in epilepsy outpatient clinics of the 28 participating centers, enrolling 809 consecutive patients with a definite diagnosis of an I/GE syndrome as defined by the International League Against Epilepsy (ILAE) 2017 criteria.[22] Patients aged 6–40 years with a minimum of 1 year of follow-up were included after they gave written informed consent.

Other inclusion criteria were having at least one electroencephalographic (EEG) recording supporting their diagnosis, such as related epileptic abnormalities (generalized spike and wave discharges, photosensitivity, or having focal spikes for idiopathic focal epilepsy syndromes). All EEGs and clinical features were re-evaluated by a panel of experienced clinical neurophysiologists (B.B., S.K.V., F.F.E., S.N.Y., S.A.) to ensure the I/GE syndrome diagnoses.

The patients had to have all other necessary biochemical, serologic, and immunologic laboratory investigations

performed for detailed differential diagnosis. Patients with additional nonepileptic psychogenic seizures were excluded.

2.2 | Data collection

Each patient was interviewed by local neurologists/epileptologists, face to face, using two structured questionnaires. The first questionnaire included detailed diagnostic questions regarding the demographic, clinical, and electrophysiologic details of their epilepsy. When an accompanying symptom of headache was concerned, another questionnaire investigating the details of their headache was administered. The second questionnaire included diagnostic questions based on the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria[23] for diagnoses of both IIH and PIH. The clinical features of headache and associated symptoms, age at headache onset, time of last headache attack, frequency of headaches, duration of pain, location and quality of headache (e.g., pressing, throbbing, stabbing), family history of headache, questions about the temporal relationship of seizures and headaches, and visual analog scale (VAS) scores for headache intensity were recorded.

After submission of the forms by the local investigator, one of the headache experts among the authors (A.Ö.) checked the diagnosis to ensure the correct standard ICHD-3 diagnosis, applying the relevant criteria.

The subgroups of I/GE were classified according to the ILAE classification of epilepsies and epileptic syndromes as childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), JME, epilepsy with generalized tonic–clonic seizures alone (GTCA), and lastly, genetic generalized epilepsy (GGE)-other (patients who could not be classified in a specific I/GE syndrome).[22,24] Idiopathic/genetic focal epilepsy syndromes were classified as follows: self-limited epilepsy with centrotemporal spikes (SLECTS; previously known as Rolandic epilepsy), and childhood epilepsy with occipital paroxysms (CEOP).[22]

Seizures were classified according to the updated ILAE terminology of 2017.[25]

A group of experienced epileptologists (B.B., S.N.Y., S.K.V., S.A., F.F.E.) verified the diagnosis of epilepsy syndrome by reviewing the electroclinical data of every patient in detail.

Patients were further grouped into two categories according to their current age at admission as adults (≥18 years of age) and children/adolescents (<18 years of age). There were more adults than children/adolescents (668 adults [82.57%] and 141 [17.43%] child/adolescents), because the child neurology centers/experts who contributed to the study were limited (only three centers).

Informed consent was obtained from all patients/legal guardians before they were included in the study. The ethics committee approved the study protocol (protocol number 2019/32).

2.3 | Statistical analysis

Demographic and clinical variables were analyzed using the Statistical Package for the Social Sciences version 22.0 statistics package. Continuous variables were summarized as means and SDs, and categorical variables as numbers and percentages.

An unsupervised K-means algorithm was used to cluster patients according to their common epilepsy and headache characteristics (variables: epilepsy type, presence of seizure types [myoclonic, generalized tonic–clonic seizures [GTCS], absence], focal, age at seizure onset, ≥5 years of remission of epilepsy, age at headache onset, location of headache, duration of headache [months], VAS score, frequency of headache [a minimum of five headache attacks], mean duration of headache attacks [hours], quality of headache [throbbing or other], and family history of headache), and to determine the factors that were effective in clustering.

K-means clustering is the best-known unsupervised machine learning algorithm, with categorical and continuous data, which works well for data with mixed numeric and categorical features. We used the chi-square test or exact test to compare categorical characteristics between clusters, and Mann–Whitney *U* tests to compare continuous characteristics between clusters. For the combined analysis of the child/adolescent and adult groups as a whole, analysis of variance was used to compare clusters for age, age at epilepsy onset, and age at headache onset. We also used the Kruskal–Wallis test for performing comparisons of headache duration (months) and VAS scores, because they did not fit the normality assumption. We summarized characteristics as count (*n*, %), mean ± SD, and median (low quartile–high quartile) where appropriate. All analyses were performed by an experienced biostatistician (B.G.T.) using the Statistica 13.5 program.[26]

3 | RESULTS

3.1 | Demographic and clinical characteristics of entire cohort

The flow chart of the study is summarized in Figure 1.

A total of 809 patients (531 females, 65.6%) with a confirmed diagnosis of I/GE were enrolled in the study.

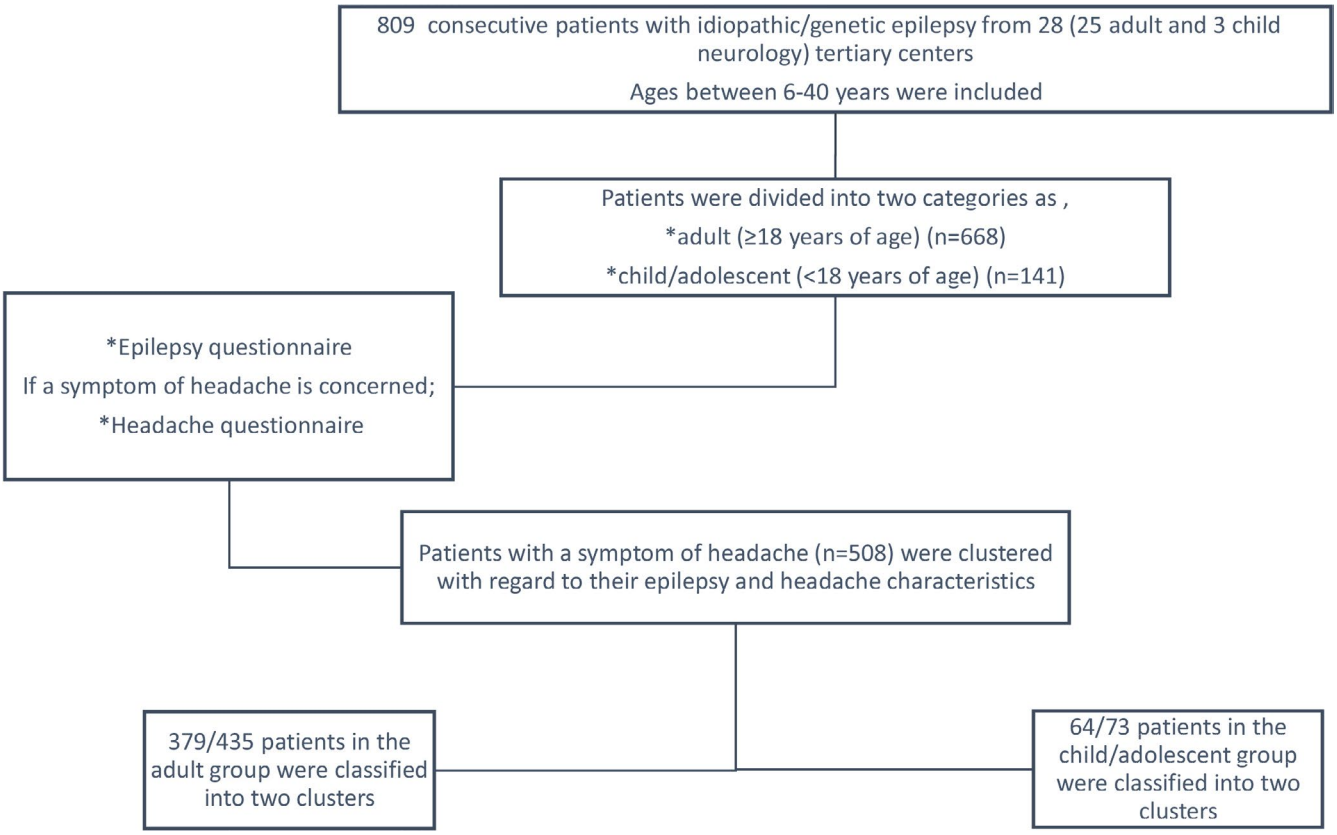


FIGURE 1 Flow chart of the study

The mean age, age at epilepsy onset, mean epilepsy duration at the interview, and the mean follow-up period were 25.35 ± 5.75, 14.27 ± 6.61, 10.58 ± 8.35, and 6.63 ± 6.38 years, respectively.

The distribution of the epilepsy syndromes was as follows: JME ($n = 337$, 41.7%), GTCA ($n = 222$, 27.4%), CAE ($n = 46$, 5.7%), JAE ($n = 91$, 11.2%), CEOP ($n = 20$, 2.5%), SLECTS ($n = 45$, 5.6%), and GGE-other ($n = 48$, 5.9%).

Among all the patients, 508 (62.8%) reported having headache (435 adults [65.11% of the adults] and 73 children/adolescents [51.77% of the child/adolescent cohort]), and in 444 (87.4%) of these, headaches had no time relationship with seizures (classified as IIH). The prevalence of IIH was found to be 54.88% (444/809). The most frequent type of IIH was migraine, with a prevalence of 41.2% (migraine with aura [MwA], 16.06%; migraine without aura [MwoA], 20.1%; chronic migraine, 1.1%; probable MwoA, 2.7%; probable MwA, 1.1%), whereas the prevalence of TTH was 13.7%. When we evaluated the adult and children/adolescent groups separately, migraine and TTH prevalence was 44.6% and 12.7% in the adult group, whereas it was 24.8% and 18.4% for the child/adolescent group, respectively.

One hundred five patients with headaches described a definite time relationship with epileptic seizures (PIH); 42 also had accompanying IIHs, and one patient had both preictal and postictal headaches.

The distribution of headache subtypes with regard to I/GE syndromes is given in Table 1.

3.2 | Cluster analysis results

K-means cluster analysis classified 443 of 508 patients with headache according to their common headache and epilepsy characteristics. Patients with incomplete data could not be included in this particular analysis, because the missing data were related to critical variables such as a family history of headache, age at headache onset, and headache duration.

The model revealed three distinct clusters for all patients with I/GE with headache. In Cluster 1 ($n = 226$), 78.76% of patients with JME, 86.28% of patients with myoclonic seizures, 63.27% of patients with a history of ≥5 headache attacks, 44.69% of patients with 1–4-h headache duration, 62.83% of patients with throbbing headache, and 63.27% of patients with a family history of headache were clustered. In contrast to Cluster 1, patients with a GTCA syndrome (50.51%), 87.88% of patients with a history of ≥5 headache attacks, 60.61% of patients with >4-h headache duration, 79.80% of patients with throbbing headache, and 65.66% of patients with a family history of headache were grouped in Cluster 2 ($n = 99$). The last cluster, Cluster 3 ($n = 118$),

TABLE 1 Distribution of headache subtypes regarding idiopathic/genetic epilepsy syndromes in the entire cohort ($n = 809$)

Epilepsy subtype, total number of patients	Headache subtype, *n* (%) within epilepsy subtype					
	MwoA	MwA	Migraine, other[a]	Migraine, all types[b]	TTH, all types[c]	PIH[d]
JME, $n = 337$	72 (21.4)	70 (20.8)	17 (5.0)	159 (47.2)	47 (13.9)	48 (14.3)
GTCA, $n = 222$	46 (20.7)	25 (11.3)	13 (3.9)	84 (37.8)	21 (9.5)	33 (14.9)
JAE, $n = 91$	20 (22.0)	12 (13.2)	2 (2.2)	34 (37.4)	18 (19.8)	10 (10.9)
CAE, $n = 46$	9 (19.6)	4 (8.7)	3 (6.5)	16 (34.8)	8 (17.4)	2 (4.3)
GGE-other, $n = 48$	5 (10.4)	13 (27.1)	3 (6.3)	21 (43.8)	8 (16.7)	4 (8.3)
CEOP, $n = 20$	3 (15)	2 (10.0)	-	5 (25.0)	2 (10.0)	6 (30)
SLECTS, $n = 45$	8 (17.8)	2 (4.4)	4 (8.9)	14 (31.1)	7 (15.6)	2 (4.4)
Total, $n = 809$	163 (20.1)	128 (15.8)	42 (5.2)	333 (41.2)	111 (13.7)	105 (12.9)

Abbreviations: CAE, childhood absence epilepsy; CEOP, childhood epilepsy with occipital paroxysms; GGE-other, other genetic generalized epilepsy; GTCA, epilepsy with generalized tonic–clonic seizures alone; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; MwA, migraine with aura; MwoA, migraine without aura; PIH, peri-ictal headache; SLECTS, self-limited epilepsy with centrotemporal spikes; TTH, tension-type headache.

[a]Represents patients with probable MwA, probable MwoA, migraine with brainstem aura, and chronic migraine.

[b]Represents patients with MwA, MwoA, and migraine, other.

[c]Represents patients with infrequent, frequent, probable, and chronic TTH.

[d]Note that some of these patients also have coexisting interictal headaches.

included patients aged <24 years (65.25%), with a GTCA syndrome (36.44%), and with focal seizures (13.56%), along with patients with attack duration of <1 h (51.69%), headache duration < 24 months (57.63%), and nonthrobbing headache (77.12%).

The median VAS scores of the patients showed significant differences between the clusters, as shown in Table 2.

We further analyzed child/adolescent and adult patients separately to achieve unbiased results, because age is an important factor for stratification in cluster analysis, as well as in clinical epileptology.

3.3 | Cluster analysis results for adult patients

K-means cluster analysis revealed two hidden distinct clusters of adult patients with I/GE according to their common headache and epilepsy characteristics, as shown in Figure 2 and Table 3. Also, the model classified 379 of 435 patients with headache in the adult group. The loss of sample size was due to incomplete data, as stated above.

For the adult group, 89.8% of patients with JME, 88.43% of patients with myoclonic seizures, 61.87% of GTCS, 81.57% of patients with a ≥5-headache attack history, 74.02% of patients with 1–4-h headache duration, 66.67% of patients with 4–24-h headache duration, 83.56% of patients with >24-h headache duration, 80% of patients with throbbing headache, and 84.34% of patients with a family history of headache were grouped in Cluster 1.

The median VAS scores of patients in Cluster 1 were significantly higher than in patients in Cluster 2 (median score = 6 [range = 4–8] for Cluster 1, and 5 [range = 4–7] for Cluster 2; $p = .004$). In addition, the median headache symptom duration was also significantly longer for patients in Cluster 1 when compared with Cluster 2 (median = 36 [range = 12–72] months for Cluster 1, and 24 [range = 12–60] months for Cluster 2; $p = .006$). The patients with SLECTS and GTCA were clustered in Cluster 2 (66.67% and 69.97%, respectively).

3.4 | Cluster analysis results for adolescents and children

In the child/adolescent group, 64 of 73 patients with complete data were included in the cluster analysis, and the patients were classified into two clusters (see Table 4, Figure 3).

In the child/adolescent group, 80% of patients with nonthrobbing headache, 82.76% patients with a headache duration of <1 h, and 72.22% with a family history of headache were clustered in Cluster 1, whereas 72.73% of patients with myoclonic seizures, 66.67% of patients with ≥5 headache attacks, 63.16% patients with a headache duration of 1–4 h, 55.56% patients with a headache duration of >4 h, and 64.29% patients with throbbing headache were clustered in Cluster 2. The median VAS scores and headache symptom duration (months) were significantly higher and longer in Cluster 2 ($p = .004$ and $p <. 001$, respectively).

TABLE 2 Cluster analysis results of all idiopathic/genetic epilepsy patients using variables related to headache and epilepsy characteristics ($n = 443$)

Characteristic	Cluster 1, $n = 226$	Cluster 2, $n = 99$	Cluster 3, $n = 118$	p
Age, years, mean ± SD	26.18 ± 8.57	25.97 ± 8.58	23.67 ± 9.95[a]	.041
≥5 headache attacks, *n* (%)	175 (77.43)	87 (87.88)	27 (22.88)	<.001
Duration of headache, *n* (%)				
<1 h	30 (13.27)	6 (6.06)	61 (51.69)	<.001
1–4 h	101 (44.69)	12 (12.12)	33 (27.97)	
>4 h	45 (19.91)	60 (60.61)	15 (12.71)	
>24 h	50 (22.12)	21 (21.21)	9 (7.63)	
Localization of headache, *n* (%)				
Unilateral	53 (23.45)	52 (52.53)	18 (15.25)	<.001
Bilateral	173 (76.55)	47 (47.47)	100 (84.75)	
Quality of headache, *n* (%)				
Throbbing	142 (62.83)	79 (79.80)	27 (22.88)	<.001
Other	84 (37.17)	20 (20.20)	91 (77.12)	
Family history of headache, *n* (%)	143 (63.27)	65 (65.66)	36 (30.51)	<.001
Type of epilepsy				
JME	178 (78.76)	13 (13.13)	16 (13.56)	<.001
CAE	4 (1.77)	4 (4.04)	14 (11.86)	
JAE	13 (5.75)	20 (20.20)	20 (16.95)	
CEOP	3 (1.33)	4 (4.04)	3 (2.54)	
SLECTS	5 (2.21)	5 (5.05)	13 (11.02)	
GTCA	11 (4.87)	50 (50.51)	43 (36.44)	
GGE-other	12 (5.31)	3 (3.03)	9 (7.63)	
Presence of myoclonic seizures, *n* (%)	195 (86.28)	11 (11.11)	21 (17.80)	<.001
Presence of absence seizures, *n* (%)	51 (22.57)	30 (30.30)	40 (33.90)	.061
Presence of GTC seizures, *n* (%)	142 (62.83)	74 (74.75)	76 (64.41)	.105
Presence of focal seizures, *n* (%)	6 (2.65)	7 (7.07)	16 (13.56)	<.001
≥5 years of epilepsy remission, *n* (%)	23 (10.18)	11 (11.11)	19 (16.10)	.263
VAS score				
Mean ± SD Median (Q1–Q2)	5.62 ± 1.94 5 (4–7)	6.55 ± 2.06[a] 7 (5–8)	4.16 ± 2.08[a,b] 4 (3–5)	<.001
Duration of headache symptom, months				
Mean ± SD Median (Q1–Q2)	47.97 ± 51.67 24 (12–60)	74.76 ± 84.48 48 (12–120)	26.04 ± 31.05[a,b] 12 (5–36)	<.001
Age at headache onset, years				
Mean ± SD Median (Q1–Q2)	22.24 ± 8.83 21.5 (16.5–28)	19.69 ± 8.07 19 (14–24)	21.52 ± 9.60 19 (15–26)	.058
Age at epilepsy onset, years				
Mean ± SD Median (Q1–Q2)	14.96 ± 4.96 15 (13–17)	15.46 ± 7.64 15 (10–19)	13.82 ± 7.99 13 (8–17)	.153

Note: Analysis of variance was used to compare clusters for age, age at epilepsy onset, and age at headache onset. Because headache duration (months) and VAS scores did not fit normality assumption, comparisons were done using the Kruskal–Wallis test.

Abbreviations: CAE, childhood absence epilepsy; CEOP, childhood epilepsy with occipital paroxysms; GGE-other, other genetic generalized epilepsy; GTC, generalized tonic–clonic; GTCA, epilepsy with generalized tonic–clonic seizures alone; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; Q1, first quartile; Q2, second quartile; SLECTS, self-limited epilepsy with centrotemporal spikes; VAS, visual analog scale.

[a]Significantly different from Cluster 1.

[b]Significantly different from Cluster 2.

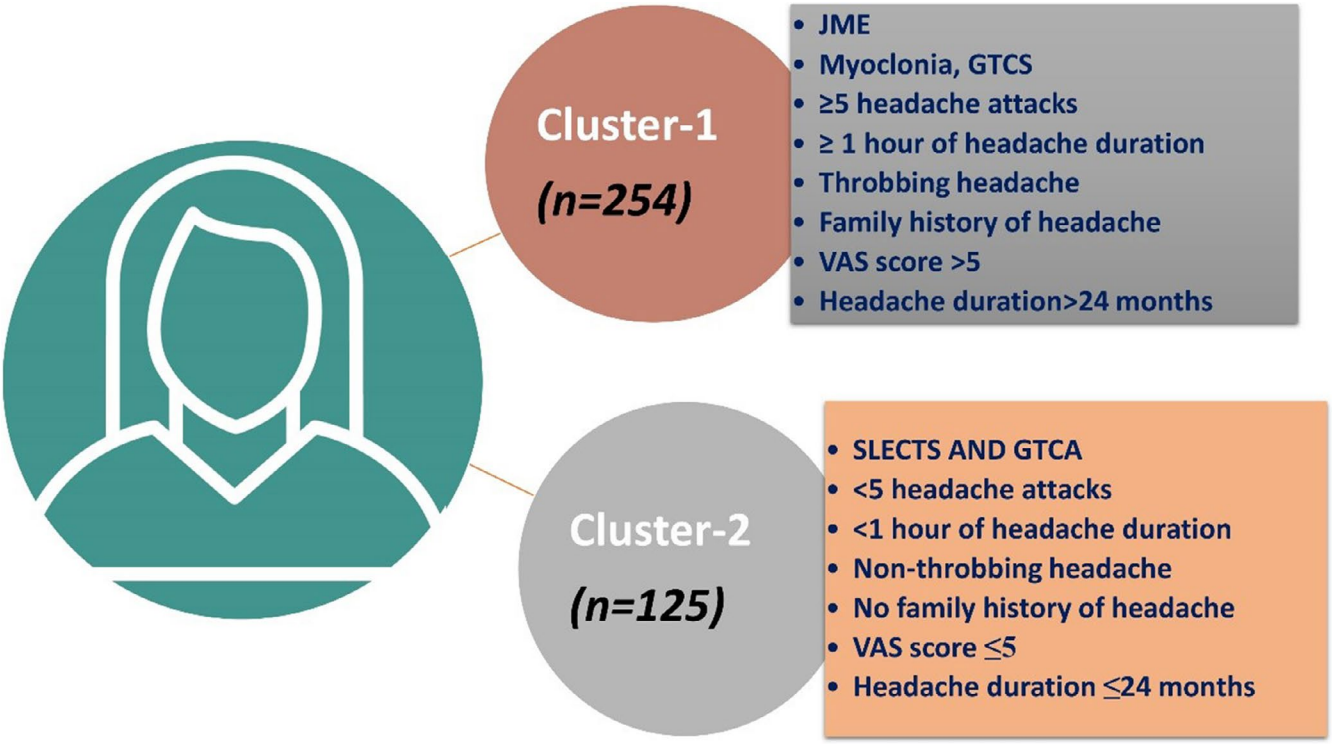


FIGURE 2 The clusters of adult patients with idiopathic/genetic epilepsy according to their headache and epilepsy characteristics. GTCA, generalized tonic–clonic seizures alone; GTCS, generalized tonic–clonic seizures; JME, juvenile myoclonic epilepsy; SLECTS, self-limited epilepsy with centrotemporal spikes; VAS, visual analog scale

4 | DISCUSSION

This is a multicenter, cross-sectional study evaluating phenotypic features of headache by experts in a large cohort of patients with I/GE. Our study revealed that headache was a very frequent symptom in these patients, with a prevalence of 62.8% (51.77% in children/adolescents, 65.11% in adults), underlining that questioning for headache in patients with I/GE should be a part of routine examinations in the clinical setting. Moreover, by using the cluster analysis method, we were able to define distinct clusters in patients with I/GE according to their headache and epilepsy characteristics for the first time. When evaluated for the adult and child/adolescent groups, two similar hidden clusters could be discriminated, separately.

4.1 | Remarkable comorbidity of primary headache in patients with I/GE

We found the prevalence of migraine to be 44.6% in the adult patients and were struck by the obviously higher prevalence of migraine compared with the general population (the highest report was 19.9%).[5,6,27–30] Prospective studies focusing on primary headache prevalence in patients with I/GE are very limited. The majority of the available studies investigated the prevalence rates of headache/migraine in nonselected groups of patients with epilepsy, and only a handful reported the headache/migraine prevalence in small subgroups of patients with I/GE. In a study from a tertiary epilepsy outpatient clinic that evaluated headache prevalence in 201 patients with various types of epilepsy, a migraine prevalence of 18% was reported in patients with I/GE, which was higher than in patients with other types of epilepsy (11%) and the general population (11%–15%).[31] The prevalence rates in our study support the previous observations of a higher prevalence of headache/migraine comorbidity in adult patients with I/GE. For the pediatric group, similar observations were reported in a prospective study on only 50 pediatric patients with a headache prevalence of 46%, and 43.5% of these headaches were diagnosed as migraine.[32] The authors hypothesized that epilepsies with a possible genetic cause (SLECTS and JME in particular) had a higher probability of comorbid migraine, because the mutations in these syndromes might influence the cortical excitability and lead to CSD and consequently migraine.[11–13] The headache prevalence of 51.77% and migraine prevalence of 24.8% in our pediatric group confirmed the higher prevalence of headache/migraine comorbidity in children with I/GE.

TABLE 3 Cluster analysis results of adult patients with idiopathic/genetic epilepsy using variables related to headache and epilepsy characteristics ($n = 379$)

Characteristic	Cluster 1, $n = 254$	Cluster 2, $n = 125$	p
≥5 headache attacks, *n* (%)	208 (81.57)	47 (18.43)	<.001
Duration of headache, *n* (%)			
<1 h	25 (36.76)	43 (63.24)	<.001
1–4 h	94 (74.02)	33 (25.98)	
>4 h	74 (66.67)	37 (33.33)	
>24 h	61 (83.56)	12 (16.44)	
Localization of headache, *n* (%)			
Unilateral	82 (73.87)	29 (26.13)	.064
Bilateral	172 (64.18)	96 (35.82)	
Quality of headache, *n* (%)			
Throbbing	176 (80.00)	44 (20.00)	<.001
Other	78 (49.06)	81 (50.94)	
Family history of headache, *n* (%)	167 (84.34)	31 (15.66)	<.001
Type of epilepsy, *n* (%)			
JME	176 (89.80)	20 (10.20)	<.001
CAE	6 (46.15)	7 (53.85)	
JAE	23 (56.10)	18 (43.90)	
CEOP	5 (71.43)	2 (28.57)	
SLECTS	1 (33.33)	2 (66.67)	
GTCA	30 (30.93)	67 (69.07)	
GGE-other	13 (59.09)	9 (40.91)	
Presence of myoclonic seizures, *n* (%)	191 (88.43)	25 (11.57)	<.001
Presence of absence seizures, *n* (%)	65 (65)	35 (35)	.618
Presence of GTC seizures, *n* (%)	172 (61.87)	106 (38.13)	<.001
Presence of focal seizures, *n* (%)	5 (55.56)	4 (44.44)	.469
≥5 years of epilepsy remission, *n* (%)	27 (61.36)	17 (38.64)	.401
VAS score			
Mean ± SD Median (Q1–Q2)	5.96 ± 2.08 6 (4–8)	4.78 ± 2.21 5 (4–7)	.004
Duration of headache symptom, months			
Mean ± SD Median (Q1–Q2)	57.55 ± 65.21 36 (12–72)	41.33 ± 52.77 24 (12–60)	.006
Age at headache onset, years			
Mean ± SD Median (Q1–Q2)	22.56 ± 8.32 21 (18–26)	24.26 ± 8.76 22 (18–28)	.421
Age at epilepsy onset, years			
Mean ± SD Median (Q1–Q2)	15.62 ± 5.62 15 (12–18)	15.97 ± 7.92 16 (13–18)	.277

Significant values are in red colour.

Abbreviations: CAE, childhood absence epilepsy; CEOP, childhood epilepsy with occipital paroxysms; GGE-other, other genetic generalized epilepsy; GTC, generalized tonic–clonic; GTCA, epilepsy with generalized tonic–clonic seizures alone; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; Q1, first quartile; SLECTS, self-limited epilepsy with centrotemporal spikes; VAS, visual analog scale.

4.2 | Clustering of all I/GE patients with a symptom of headache

The cluster analysis of the entire cohort with symptoms of headache (child/adolescents and adults combined) revealed three hidden clusters with regard to their headache and epilepsy characteristics. Cluster 1 included patients with frequent and moderate–severe headaches (VAS ≥ 5), and the majority had a family history, indicating a migraine-type primary headache. This cluster consisted mostly of patients with JME

TABLE 4 Cluster analysis results of child/adolescent group with idiopathic/genetic epilepsy patients ($n = 64$)

Characteristic	Cluster 1, $n = 39$	Cluster 2, $n = 25$	p
≥5 headache attacks, *n* (%)	11 (33.33)	22 (66.66)	<.001
Duration of headache, *n* (%)			
<1 h	24 (82.76)	5 (17.24)	.007
1–4 h	7 (36.84)	12 (63.16)	
>4 h	4 (44.44)	5 (55.56)	
>24 h	4 (57.14)	3 (42.86)	
Localization of headache, *n* (%)			
Unilateral	8 (66.67)	4 (33.33)	.649
Bilateral	31 (59.62)	21 (40.38)	
Quality of headache, *n* (%)			
Throbbing	10 (35.71)	18 (64.29)	<.001
Other	29 (80.56)	7 (19.44)	
Family history of headache, *n* (%)	13 (72.22)	5 (27.78)	
Type of epilepsy			
JME	3 (27.27)	8 (72.73)	.167
CAE	7 (77.78)	2 (22.22)	
JAE	6 (50.00)	6 (50.00)	
CEOP	2 (66.67)	1 (33.33)	
SLECTS	15 (75.00)	5 (25.00)	
GTCA	5 (71.43)	2 (28.57)	
GGE-other	1 (50.00)	1 (50.00)	
Presence of myoclonic seizures, *n* (%)	3 (27.27)	8 (72.73)	.012
Presence of absence seizures, *n* (%)	13 (61.90)	8 (38.10)	.912
Presence of GTC seizures, *n* (%)	8 (57.14)	6 (42.86)	.742
Presence of focal seizures, *n* (%)	16 (80.00)	4 (20.00)	.029
≥5 years of epilepsy remission, *n* (%)	6 (66.67)	3 (33.33)	.701
VAS score			
Mean ± SD Median (Q1–Q2)	5.44 ± 1.66 4 (2–6)	4.10 ± 1.80 6 (5–6)	.004
Duration of headache symptom, months			
Mean ± SD Median (Q1–Q2)	11.79 ± 12.59 12 (3–12)	42.76 ± 37.03 24 (18–60)	<.001
Age at headache onset, years			
Mean ± SD Median (Q1–Q2)	12.38 ± 3.09 13 (10–15)	10.70 ± 3.62 11 (9–14)	.078
Age at epilepsy onset, years			
Mean ± SD Median (Q1–Q2)	8.61 ± 3.30 9 (6–11)	9.64 ± 3.96 9 (7–12)	.359

Significant values are in red colour.

Abbreviations: CAE, childhood absence epilepsy; CEOP, childhood epilepsy with occipital paroxysms; GGE-other, other genetic generalized epilepsy; GTC, generalized tonic–clonic; GTCA, epilepsy with generalized tonic–clonic seizures alone; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; Q1, first quartile; SLECTS, self-limited epilepsy with centrotemporal spikes; VAS, visual analog scale.

and those with myoclonic seizures, accordingly. On the other hand, Cluster 3 mainly consisted of patients with focal seizures and a GTCA epilepsy syndrome. Furthermore, patients with shorter headache duration (<1 h) and a shorter headache symptom duration (<24 months), with nonthrobbing headaches, indicating TTH, were also clustered in this group.

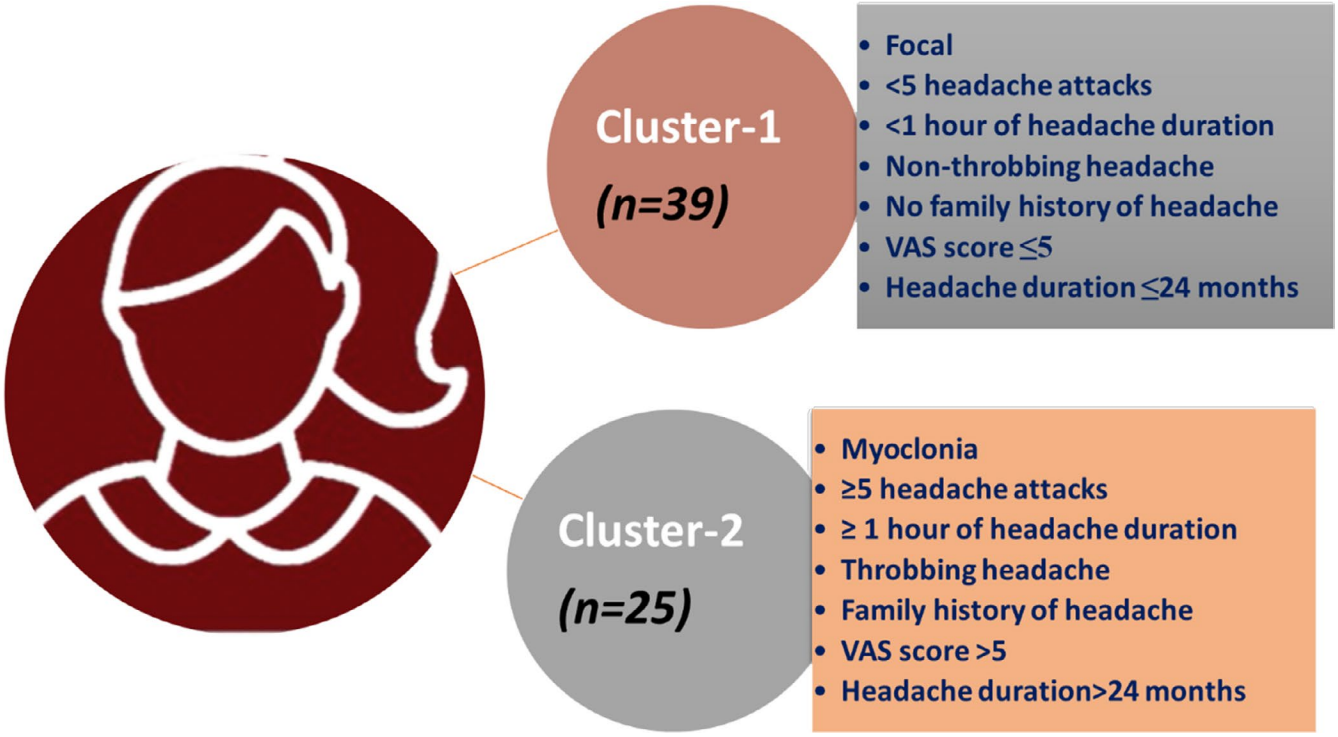


FIGURE 3 The clusters of child/adolescent patients with idiopathic/genetic epilepsy according to their headache and epilepsy characteristics. VAS, visual analog scale

The majority were aged <24 years (65.25%), as expected from the data. These two clusters represented two distinct groups having opposite characteristics within our cohort of patients with I/GE with headaches. Apart from these two different clusters, a small intermediary group of patients with a GTCA syndrome and migrainous headache characteristics was represented in a separate cluster (Cluster 2) in this analysis. The patients in this group had similar characteristics to Cluster 1 in terms of headache quality (throbbing headaches), severity, frequency, and duration, with a definite family of headache history, underlining the migrainous properties of headaches in this group. We believe this is a border zone (a transition zone) between Clusters 1 and 3, where patients with migraine but without a JME syndrome are cumulated. The transition from adolescence age to adulthood and the new onset of migraine within this transition phase might be effective in the development of this separate group.[33] The formation of a separate group including these patients is not surprising in the entire cohort, because migraine is already a very common neurologic disease in the general community.[5,27,28]

4.3 | Cluster analyses of adult and child/adolescent patients with symptom of headache seperately

In adults, Cluster 1 was characterized by more severe, frequent, and throbbing headaches with a longer pain duration, a phenotype of definite migrainous features compatible with studies reporting the close relationship of migraine and epilepsy.[21,34] These adults had symptoms of headache for >24 months. Moreover, patients with a family history of headache were also classified in this group, emphasizing the important role of a possible genetic susceptibility underlying the comorbidity of headaches. The majority had myoclonic seizures and GTCS, compatible with a diagnosis of JME, which showed strong evidence of a genetic background.[17,35] On the other hand, Cluster 2 included patients with moderate, less severe, nonthrobbing, and less frequent headaches, with a shorter duration of pain and a shorter history of headache. These patients had no family history of headache, and the majority were diagnosed as having SLECTS or GTCA, remarkably.

The majority of the patients in Cluster 1 had a syndrome of JME, which is not surprising because a strong link has also been reported between JME and migraine previously.[17, 36] In a small study by Schankin et al., 75 patients with JME were assessed, and a significantly higher prevalence of migraine (41%) was reported. The rate of MwA (15%) was also found to be higher than the general population, which is in line with the MwA rates of the JME group (15.8%) in our study, including 337 patients with JME. They highlighted the role of having a family history of migraine as a strong risk factor for migraine comorbidity, similarly.[17] In another cross-sectional study, the migraine prevalence was found to be 23.5% in patients with JME, whereas it

was 16% in the healthy controls.[37] A plausible explanation for this close relationship between JME and migraine may be through common genetic traits. The coexistence of alterations in the genes encoding ion channel proteins such as *CACNA1A*, *ATP1A2*, *SCN1A*, and *PRRT2* in familial hemiplegic migraine and genetic epilepsies have been extensively documented before.[11,12,38–41]. This shared genetic liability may lead to a neuronal hyperexcitability state by increasing excitatory neurotransmitters such as glutamate, or affecting ion channel functioning such as the Na^+/K^+-ATPase pump, which results in the onset of CSD when it reaches the required threshold.[11,38] The triggering of CSD may eventually facilitate the onset of a migraine attack or epileptic seizure, depending on the type and velocity of the propagation, as the recruitment of trigeminal nuclei can result in central sensitization and pain for migraine or synchronous firing of larger neuronal populations, followed by an epileptic seizure.[11,38] It is also possible that epileptic discharges in patients with JME may facilitate the onset of CSD, which propagates to and activates the trigeminovascular system, which is accepted as the key mechanism of migraine attacks.[42,43] Patients with comorbid headache may be appropriate candidates for future studies focused on JME genetics also stratified by headache phenotypes, because JME is a multigenic disorder comprising distinct genetically determined endophenotypes, as shown by heritability and linkage analysis studies.[44–46]

As a result, we believe the cumulation of patients with JME with migraine in a separate cluster supports the hypothesis that an endophenotype with headache exists in patients with I/GE with a stronger genetic susceptibility. In addition, we showed that milder nonmigraine headaches were cumulated in a separate group and were more closely associated with focal Idiopathic Epilepsies and Migraine and GTCA.

Evaluating patients with I/GE with regard to headache phenotypes may be valuable in clinical management. Treatment with antiseizure medications (ASMs) with antimigraine effects may be more efficient in Cluster 1 patients, because these drugs are effective by restoring the central overexcitation/inhibition imbalance due to the ion channel dysfunction and genetic heritability.[47,48]

Many factors such as genetic background, gradual development of pathophysiologic pathways, myelination, and maturation of cerebral networks may impact the presentation of headache during childhood.[49] We believe that, keeping the potential neurodevelopmental phenotypic changes in the background, our results might help to evaluate child/adolescent patients with I/GE with comorbid headache. After puberty, migraine-like headaches may be incorporated into clinical phenotypes.[50]

It is striking that Cluster 2 in children/adolescents shows migrainous characteristics similar to Cluster 1 in adults. A possible explanation is that, similar to the adult population, genetics may be responsible for the etiopathogenesis of headache in this group.[51,52] Although children/adolescents in Cluster 2 had myoclonic seizures as the main seizure type, similar to Cluster 1 in the adult group, we could not show any specific relationship between headache and JME here, probably due to the small sample size.

Remarkably, however, focal seizures were cumulated in Cluster 1 along with mild/moderate and shorter headaches. Thus, children with idiopathic/genetic "focal" epilepsy experience less disabling headaches, which might not negatively influence quality of life. Our results should be evaluated with caution, and further studies with larger sample sizes are needed due to the limited number of our sample size in the child/adolescent group.

5 | STRENGTHS AND LIMITATIONS

A major limitation of our study might be the recall bias of the patients about the details of their headaches and seizures, but because all patients were regularly followed up, the available data of each patient were rechecked by the physicians. Another limitation is the smaller number of child/adolescent patients when compared with the adult patient cohort, owing to the limited contribution of child neurology centers/experts. However, the main strength of our study is the confirmed epilepsy and headache diagnoses based on the specified-tertiary center data, by experts. Another strong point is the comprehensive dataset including potential bias comparisons and checking all of the required developmental and comorbid issues.

6 | CONCLUSIONS AND FUTURE DIRECTIONS

Headache is a very frequent (62.8%) but a neglected symptom in both adult and pediatric patients with I/GE. This is the first attempt to categorize patients with I/GE in clusters concerning the different characteristics of their headaches. We think that this approach enables the more accurate management of individuals in terms of diagnosis and treatment options. Patients with migrainous features may require carefully selected ASMs and other treatments, effective also on their headaches, rather than over-the-counter medications, whereas other patients can benefit from regular medications and daily life regulation. Further studies addressing the association of headache and epilepsy comorbidity are needed to uncover the hidden mechanisms and genetic links, which could further improve our treatment options.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. 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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