Research Square

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Clinical Profile of Primary Headache Disorders in Patients with Epilepsy and Response to Standard-of-Care Migraine Preventive Treatment: A South Asian Cohort

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Abstract

Background

Headache is among the most frequent comorbidities of epilepsy, yet its clinical profile is poorly characterised and prospective data on treatment response are scarce, particularly from South Asia. This study aimed to characterise the prevalence, profile and predictors of primary headache disorders (PHD) in patients with epilepsy (PWE), and the response of comorbid migraine to 3 months of preventive treatment.

Methods

Over 18 months at a tertiary-care centre in northern India, PWE were prospectively screened for a co-existing PHD. Headaches were classified by ICHD-3 and their temporal relationship to seizures. Predictors of headaches were identified by multivariable logistic regression. Patients with comorbid migraine received standard preventive treatment, reviewed monthly for 3 months; monthly headache-day, migraine-day and seizure counts were compared across visits with the Friedman test (post-hoc Wilcoxon signed-rank), and ≥ 50%-responder proportions with Cochran's Q, with intention-to-treat sensitivity analysis.

Results

Of 814 PWE screened, 346 (42.5%; 95% CI 39.2–45.9) had a PHD. Interictal headache predominated (314; 90.8%), most often migraine (218; 69.4%). Female sex (adjusted OR 2.41; 95% CI 1.46–3.99) and poorer seizure control (adjusted OR 1.63 per category; 1.05–2.51) were independently associated with migraine; antiseizure medication count was not. With migraine preventive treatment, median migraine days progressively fell from 4 to 1 and headache days from 14 to 6 over 3 months (Friedman $p < 0.001$; Kendall's $W = 0.70$ and 0.87), with 79.6% achieving ≥ 50% responder rate; seizure frequency fell only slightly ($W = 0.15$).

Conclusions

Migraine is the predominant interictal headache in PWE; female sex and poorer seizure control independently mark higher migraine risk. Standard preventive treatment was associated with significant, progressive reductions in headache and migraine days, supporting routine headache screening in this subset of population.

Trial registration:

Not applicable. This was an observational study; migraine preventive treatment was prescribed as standard of care and was not allocated by the study protocol.

Background

Epilepsy affects approximately 50 million people worldwide, nearly 80% of whom live in low- and middle-income countries (LMICs) [1], and, together with migraine, ranks among the leading neurological contributors to global disability [2]; headache disorders alone affect 2.9 billion people worldwide, with migraine accounting for about 90% of headache-attributed disability [3]. Headaches are one of the most frequent, yet least systematically examined, comorbidities of epilepsy. A 2026 systematic review and meta-analysis of 73 studies comprising more than 103,000 people with epilepsy (PWE) estimated a pooled headache prevalence of 40%, with interictal (≈ 35%) and postictal (≈ 27%) headache the most frequently reported subtypes [4]. An earlier meta-analysis reported a higher pooled estimate of 48%, and prevalence across individual studies varies widely, underscoring substantial geographic and methodological heterogeneity [5].

The relationship between epilepsy and headache, particularly migraine, is increasingly understood as bidirectional rather than coincidental [6]. Both disorders converge on a shared substrate of cortical hyperexcitability, ion-channel dysfunction, cortical spreading depression and overlapping genetic susceptibility, which plausibly explains their co-occurrence and their common responsiveness to several antiseizure medications [7, 8]. Comorbidity is also clinically consequential: in PWE, coexistent migraine has been associated with a longer duration of epilepsy, a poorer early treatment response and a higher likelihood of drug-refractory disease [9]. Despite this, the visible and more alarming nature of seizures tends to overshadow headaches in routine care, leaving it under-recognised and under-treated, even though contemporary evidence explicitly calls for standardised headache assessment to be integrated into epilepsy management [4, 10].

Beyond prevalence, the detailed clinical phenotype of primary headache disorders (PHD) in PWE remains poorly characterised. The relative distribution of various PHD's varies considerably between cohorts, and their interictal versus peri-ictal patterning, laterality, quality and anatomical location, together with their relationship to seizure type, seizure frequency, antiseizure-medication burden and epilepsy duration, have been described only sparingly and inconsistently. Most available data derive from high-income settings and cannot be directly extrapolated to LMICs, where the majority of the global epilepsy burden resides and where prospectively collected Indian data are particularly scarce [1, 10, 11].

The most consequential gap, however, concerns treatment. In the general population, the efficacy of migraine preventive drugs against placebo is established in randomised trials, and their comparative effectiveness has been synthesised by network meta-analysis [12]. This evidence base, however, does not specifically address PWE, and the few epilepsy-specific reports are small and largely confined to individual antiseizure agents used opportunistically for their dual anti-seizure and anti-migraine action, such as a 31-patient observational study of perampanel [13], though it is not still the standard of care for

migraine preventive treatment. Consequently, to our knowledge, no longitudinal study has tracked how PWE with comorbid migraine respond, over time, to standard-of-care migraine preventive treatment delivered alongside ongoing seizure management.

We therefore conducted a longitudinal study at a tertiary-care neurology centre to characterise the clinical profile of primary headache disorders in patients with epilepsy and to evaluate the response to standard-of-care migraine preventive treatment over a three-month follow-up period.

Methods

Study design and setting

This was a hospital-based, prospective longitudinal study conducted in the Department of Neurology of the Govind Ballabh Pant Institute of Postgraduate Medical Education and Research (GIPMER), a tertiary-care teaching hospital in New Delhi, northern India, over an 18-month period (January 2025 to June 2026). The study protocol was approved by the Institutional Ethics Committee of the Govind Ballabh Pant Institute of Postgraduate Medical Education and Research (GIPMER), New Delhi, India, in accordance with the guidelines of the Declaration of Helsinki. Written informed consent to participate and written informed consent to publish were obtained from every participant, or from a parent or legal guardian for participants younger than 18 years.

Participants

Patients with epilepsy aged 5 years or older attending the neurology outpatient department were screened for a co-existing primary headache disorder. Epilepsy was diagnosed and classified according to the 2017 International League Against Epilepsy (ILAE) classifications of seizure types and of the epilepsies [14, 15]. Eligible participants were those with epilepsy and one or more co-existing symptomatic primary headache disorders. Patients were excluded if they had (i) a secondary headache of non-epileptic cause identified on clinical and/or neuroimaging evaluation, (ii) an inability or unwillingness to provide a reliable headache history, (iii) isolated ictal epileptic headache (headache occurring as a seizure aura), or (iv) age younger than 5 years. Participants were enrolled by random (lottery) sampling from the weekly outpatient epilepsy census.

Sample size

The sample size was based on a previous hospital-based study by Çilliler et al. [16], in which the proportions of migraine and tension-type headache among patients with epilepsy were 26.9% and 17.2%, respectively. Using the formula for a single proportion ($n = Z^2p(1 - p)/d^2$) with a 95% confidence level and 5% absolute precision, the larger estimate yielded a minimum of 302 participants. After inflating this figure by 10% to allow for non-response, the target sample size was 332.

Clinical assessment and data collection

Eligible participants were evaluated using a structured proforma that captured demographic details and a detailed history of both epilepsy and the co-existing headache disorder(s). Epilepsy variables comprised age at seizure onset, seizure type and epilepsy type (per ILAE 2017) [14, 15], average seizure frequency per month over the preceding 3 months, and the number (polytherapy ≥ 2 ASM's), class and duration of antiseizure medications (ASMs). Headache variables comprised age at headache onset, temporal relationship to seizures (interictal, pre-ictal or post-ictal), headache type (per the International Classification of Headache Disorders, 3rd edition [ICHD-3]) [17], average headache frequency per month over the preceding 3 months, duration of individual headache events, laterality, quality, anatomical location and associated aura. Headaches that could not be assigned to a specific ICHD-3 category were recorded as "unclassified." Findings from electroencephalography (EEG) and neuroimaging performed as part of the routine epilepsy workup were documented.

Definitions

Headaches were defined by their temporal relationship to seizures in accordance with established criteria [17, 18]: interictal headache, occurring independently of seizures (more than 24 h before or more than 72 h after a seizure); pre-ictal headache, beginning within 24 h before a seizure and continuing until its onset; ictal headache, occurring exclusively during a seizure; and post-ictal headache, beginning within 3 h after a seizure and resolving within 72 h. Seizure control over the preceding 3 months was categorised as good (no seizures), fair (1–2 seizures/month) or poor (≥ 3 seizures/month). In accordance with ICHD-3 criteria [17], migraine was classified as chronic when headache occurred on ≥ 15 days/month (with migraine features on ≥ 8 days/month) and as episodic otherwise. The duration of individual headache events was recorded as a binary variable, less than 12 h or 12 h or more, rather than in hours.

Treatment protocol and follow-up

Participants with epilepsy and co-existing migraine were managed according to standard migraine-preventive recommendations [19, 20]. Those already receiving a standard preventive agent with adequate benefit continued the same treatment; those with an inadequate response had the agent or dose modified; and those whose headache worsened were switched to an alternative standard preventive agent. Preventive agents used included propranolol, amitriptyline, valproate and topiramate, selected according to guideline recommendations and individual patient factors. Participants with migraines were reviewed at 1, 2 and 3 months. A favorable response was defined a priori as a ≥ 50% reduction from baseline in (i) seizure frequency and (ii) monthly headache days and monthly migraine days.

Outcomes

The primary outcome was the proportion of the different types of primary headache disorder (by temporal relationship to seizures and by ICHD-3 subtype) among patients with epilepsy. The secondary outcome was the response to standard-of-care migraine preventive treatment at 3 months in patients with epilepsy and co-existing migraine.

Statistical analysis

Data were analysed using R version 4.5.3 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were summarised as frequencies and percentages, and continuous variables as mean ± standard deviation or median (interquartile range) according to their distribution. Categorical variables were compared using the chi-square test or the Fisher exact test, and continuous variables using the Mann–Whitney U test (two groups) or the Kruskal–Wallis test (three groups), as appropriate. Where an omnibus Kruskal–Wallis test was significant, post-hoc pairwise comparisons were performed using the Wilcoxon rank-sum test. Associations between two quantitative variables were assessed using the Spearman rank correlation coefficient. Effect sizes were summarised using Cramér's V for categorical associations and odds ratios with 95% confidence intervals. Independent predictors of interictal migraine, relative to the other interictal headache subtypes, were identified using multivariable binary logistic regression with sex, age, duration of epilepsy, seizure type, etiology, seizure-control category and number of antiseizure medications entered as covariates. To address multiple testing, p-values for the subtype comparisons were additionally adjusted using the Benjamini–Hochberg false-discovery-rate procedure. Longitudinal treatment response was analysed from patient-level monthly counts: headache days, migraine days and seizure frequency at baseline and at each of the three follow-up visits were compared using the Friedman test, with post-hoc pairwise Wilcoxon signed-rank tests (Holm-adjusted) and Kendall's W as the effect size; the change across visits in the proportion of patients achieving a ≥ 50% reduction was assessed using Cochran's Q, corroborated by an intention-to-treat analysis in which withdrawals were classified as non-responders. Proportions are reported with 95% Wilson confidence intervals; a two-sided p-value < 0.05 was considered statistically significant.

Use of generative artificial intelligence

During the preparation of this work the authors used Claude (Anthropic) to assist with language editing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Results

Prevalence and distribution of primary headache disorders

During the study period, 814 patients with epilepsy were screened, of whom 346 (42.5%; 95% CI 39.2–45.9), had a co-existing primary headache disorder and constituted the study cohort (Fig. 1). Interictal headache was present in 314 (90.8%) and post-ictal headache in 107 (30.9%) patients; 75 had both, and no patient reported pre-ictal headache. Among patients with interictal headache, migraine was the most

frequent subtype (218; 69.4%), followed by unclassified headache (70; 22.3%) and tension-type headache (TTH; 26; 8.3%); no trigeminal autonomic cephalalgia was identified. Among patients with post-ictal headache, unclassified headache (58; 54.2%) was slightly more frequent than migraine (49; 45.8%), with no TTH or trigeminal autonomic cephalalgia. Relative to the total screened epilepsy population, interictal headache occurred in 38.6% (314/814), post-ictal headache in 13.1% (107/814), migraine in 26.8% (218/814), TTH in 3.2% (26/814) and unclassified interictal headache in 8.6% (70/814).

Demographic and epilepsy characteristics of the headache cohort

Among the 346 patients with a primary headache disorder, 187 (54.0%) were female and 159 (46.0%) were male. with a mean age of 26.2 ± 11.0 years (range 5 to 70); the 21-to-30-year band was the largest (126; 36.4%), followed by 11 to 20 years (108; 31.2%). The mean age at seizure onset was 16.0 ± 10.0 years and the mean duration of epilepsy was 10.2 ± 8.2 years.

Focal seizures were the most common seizure type (177; 51.2%), followed by generalised (90; 26.0%) and unknown onset (79; 22.8%). The etiology of epilepsy was structural in 144 (41.6%), genetic in 101 (29.2%) and unknown in 101 (29.2%). At presentation, 190 patients (54.9%) had good seizure control, 128 (37.0%) fair and 28 (8.1%) poor. Antiseizure-medication (ASM) polytherapy were used in 178 (51.4%) patients, respectively (Table 1). Seizure type did not differ by sex (focal 49.2% vs 53.5%, generalised 28.9% vs 22.6%, unknown 21.9% vs 23.9% in females and males respectively; $\chi^2 = 1.74$, $p = 0.420$) or across age bands ($\chi^2 = 6.87$, $p = 0.143$). Neither current age, age at seizure onset, nor duration of epilepsy differed significantly across the three seizure types (Kruskal–Wallis $p = 0.080$, 0.146 and 0.937 respectively).

Table 1
Demographic and epilepsy characteristics of the study cohort (n = 346).

Characteristic	Value
Age (years), mean ± SD	26.2 ± 11.0
Female sex	187 (54.0)
Age at seizure onset (years), mean ± SD	16.0 ± 10.0
Duration of epilepsy (years), mean ± SD	10.2 ± 8.2
Seizure type, n (%)	
Focal	177 (51.2)
Generalised	90 (26.0)
Unknown	79 (22.8)
Epilepsy etiology, n (%)	
Structural	144 (41.6)
Genetic	101 (29.2)
Unknown	101 (29.2)
Seizure control, last 3 months, n (%)	
Good (0/month)	190 (54.9)
Fair (1–2/month)	128 (37.0)
Poor (≥ 3/month)	28 (8.1)
Antiseizure medication, n (%)	
Polytherapy	178 (51.4)

SD, standard deviation.

Clinical profile of interictal headache

Most common was Interictal migraine (69.4%, 218) predominantly affected females (62.4%; mean age 26.4 ± 11.0 years) and was episodic in 85.3% and chronic in 14.7%. It was typically bilateral (86.2%), pulsating (93.6%) and holocranial (56.4%), with a posterior/parieto-occipital location in 36.2%; aura was infrequent (2.3%). Interictal TTH (n = 26) showed a male predominance (61.5%), was bilateral in all patients, predominantly pressing in quality (84.6%), and most often holocranial (50.0%) or frontal (19.2%). Interictal unclassified headache (n = 70) was also male-predominant (57.1%) and bilateral (85.7%), and event duration mostly short lasting (< 12 h in 97.1%) and a predominantly posterior/parieto-occipital location (50.0%).

On comparison across the three interictal subtypes (Table 2), migraine was significantly more frequent in females ($p < 0.01$), more often involved ≥ 15 headache days/month ($p < 0.001$), longer lasting (> 12 h, $p < 0.001$), was more often pulsating ($p < 0.001$). Headache location also differed significantly ($p = 0.028$), with a frontal location more typical of TTH and a posterior location of unclassified headache and migraine. The subtypes did not differ significantly by epilepsy etiology, seizure type, seizure frequency, headache laterality, age of epilepsy or headache onset, duration of epilepsy or number of ASMs.

Table 2
Comparison of clinical characteristics across interictal headache subtypes.

Variable	Migraine (n = 218)	TTH (n = 26)	Unclassified (n = 70)	p
Female sex, n (%)	136 (62.4)	10 (38.5)	30 (42.9)	< 0.01
Seizure type, n (%)				0.52
Focal	114 (52.3)	17 (65.4)	33 (47.1)	
Generalised	53 (24.3)	6 (23.1)	20 (28.6)	
Unknown	51 (23.4)	3 (11.5)	17 (24.3)	
Epilepsy etiology, n (%)				0.87
Structural	97 (44.5)	12 (46.2)	28 (40.0)	
Genetic	57 (26.1)	8 (30.8)	22 (31.4)	
Unknown	64 (29.4)	6 (23.1)	20 (28.6)	
≥ 15 headache days/month, n (%)	105 (48.2)	6 (23.1)	8 (11.4)	< 0.001
Event duration > 12 h, n (%)	84 (38.5)	1 (3.8)	2 (2.9)	< 0.001
Quality, n (%)				< 0.001
Pulsating	204 (93.6)	4 (15.4)	24 (34.3)	
Pressing	8 (3.7)	22 (84.6)	14 (20.0)	
Dull aching	5 (2.3)	0 (0.0)	10 (14.3)	
Other	1 (0.5)	0 (0.0)	22 (31.4)	
Location, n (%)				0.028
Holocranial	123 (56.4)	13 (50.0)	31 (44.3)	
Posterior/parieto-occipital	79 (36.2)	7 (26.9)	35 (50.0)	
Frontal	8 (3.7)	5 (19.2)	4 (5.7)	
Other	7 (3.2)	1 (3.8)	0 (0.0)	
Headache duration (years), median (IQR)	5 (2–10)	2 (1–6.75)	2 (0–7)	< 0.001

TTH, tension-type headache; IQR, interquartile range. p-values from the chi-square or Fisher exact test (categorical variables) and the Kruskal–Wallis test (continuous variables). Effect sizes for the significant

categorical associations (Cramér's V): headache quality 0.62, event duration 0.36, ≥ 15 headache days/month 0.32, location 0.17.

Post-ictal headache

Post-ictal headache (n = 107) was either migrainous (49; 45.8%) or unclassified (58; 54.2%) and none were TTH in character (Table 3). Generalised-onset seizures tended to be associated with migraine-type post-ictal headache, although this did not reach statistical significance (p = 0.06). Migrainous post-ictal headaches more often lasted > 12 h (61.2% vs 43.1%; p = 0.05) and were more often pulsating (71.4% vs 27.6%; p < 0.001) than unclassified post-ictal headaches. The two subtypes did not differ significantly by gender, etiology, seizure frequency, laterality, location, age at onset, duration of epilepsy or headache, or number of ASMs. After Benjamini–Hochberg correction for multiple comparisons, neither of the borderline post-ictal associations (seizure type and event duration) remained significant (both adjusted p = 0.07).

Table 3
Comparison of post-ictal headache subtypes (n = 107).

Variable	Migraine (n = 49)	Unclassified (n = 58)	p
Seizure type, n (%)			0.06
Focal	23 (46.9)	33 (56.9)	
Generalised	20 (40.8)	12 (20.7)	
Unknown	6 (12.2)	13 (22.4)	
Event duration > 12 h, n (%)	30 (61.2)	25 (43.1)	0.05
Quality, n (%)			< 0.001
Pulsating	35 (71.4)	16 (27.6)	
Pressing	3 (6.1)	12 (20.7)	
Dull aching	3 (6.1)	2 (3.4)	
Other	8 (16.3)	27 (46.6)	

p-values from the chi-square or Fisher exact test (categorical variables) and the Mann–Whitney U test (continuous variables).

Correlations

In the whole cohort, years since headache onset correlated with duration of epilepsy (r = 0.39, p < 0.001), attenuating to r = 0.27 (p < 0.001) after adjustment for current age, and monthly headache days correlated negligibly with baseline seizure frequency (r = 0.11, p = 0.04). Within the interictal migraine subgroup, monthly migraine days correlated weakly with baseline seizure frequency (r = 0.26, p < 0.001) and with the number of ASMs (r = 0.17, p = 0.01), while years since migraine onset correlated with

duration of epilepsy (r = 0.33, p < 0.001; r = 0.18, p = 0.007 after adjustment for age). All correlations were weak in magnitude.

Independent predictors of interictal migraine

To identify factors independently associated with the migraine phenotype, a multivariable logistic regression model was fitted comparing interictal migraine with the other interictal headache subtypes (n = 314). Only female sex (adjusted OR 2.41, 95% CI 1.46–3.99; p = 0.001) and poorer seizure control (adjusted OR 1.63 per category, 95% CI 1.05–2.51; p = 0.029) were independently associated with migraine; age, duration of epilepsy, seizure type, etiology and the number of ASMs were not (Table 4).

Table 4
Multivariable logistic regression: predictors of interictal migraine versus other interictal headache subtypes (n = 314).

Predictor	Adjusted OR	95% CI	p
Female sex	2.41	1.46–3.99	0.001
Age (per year)	1.01	0.99–1.04	0.37
Duration of epilepsy (per year)	1.01	0.97–1.04	0.80
Seizure type (ref. unknown)			
Focal	0.83	0.42–1.63	0.58
Generalised	0.94	0.32–2.71	0.90
Aetiology (ref. unknown)			
Structural	0.87	0.47–1.60	0.66
Genetic	0.60	0.20–1.81	0.36
Poorer seizure control (per category)	1.63	1.05–2.51	0.029
Number of ASMs	0.69	0.41–1.18	0.18

OR, odds ratio; CI, confidence interval; ASM, antiseizure medication. Reference categories are male sex and unknown seizure type/etiology. Seizure control was modelled as an ordinal category (good, fair, poor).

Response to migraine preventive treatment

Of the 218 patients with epilepsy and interictal migraine, 174 (79.8%) required a migraine-preventive drug, while 44 (20.2%) were managed with acute treatment alone. 11, 18 and 22 patients had withdrawn by months 1, 2 and 3, respectively. Median monthly headache days fell from 14 (IQR 14–30) at baseline to 10 (7–24), 8 (6–14) and 6 (4–14) at months 1, 2 and 3, and median migraine days from 4 (2–6) to 2 (1–4), 2 (1–3) and 1 (0–2); both reductions were highly significant across visits (Friedman test, headache days $\chi^2 = 512.3$, migraine days $\chi^2 = 409.6$, both $p < 0.001$), with large effect sizes (Kendall's W = 0.87 and 0.70) and significant improvement at every successive visit (post-hoc Wilcoxon signed-rank,

all Holm-adjusted p < 0.001). Correspondingly, a ≥ 50% reduction in monthly headache days was achieved in 35.7% (74/207), 70.0% (140/200) and 79.6% (156/196) of patients, and in monthly migraine days in 44.9% (93/207), 71.5% (143/200) and 79.6% (156/196), at months 1, 2 and 3 (Table 5); this increase was significant (Cochran's Q, headache days Q = 139.0, migraine days Q = 94.7, both p < 0.001) and remained significant in an intention-to-treat analysis classifying all withdrawals as non-responders (p < 0.001). Seizure frequency before treatment was low: 119 of the 218 patients (54.6%) had had no seizure in the preceding month, and the median was 0 seizures per month (IQR 0 to 1; mean 0.81). Among the 99 patients (45.4%) who had seizures at baseline, the median was 1 per month (IQR 1 to 2; mean 1.79, range 1 to 15). Over follow-up the proportion of patients who were seizure-free rose from 54.6% at baseline to 83.1% (172/207), 84.0% (168/200) and 84.7% (166/196) at months 1, 2 and 3, and the mean monthly seizure frequency fell from 0.81 to 0.52, 0.43 and 0.42, while the median remained 0 at every visit. This change was statistically significant but small (Friedman $\chi^2 = 86.8$, p < 0.001; Kendall's W = 0.15, indicating a far smaller effect than for headache or migraine days) and was confined to the interval between baseline and month 1 (Holm-adjusted p < 0.001), with no further change between months 1 and 2 (p = 0.19) or months 2 and 3 (p = 0.41). A reduction of at least 50% in seizure frequency, which can be assessed only in patients who had seizures at baseline, was achieved by 68.1% (62/91), 69.3% (61/88) and 70.9% (61/86) at months 1, 2 and 3 (Table 5). Change in seizure frequency correlated only weakly with change in monthly migraine days at month 2 (r = 0.22, p = 0.001) and month 3 (r = 0.20, p = 0.006).

Table 5
Proportion of patients achieving ≥ 50% responder rate over 3 months.

Outcome (≥ 50% reduction)	Month 1 (n = 207)	Month 2 (n = 200)	Month 3 (n = 196)
Monthly headache days, n (%)	74 (35.7)	140 (70.0)	156 (79.6)
Monthly migraine days, n (%)	93 (44.9)	143 (71.5)	156 (79.6)
Seizure frequency, n/N (%)[]	62/91 (68.1)	61/88 (69.3)	61/86 (70.9)

Denominators for headache and migraine days reflect attrition (11, 18 and 22 withdrawals by months 1, 2 and 3). The increase across visits in headache-day and migraine-day responder proportions was significant (Cochran's Q, p < 0.001) and robust to an intention-to-treat analysis. []Seizure-frequency response could be assessed only in the 99 patients who had at least one seizure in the month before treatment, since a reduction of 50% cannot be defined from a baseline of zero; denominators are those of this subgroup with available data at each visit.

Discussion

Among 814 people with epilepsy screened, primary headache disorders were identified in 346 (42.5%), and interictal headache predominated, with migraine the most frequent interictal subtype. On multivariable analysis, female sex and poorer seizure control were the only independent predictors of interictal migraine, whereas the number of antiseizure medications was not. Over three months of

guideline-based preventive treatment, monthly headache days and migraine days fell significantly and progressively, and nearly 80% of patients achieved a reduction of at least 50% in both. Together these findings characterise the burden and clinical determinants of headache in epilepsy and add prospective longitudinal data on treatment response.

PHD in epilepsy, especially Migraine and epilepsy co-occur more often than chance alone would predict; meta-analysis estimates an approximately 80% higher lifetime prevalence of migraine among people with epilepsy, and of epilepsy among people with migraine [21]. Cortical hyperexcitability is a feature of both disorders and is the mechanism most often invoked to explain this overlap [6, 18]. A shared genetic basis has been proposed [4], with variants in ion-channel genes such as CACNA1A, SCN1A and ATP1A2 cited in support of a common channelopathy model [7]. Direct genetic evidence of causation is nevertheless lacking, as a recent bidirectional Mendelian randomisation analysis found no evidence that either condition causes the other [22]. A dual-control study offers an alternative explanation, reporting migraine to be more frequent in patients with epilepsy than in unrelated controls (OR 2.87, 95% CI 1.42–5.81) and equally frequent in their first-degree relatives, whereas tension-type headache showed no such association [23]; this pattern of selective, familially aggregated migraine favours shared susceptibility over an effect of epilepsy itself. The relationship may also run in the opposite direction, since comorbid migraine has been linked to longer epilepsy duration, poorer early treatment response and a higher incidence of intractable epilepsy [9]. Our cross-sectional design can describe this association as our data showed migraine was prevalent in 26.8% of patients with epilepsy, but cannot explain the mechanism behind it.

Despite this well-recognised comorbidity, headache in epilepsy is easily overlooked [10]. Consultations are usually dominated by seizure control and drug safety, and headache remains a frequently ignored and underreported comorbidity in people living with epilepsy. The consequences are not trivial. Among 280 adults with epilepsy assessed with the Headache-Attributed Lost Time index, half reported grade 3 or grade 4 disability, and the authors concluded that headache imposes a moderate to severe burden on quality of life and represents a clear clinical need [24]. In children with epilepsy, quality of life is significantly lower in those with headache on both patient and parent report [25]. Migraine is the principal driver of this burden, accounting for approximately 90% of headache-attributed disability worldwide [3]. Systematic screening and appropriate management of headache in people with epilepsy have accordingly been called for [5], yet prospective data on whether such treatment helps have remained limited.

Our prevalence of 42.5% lies within the wide range reported from epilepsy-clinic cohorts, which spans approximately 26% [26] to over 70% [27], and is close to pooled estimates of 48.4% [5] and 40.4% [4]. Interictal headache predominated (90.8%), consistent with the 74.8% reported by Mutlu [26]. Within interictal headache, however, our subtype distribution was unusual: migraine accounted for 69.4% and tension-type headache for only 8.3%. Migraine and tension-type headache were equally frequent (33.1% each) in a prospective cohort of 500 patients with epilepsy [28], tension-type headache accounted for 39% in a Lithuanian series [24], and pooled estimates place it at 26.2% [5]. The migraine-predominant

distribution is nonetheless consistent with the selective association of migraine, but not tension-type headache, demonstrated against controls [23].

The interictal migraine phenotype also departed from the classical description. Pain was bilateral in 86.2% and most often holocranial (56.4%) or posterior (36.2%), although the pulsating quality typical of migraine was preserved in 93.6%. Aura, which affects up to 30% of people with migraine in general populations [8, 29], was recorded in only 2.3%. The bilateral predominance contrasts with a recent prospective cohort in which interictal migraine in epilepsy was mainly unilateral (76.3%) [30], indicating that pain topography in this population is not consistent across settings.

Our multivariable findings both confirm and refine earlier reports. The associations of female sex and higher seizure frequency with migraine described by Çilliler et al. [16] persisted after adjustment, identifying women and patients with poorer seizure control as the groups in whom screening is most likely to be productive. By contrast, the association between antiseizure polytherapy and headache reported in three previous cohorts [16, 28, 31] was not independent once seizure control was included in the model, suggesting that it may be partly confounded by seizure burden rather than reflecting a direct pharmacological effect. Whether headache is genuinely over-represented in epilepsy remains contested at the level of individual cohorts, with elevated migraine prevalence in some studies using general-population comparison [27] but no excess in others [31, 32]; our uncontrolled design cannot resolve this question.

Post-ictal headache affected 30.9% of the cohort, closely matching the pooled prevalence of 27.1% (95% CI 22.5–32.1) in the most recent meta-analysis [4]. That pooled estimate carries near-maximal statistical heterogeneity (I^2 = 96.0%) [4], and individual series diverge widely, one tertiary epilepsy centre reporting post-ictal headache in 78.5% of patients with headache [33]; post-ictal estimates therefore appear strongly dependent on setting and ascertainment. ICHD-3 recognises post-ictal headache as a secondary headache in its own right (code 7.6.2) [17]; we additionally sub-classified these episodes by phenotype, and more than half (54.2%) did not meet the symptom profile of a recognised primary headache type. Where a phenotype could be assigned, migrainous post-ictal headache more often lasted beyond 12 h (61.2% versus 43.1%) and was pulsating (71.4% versus 27.6%). Duchaczek et al. identified generalised tonic-clonic seizures, antiseizure polytherapy and young age at epilepsy onset as predictors of post-ictal headache [31]; in our cohort the association with seizure type did not survive correction for multiple comparisons. Taken with the finding that only five studies of post-ictal headache treatment exist, none providing good-quality evidence [34], post-ictal headache remains the least characterised component of headache in epilepsy.

Prospective treatment data in this population remain scarce, and Duchaczek et al. specifically called for studies using headache and seizure diaries [31]. In our cohort median monthly migraine days fell from 4 to 1 and headache days from 14 to 6 over three months, with 79.6% of patients achieving a reduction of at least 50% in both. This is closely comparable to the only similar study in this population, a 12-month observational study of perampanel in which 22 of 27 patients continuing treatment achieved at least a

50% reduction in migraine attacks and 10 became attack-free [13]. That study, however, used perampanel, an antiseizure medication licensed only for epilepsy and used off-label in migraine, whereas our patients received guideline-recommended preventive agents; our findings therefore speak more directly to what can be expected from standard care in this population. To our knowledge, this is the first prospective study to report the response of migraine to guideline-recommended preventive treatment in an adult cohort with epilepsy. An uncontrolled responder proportion of this size cannot, however, be equated with drug effect. In placebo-controlled trials the increment attributable to topiramate over placebo is approximately 17 percentage points, or 168 additional responders per 1000 treated [35], and of the four agents used here only topiramate is supported by high-certainty evidence, propranolol, valproate and amitriptyline carrying moderate-certainty evidence of benefit [12]. Much of the improvement we observed is therefore likely to reflect the absence of blinding and of a placebo arm, since regression to the mean, spontaneous fluctuation in what is a cyclic disorder, and expectation effects all inflate apparent response in an open-label design. Improvement was also front-loaded, the proportion of migraine-day responders rising by 27 percentage points between months 1 and 2 but by only 8 thereafter; this bears on a question the International Headache Society regards as unsettled, since guidelines advise a minimum preventive trial of four to twelve weeks, most studies assess response at three months, and delayed responses are recognised [36]. Several agents used here are simultaneously anti-seizure medications and migraine preventives, so improvement cannot be attributed to headache-specific treatment, and placebo-controlled trials remain the benchmark against which preventive efficacy is judged.

Strengths and limitations

Strengths of this study include a prospective design with structured three-month follow-up, the use of current ICHD-3 criteria, multivariable adjustment that isolates independent predictors, and longitudinal analysis of patient-level counts (Friedman and Cochran's Q tests) with intention-to-treat sensitivity analysis and false-discovery-rate control.

Several limitations temper interpretation. First, recruitment from a single tertiary centre introduces referral and selection bias and limits generalisability. Second, the absence of a headache-free or non-epilepsy control group precludes estimation of the headache excess attributable to epilepsy; notably, prior studies making such comparisons themselves diverge [27, 31, 32]. Third, the treatment analysis is observational and uncontrolled, so no efficacy or causal inference is warranted. Baseline headache and seizure frequencies were recorded as monthly averages recalled over the preceding 3 months rather than from prospective daily diaries, and are therefore subject to recall bias. Finally, some subgroups (notably interictal tension-type headache) were small, and headache subtyping relied on clinical ICHD-3 assessment without formal inter-rater reliability testing, with a proportion of post-ictal headaches remaining unclassifiable.

Conclusions

Primary headache disorders, predominantly interictal migraine, affect over 40% of people with epilepsy attending neurology services, yet are easily overlooked in consultations focused on seizure control. Female sex and poorer seizure control identify those at highest risk. Because headache in this population carries a measurable burden on quality of life and improved substantially during three months of standard preventive treatment, systematic enquiry about headache should form part of routine epilepsy care. Adequately controlled trials are required to establish how much of the observed improvement is attributable to treatment itself.

Abbreviations

ASM
antiseizure medication
CI
confidence interval
EEG
electroencephalography
GIPMER
Govind Ballabh Pant Institute of Postgraduate Medical Education and Research
ICHD-3
International Classification of Headache Disorders,3rd edition
ILAE
International League Against Epilepsy
IQR
interquartile range
LMIC
low- and middle-income country
OR
odds ratio
PHD
primary headache disorder
PWE
people with epilepsy
SD
standard deviation
TTH
tension-type headache.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Ethics Committee of the Govind Ballabh Pant Institute of Postgraduate Medical Education and Research (GIPMER), New Delhi, India, in accordance with the guidelines of the Declaration of Helsinki. Written informed consent to participate was obtained from every participant, or from a parent or legal guardian for participants younger than 18 years.

Consent for publication

Written informed consent to publish was obtained from every participant, or from a parent or legal guardian for participants younger than 18 years.

Competing interests

The authors declare that they have no competing interests.

Authors' information

Not applicable.

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Author Contribution

BKS contributed to Methodology, Investigation, Formal Analysis, Data Curation, Validation and Writing Original Draft. SML contributed to Writing Original Draft, Formal Analysis, Data Curation and Visualization. SR contributed to Methodology, Validation and Reviewing and Editing. SG contributed to conceptualization, methodology, Supervision, Writing- Reviewing and Editing and Project Administration. All authors read and approved the final manuscript.

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Data Availability

De-identified individual patient data and analysis code are available from the corresponding author upon reasonable request.

References

1. World Health Organization Epilepsy [Internet]. Geneva: World Health Organization; 2024 [cited 2026 Jun 27]. Available from: https://www.who.int/news-room/fact-sheets/detail/epilepsy
2. GBD 2021 Nervous System Disorders Collaborators (2024) Global, regional, and national burden of disorders affecting the nervous system, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Neurol 23(4):344–381. https://doi.org/10.1016/S1474-4422(24)00038-3
3. GBD 2023 Headache Collaborators (2025) Global, regional, and national burden of headache disorders, 1990–2023: a systematic analysis for the Global Burden of Disease Study 2023. Lancet Neurol 24(12):1005–1015. https://doi.org/10.1016/S1474-4422(25)00402-8
4. Sharma A, Paruchuri A, Kola PR, Pal PN, Agarwal A (2026) Burden of headache among people with epilepsy: a systematic review and meta-analysis. Seizure 138:71–83. https://doi.org/10.1016/j.seizure.2026.02.015
5. Duko B, Ayalew M, Toma A (2020) The epidemiology of headaches among patients with epilepsy: a systematic review and meta-analysis. J Headache Pain 21(1):3. https://doi.org/10.1186/s10194-020-1074-0
6. Pelzer N, de Boer I, van den Maagdenberg AMJM, Terwindt GM (2023) Neurological and psychiatric comorbidities of migraine: concepts and future perspectives. Cephalalgia 43(6):3331024231180564. https://doi.org/10.1177/03331024231180564
7. Pascarella A, Marsico O, Abelardo D, Cutellè R, Bulgari A, Mummolo C et al (2025) Epilepsy and migraine: a diagnostic and therapeutic challenge. Front Pharmacol 16:1649543. https://doi.org/10.3389/fphar.2025.1649543
8. Ferrari MD, Goadsby PJ, Burstein R, Kurth T, Ayata C, Charles A et al (2022) Migraine Nat Rev Dis Primers 8(1):2. https://doi.org/10.1038/s41572-021-00328-4
9. Velioğlu SK, Boz C, Özmenoğlu M (2005) The impact of migraine on epilepsy: a prospective prognosis study. Cephalalgia 25(7):528–535. https://doi.org/10.1111/j.1468-2982.2005.00912.x
10. Chovatiya H, Yajnik K, Desai S (2023) Prevalence of headache disorders in patients living with epilepsy in rural region in western part of India. Epilepsy Behav 139:109063. https://doi.org/10.1016/j.yebeh.2022.109063
11. Dhiman V, Menon GR, Kaur S, Mishra A, John D, Rao Vishnu MV et al (2021) A systematic review and meta-analysis of prevalence of epilepsy, dementia, headache, and Parkinson disease in India. Neurol India 69(2):294–301. https://doi.org/10.4103/0028-3886.314588
12. Lampl C, MaassenVanDenBrink A, Deligianni CI, Gil-Gouveia R, Jassal T, Sanchez-Del-Rio M et al (2023) The comparative effectiveness of migraine preventive drugs: a systematic review and

network meta-analysis. J Headache Pain 24(1):56. https://doi.org/10.1186/s10194-023-01594-1

13. Fernandes M, Dono F, Dainese F, Renna R, Consoli S, Gaspari C et al (2021) Perampanel may represent an effective treatment for the prevention of migraine comorbid with epilepsy. Epilepsy Behav 125:108391. https://doi.org/10.1016/j.yebeh.2021.108391
14. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE et al (2017) Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 58(4):522–530. https://doi.org/10.1111/epi.13670
15. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L et al (2017) ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 58(4):512–521. https://doi.org/10.1111/epi.13709
16. Çilliler AE, Güven H, Çomoğlu SS (2017) Epilepsy and headaches: further evidence of a link. Epilepsy Behav 70(Pt A):161–165. https://doi.org/10.1016/j.yebeh.2017.03.009
17. Headache Classification Committee of the International Headache Society (IHS) (2018) ;38(1):1–211. https://doi.org/10.1177/0333102417738202
18. Bauer PR, Tolner EA, Keezer MR, Ferrari MD, Sander JW (2021) Headache in people with epilepsy. Nat Rev Neurol 17(9):529–544. https://doi.org/10.1038/s41582-021-00516-6
19. Ailani J, Burch RC, Robbins MS, Board of Directors of the American Headache Society (2021) The American Headache Society Consensus Statement: update on integrating new migraine treatments into clinical practice. Headache 61(7):1021–1039. https://doi.org/10.1111/head.14153
20. Ravishankar K, Chakravarty A, Chowdhury D, Shukla R, Singh S (2011) Guidelines on the diagnosis and the current management of headache and related disorders. Ann Indian Acad Neurol 14(Suppl 1):S40–59. https://doi.org/10.4103/0972-2327.83100
21. Wu X, Zhuang J (2024) Association between migraine and epilepsy: a meta-analysis. Front Neurol 14:1276663. https://doi.org/10.3389/fneur.2023.1276663
22. Chen F, Sun J, Lei J, Wang Y (2025) Epilepsy and migraine: a bidirectional Mendelian randomization study. Epilepsy Behav 172:110723. https://doi.org/10.1016/j.yebeh.2025.110723
23. Rathore C, Joshi H, Vadodaria V, Yadav M, Prakash S (2026) Selective association and familial aggregation of migraine in epilepsy: evidence from a dual-control study. Epilepsy Behav 182:111093. https://doi.org/10.1016/j.yebeh.2026.111093
24. Mameniškienė R, Karmonaitė I, Zagorskis R (2016) The burden of headache in people with epilepsy. Seizure 41:120–126. https://doi.org/10.1016/j.seizure.2016.07.018
25. Schiller K, Schiller V, Kortas A, Unterholzner G, Raffler S, Schimmel M et al (2024) Primary headache is related to reduced health-related quality of life in children with epilepsy. Healthc (Basel) 12(4):426. https://doi.org/10.3390/healthcare12040426
26. Mutlu A (2018) Association between epilepsy and headache. Neurol Sci 39(12):2129–2134. https://doi.org/10.1007/s10072-018-3558-0

27. Hofstra WA, Hageman G, de Weerd AW (2015) Periictal and interictal headache including migraine in Dutch patients with epilepsy: a cross-sectional study. Epilepsy Behav 44:155–158. https://doi.org/10.1016/j.yebeh.2014.12.025
28. Schiller K, Rauchenzauner M, Avidgor T, Hannan S, Lorenzen C, Kaml M et al (2023) Primary headache types in adult epilepsy patients. Eur J Med Res 28(1):49. https://doi.org/10.1186/s40001-023-01023-8
29. Joppeková Ľ, Pinto MJ, Dias da Costa M, Boček R, Berman G, Salim Y et al (2025) What does a migraine aura look like? A systematic review. J Headache Pain 26(1):149. https://doi.org/10.1186/s10194-025-02080-6
30. Chen Y, Wang C, Zhang H, Zheng Y, Cheng W, Wang Y et al (2025) The characteristics of headache in patients with epilepsy. Cephalalgia 45(7):3331024251352855. https://doi.org/10.1177/03331024251352855
31. Duchaczek B, Ghaeni L, Matzen J, Holtkamp M (2013) Interictal and periictal headache in patients with epilepsy. Eur J Neurol 20(10):1360–1366. https://doi.org/10.1111/ene.12049
32. Tonini MC, Giordano L, Atzeni L, Bogliun G, Perri G, Saracco MG et al (2012) Primary headache and epilepsy: a multicenter cross-sectional study. Epilepsy Behav 23(3):342–347. https://doi.org/10.1016/j.yebeh.2012.01.017
33. Zhang S, Lv Z, Li J, Zhou D (2025) Clinical characteristics of headache related to epilepsy: experience from a tertiary epilepsy center. BMC Neurol 25(1):223. https://doi.org/10.1186/s12883-025-04217-1
34. Shahisavandi M, Zeraatpisheh Z, Rostaminejad M, Asadi-Pooya AA (2021) Treatment of postictal headache: a systematic review and future directions. Epilepsy Behav 119:107971. https://doi.org/10.1016/j.yebeh.2021.107971
35. Raffaelli B, García-Azorín D, Boucherie DM, Amin FM, Deligianni CI, Gil-Gouveia R et al (2023) European Headache Federation (EHF) critical reappraisal and meta-analysis of oral drugs in migraine prevention - part 3: topiramate. J Headache Pain 24(1):134. https://doi.org/10.1186/s10194-023-01671-5
36. Puledda F, Sacco S, Diener HC, Ashina M, Al-Khazali HM, Ashina S et al (2024) International Headache Society global practice recommendations for preventive pharmacological treatment of migraine. Cephalalgia 44(9):3331024241269735. https://doi.org/10.1177/03331024241269735

Figures

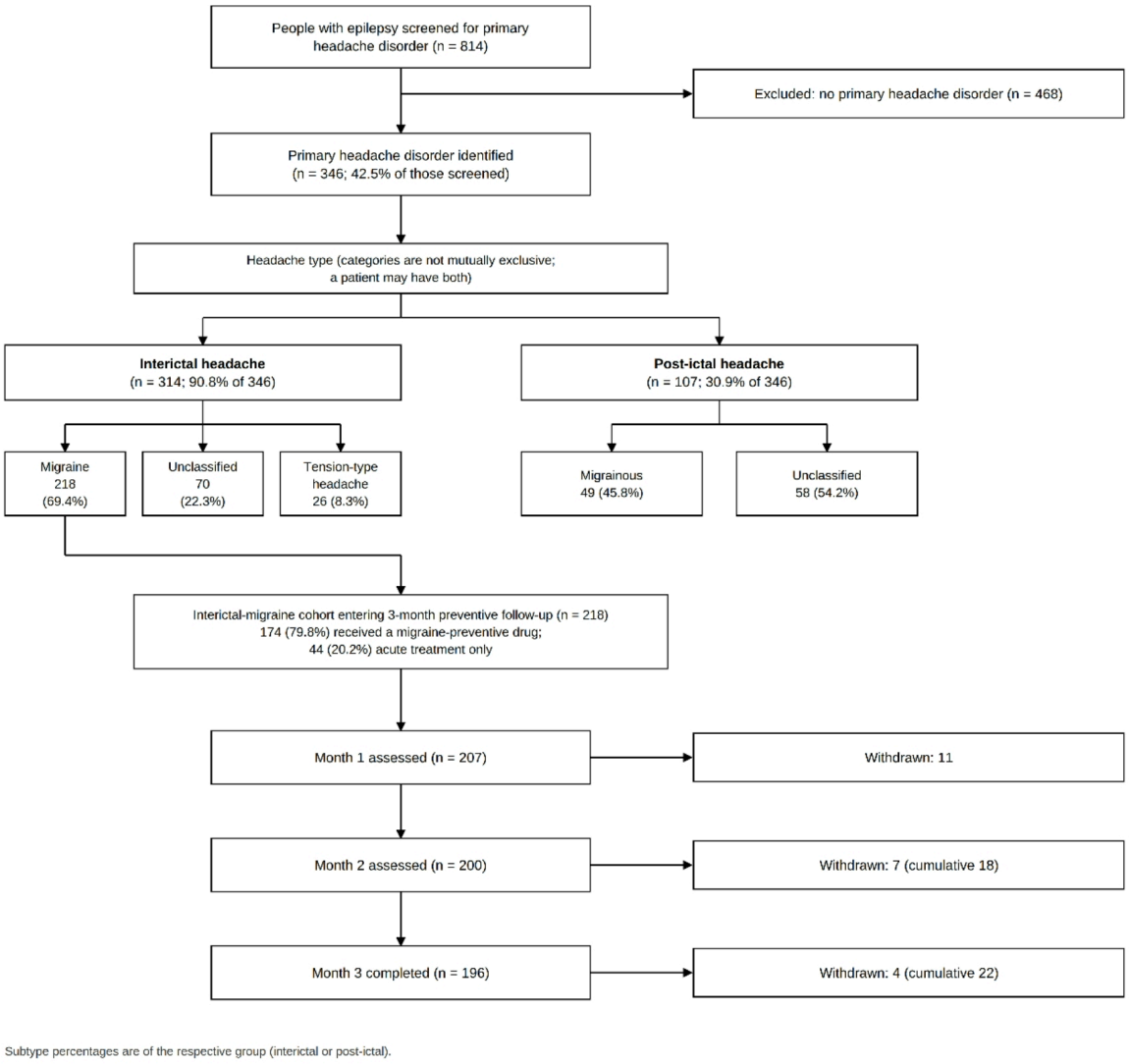


Figure 1

Flow of participants through screening, headache classification and 3-month follow-up.

Supplementary Files

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