

prevalence of interictal migraine among patients with epilepsy

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Research Article

Keywords: Epilepsy, Interictal migraine, Drug-resistant epilepsy

Posted Date: August 11th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10363020/v1>

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Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at The Egyptian Journal of Neurology, Psychiatry and Neurosurgery on October 12th, 2026. See the published version at <https://doi.org/10.1186/s41983-026-01265-3>.

Abstract

Background

Migraine and epilepsy are common neurological disorders that share several pathophysiological mechanisms, including cortical hyperexcitability. Migraine is more frequent in patients with epilepsy than in the general population. This study aimed to determine the prevalence of interictal migraine among adults with epilepsy and evaluate its association with epilepsy characteristics and demographic factors.

Results

This cross-sectional study included 100 adult patients with epilepsy attending the neurology outpatient clinic at Kafr Elsheikh university hospitals. Clinical evaluation, EEG, brain MRI, and migraine assessment according to ICHD-3 criteria were performed. Only interictal migraine was included. Migraine was identified in 25% of patients, with migraine without aura being the most common subtype (76%). Migraine was significantly associated with female sex, earlier age at epilepsy onset, higher seizure frequency, longer seizure duration, drug-resistant epilepsy, multiple antiepileptic drug use, and focal epileptiform EEG abnormalities (all $p < 0.05$). Logistic regression identified female sex, earlier epilepsy onset, prolonged seizure duration, and drug-resistant epilepsy as independent predictors of migraine.

Conclusion

Interictal migraine is a frequent comorbidity in epilepsy, particularly among patients with more severe disease. Early recognition of migraine may improve the comprehensive management and quality of life of patients with epilepsy.

Background

Migraine and epilepsy are among the most common chronic neurological disorders worldwide and constitute major causes of disability. [1].

Historically, migraine and epilepsy have been considered separate neurological diseases with different diagnostic features and clinical presentations. However, accumulating evidence from epidemiological, genetic, and neurophysiological research has demonstrated important biological links between the two disorders, suggesting a reciprocal and multifaceted relationship [2]

Several studies indicate that migraine and epilepsy share common mechanisms involving abnormal neuronal excitability. Alterations in neuronal networks, together with overlapping genetic and molecular pathways, have strengthened the concept that both disorders arise from disturbances in cortical excitability, despite their different clinical outcomes [3].

The hallmark of epilepsy is the occurrence of seizures caused by excessive and synchronized electrical activity within neuronal populations. These abnormal discharges originate from hyperexcitable cortical regions and may either remain confined to a specific area, producing focal seizures, or spread to involve both cerebral hemispheres, resulting in generalized seizures [4].

The mechanisms responsible for migraine are less clearly defined and continue to be the focus of ongoing research. Current evidence suggests that dysfunction of cortical neuronal networks, leading to increased cortical excitability, plays an important role in initiating migraine attacks in susceptible individuals [5].

One of the best-recognized neurophysiological phenomena associated with migraine, particularly migraine with aura, is cortical spreading depression (CSD). This process consists of a slowly advancing wave of neuronal and glial depolarization that travels across the cerebral cortex at approximately 2–3 mm/min. The depolarization phase is preceded by transient neuronal hyperactivity and followed by prolonged suppression of neuronal electrical activity [6].

Experimental and clinical studies have demonstrated that CSD activates the trigeminovascular system, initiating a cascade of neurovascular events. This activation promotes the release of calcitonin gene-related peptide (CGRP), a key neuropeptide involved in migraine pathogenesis, which contributes to headache generation through vasodilation and sterile neurogenic inflammation of the meninges [7].

Methods

This was a cross-sectional observational study conducted on 100 adult patients diagnosed with epilepsy according to the criteria of the International League Against Epilepsy 2025. The study was carried out at the Neurology outpatient Clinic at Kafr Elsheikh university hospitals.

The study specifically focused on interictal migraine occurring independently of seizure episodes. Only headaches fulfilling the diagnostic criteria for migraine and occurring outside the temporal relationship with seizures were included in the analysis.

Patients presenting with isolated peri-ictal headaches, including pre-ictal, ictal, or post-ictal headaches, without evidence of independent interictal migraine were excluded. In addition, patients whose headaches occurred exclusively in direct temporal relation to seizure episodes were not included in the study.

The study protocol was reviewed and approved by the Institutional Ethics Committee of Kafrelsheikh Faculty of Medicine. Written informed consent was obtained from all enrolled participants prior to inclusion in the study. Patients were recruited during the period from January 2026 to June 2026.

Patients aged ≥ 18 years who were diagnosed with epilepsy according to the 2025 criteria of the International League Against Epilepsy and had a documented electroencephalogram result were included.

Exclusion criteria patients younger than 18 years, patients who refused to participate in the study, patients with symptomatic epilepsy secondary to craniocerebral injury, cerebral haemorrhage, cerebral infarction, intracranial space-occupying lesions, or inherited metabolic diseases, patients with a history of intellectual disability or other serious developmental disorders, patients with progressive central nervous system disorders (e.g., Dementia, demyelinating disorders, or Parkinson's Disease), patients with significant hepatic, renal, or cardiopulmonary disease, patients with acute symptomatic seizures, patients with psychogenic non-epileptic seizures, and patients presenting with peri-ictal headache only (pre-ictal, ictal, or post-ictal headache).

.All patients were subjected to complete history taking: (age at onset of disease), (sex), (frequency of seizures), (duration of epilepsy), (quantity of AEDs of epileptic patients), complete general and neurological examination

Magnetic Resonance Imaging of brain

MRI Technique: The brain MR imaging examinations were done by using a 3-tesla scanner (Acheiva; Philips Medical Systems, Best, Netherlands) at radiology department, Kafrelsheikh University Hospital. All patients were examined in the supine position using head coil. Routine images (T2, T1, FLAIR) were done to all patients: repetition time (TR) _ 9583 sec, echo time (TE) _ 25 sec, inversion time (TI) _ 3400 sec, IR delay _ 325 sec, echo train length (ETL) _ 17, 50 contiguous axial slices, thickness _ 3 mm, matrix size 240× 142 mm², field of view (FOV) 230× 184 mm².

Electroencephalogram (EEG)

EEG recordings were performed in the Neurology department using Nihon Kohden (model EEG 1200K), 21 EEG channels, using hyperventilation and photic stimulation as provocative procedures. EEGs were recorded while the subjects were awake with their eyes closed. The electrode placement was done in accordance with the international standard 10–20.

Migraine Assessment

Migraine diagnosis was based on the criteria of the International Headache Society and the International Classification of Headache Disorders, 3rd Edition (ICHD-3).

Patients were evaluated regarding the presence of migraine, migraine subtype (migraine with aura or migraine without aura), and the frequency and duration of migraine attacks. The study mainly focused on interictal migraine occurring independently of seizure episodes.

Statistical analysis and data interpretation

Data analysis was performed by SPSS software, version 26 (SPSS Inc., PASW statistics for windows version 26. Chicago: SPSS Inc.). Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non-normally distributed data and mean $\pm$ Standard deviation for normally distributed data after testing normality using Kolmogorov-Smirnov test. Significance of the obtained results was judged at the (0.05) level.

- Chi-Square, Monte Carlo tests were used to compare qualitative data between groups as appropriate
- Mann Whitney U test was used to compare between 2 studied groups for non-normally distributed data.
- Student t test was used to compare 2 independent groups for normally distributed data.
- The Spearman's rank-order correlation is used to determine the strength and direction of a linear relationship between two non-normally distributed continuous variables and / or ordinal variables.
- Binary logistic regression was used to assess the effect of combination of more than 2 independent variables on dichotomous outcome using Stepwise / forward Wald / Enter technique.

Results

A total of 100 patients diagnosed with epilepsy were enrolled in the study. The mean age of participants was 32.12 ± 5.71 years, ranging from 22 to 43 years. Males represented 57% of the studied population, while females accounted for 43%. The mean age at disease onset was 26.15 ± 6.20 years (**Table 1**). .

Migraine was present in 25% of patients, while 75% had no history of migraine. Among migraine-positive patients, 76% had migraine without aura, whereas 24% had migraine with aura. The median migraine attack frequency was 5 attacks per month (range: 2–7), with a median attack duration of 8 hours (range: 5–12 hours) (**Table 2**).

Among epilepsy patients diagnosed with migraine, no statistically significant difference was observed between patients with migraine with aura and those with migraine without aura regarding age ($p = 0.571$) or age at epilepsy onset ($p = 0.09$) (**Table 3**).

Regarding migraine attack duration, a significant positive correlation was observed with patients' age ($r = 0.454$, $p = 0.023$), indicating that older patients tended to experience migraine attacks of longer duration. However, no statistically significant correlations were detected between migraine attack duration and age at onset of epilepsy, duration of epilepsy, or frequency of epileptic seizures, suggesting that these epilepsy-related factors were associated mainly with migraine recurrence rather than the duration of individual migraine episodes (**Table 4**).

Within the subgroup of epilepsy patients with comorbid migraine, female sex emerged as the only categorical factor significantly associated with increased migraine attack frequency, indicating a possible sex-related influence on migraine expression. However, neither drug resistance, AED burden, nor

EEG abnormalities demonstrated any significant relationship with migraine attack frequency or duration. This pattern suggests that while epilepsy-related clinical factors may increase susceptibility to migraine development, they do not appear to substantially influence migraine severity once the condition is established, supporting the concept that migraine expression may be driven by partially independent neurobiological mechanisms (**Table 5**).

This table demonstrates that female sex, earlier onset of Epilepsy, prolonged seizure duration, and drug-resistant epilepsy were significant independent predictors of comorbid Migraine. Female patients had a 5.14-fold higher risk of migraine (OR = 5.14, 95% CI: 1.89–13.92, $p = 0.001$), while drug-resistant epilepsy increased the risk by 5.24-fold (OR = 5.24, 95% CI: 1.99–13.79, $p = 0.001$).

In addition, each later one-year increase in age of epilepsy onset was associated with a lower probability of migraine (OR = 0.738, 95% CI: 0.643–0.847, $p = 0.001$), whereas longer seizure duration was associated with a markedly increased risk (OR = 4.58, 95% CI: 2.25–9.29, $p = 0.001$). Age was not significantly associated with migraine occurrence ($p = 0.100$) (**Table 6**).

Discussion

The present study investigated the prevalence, clinical characteristics, associated factors, and predictors of interictal migraine among patients with epilepsy, aiming to better characterize the relationship between these two highly prevalent neurological disorders that are believed to share overlapping pathophysiological mechanisms. Our findings demonstrated a relatively high burden of migraine among epilepsy patients, with significant associations between migraine occurrence and several demographic, clinical, electrophysiological, and disease severity variables.

In our study, 100 patients with epilepsy were included, with a mean age of 32.12 ± 5.71 years, ranging from 22 to 43 years. Male patients represented 57% of the studied population, while females accounted for 43%. The mean age at onset of epilepsy was 26.15 ± 6.20 years, median disease duration was 5 years, and median seizure frequency was one attack per month. Drug-resistant epilepsy was identified in 65% of patients, while focal epileptogenic abnormalities represented the most common EEG finding, observed in 47% of patients. These baseline epidemiological findings were generally comparable to those reported by **Shi et al.** [6] who studied 1326 patients with epilepsy and reported a median age of 32 years, male predominance of 52.1%, and drug-resistant epilepsy prevalence of 23.5%, although their cohort demonstrated a longer median disease duration of 10 years .

Our study demonstrated that migraine was present in 25% of epilepsy patients, while 75% had no history of migraine. Among migraine-positive patients, migraine without aura represented the predominant subtype accounting for 76% of cases, while migraine with aura accounted for only 24%. This prevalence was higher than that reported by **Shi et al.** [6] who identified migraine in 19.2% of epilepsy patients. Similar findings were reported by **HELP** [8] who found migraine prevalence of 12.4% among 597 epilepsy patients, while **Wang et al.** [9] reported interictal migraine in 12.53% of 1109 patients with epilepsy.

Collectively, these findings strongly support that migraine occurs significantly more frequently among epilepsy patients than in the general population, suggesting the presence of shared pathophysiological mechanisms linking both disorders [10].

Regarding demographic associations, female sex showed a highly significant association with migraine occurrence in our study, where females represented 72% of migraine-positive patients compared with only 33.3% among non-migraine patients ($p = 0.001$). Similar observations were reported by **Shi et al.** [6] who found females accounted for 55.1% of migraine-positive patients ($p = 0.010$), while **HELP** [8] reported female predominance reaching 68.9% among migraine patients ($p < 0.001$) [2]. Wang et al. similarly reported that headache disorders were more common among female epilepsy patients than males (63.75% versus 57.17%). This consistent female predominance may be explained by hormonal influences, particularly estrogen-mediated modulation of trigeminovascular activation and cortical excitability, which increase migraine susceptibility among female patients [11].

Concerning age-related variables, our study demonstrated no statistically significant difference regarding current age between migraine-positive and migraine-negative patients (32.67 ± 6.08 vs 30.48 ± 4.11 years, $p = 0.098$), which is partially comparable to **Shi et al.** [6] who reported only a slight difference between both groups (median 31 vs 32 years, $p = 0.046$). In contrast, age at onset of epilepsy demonstrated a highly significant association with migraine occurrence in our study. Patients with migraine had significantly earlier epilepsy onset compared with patients without migraine (20.44 ± 4.21 vs 28.05 ± 5.58 years, $p < 0.001$). Similar findings were reported by **HELP** [8] who demonstrated significantly earlier epilepsy onset among migraine patients .

Seizure burden was strongly associated with migraine occurrence in our study. Patients with migraine demonstrated significantly higher seizure frequency compared with patients without migraine, with median seizure frequency reaching 10 attacks per week compared with 4 attacks per week among non-migraine patients ($p = 0.001$). Similarly, **Shi et al.** [6] demonstrated that migraine-positive patients were significantly more likely to experience seizures during the preceding three months (74.4% versus 59.9%, $p < 0.0001$). In addition, seizure duration was significantly longer among migraine patients in our study (10.04 ± 2.30 vs 4.61 ± 1.27 minutes, $p < 0.001$). These findings suggest that increased epileptic activity may facilitate cortical spreading depolarization and activation of trigeminovascular pathways involved in migraine pathogenesis [10]

Drug-resistant epilepsy represented another major associated factor in our study. Among migraine-positive patients, 64% had drug-resistant epilepsy compared with only 25.3% among non-migraine patients ($p < 0.001$). Similar findings were reported by **Shi et al.** [6] who observed significantly poorer seizure outcomes among migraine patients, with drug-resistant epilepsy being more frequent in migraine-positive patients (29.1% vs 22.1%, $p = 0.007$). Furthermore, treatment burden was significantly higher among migraine patients in our study, as 92% of migraine-positive patients were receiving three antiseizure medications compared with only 9.3% among non-migraine patients ($p < 0.001$). Similarly, **Schiller et al.** [12] demonstrated that patients receiving polytherapy were significantly more likely to

report migraine than patients receiving monotherapy ($p = 0.028$). These observations suggest that more severe epilepsy phenotypes and poor seizure control may contribute significantly to migraine susceptibility.

EEG findings further supported this relationship. Focal epileptogenic abnormalities were significantly more frequent among migraine-positive patients, observed in 80% compared with 36% among non-migraine patients, while none of migraine-positive patients demonstrated normal EEG findings ($p < 0.001$). Comparable findings were reported by Shi et al., who demonstrated significantly higher migraine prevalence among patients with focal epilepsy and focal-to-bilateral tonic-clonic seizures (24.5% versus 17.6%, $p = 0.023$). These findings support the hypothesis that focal cortical dysfunction may represent an important shared pathophysiological substrate linking epilepsy and migraine [6].

Regarding migraine subtype analysis, our study demonstrated that migraine without aura represented the predominant subtype and was associated with significantly greater disease burden. Patients with migraine without aura demonstrated significantly longer attack duration compared with migraine with aura patients (10.58 ± 2.27 vs 8.33 ± 1.51 hours, $p = 0.036$), while migraine frequency was significantly higher (median 5 vs 2.5 attacks/week, $p = 0.001$). Interestingly, all patients with migraine with aura were males, whereas 94.7% of migraine without aura patients were females ($p = 0.001$). These findings may suggest more sustained trigeminovascular activation in migraine without aura, resulting in more frequent and prolonged headache attacks [6].

Correlation analysis provided additional important findings. Migraine attack frequency demonstrated significant negative correlation with age at epilepsy onset ($r = -0.415$, $p = 0.039$), significant positive correlation with epilepsy duration ($r = 0.732$, $p = 0.001$), and the strongest positive correlation with seizure frequency ($r = 0.941$, $p = 0.001$). Female patients also demonstrated significantly higher migraine frequency than males (median 5 vs 3 attacks/month, $p = 0.001$). In contrast, migraine attack duration showed significant positive correlation only with patient age ($r = 0.454$, $p = 0.023$). These findings suggest that epilepsy severity mainly influences migraine recurrence rather than duration of individual headache episodes.

Finally, multivariable logistic regression analysis identified female sex, earlier age at epilepsy onset, prolonged seizure duration, and drug-resistant epilepsy as independent predictors of migraine occurrence. Female sex increased migraine risk by more than fivefold (OR = 5.14, 95% CI 1.89–13.92, $p = 0.001$), while drug-resistant epilepsy similarly increased migraine risk by approximately five times (OR = 5.24, 95% CI 1.99–13.79, $p = 0.001$). Each one-year increase in age at epilepsy onset reduced migraine probability (OR = 0.738, $p = 0.001$), whereas prolonged seizure duration significantly increased migraine risk (OR = 4.58, $p = 0.001$). Similar findings were reported by **Shi et al.** [6] whose multivariable analysis identified female sex, focal-to-bilateral seizure propagation, and recent seizure activity as independent predictors of migraine occurrence. Overall, our findings strongly suggest that migraine among epilepsy patients is closely associated with markers of disease severity including poor seizure control, prolonged seizure duration, early disease onset, focal epileptiform abnormalities, and drug resistance, further

supporting the hypothesis that both disorders share common neurobiological mechanisms involving cortical hyperexcitability, altered ion channel function, glutamatergic dysregulation, and cortical spreading depression [10]

Several mechanisms may explain the observed association between epilepsy and migraine. Both disorders share common pathophysiological pathways including cortical hyperexcitability, ion channel dysfunction, glutamatergic neurotransmission abnormalities, altered serotonin signaling, and cortical spreading depolarization. Repeated seizure activity may progressively sensitize trigeminovascular pain pathways, thereby increasing susceptibility to migraine attacks. Furthermore, the predominance of focal epileptic abnormalities among migraine patients supports the hypothesis that focal cortical dysfunction may contribute directly to coexistence of both disorders.

Limitations

The relatively small sample size and single-center design may limit generalizability. In addition, the cross-sectional design prevents establishment of causal relationships between epilepsy severity and migraine occurrence. Larger multicenter prospective studies are required to better clarify temporal relationships and identify optimal therapeutic strategies for patients suffering from both disorders.

Conclusion

Migraine represents a frequent and clinically important comorbidity among patients with epilepsy. Female sex, earlier epilepsy onset, longer seizure duration, higher seizure frequency, drug-resistant epilepsy, focal epileptiform EEG abnormalities, and greater antiseizure medication burden were all strongly associated with migraine occurrence. These findings emphasize the importance of routine migraine screening among epilepsy patients, particularly those with poorly controlled seizures, and further support the concept of shared neurobiological mechanisms underlying both epilepsy and migraine.

Abbreviations

- CSD
Cortical spreading depression
- CGRP
Calcitonin gene-related peptide
- AEDs
antiepileptic drugs
- EEG
Electroencephalogram
- MRI
Magnetic Resonance Imaging

• SD
standard deviation

Declarations

Author Contribution

IS: Organization of the data, execution of the project, analysis of the data, review, writing of the first draft, and review and critique. SE: organization of data, execution of the project and statistical analysis, writing of first draft, and reviewing and critique. IB: Organization of the data, execution of the project and statistical analysis, writing of the first draft, and review and critique. supervision of the research, design of the statistical analysis, execution of the statistical analysis, review of the results, writing of the first draft of the manuscript, review of the first draft of the manuscript and critique. All authors reviewed the manuscript and approved the final manuscript.

Acknowledgement

THANKS

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Tables

Table 1 to 6 are available in the Supplementary Files section.

Supplementary Files

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