

## A Cross-sectional Study of Clinical Characteristics of Headache in Patients with Idiopathic Epilepsy

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### ABSTRACT

**Background:** Headache and epilepsy are common neurological disorders and their relationship is still incompletely known. The purpose of our work was to estimate the most common types of primary headache syndromes and its relation to seizure timing in epileptic patients.

**Patients & Methods:** In a cross-sectional study, we evaluated headaches in 100 consecutive patients with idiopathic epilepsy attending the medicine and neurology outpatient department at Darbhanga Medical College and Hospital, Laheriasarai, Bihar by complete medical history, physical and neurologic examination EEG and CT brain.

**Results:** Of our study population, 78% of patients with epilepsy reported headaches. Migraine occurred in 70.6% of patients with headache followed by tension-type headache in 25.58% of patients and other types of headaches occurred in 2.56% of patients. There were 8 patients (10.1%) had a pre-ictal headache, 52 patients (66.5%) had a postictal headache and 39 patients (50%) had an interictal headache. In our study, we found that the occurrence of headache being linked to the female sex, lower mean age, lower mean age at the onset of epilepsy, focal epilepsy, longer duration of epilepsy, high frequency of seizures and the use of polytherapy of antiepileptics.

**Conclusion:** Headache especially migraine is an important comorbidity of epilepsy and should receive more attention especially in female patients, patients with younger age, lower mean age at epilepsy onset, longer duration of the disease, patients on polytherapy, patients with higher frequency of seizures and patients with focal epilepsy.

**Keywords:** Epilepsy, Headache, Migraine, Preictal Headache, Interictal Headache, Postictal Headache

### INTRODUCTION

More than 70 million people of variable ages, races, and social classes, especially in low and middle-income countries suffer from epilepsy worldwide <sup>[1]</sup>. It was reported that the lifetime incidence of epilepsy is ranging from 1 to 26 with a peak age ranges from 30 to 50 years. Variability in the prevalence rates of neurological disorders has been observed across various

epidemiological studies in the country. For example, the prevalence of epilepsy has been reported between 2.2 and 10.4 per 1,000 population across different regions in India. This variation in the prevalence rates of neurological disorders attributes to differences in the manner the cases are defined and identified in each study, and the inclusion and exclusion criteria's used, which poses a problem to understand the actual burden of neurological disorders. A meta-analysis of 20 studies to estimate the prevalence of epilepsy was published in 1999 but thereafter no meta-analysis has been published on the prevalence of common neurological disorders in India.<sup>[3] [4]</sup>

Both epilepsy and headache are very common neurological disorders with episodic attacks. Patients with epilepsy may suffer from disabling headaches as one of the most common comorbidities that may add more burdens to those patients.

A headache is often under diagnosed because both physicians and patients are often paying more attention to epilepsy rather than a headache <sup>[5] [6] [7]</sup>.

Present study aimed to estimate the most common types of primary headache syndromes and its relation to seizure timing in epileptic patients.

## **MATERIALS AND METHODS**

Across-sectional study was conducted at Department of Medicine and Neurology. The study participants were recruited from the neurology outpatient of Darbhanga Medical College and Hospital, Laheriasarai, Bihar in the period from January 2020 to December 2020. The study included 100 consecutive patients with idiopathic epilepsy with disease duration of more than one year. Idiopathic epilepsy is defined as epilepsy in absence of significant past history of etiologic cause, abnormal neurological examination and/or structural brain abnormalities detected by brain imaging (CT or MRI).

Patients with mental retardation, learning disabilities, behavioral disorders or other evident abnormalities that could compromise the ability to respond to the questionnaires and patients with secondary (symptomatic) epilepsy were excluded from the study by performing mini-mental state and CT brain. Informed consent was given by all patients.

Complete medical history, physical and neurologic examination was done for all patients. Electroencephalography in resting awake condition with eyes closed was done for all patients. The EEG data were acquired by a computer-based system. Brain imaging (CT or MRI) and other laboratory investigations including complete blood count, renal functions, liver functions, random blood glucose, and serum electrolytes were done to exclude patients with symptomatic causes of epilepsy.

### **Assessment of Epilepsy**

Direct interview with patients with epilepsy was done and the type of epilepsy was determined according to the criteria of the International League Against Epilepsy 2010, the seizure frequency divided into four grades (<1/year; ≥1/year to <1/month; ≥1/month to <1/week and ≥1/week) <sup>[8]</sup> the used medications, the predisposing factors, positive family history of headache and epilepsy, history of febrile convulsions and the use of analgesic and its type were taken for each of the study participants.

### **Assessment of Headache**

The type of headache was determined according to the International-Headache-Classification-III-ICHD-III-2013-Beta. According to the temporal relationship with seizures 1) a Peri-ictal headache which is further divided into a preictal headache, ictal and post-ictal headache. A pre-

ictal headache was defined as a headache appearing within 24 hours before the seizure. An ictal headache was present exclusively during the seizure. A post-ictal headache was defined as a headache which develops within 3 hours following a partial or generalized seizure and resolves within 72 hours after the end of the seizure. 2) An inter-ictal headache includes all headaches that manifested within a time period of the epileptic disease and whose attacks were not temporally related to an epileptic seizure (within more than 72 hours of the last seizure).

### Statistical Analysis

Data were analyzed using Microsoft Excel Ver. 12.0. Quantitative data were represented as mean  $\pm$ SD for normally distributed data, and median (range) for abnormally distributed data. Student t-test or Mann-Whitney test were used for data analysis according to the normality of the distribution of the data. Qualitative data were presented as number and percentage and compared using either Chi square or Fisher exact tests. P value was considered significant if it was less than 0.05.

## RESULTS

One hundred patients with idiopathic epilepsy (mean age =  $24.7 \pm 8.20$  years) participated in the study, 59% percent of the patients were females and 41% were males.

### Epilepsy Related Data

Seventy-four percent of the patients suffer focal seizures, 25% suffer generalized seizures, and one patient (1%) suffers unclassified seizures depending on the clinical history. The mean age at the onset of epilepsy is  $16.26 \pm 8.88$  years. The mean duration of epilepsy is  $8.39 \pm 5.33$  years. Three patients (3%) do not take antiepileptic medications, fifty patients (50%) take one antiepileptic drug (mono-therapy) for treatment and forty-seven patients (47%) were taking more than one antiepileptic drug (polytherapy). Nineteen patients (19%) had a seizure frequency of  $<1$  seizure per year, 17 patients (17%) had a seizure frequency of  $\geq 1$ /year to  $<1$ /month, 44 patients (44%) had a seizure frequency of  $\geq 1$ /month to  $<1$ /week and 20 patients (20%) had a seizure frequency of  $\geq 1$  seizure per week. Eleven patients (11%) had a previous history of febrile convulsions. Eighteen patients (18%) had a positive family history of epilepsy. Twelve patients (12%) had a positive family history of a chronic headache including migraine and its subtypes.

Inter-ictal EEG was normal in 41 patients (41%), showed focal epileptic form discharges in 51 patients (51%) while 8 patients (8%) have generalized epileptic form discharges. Of patients with focal epileptic form discharges, left hemispheric discharges were present in 27 patients (51%) and right hemispheric discharges in 24 patients (49%), temporal discharges in 23 patients (45%), frontal discharges in 23 patients (45%) and occipital discharges in 5 patients (10%).

### Headache Related Data

Seventy-eight patients with epilepsy (78%) were suffering from headache. Migraine was diagnosed in 56 patients (70.6%; 6 patients suffered a migraine with aura, 45 patients suffered a migraine without aura, and 5 patients suffered probable migraine). The second most prevalent headache was tension type headache that occurred in 20 patients (25.58%) including 18 patients (23.08%) with tension type headache and 2 patients (2.56%) with probable tension headache. Only 2 patients (2.56%) had other types of headaches; one patient had episodic cluster headache and the other had a probable cluster headache. The degree of severity of headache in patients with headache was as the following: Mild degree in 10 patients (12.82%), moderate degree in 50 patients (64.10%) and severe degree in 18 patients (23.08%)<sup>[9]</sup>.

### Relation of Headache to Seizure Timing

There were 8 patients (10.1%) had a pre-ictal headache that evolved into seizures including 4 patients had only pre-ictal headache, 2 patients had both pre-ictal and post-ictal headaches and 2 patients had pre-ictal, post-ictal and inter-ictal headaches. There were 52 patients (66.5%) had a post-ictal headache who reported a headache after seizure including 33 patients (42.31%) had only post-ictal headache, 15 patients (19.23%) had a post-ictal and inter-ictal headache, 2 patients (2.56%) had post-ictal and pre-ictal and 2 patients (2.56%) had three types of pre-ictal, post-ictal and inter-ictal headaches. There were 39 patients (50%) had inter ictal headache who reported a headache in between seizures and no related to them including 22 patients (28.21%) had only inter-ictal headache, 15 patients (19.23%) had post-ictal and inter-ictal headache and 2 patients (2.56%) had post-ictal, inter-ictal and pre-ictal headache (Table 1).

### Comparison between Headache Group and Non-Headache Group

Population characteristics and intergroup differences analysis results regarding headache existence are shown in (Table 2). There were statistically significant differences in age, gender, age at onset of epilepsy, epilepsy duration, epilepsy type, the frequency of seizures and EEG finding between both groups. But there were no statistically significant differences in family history of a headache and epilepsy and history of febrile convulsions between both groups.

**Table 1 : The Timing of Headache in relation to the epileptic seizures**

Patients	Timing of Headache					
	Peri-ictal			Inter-ictal		
	Pre-ictal	Pre & post-ictal	Post-ictal	Pre-ictal	Pre & post-ictal	Post-ictal
Number	4	2	33	22	15	2
Percentage	5.13%	2.56%	42.31%	28.21%	19.23%	2.56%

**Table 2 : Relationship between presence of headache and epilepsy characteristics**

Variables	No Headache	Headache	P value
<b>Gender</b>			
• Male	2(9.09%)	57(73.08%)	<0.0001
• Female	20(90.91%)	21(26.92%)	
<b>Age/years</b>			
• Mean±SD	28.05±7.26	23.76±8.25	0.02
• Median (range)	29.5(15-40)	21(12-50)	
<b>Epilepsy type</b>			
• Focal	12(54.55%)	62(79.49%)	0.02
• Generalized	9(40.91%)	16(20.51%)	
• Unclassified	1(4.55%)	0	
<b>Age of onset of epilepsy</b>			
• Mean±SD	24.64±6.94	13.90±7.92	<0.0001
<b>Epilepsy Duration</b>			
• Mean±SD	3.41±2.41	9.79±5.09	<0.0001
<b>Type of therapy</b>			

<ul style="list-style-type: none"> <li>No therapy</li> <li>Monotherapy</li> <li>Poly therapy</li> </ul>	0 20(90.91%) 2(9.09%)	3(3.85%) 30(38.46%) 45(57.69%)	<0.0001
<b>Frequency of epilepsy</b> <ul style="list-style-type: none"> <li>&lt;1/year</li> <li>≥1/year,&lt;1month</li> <li>≥1/month,&lt;1week</li> <li>≥1/week</li> </ul>	9(40.91%) 8(36.36%) 3(13.64%) 2(9.09%)	10(12.82%) 9(11.54%) 41(52.56%) 18(23.08%)	<0.0001
<b>History of febrile convulsions</b> <ul style="list-style-type: none"> <li>No</li> <li>Yes</li> </ul>	21(95.45%) 1(4.55%)	68(87.18%) 10(12.82%)	0.45
<b>EEG finding</b> <ul style="list-style-type: none"> <li>Normal</li> <li>Generalized</li> <li>Focal</li> </ul>	18(81.82%) 1(4.55%) 3(13.64%)	23(29.49%) 7(8.97%) 48(61.54%)	<0.0001
<b>Family history of epilepsy</b> <ul style="list-style-type: none"> <li>No</li> <li>Yes</li> </ul>	18(81.82%) 4(18.18%)	64(82.05%) 14(17.95%)	1.00
<b>Family history of headache</b> <ul style="list-style-type: none"> <li>No</li> <li>Yes</li> </ul>	22(100%) 0	66(84.62%) 12(15.38%)	0.06

### Antiepileptic and Analgesic Drugs

Patients suffering from headaches were more commonly polytherapy as regard antiepileptic drugs (57.69%) compared to those without headaches (9.09%) ( $P = <0.0001$ ). Among patients with a headache only 34 patients (43.59%) use analgesic for the treatment of a headache and 44 patients (56.41%) didn't use any medications for treatment. The majority of patients 26 patients (76.47%) used analgesics without seeking medical advice and only 8 patients (23.53%) used analgesics prescribed by a doctor after seeking medical advice.

### DISCUSSION

Headache is very common among patients with epilepsy. However, its frequency is very variable among various studies. Some studies reported similar frequency and other studies reported lower frequency compared to our study. Mameniskiene et al. reported that 82.2% of patients with epilepsy suffered from headache in his study population <sup>[10]</sup>. However, lower frequencies were reported in other studies; 22% by Kwan et al., 2008 or 34% by Kanemura et al., 2013 <sup>[11][12]</sup>. These differences can be explained by variations in the characteristics of the recruited patients with epilepsy including age; newly diagnosed patients; patients with less refractory epilepsy; patients referred to tertiary centers; study design and/or diagnostic criteria <sup>[13]</sup>.

As regard the type of headache, we found that migraine was the most frequent type of headache in patients with epilepsy including (57.69%) migraine with outaura (6.69%), a migraine with aura and (6.41%) probable migraine and the second most frequent type is tension-type headache (25.64%). Similar findings were found in several studies <sup>[3] [4] [12] [14] [15] [16]</sup> and those results

suggest the relationship and common pathophysiological mechanisms of both epilepsy and migraine.

Seo et al., 2016 recorded that the most common headache type identified was tension type headache and the high prevalence of tension-type headaches may be explained by frequent use of valproate and to piramate in the study sample as these drugs are used and approved in the prophylaxis of migraine and could prevent its occurrence [13]. As regard the time of headache we found that post-ictal headache is the commonest type of headache followed by the inter-ictal and less commonly the pre-ictal type and this result is in agreement with many studies [6] [7] [14] [15] [17] [18]. This could be explained by the triggering effect of epileptic seizure on headache occurrence and the greater ease by which cortical spreading depression can be reached in the post-seizure period.

On the other hand, some studies found that inter-ictal headache is the most common [3] [15].

We found that younger patients with epilepsy, especially females, are more liable to develop headache compared to older ones. This finding is similar to other studies [7] [8] [11] [19] [20] [21] [22] and can be explained by the fact that headache in general usually occurs in younger age groups and more common in females [18] [23]. In contrast to our result, few studies reported no statistically significant differences in age and sex between patients with headaches compared to those without [5] [10].

Patients with epilepsy associated with headaches have a significantly lower age of onset and longer duration of epilepsy compared to those without headache.

Many studies showed similar results to our study [2] [15] [19] [24] which maybe explained by the fact that a headache especially migraine is more common in younger ages. Moreover, headache is more common with intractable epilepsy with a long duration. In contrast to our result, Forderreuther et al. , 2002 found no statistically significant differences in the age of onset or the duration of epilepsy between headache and non-headache groups [5].

Similar to the results of other studies [5] [8] [12] [14] [16] [19] [22] [24], patients with epilepsy in whom the seizure frequency is high, and those receiving polytherapy suffers significantly more headaches compared to those with lower seizure frequency and mono-therapy for epilepsy treatment. These results suggest that intractable seizures which are more frequent and need polytherapy for control act as a trigger for cortical spreading depression and frequent migraine headaches.

Moreover, repeated seizures and difficulty of control of the mare usually associated with more psychological stress which may increase the incidence of tension-type headache.

In our study, we found that there was no significant association between headache and family history of headache or epilepsy and the same findings were reported by some studies [12] [13] [21].

On the other hand, fewer studies reported a significant association between the occurrence of headache and family history of headache and epilepsy [20]. Also, we found that there was no significant association between headache and previous history of febrile convulsions and this was the same findings by Seo et al. , 2016.

We found a significant association between headache and the focal onset seizures and this was reported also by many studies [12] [20] [25] [26]. Neuronal discharges in partial seizures may trigger vascular changes and that partial seizures, which spread to brainstem and hypothalamus, may induce headaches [12] [27] [28]. Other studies found no significant association between the occurrence of headache and type of epilepsy [5] [21]. Our results also showed that abnormal EEG, especially those with focal discharges, is more common in patients with headache compared to those without. Similar results were also reported in some studies [20] [25].

In this study has some limitations. First, our interview was dependent on patients' memory of headaches. Second, the findings reported here were based on a sample size of 100 participants. Accordingly, future studies should focus on a larger pool. Thirdly, the use of routine EEG recording which gave us limited information about focality of epilepsy so in the next studies we will need other investigations to accurately assess seizure focality and correlates these findings with seizure semiology.

## CONCLUSION

In conclusion, our study showed that patients with epilepsy frequently experience headaches. Migraine is the most prevalent type of headache in patients with epilepsy. Post-ictal headache occurs more frequently compared to inter-ictal headache. Pre-ictal and ictal headaches were rare. In our study we found that the occurrence of headaches was more in the female sex, lower mean age of the patient and lower mean age at the onset of epilepsy. Patients with focal epilepsy, longer duration of epilepsy, higher frequency of seizures and those in whom poly therapy is used suffer more headaches. Patient with abnormal EEG, especially those with focal abnormalities, were more commonly suffering from headache.

The comorbidity between headache and epilepsy is extremely important, as headaches often receive less attention than the more dramatic symptoms of seizures.

In epilepsy, questions concerning headache should be an integral part of the history as comorbidity may influence the antiepileptic drug choice, and the migraine may need specific treatment.

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