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Seizure Associated Headache in Epilepsy

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ABSTRACT

Background: Headache is a commonly reported comorbidity in individuals with epilepsy and their relationship is still incompletely known.

Objective: To assess the most prevalent kinds of primary headache and their connection to seizure timing among patients with epilepsy.

Patients and methods: This is cross sectional study, we assessed headaches using a comprehensive medical history, physical and neurologic examination, EEG, CT, and MRI brain scans in 200 patients with idiopathic epilepsy who were seen at the Mansoura University Hospital's neurology outpatient clinic and epilepsy clinic.

Results: Of our study population, tension-type headache (TTH) occurred in 57% of patients, unclassified headache in 22% of patients, migraine occurred in 19% of patients, migraine and TTH in 2% of patients. There were 4 patients (2%) had a pre-ictal headache, 2 patients (1%) had an ictal headache, 156 patients (78%) had a postictal headache and 31 patients (15.5%) had an interictal headache and 7 patients (3.5%) had an inter-ictal-post-ictal headache. Headache frequency was associated with female sex, anxiety, sadness, generalized tonic-clonic epilepsy, high seizure frequency, and antiepileptic polytherapy usage.

Conclusion: A major comorbidity of epilepsy is headache, particularly TTH, which should be given extra attention, particularly in female patients, patients receiving polytherapy, patients experiencing more frequent seizures, and patients with generalized tonic-clonic epilepsy.

Keywords: Epilepsy, Migraine, Headache, Tension-type Headache.

INTRODUCTION

In their lifetime, about 10% of people will have a seizure. With 65 million cases globally, epilepsy ranks third in terms of neurological illnesses' global burden of disease [(1)]. A researchs from throughout the globe indicates that the yearly incidence of epilepsy is 67.8 cases per 100,000 person-years, whereas the prevalence is 6.4 cases per 1,000 people. Compared to high-income nations, low-and middle-income countries have greater rates of both prevalence and incidence [(2)].

Headaches are more common in people with epilepsy than in people without the condition. Seizures and migraine episodes are often not temporally associated. However, headaches may occur before to, during, or after an episode[(3)].

Numerous pathophysiological pathways are similar in headaches and seizures. Ion channel malfunctions and neurotransmitters are involved in these pathways. Additionally, it appears that photosensitivity influences the relationships [(4)]. Additionally, there is a hereditary propensity for seizures and headaches because certain genetic abnormalities, such those in ATP1A2 and CACNA1A, are present in both migraine and epilepsy families. Patients who have these genetic mutations may benefit from the "channelopathy" idea [(5)].

While the normal population's migraine prevalence ranges from 10% to 18%, investigations conducted on epileptic patients have indicated that the prevalence is between 8% and 24%. Conversely, the incidence of epilepsy in the general population is between 0.5% and 1.5%, while in migraineurs, it has been reported to be as high as 17% [(6)]. In addition, a number of anti-epileptic medications (AEDs) are popular and successful in preventing migraines [(7)].

Precise categorization of epilepsy and headache necessitates a thorough description of the symptoms and their temporal correlation in order to start appropriate, prompt, and effective therapy [(3)]. There is no class of seizures in the ILAE seizure categorization scheme with symptoms similar to headaches. Nonetheless, ictal epileptic headache, post-ictal headache, and migraine aura-triggered seizure are among the various types of seizure-related headaches included in the ICHD-3 [(8)].

This study aimed to assess the most prevalent kinds of primary headache and their connection to seizure timing among patients with epilepsy.

PATIENTS AND METHODS

In the Egyptian University Hospital in Mansoura, a cross sectional study was carried out. Between September 2021 and June 2023, participants in the research were gathered from the Mansoura University Hospital's epilepsy and neurology outpatient clinics.

Two hundred patiens with primary headaches and idiopathic epilepsy who had been ill for at least six months were included in the trial. The term "idiopathic epilepsy" refers to epilepsy that has not been significantly associated with a known etiology, abnormal neurological examination, or structural abnormalities of the brain identified by brain imaging (MRI or CT scan).

Inclusion criteria: Age: 18 years and more. Gender: Both genders. Patients have been diagnosed with primary epilepsy with disease duration of six months or

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more according to the International League Against Epilepsy (ILAE) 2017. Patients complaining of primary headache according to Headache Classification Committee of the International Headache Society (HIS, 2018) ICHD-3 criteria

Exclusion criteria: Age: less than 18 years. Patients who refused to participate in the study. Secondary epilepsy. Secondary headache. Patients complaining of epilepsy less than 6 months ago. Major mental or psychiatric disorders. History of drug abuse.

All subjects underwent the following:

1. **History taking:** Detailed history was obtained from the patients and their families including identifying data, seizure history (duration of epilepsy and seizure semiology), past medical and surgical history and family history. Also details about medication used for treatment of epilepsy were taken.
   - **Epilepsy analysis:** onset, course, duration of seizure. Age of onset of first seizure. Pre-ictal, ictal and post-ictal events in details and their duration. Medication taken for treatment of seizures.
   - **Headache analysis:** onset, course, duration of headache. Distribution of pain, associated symptoms, relieving and precipitating factors, timing and type of aura in case of migraine headache. Relation to timing of epileptic attack and type of epileptic attack.

     The HIS-2018 ICHD-3 criteria were used to diagnose headaches. The International League Against Epilepsy-2017 operational categorization of seizure type separated the seizures into four groups: focal onset, generalized onset, focal + secondary generalized seizure, and undetermined onset seizures[(9)].

     There are three categories for the temporal link between a headache and a seizure: pre-, inter-, and post-ictal.

     Pre-ictal headaches were defined as those that began more than twenty-four hours before a seizure started.

     Inter-ictal headaches were those that occurred at least twenty-four hours following the conclusion of a seizure.

     Post-ictal headache is defined as headache that occurs three hours after a partial or generalized seizure and goes away seventy-two hours later.
2. **Neurological and general examination:** To detect any focal neurological deficits or general medical illness.
3. **Interictal electroencephalography (EEG):**

EEG recording were done in the Neurology Department using Nihon Kohden, 21EEG channels (model 65178, USA), using hyperventilation and photic stimulation as triggering procedures. EEG was collected while the subjects were awake with their eye closed. Electrodes were placed according to the standard 10-20 system, over the following sites: Fp1, Fp2, F7, F3, Fz, F4, F8,T3, T4, T5, T6, C3, Cz, C4, P3, Pz, P4, O1 and O2. Noise and any interference were avoided. The skin was cleaned using alcohol before placing the electrodes to minimize their impedance. Then, conductive gel was applied, which allowed electrodes to be kept in place. The skin electrodes impedance was verified to be higher than 20 K. Several montages were done. Bipolar transvers montage was applied to minimize the contamination caused by vertical eye movement artifacts in the frontal delta activity. Photic stimulation and hyperventilation were done over one minute. Recordings were done for 10 minutes on awake resting subjects.

4. MRI:

The brain was imaged using 1.5 tesla units (Magnetom Symphony, Siemens Medical Solution, Version VA 12A, Erlangen, Germany). MRI protocol was supplied; T1-WIs (TR/TE=500-800/14-20 msec), T2-Wis (TR/TE=2500-4490/82-90 msec), and flair pictures (TR/TE=9000-14/2500 msec). The slide was 6 mm thick, with a matrix size of 256x256 and a field of view of 230 mm.

Ethical approval:

Mansoura University Faculty of Medicine's local Ethics Committee gave the project approval. Every patient provided written informed permission, and the study was conducted in agreement with the guidelines outlined in the Declaration of Helsinki.

Statistical analysis

The computer was given data, and SPSS software package version 20.0 was used for analysis. Numbers and percentages were used to describe the qualitative data, which were compared by Monte Carlo test. To confirm the distribution's normality, the Shapiro-Wilk test was performed. The terms range (minimum and maximum), mean±standard deviation (SD), median, and interquartile range (IQR) were used to represent quantitative data. Kruskal-Wallis was used to compare between groups for quantitative variables, which were with aberrant distributions. If the p value for any of the tests was less than 0.05, the findings were deemed statistically significant.

RESULTS

This based cross sectional study was designed to involve 200 epileptic patients complaining of headache; 78 male and 122 female patients, with median age of 37 years ranging from 18 to 70 years (Table 1).

Table (1): Distribution of the studied cases according to demographic data, family history and medical history (n = 200)

	No.	%
Sex		
Male	78	39.0
Female	122	61.0
Age (years)		
Min. – Max.	18.0 – 70.0	
Mean ± SD.	37.58 ± 10.48	
Median (IQR)	37.0 (29.50 – 43.0)	
Special habits (Smoking)	28	14.0
Family history of migraine	9	4.5
Family history of epilepsy	28	14.0
HTN	22	11.0
DM	9	4.5
Obesity	79	39.5
Anxiety	13	6.5
Depression	37	18.5
Sleep disorders	39	19.5
GIT disorders	19	9.5

According to epileptic seizure characters, type of seizure was mainly generalized tonic-clonic (61.5%), followed by focal seizures (34%). Regarding antiseizure (45%) of patients were treated with dual antiseizure drugs and (40.5%) were treated by more than two antiseizure drugs (Table 2).

Table (2): Distribution of the studied cases according to epileptic seizure characters (n = 200)

Epileptic seizure characters	No.	%
Onset of seizure		
Childhood	87	43.5
Adulthood	113	56.5
Course of seizure		
Excellent	6	3.0
Improving	60	30.0
Relapsing	124	62.0
Poor	10	5.0
Duration of seizure (years)		
Min. – Max.	1.0 – 50.0	
Mean ± SD.	15.65 ± 10.49	
Median (IQR)	13.50 (8.0 – 22.50)	
Type of seizure		
Focal onset	68	34.0
Generalized tonic-clonic	123	61.5
Impaired awareness seizure TLE	3	1.5
Focal to bilateral tonic-clonic	6	3.0
Antiseizure medications		
With single antiseizure drug	29	14.5
With dual antiseizure drugs	90	45.0
With more than two antiseizure drugs	81	40.5
Age of onset of first seizure (years)		
Min. – Max.	1.0 – 57.0	
Mean ± SD.	21.77 ± 12.77	
Median (IQR)	20.0 (12.50 – 30.0)	

Regarding headache types in epileptic patients, the prominent type of headache was TTH (57%), followed by migraine (19%), migraine and TTH (2%) and headache type was not classifiable in (22%) (Table 3).

Table (3): Distribution of the studied cases according to headache characters (n = 200)

	Headache characters	No.	%
Type of Headache	TTH	114	57.0
	Migraine	38	19.0
	Migraine and TTH	4	2.0
	Unclassified headache	44	22.0
Onset	Childhood	14	7.0
	Adulthood	186	93.0
Course	Episodic	149	74.5
	Chronic	51	25.5
Duration (years)	Min. – Max.	1.0 – 15.0	
	Mean ± SD.	3.23 ± 2.28	
	Median (IQR)	3.0 (2.0 – 4.0)	

On studying correlation between type of headache and demographic data, family history and medical history in epileptic patients; it showed statistically significant correlation between headache and anxiety and depression (Table 4).

Table (4): Relation between type of headache and demographic data, family history and medical history (n = 200)

	Type of headache								P
	Unclassified headache (n= 44)		TTH (n= 114)		Migraine (n= 38)		Migraine and TTH (n= 4)		
	No.	%	No.	%	No.	%	No.	%	
Sex									
Male	14	31.8	52	45.6	11	28.9	1	25.0	0.165
Female	30	68.2	62	54.4	27	71.1	3	75.0	
Age (years)									
Mean ± SD.	37.66 ± 9.75		38.17 ± 11.27		35.87 ± 8.18		36.50 ± 15.93		0.669
Median (Min. – Max)	37.0(23.0 – 70.0)		39.0(18.0 – 65.0		37.0(22.0 – 55.0)		33.50(21.0–58.0)		
Special habits (Smoking)	2	4.5	22	19.3	4	10.5	0	0.0	0.079
Family history of migraine	4	9.1	4	3.5	1	2.6	0	0.0	0.432
Family history of epilepsy	3	6.8	16	14.0	8	21.1	1	25.0	0.192
HTN	3	6.8	15	13.2	4	10.5	0	0.0	0.736
DM	2	4.5	6	5.3	0	0.0	1	25.0	0.146
Obesity	22	50.0	45	39.5	11	28.9	1	25.0	0.235
Anxiety	6	13.6	3	2.6	4	10.5	0	0.0	0.038*
Depression	5	11.4	17	14.9	13	34.2	2	50.0	0.012*
Sleep disorders	11	25.0	17	14.9	9	23.7	2	50.0	0.119
GIT disorders	6	13.6	8	7.0	4	10.5	1	25.0	0.261

*: Significant

In terms of headache timing in relation to epileptic seizures, post-ictal headache was the most prevalent kind (78%) followed by inter-ictal headache (15.5%) (Table 5).

Table (5): Distribution of the studied cases according to timing of headache in relation to seizures (n = 200)

Timing of headache	No.	%
Pre- ictal	4	2.0
Ictal	2	1.0
Post- ictal	156	78.0
Inter- ictal	31	15.5
Inter-ictal-post-ictal	7	3.5

There was significant positive correlation between frequency of seizures and frequency of headache (Table 6).

Table (6): Correlation between frequency of seizures and frequency of headache (n = 200)

	Frequency Seizures	
	r_s	P
Frequency Headache	0.838*	<0.001*

*: Significant

On studying correlation between timing of headache and antiseizure medications, there was significant correlation between incidence of headache in relation to seizure and antiseizure polytherapy (Table 7).

Table (7): Relation between timing of headache in relation to epileptic seizures and antiseizure medications (n = 200)

Temporal relation of headache	Antiseizure medications						p
	With single antiseizure drug (n = 22)		With dual antiseizure drugs (n = 68)		With more than 2 antiseizure drugs (polytherapy) (n = 66)		
	No.	%	No.	%	No.	%	
Pre- ictal	0	0.0	4	5.9	0	0.0	
Ictal	1	4.5	0	0.0	1	1.5	
Post –ictal	35	22.4	63	40.3	58	37.1	
Inter- ictal	7	31.8	10	14.7	14	21.2	0.014*
Inter-ictal-post-ictal	3	13.6	1	1.5	3	4.5	

*: Significant.

DISCUSION

Headache is a commonly reported comorbidity in individuals with epilepsy [(10)]. Seizures and headaches share several physiological processes, particularly migraine, as well as the impact of genetic factors [(7)].

Primary headaches and secondary headaches are distinct categories of headache. Primary headaches have no obvious origin, but secondary headaches are caused by a different illness, such as neck trauma, vascular problems, or brain hemorrhage. The most recent edition of the ICHD-3b divides primary headaches into four types: migraine, TTH, trigeminal autonomic cephalgia, and neuralgias [(8)].

In the current study, we aimed to assess the prevalence and type of headache among epileptic patients, assess the precipitating factors for headache in epileptic patients, evaluate the temporal relation of headache and epileptic focus and assess headache severity among patients with epilepsy.

We enrolled 200 patients diagnosed by primary epilepsy with disease duration of six months or more and complaining of primary headache.

The mean age of cases in our study was 37.58 ± 10.48, which is in comparable with many studies discussed headache in epileptic patients as their cases mean age was 37.8 ± 14.5[(11)], 41.25 ± 15.70[(12)] and 42.8 ± 14.9[(13)].

In our study, there was female predominance in epileptic patients with headache (61% of the patients) in harmony with [(14-16)]. This is because primary headaches, such as migraines, are linked to female sex hormones [(17)]. This study discovered that sex hormones in females affect cells around the trigeminal nerve as well as blood arteries in the skull. Estrogens, hormones responsible for reproductive and sexual development in females, are especially important in sensitizing these cells to migraine triggers in females of childbearing age [(18)].

In contrast to female epileptic patients, **Schiller *et al.*** [(13)] discovered that a somewhat greater number of male epileptic patients reported TTH. There was no correlation found by **Mameniškienė *et al.*** [(11)] between the age or sex of the patient and the headache related to epilepsy.

In our study, type of seizure was mainly generalised tonic-clonic (61.5%), followed by focal seizures (34%), focal to bilateral tonic-clonic (3%) and impaired awareness seizure TLE was reported in 1.5% of cases. This result is in agreement with **Kaur *et al.*** [(19)] who illustrated that overall, 59% of patients experienced generalized tonic-clonic seizures, which were the most common kind of seizures in adults. Furthermore, **Kanitkar *et al.*** [(20)] **and Sendil *et al.*** [(21)] found that generalized tonic-clonic seizures were shown to be more common in adults (70% and 64%, respectively).

However, according to a research by **Sayed *et al.*** [(22)] 74% of the patients have focal seizures, 25% experience generalized seizures, and 1% of patients experience seizures that cannot be categorized based on their clinical history. One hundred consecutive individuals with idiopathic epilepsy who had been ill for longer than a year were included in this research.

Regarding headache types in the epileptic patients in our study, the prominent type of headache was TTH (57%), followed by migraine (19%), migraine and TTH (2%). Headache type was not classifiable in (22%).

Similarly, in **Osama *et al.*** [(16)] research, TTH was the most common main headache problem among epileptic patients, accounting for 45.2% of cases. Also, in their investigation, **Seo *et al.*** [(23)] discovered that 50% of epileptic patients had TTH.

Mameniškienė *et al.* [(11)] reported that incidence of TTH was (39%), migraine was (31.7%), medication-overuse headache was (7.8%) and potentially ongoing headache caused by a traumatic brain damage was (16%).

Conversely, **Mainieri *et al.*** [(12)] **and Çilliler *et al.*** [(24)] noted a significantly lower incidence of TTH (17.2%) and (18.56%), respectively, and clarified that no theories about the relationship between TTH and epilepsy have been proposed.

In our research, migraine (19%) was the second most prevalent main headache type. This finding was in consistence with **Osama *et al.*** [16] study, as migraine represented (12.9%). The frequent usage of valproate (53.3%) in the research population, which is indicated as one of the preventative therapies for migraine, may account for the low prevalence of migraine headaches. Up to 32.9% of the individuals in the **Gameleira *et al.*** [25] trial also reported having a headache similar to a migraine.

On the other hand, **Khedr *et al.*** [26] **and Fawi *et al.*** [27] discovered that TTH (25.64%) is the second most common kind of headache among people with epilepsy, behind migraines.

In our study, there was significant correlation between headache occurrence, anxiety and depression. This is in agreement with **Song *et al.*** [28] study, as individuals with TTH were more likely than non-headache individuals to experience anxiety and sadness. In those with TTH, these two disorders were linked to a worsening of headache symptoms. The explanation for this is that genetic or shared environmental risk factors may be at play. Models of migraine and panic disorder's pathophysiology identify certain neurotransmitters, such as the serotonin system [29].

Timing of headache to epileptic seizure in the current study was mainly post ictal headache (78%) followed by inter- ictal headache (15.5%), inter-ictal-post-ictal headache (3.5%), pre-ictal headache (2%) then ictal headache (1%). This is in accordance with **Schiller *et al.*** [13] who discovered that the most frequent headache linked with seizures was postictal headache

Also, **Sayed *et al.*** [22] discovered that 52 patients (66.5%) who reported having a headache after a seizure had post-ictal headaches. Of these, 33 patients (42.31%) had only post-ictal headaches, 15 patients (19.23%) had both post-ictal and inter-ictal headaches, 2 patients (2.56%) had post-ictal and pre-ictal headaches, and 2 patients (2.56%) had three different types of headaches: post-ictal, post-ictal, and inter-ictal.

This is in agreement with **Osama *et al.*** [16] who found that post-ictal headaches (29%) and inter-ictal headaches (19.4%) were the most common types of headaches experienced by epilepsy patients. They noticed that TTH was present in instances of post-ictal headache. This implies that proprioceptive stimulation from muscles resulting from motor symptoms experienced during a seizure may be the etiology of TTH [30].

Furthermore, the percentages of 19.7–41% for post-ictal headaches were found from earlier research by **Mainieri *et al.*** [12]**, Çilliler *et al.*** [24] **and Wang *et al.*** [31]**.** This may be explained by the increased ease with which cortical spreading depression may be attained in the post-seizure phase and the triggering influence of epileptic seizures on headache onset. However, other research indicates that interictal headache is the most prevalent kind [27,32]. Patients may fail to disclose pre-ictal headaches because the epileptic seizure masks them and makes it difficult for them to remember the exact events that preceded them [3].

In the present study, there was significant correlation between frequency of seizures with frequency of headache.

Our findings are in line with the results of **Caprara *et al.*** [14] in adult patients with epilepsy. This study reported that patients with headaches were more likely to not be seizure-free than patients without headaches, and this finding is consistent with our own. There was a modest correlation between headache and seizure freedom.

Regarding treatment, (45%) of our patients were treated with dual AEDs, (40.5%) were treated by more than 2 AEDs and (14.5 %) were treated by single antiepileptic drug. This is in agreement with **Osama *et al.*** [16]**,** as patients on polytherapy experienced headaches at a rate of 69.2% compared to 52.9% in those on monotherapy. **Wang *et al.*** [31] **and Duchaczek *et al.*** [33] also found that polytherapy patients experienced headaches more frequently, and implying that refractory patients undergoing multiple treatments may have headaches frequently.

On the other hand, in **Schiller *et al.*** [13] study, as 157 out of 163 epileptic patients who said they had headaches at least once a month, used AEDs. At the time of the interview, 52 (33.2%) of those patients had undergone polytherapy, whereas 105 (66.9%) had received monotherapy. In their research, individuals receiving these AEDs in monotherapy experienced migraine less frequently than those receiving them in polytherapy. They clarified that because monotherapy has fewer side effects than polytherapy, it helps people with epilepsy have fewer migraine attacks.

CONCLUSION

Headaches are common in patients with epilepsy. The most common kind of headache experienced by epilepsy sufferers is TTH. Inter-ictal headache is less common than post-ictal headache. Ictal and pre-ictal headaches were uncommon. According to our research, headaches were more common in women, and patients also reported feeling depressed and anxious. Headaches are more common in patients with generalized tonic-clonic epilepsy, increased seizure frequency, and polytherapy-treated patients.

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