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Headaches and their relationships to epileptic seizures

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ABSTRACT

Purpose: The frequent association between headache and epilepsy has been increasingly studied in recent years. Through this study, we attempted to study possible temporal associations between epileptic seizures and headaches. We also tried to describe clinical aspects of headache in our patients with epilepsy.
Patients and methods: We included patients with epilepsy and patients without epilepsy who presented for a first neurologic episode suggestive of epileptic seizure or unusual headache. These patients were invited to answer a standardized questionnaire screening for headache characteristics. Patients with epilepsy were asked for further data about their epilepsy. Electroencephalogram (EEG) was performed in all patients. Brain Magnetic resonance imaging MRI was reserved for patients in whom we suspected a structural lesion.
Results: Overall, we included 47 patients with a mean age of about 39 ± 15 years (19 to 68 years old) and a female predominance (Sex Ratio: SR = 1.47). Most frequently, our patients documented periictal headache (Peri-IH) (85.1%) including respectively ictal headache (IH: 31.9%); postictal headache (Post-IH: 21.3%), and preictal headache (Pre-IH: 4.3%). Less frequently, our patients noted interictal headache (Inter-IH: 31.9%). Interestingly, these subgroups exhibited different headache patterns with predominantly unclassified-type headache (U-TH) in patients with IH (72.7%), tension-type headache (T-TH) in patients with Post-IH (73.3%), and migraine-type headache (M-TH) in patients with Inter-IH (60%).
Conclusions: Our results suggest that patients with epilepsy could exhibit different headache types. The clinical pattern of headache seemed to be linked to the time of seizure onset.

1. Introduction

Epilepsy is considered one of the major neurologic problems, and the mean prevalence rate is 8% worldwide [1]. It is associated with a stigma, psychiatric comorbidity, and subsequently, a poor quality of life [2]. Epilepsy comorbidities include various neurologic conditions like headache. Numerous reports raised the question of possible association between both neurologic conditions. Nevertheless, the likely relationship between headache and epilepsy remains poorly understood [3–6].

Previous studies focused particularly on the association between migraine-type headaches (M-TH) and epilepsy. The reported prevalence of migraine in patients with epilepsy ranges from 14 to 24%, and the prevalence of epilepsy in migraine subjects ranges from 1.1 to 17% [3].

The purpose of this study was to describe the characteristics of headaches in patients with epilepsy and to define precisely the possible association between these two neurological conditions.

2. Patients and methods

2.1. Patients

We included patients with epilepsy who were interviewed during their follow-up visit. We also recruited patients without epilepsy who presented for a first neurologic episode suggestive of epileptic seizure or onset of unusual headache.

Patients with mental retardation, learning disabilities, behavioral or mood disorders, and other evident abnormalities that could compromise cooperation and the ability to respond to the questionnaires were excluded.

Patients with acute symptomatic seizures (metabolic disturbances, brain vascular and infectious diseases), epilepsy related to extensive malformations of cortical development, and brain tumor were excluded.

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2.2. Methods

❖ For each patient, we collected:
- Demographic data: age, gender;
- Anamnestic data: family history (epilepsy, headache), neonatal and childhood period, schooling.

❖ All patients completed a questionnaire regarding:

1. Epilepsy: age at onset, seizure (type, semiology, time of occurrence, frequency, control with antiepileptic drugs (AEDs));
2. Headache: localization, quality, lateralization, radiating patterns, associated features, duration, intensity (**mild**: *maintaining normal activities without problems*; **moderate**: *maintaining normal activities with difficulty*; **severe**: *must give up normal activities and lie down*; or **extremely severe**: *impossible to stay still*), pattern (M-TH; tension-type headache (T-TH); or unclassified-type headache (U-TH)), response to (analgesic/antiepileptic) drugs;
3. Chronologic link between epilepsy and headache (headache timing in relation to seizures):
   - 3.1 Preictal headache (Pre-IH): when a headache starts 24 h before the seizure and continues until the onset of the seizure.
   - 3.2 Ictal headache (IH): in this group, we included patients with "Ictal Epileptic Headache" (IEH), whose criteria were published 6 years ago by the group of Parisi et al. [7–9]. We also considered patients with "Hemicrania Epileptica" (HE), whose headache appeared simultaneously or sequentially, with other epileptic manifestations [10].
     We specified the number of patients with IH, which led to the diagnosis of epilepsy or revealed a poor control of epileptic seizures.
   - 3.3 Postictal headache (Post-IH): when headache develops within 3 h following the seizure and resolves within 72 h after onset.
   - 3.4 Interictal headache (Inter-IH): when headache was unrelated to seizure occurrence.

❖ The term periictal headache (Peri-IH) was used to designate patients with seizure-related headache including Pre-IH, IH, and Post-IH.

❖ The epilepsy was classified according to the criteria of the International League Against Epilepsy's Classification of Epileptic Seizures (2017) [11].

❖ Headache pattern was defined based on The International Classification of Headache Disorders, third edition (ICHD-3) [12]. Patients whose headache did not match with any known headache type were considered unclassifiable.

❖ Investigation included electroencephalogram (EEG) and brain MRI, or brain computed tomography (CT) scan. Neuroimaging was performed only when we suspected structural epilepsy.

3. Statistics

For statistical analyses, we used the Statistical Package for the Social Sciences (SPSS) version 20. Continuous variables were summarized as means and standard deviations and categorical variables as numbers and percentages. Chi-square tests were used to compare the distributions of categorical variables between groups. Paired-sample t-tests were used to compare continuous variables. Statistical significance was set at $p < 0.05$.

4. Results

4.1. Demographic and anamnestic data

In total, 47 patients were included in this study. The mean age was about 39 ± 15 years ranging from 19 to 68 years old. Females outnumbered males (59.6% *vs* 40.4%; SR = 1.47). Overall, 83% of patients were interviewed during a follow-up visit as a part of their epilepsy care. In this group, the median period of follow-up was 10 years (3–26 years). The remaining 17% of patients have no previous history of epilepsy; they were initially referred for headache. In patients with a previous history of epilepsy, patients were diagnosed with temporal lobe epilepsy (TLE) in 34% of cases, frontal lobe epilepsy (FLE) in 17% of cases, central epilepsy (CE) in 12.8% of cases, parietal lobe epilepsy (PLE) in 4.3% of cases, occipital lobe epilepsy (OLE) in 2.1% of cases, and generalized onset in 12.7% of cases.

Nearly one-half of the patients (21.3%) noted more than one type of headache while others (78.7%) experienced only one type of headache. There was no significant difference in gender, disease duration, seizure frequency, and response to AEDs between patients with one and two headache types. Most frequently, our patients exhibited Peri-IH (85.1%) including respectively IH (31.9%), Post-IH (21.3%), and Pre-IH (4.3%). Less frequently, our patients displayed Inter-IH (31.9%).

4.2. Inter-IH

Inter-IH was reported by 15 cases (31.9%). In these patients, headache was consistent with the M-TH pattern in 60% of cases and T-TH in 40% of patients. Headache was more often severe (73.3%); in 26.7% of patients, headache was moderate. The clinical characteristics of the headaches are summarized in Table 1. About half of patients (53.3%) did not show headache improvement after analgesic drug intake. The use of a higher number of AEDs was not associated with Inter-IH. Thus, the use of two or more AEDs was noted in 14 patients (53.8%) without Inter-IH and 2 patients (15.4%) with Inter-IH. However, the difference between both groups did not reach the threshold of significance ($p = 0.068$). Inter-IH did not correlate with gender, seizure type, or seizure frequency. Electroencephalogram recording showed interictal focal abnormalities in 66.7% of patients. These abnormalities originated mainly from frontal regions (36.4%) and showed mostly right lateralization (54.5%). Brain MRI was normal in 40% of patients; it showed brain atrophy in 20% of patients and mesial temporal sclerosis in 13.3% of patients. The CT scan performed in the remaining patients (26.7%) was normal.

Table 1
Clinical characteristics of headaches.

	Inter-IH	IH	Post-IH
Localization (%)			
Forehead	33.3	59.1	30
Vertex	6.7	22.7	0
Unilateral	40	0	10
Whole brain	0	0	50
Others	20.1	18.2	10
Quality (%)			
Tightening	26.7	59.1	10
Pulsating	66.7	13.6	10
Shock	6.7	22.7	0
Heaviness	0	0	80
Others	0	4.5	0
Lateralization (%)			
Right	13.3	9.1	0
Left	26.7	9.1	10
Bilateral	60	81.8	90
Associated features (%)			
Hypotonia	6.7	0	0
Sensory	6.7	49.8	0
Dizziness	0	31.8	0
Vomiting/nausea	33.3	0	10
Photo/phonophobia	6.7	0	0
Drowsiness	0	0	20
None	46.7	18.2	60
Duration			
0–15 min	6.7	86.4	0
15–60 min	6.4	4.5	10
1–12 h	33.3	9.1	10
>12 h	53.3	0	80

4.3. Pre-IH

Pre-IH was identified in only two patients. The headache started within 24 h prior to the seizure occurrence. Both patients reported extremely severe pain, which was pulsating in quality and predominated in the forehead. Headache was associated with dizziness in one case and vomiting in the other case. Headache did not resolve after analgesic intake and lasted until seizure onset. In both patients, seizure semiology was consistent with mesial temporal origin. Scalp EEG recording did not show any abnormal electrical activity.

4.4. IH

Ictal headache was reported in 22 patients (46.8%). The diagnosis of IH was delayed in 8 patients (36.4%) with a median time to diagnosis around 24 months (6–48 months). Headache manifested as the sole ictal symptom (IEH) in 22.7% of patients and was one of the symptoms at the seizure onset (HE) in the remaining 77.3% of patients. Ictal headache led to the diagnosis of epilepsy in 31.8% and was associated with poor seizure control in 45.5% of patients. Six patients (27.3%) among patients with IH exhibited another headache type (Inter-IH, Post-IH).

In patients with previous history of epilepsy (77.2%), IH was associated with focal onset epilepsy in 70.6% of patients. Temporal lobe epilepsy was the most frequent (58.3%) followed by CE (16.7%) and PLE (16.7%) and then OLE (8.3%).

Patients with this type of headache more often had U-TH (72.7%) and, less frequently, T-TH (22.7%) and M-TH (4.5%). We identified two particular patterns among patients with U-TH (U-TH1 and U-TH2). Patients with U-TH1 (45.5%) described headache as a bilateral frontal pain, constrictive in quality. In this group, patients reported some symptoms suggestive of epileptic origin concomitant with headache such as sensory features (40.9%) and dizziness (31.8%). Sensory features included mainly visual and auditory hallucinations (27.2%) and paresthesia (22.6%). Patients with U-TH2 (22.7%) perceived their headache as an electric shock located in the vertex with possible paresthesia of the scalp all around. Ictal headache was graded extremely severe in 13.6% of patients, severe in 77.3% of patients, and mild to moderate in 9% of patients. Overall, 40.9% of patients experienced postictal confusion. Detailed clinical characteristics of the headaches are recapitulated in Table 1.

When we compared IH clinical characteristics between patients whose headache manifested as the sole ictal symptom (subgroup 1: IEH) and patients whose headache appeared simultaneously or sequentially with other epileptic manifestations (subgroup 2: HE), we did not find differences between both subgroups (Table 2).

Interictal EEG in patients with IH showed focal abnormalities in 81.9%. These abnormalities were identified mainly in the frontal area (68.2%) and less frequently in the temporal (9.1%) and parietal (4.5%) areas. We also noted predominant right lateralization of interictal discharges (50%). Ictal discharges were identified in two patients whose IH occurred simultaneously with epileptiform discharges consisting of right temporal spikes in one of these patients and right occipital spikes and waves in the other patient.

Brain MRI showed mesial temporal sclerosis in 22.7% of cases, brain atrophy in 9.1% of cases, and focal dysplasia in 4.5% of cases.

4.5. Post-IH

Ten patients (21.3%) reported Post-IH. All of them had focal seizure onset (TLE: 60%, FLE: 30%, and CE: 10%). Post-IH was consistent with T-TH in the majority of patients (73.3%) and M-TH in 10% of patients. In the remaining patients (16.7%), headache was discordant with these two common types of headache and thus, considered as U-TH3. Patients with U-TH3 perceived headache as unusual heaviness involving the whole head. The headache was graded as moderate by 1 patient (10%) and severe by 9 (90%) patients. Table 1 details clinical characteristics of the headaches. On EEG recording, most patients demonstrated frontal or occipital interictal discharges (40%), and less frequently, interictal discharges were detected in parietal regions. Brain MRI showed mesial temporal sclerosis in 20% of patients, perinatal ischemic stroke in 10 cases, and focal dysplasia in 10% of patients. Neuroimaging was normal in the remaining patients.

Table 2
Clinical characteristics of patients with IEH and those with HE.

	Subgroup 1 Patients with IEH	Subgroup 2 Patients with HE	p
Localization (%)			
Forehead	80	52.9	
Vertex	20	23.5	0.3
Unilateral	0	0	
Whole head	0	11.8	
Other	0	11.8	
Quality (%)			
Tightening	60	58.8	
Pulsating	0	17.6	0.9
Shock	40	17.6	
Heaviness	0	0	
Other	0	5.9	
Lateralization (%)			
Right	20	5.9	0.6
Left	0	11.8	
Bilateral	80	82.4	
Associated features (%)			
Hypotonia	0	0	
Sensory	0	52.9	
Dizziness	0	29.4	
Vomiting/nausea	0	0	–
Photo/phonophobia	0	0	
Drowsiness	0	0	
None	100	17.6	
Duration			
0–15 min	80	88.2	
15–60 min	0	5.9	0.4
1–12 h	20	5.9	
>12 h	0	0	

IEH: Ictal epileptic headache; HE: Hemicrania epileptica.

4.6. Headache with probable epileptic origin (Probable-IH)

The epileptic origin of headache was uncertain in 8 patients (17%). In these patients, headache did not fulfill the proposed criteria for IH [7]. There was no previous history of epilepsy. There was no awareness impairment or cognitive disturbance during headache occurrence. Headache was mostly consistent with U-TH1 (75%). Features associated with the onset of headache included minor sensory symptoms (50%) and dizziness (25%). Headache was graded moderate (25%) to severe (75%). Further clinical characteristics are provided in Table 1. Interictal EEG demonstrated frontal discharges in 62.5% of cases and less frequently temporal (12.5%), parietal (12.5%), and occipital (12.5%) discharges. Paroxysmal abnormalities were mostly bilateral (50%).

5. Discussion

Both headache and epilepsy are known as neurologic conditions with paroxysmal expression [13]. Recently, there has been an increasing number of published papers focusing on the prevalence of headache among patients with epilepsy [3,4,6,14]. Nevertheless, the epidemiological data available in this regard are discordant among different studies [15]. This discordance is probably related to the difference in inclusion criteria used and the age group studied. In addition, it seems that the proposed criteria for IH diagnosis lack clinical accuracy, and thus, some patients with IH may not be diagnosed with epilepsy and therefore not started on antiepileptic drugs [16]. In fact, the diagnosis of IH was delayed in 36.4% of patients in our series, with a median time to diagnosis around 24 months. We highlight that the diagnosis of IH

associated, simultaneously or sequentially, with other epileptic manifestations known as "HE" according to the previous edition of ICHD is more often based on clinical evidence [10]. In contrast, the concepts of IEH define a condition in which headache is the "sole" ictal epileptic manifestation associated with EEG anomalies and both are responsive to intravenous AED administration [7,16]. Thus, IH is rather underestimated since EEG recording in patients with isolated headache is not recommended. In this context, the recent revision of International Classification of Headache Disorders published in 2018 has created even more confusion than previously as it ignores the contribution of EEG to show the epileptic origin of headaches [17,18]. Moreover, IH may occasionally be unresponsive to AED treatment as is the case for other types of seizures. Usually, patients do not use an AED for headaches because they are not aware of its epileptic origin or because seizures prevent them from taking their treatment. Besides, headache may be associated with epileptic seizures in different ways; so IH may remain unrecognized in patients with previous history of nonictal headache. This situation was encountered among 27.3% of cases in our series. In addition, IH did not display a specific clinical or electric pattern, which made the diagnosis of IH more difficult. In fact, in a previous study carried among a pediatric population with M-TH and T-TH, EEG abnormalities during headache-free periods were found in 16% of patients with M-TH and 2% of patients with T-TH [19]. For these reasons, the main aim of this study was to describe clinical features of headaches in patients with epilepsy. We also tried to clarify the likely link between headaches and epilepsy.

Most often, our patients had Peri-IH. These results were discordant with previous reports such as that of Hofstra et al. where Inter-IH was the most frequent headache reported in patients with epilepsy [20]. However, the authors did not include patients who had more than one type of headache among the subgroups of patients with Peri-IH. In their study published in 2013, Duchaczek et al. also reported different results with more patients with Inter-IH than with Peri-IH [21].

In our series, about 31.9% of patients experienced Inter-IH, which is in accordance with previous studies in which the frequency of this headache type ranged from 5.9% to 57.8% [21–23]. Most patients with Inter-IH (60%) exhibited M-TH while others (40%) presented T-TH. These results are consistent with earlier reports in which the authors demonstrated that migraine is the commonest headache type among patients with epilepsy with headache/epilepsy comorbidity [23,24]. Our study did not reveal a tendency to a higher frequency of seizures or an association with a particular seizure type in patients with Inter-IH. Thus, it seems that comorbid headache is independent from epilepsy-related variables. We therefore suggest that headache shares a pathogenic molecular basis with epilepsy. Indeed, according to our results, the combination of two or three AEDs seemed to be associated with a lower risk of developing Inter-IH. Accordingly, we speculate that AEDs act not only through pathways involved in seizure generation but also through pathways involved in headache generation in a synergistic mode; however, we whether AEDs activate both pathways in a similar or different manner is not clear. In our study, interictal EEG revealed frontal predominance of abnormalities among patients with nonseizure-related headache. This may be related to the fact that M-TH was the most frequent pattern of headache in these patients. In fact, recurrent migraine attacks result from spreading depression (SD) waves though trigeminovascular activation, leading to pain and blood flow changes [25,26]. This neurophysiological phenomenon is responsible for sustained depolarization of neurons and leads to the loss of electrical activity and changes in the synaptic architecture. The impaired ion homeostasis associated with SD triggers a cascade of cellular events leading to toxic release of glutamate [25]. Spreading depression preferentially involves occipital cortex, creating a blocked neuronal state with an excitotoxic environment, which may be harmful for neurons spared by SD and thus reacting to glutamate release [25,26]. We further speculate that SD promotes epileptiform activity by modifying the density of neurotransmitter receptors and their distribution in the anterior area of the cortex [25]. Indeed, the putative role of occipital cortex in the generation of both epilepsy and headache has been widely demonstrated in studies published by Piccioli et al. and Parisi respectively in 2009 and 2015, in which the authors studied photosensitivity in patients with headache and epilepsy [27,28].

Migraine-type headache was also the sole headache pattern among our two patients with Pre-IH and mesial temporal epilepsy; this is in agreement with Verrotti et al.'s study where M-TH was the most frequent headache pattern among patients with Pre-IH (86%). Contrary to our study, the authors did not find correlation between Pre-IH and a particular focal seizure type [29].

In our study, TLE was also the most common type of epilepsy among patients with IH. This is probably because the majority of our population (34%) had TLE. In this context, previous reports also documented the main involvement of the temporooccipital regions in patients with IH and focal symptomatic epilepsy based on electroclinical data and MRI findings [30,31]. Unlike previous studies where IH was associated with M-TH, the majority of our patients with IH exhibited U-TH. This headache pattern, albeit not yet well described, had already been reported in a previous study [30]. The authors, similarly, noted the association of headache with further elementary clinical features such as sensory and autonomic symptoms. It is a peculiar presentation, which was called by some authors as "ictal headache followed by other epileptic manifestations" or "epileptic seizure beginning with headache". They also considered headache as an aura for this kind of seizure beginning with headache [30,32]. Our ictal EEG findings are similar to of previous studies where temporal and occipital ictal discharges were noted [30,32]. We therefore think that a seizure manifesting as IH takes its origin in the posterior cortex with mainly temporo–parieto-occipital substratum. We also do not differentiate in terms of seizure origin between patients with "IEH" and "HE". In fact, patients of both subgroups showed similar electroclinical characteristics.

Contrary to Wang et al. who found that Post-IH was more frequent among patients with generalized epilepsy, the majority of our patients who experienced Post-IH had focal epilepsy with mainly temporal (60%) or frontal origin (30%) [33]. We explain this association by the recognized longer duration of seizures with temporal origin and the complex networks relating the temporal lobe to other brain areas leading to widespread ictal activity. Concerning seizures with frontal origin, they rapidly propagate widely as the frontal lobe occupies a substantial portion of the brain. Indeed, previous reports demonstrated that longer seizures correlated with a greater risk to develop Post-IH [29]. In our study, Post-IH was more frequently associated with T-TH. Literature data in this regard are widely discordant. Thus, some authors reported similar findings while according to others, M-TH is the most frequent pattern of headache in patients with Post-IH [21,33].

The major limitation of this study is its descriptive nature. The other main limitation is the absence of an objective tool to evaluate headache characteristics, and clinical data collection was therefore based on patients' self-reports using a questionnaire. This probably led to some limitations. For example, it was difficult to differentiate between IEH and ictal nonepileptic headache (when IH onset clearly precedes and/or continues after cessation of the seizure) when the patient was unable to define with accuracy the timing of headache onset compared with seizure occurrence [13].

6. Conclusion

Our study was an attempt to investigate the characteristics of headaches in patients with epilepsy. The relationships between headaches and epileptic seizures do not apparently depend on the cause of epilepsy or specific epilepsy syndromes, nor site of seizure onset or seizure frequency. However, headache should be explored using EEG in the presence of some indicators suggesting that a patient may have IH. We particularly emphasize the following:

1. A previous history of epilepsy.
2. A headache with different characteristics in patients with previous history of any headache type.
3. A headache discordant with a recognized pattern according to ICHD-3.
4. A headache refractory to analgesic medication.
5. A headache accompanying or followed by sensory, autonomic, cognitive, or elementary motor features.
6. A headache occurring during complete or incomplete impairment of awareness.

Taking into consideration these indicators, we recommend EEG recordings in patients with headache since the diagnosis of seizure-related headache requires supportive electroencephalographic evidence. We stress the importance of diagnosing IH in patients who may potentially benefit from AED therapy. This treatment decision may improve the quality of life of patients with epilepsy whose headache may directly impact the quality of life of patients with epilepsy, especially those whose headaches are severe and interfere with daily activities.

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