Headache and Epilepsy: Prevalence and Clinical Types

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Many patients with epilepsy report headaches which may occur in the interictal period or have various temporal relationships with epileptic seizures, occurring before, during or after a seizure. Clinical types of headache associated with epilepsy are included in the International Classification of Headache Disorders, but not in the classification of epileptic seizures and types of epilepsy. Meanwhile, the presence of comorbid headache and its clinical phenotype should be taken into account by clinicians treating epileptic patients.

The article contains data on the prevalence of different types of headache in patients with epilepsy and the current classification of headaches according to the temporal relationship with an epileptic seizure. Diagnostic criteria of 4 clinical types of headache (interictal, preictal, ictal and postictal) are given. The comorbid relationship between epilepsy and migraine is discussed in more detail, including the pathophysiologic mechanisms shared by these paroxysmal conditions.

Keywords: *headache; epilepsy; migraine; tension-type headache; comorbidity.*

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The relationship between epilepsy and headache (in particular, migraine) was first hypothesized by the British neurologist W. Gowers in 1907 [1]. A few case reports of headache associated with epilepsy were published in the 1950s [2, 3]. In 1960, W. Lennox and M. Lennox first presented a case report of "migralepsy" in a female patient with ophthalmic migraine (currently referred to as migraine with aura) who had a visual aura followed by typical migraine and a typical epileptic seizure [4]. The concept of migralepsy had been widely used in the literature until the beginning of the 21st century. It was criticized in the literature for failing to reflect the pathophysiologic mechanisms of headache associated with epilepsy and was rejected [5–8].

The temporal relationship between headache and an epileptic seizure is an important parameter in epileptic patients with comorbid headache [9]. If a headache occurs at the time around a seizure, it is defined as periictal headache [10, 11], which can occur either before (preictal), during (ictal) or after (postictal) the seizure [12–19]. When the headache does not occur at the time around a seizure, it is defined as interictal headache.

Over the past two decades, studies showed that headache in patients with epilepsy may follow different patterns, but in most cases, they meet the diagnostic criteria for migraine [20, 21]. An Italian study of types of headache associated with epilepsy included 388 patients aged 17 to 74 years (mean age 41.2 years, women 54%) with a confirmed diagnosis of epilepsy who reported recurrent headaches [22]. Focal, generalized and unclassified epilepsy was diagnosed in 72.2%, 26.0%, and 1.8% of patients. In total, 47.7% of patients received antiepileptic drug (AED) monotherapy, 48.4% received polytherapy (⩾2 AEDs), and 3.9% received no AED therapy. The lifetime occurrence rate of epilepsy in this study was 54%. Interictal and periictal headache was reported by 48.4% and 23.7% of patients, respectively. In the latter group, 5.4% had only periictal headache while 18% also had interictal headache. Ninety percent of patients did not report headaches in the past 3 months. Thus, the authors concluded that interictal headache is the most common type in the epileptic population.

An analysis of interictal headaches showed that 26.3% of patients had migraine (including migraine with aura in 1.5% and possible migraine in 4%), 19% had tension-type headache (TTH), 0.5% had cluster headache, 0.03% had primary stabbing headache, and 2.3% had headache that did not meet the diagnostic criteria for any type defined in the International Classification of Headache Disorders [20]. The authors also pointed out that patients with interictal migraine or TTH are prone to ictal headache that has the features of migraine or TTH.

The relationship between primary headache and epilepsy was assessed in another study that included 1167 patients with epilepsy aged 18 to 81 years (most of whom had focal epilepsy). In total, 28.8% of patients reported interictal headache. Migraine was the most common headache type (68.8%, most of whom had migraine without aura) followed by TTH (27.9%) [23].

A few papers have reported different distributions of headache types. In a Lithuanian study of 280 patients with epilepsy (mean age 37.8 years, duration of epilepsy 13.2 years), 83.2% of respondents reported some type of headache. Of those with interictal headaches (77.9%), 39% reported TTH, 31.7% reported migraine, 7.8% reported medication-overuse headache (the primary type of headache was not stated) and 16% reported possible persistent headache attributed to traumatic head injury [24]. Thus, in this study, TTH was more common than migraine in epileptic patients.

It has been repeatedly hypothesized in the literature that recurrent headaches and epileptic seizures may share a common etiology in patients who have both [25–27]. Both headache and seizures may be observed in the diseases listed below [28], with interictal headache being more common.

Diseases that may present with headaches and epileptic seizures [28

- Alexander disease
- Neurocutaneous syndromes
- Sturge-Weber syndrome
- Tuberous sclerosis complex
- Vascular malformations (arteriovenous malformations, cavernomas)
- Infection
- MELAS* syndrome
- Idiopathic childhood occipital epilepsy of Gastaut
- Idiopathic photosensitive occipital lobe epilepsy
- Encephalitis
- Cerebral abscesses
- Post-meningitis syndromes
- Hydrocephalus
- Brain tumors
- Head trauma
- Post-traumatic syndromes
- Idiopathic photosensitive occipital lobe epilepsy
- Familial hemiplegic migraine
- Episodic ataxia type 2

Despite the inconsistency of epidemiological data, most studies of the relationship between headache and epilepsy were focused on migraine. The concept of comorbidity of migraine and epilepsy was formulated at the beginning of the 20th century and elaborated considerably, including the framework of the theory of "paroxysmal brain" [1, 29–34].

It is well known that migraine and epilepsy are common paroxysmal conditions that share many clinical and pathogenic features [35]. Both diseases are characterized by recurring seizures with typical symptoms, aura, and triggers such as visual stimuli, alcohol, sleep-wake cycle disturbances, vigorous exercise, and menstruations [35–39]. An imbalance between excitatory and inhibitory mediators leading to cerebral hyperexcitability and the involvement of channelopathy mechanisms play a role in the pathophysiology of both diseases [40–44]. In both epilepsy and migraine, pathophysiological changes occur in the glutamatergic [40], serotonergic, and dopaminergic systems of the brain,41 as well as in sodium, potassium, and chloride ion channels [42]. The imbalance may also be due to abnormal GABA transmission [43, 44].

A role of central sensitization with an increasing frequency of migraine attacks and seizures causing chronic disease with treatment-resistant course and overuse of medications is also being discussed for both diseases [45, 46].

Cortical hyperexcitability is thought to play an important role in the pathophysiology of both diseases [47]. In patients with migraine, changes in the excitability of the occipital cortex may lower the threshold for cortical spreading depression (CSD) [48]. The changes in excitability were reported in patients with migraine with/without aura [49, 50]. The proposed mechanisms of hyperexcitability include impaired mitochondrial metabolism, impaired ion channel activity, and reduced magnesium levels [51, 52]. The hyperexcitability is translated into hypersynchronous activity in epileptic patients and in CSD in patients with migraine [7, 53–55]. The key role of the imbalance between inhibition and excitation in cerebral neurons in triggering epileptic seizures and migraine attacks has also been confirmed [56, 57].

Moreover, it has been suggested that genetic and environmental factors may lower the threshold of cortical excitability, thus facilitating both seizures and migraine attacks [25, 26]. The alterations in ion channel-encoding genes CACNAIA, ATP1A2, and SCNIA have been found to be involved in the development of familial hemiplegic migraine, as well as generalized epilepsy and some cases of focal epilepsy as well [58]. On the other hand, CSD occurring at the start of a migraine attack and an epileptic focus can be mutually inducing. Finally, AEDs (valproate, topiramate, gabapentin, and levetiracetam) which reduce the frequency of epileptic seizures and migraine attacks by suppressing cerebral excitability are widely and successfully used for their prevention [59]. Thus, several AEDs have been included in international and Russian clinical guidelines on migraine prevention (the Prevention section): topiramate as a drug of the first choice (level of recommendation B; level of evidence 1), valproic acid as a drug of the second choice (*level of recommendation B; level of evidence 2*) [60, 61].

Relevant data were obtained in studies of the frequency of migraine in the epileptic population and frequency of epilepsy in patients with migraine. In several studies, the frequency of migraine in adult patients with epilepsy ranged between 9% and 30% (similar to that in the general population) [35] and was higher in children and adolescents, ranging from 25% to 44.6% [62, 63]. Moreover, the risk of migraine in patients with epilepsy has been shown to be twice as high as in their relatives without epilepsy [64].

At the same time, the frequency of epilepsy was not increased in the population of patients with migraine compared with their relatives without migraine. Thus, in a study of 500 patients with different types of headaches, the frequency of epilepsy in patients with migraine was lower compared with the general (<1%) and TTH population (1.6% and 2%, respectively) [65]. Only one study reported the frequency of epilepsy in patients with migraine higher than in the general population (5.9% vs. 0.5%) [66].

Therefore, migraine is more common in patients with epilepsy than in the general population, but not vice versa [65, 67]. A putative pathophysiological explanation for the one-way comorbid relationship between migraine and epilepsy is a lower threshold for CSD activation compared to the seizure threshold. Therefore, headache occurs more easily during an epileptic seizure than a seizure occurs during a migraine attack [25, 26].

Do current classifications recognize the relationship between headache and epilepsy? Curiously enough, this relationship is reflected only in the International Classification of Headache Disorders (ICHD-3 as updated by the International Headache Society in 2018) [20] and is not mentioned in the 2017 International League Against Epilepsy classification of epilepsy [68].

In ICHD-3, the relationship between epilepsy and headache is discussed in Section 1.4 *Complications of migraine and Section 7.6. Headache attributed to epileptic seizure*.

1.4. Complications of migraine [20]

1.4.1. Status migrainosus
1.4.2. Persistent aura without infarction
1.4.3. Migrainous infarction
1.4.4. Migraine aura-triggered seizure

Migraine aura-triggered seizure is one of the complications of migraine when a seizure occurs during or within 1 hour after an attack of migraine with aura. Earlier, this clinical type was referred to as migralepsy. Its diagnostic criteria are shown below.

Diagnostic criteria of migraine aura-triggered seizure [20]

A. A seizure fulfilling diagnostic criteria for one type of epileptic attack, and criterion B below
B. Occurring in a patient with migraine with aura, and during or within 1 hour after an attack of migraine with aura
C. Not better accounted for by another ICHD-3 diagnosis

In an Italian study [5], most patients had an epileptic seizure within 1 hour after the onset of a migraine attack. Most of the reported cases were epileptic seizures originating from the occipital cortex according to electroencephalography (EEG) data. The absence of epileptic EEG changes before the seizure was an important feature suggesting that epilepsy is secondary to the migraine attack. This study also described cases of epileptic seizures in patients with migraine without aura, with seizures occurring shortly after the onset of typical migraine without aura.

The differential diagnosis of the aura discussed in this study is of interest. The authors state that *migraine aura-triggered seizure* can be a valid diagnosis when the visual aura is caused by migraine rather than epilepsy. The migrainous origin of aura is confirmed by the absence of typical epileptic changes on the EEG during the aura and in the subsequent phase of headache. The aura and headache caused by epilepsy are also characterized by epileptic EEG changes (e.g., spike waves) during the visual aura and headache phase, clinical manifestations of an epileptic seizure, and cessation of headache with normalization of the EEG changes as soon as the seizure stops. Similar EEG findings were also found in other studies [69–71].

According to ICHD-3 (Section 7.6), *headache attributed to epileptic seizure* is described as a headache caused by an epileptic seizure, occurring during and/or after the seizure and remitting spontaneously within hours or up to three days. Its diagnostic criteria are given below. The EEG findings characteristic of headache attributed to epileptic seizure are given above.

Diagnostic criteria of headache attributed to epileptic seizure [20]

A. Any headache fulfilling criterion C
B. The patient is having or has recently had an epileptic seizure
C. Evidence of causation demonstrated by both of the following:
   1) headache has developed simultaneously with or soon after onset of the seizure
   2) headache has resolved spontaneously after the seizure has terminated
D. Not better accounted for by another ICHD-3 diagnosis

Headache attributed to epileptic seizure is divided into ictal headache (ICHD-3 code 7.6.1) and postictal headache, which occurs after an epileptic seizure (ICHD-3 code 7.6.2); both types are well described in the literature [13, 14, 16, 20]. *Ictal headache* occurs during an epileptic seizure, ipsilateral to the epileptic discharge and resolves immediately or shortly after the seizure. The diagnosis of ictal headache is confirmed by the co-occurrence of epileptic discharges on EEG and headache. Ictal headache may be an isolated manifestation ("true ictal headache") or accompanied by other symptoms of epilepsy (motor, sensory, autonomic), in which case it should be differentiated with other types of headache. *Hemicrania epileptica* is a rare subtype in which headache occurs during an epileptic seizure ipsilateral to the epileptic discharge [72].

Postictal headache occurs within 3 hours of an epileptic seizure and resolves spontaneously within 72 hours [20]. Several studies have reported that postictal headache may be accompanied by migrainous symptoms (nausea, vomiting) and, like migraine, respond to sumatriptan. It has been suggested that migraine-type headache is caused by epileptic discharges in the occipital cortex which activate the trigeminovascular and stem pain centers, triggering a migraine attack [15, 73].

A Korean study [74] has addressed the incidence of headache as an epileptic aura (preictal, postictal, and ictal headache). The incidence of ictal, pre- and post-ictal headache was 1.5%, 4.4%, and 24.5%, respectively. Despite some differences between the studies, the frequency of postictal headache was the highest in all of them, ranging from 24% to 70% [54, 70, 72, 74].

The HELP study showed an increasing risk of headache, primarily migraine, as the duration of epilepsy increases [75]. Although the relationship between the headache phenotype and location of the epileptic focus is poorly investigated in that paper, the authors suggested that the risk of headache/migraine may be higher in patients with occipital epilepsy, which is consistent with the hypothesized comorbid relationship between epilepsy and migraine (in particular, with the CSD mechanism discussed above).

The relationship between epilepsy and other types of headache is much less understood [76]. TTH is the second most common type of headache in patients with epilepsy according to case reports and single epidemiological studies. TTH is significantly less common in epileptic patients compared with the general population (19% versus 70%) [11, 21–23]. There are no publications on the hypothesis of the comorbidity of TTH and epilepsy; shared pathophysiological mechanisms have not been identified and are unlikely. However, some authors suggest that many patients with epilepsy have TTH in the interictal period which may be due to emotional stress of having such severe chronic disease as epilepsy, comorbid psychiatric disorders, and stigmatization [77, 78]. The latter has been reported in more than 50% of epileptic patients [77]. Twenty-one percent of individuals with epilepsy in remission for a minimum of two years reported a feeling of stigma [78]. In epileptic patients, the feelings of shame and insecurity result in social distancing [79, 80]. Relationships between levels of stigma and depression [81, 82], anxiety [83, 84], neuroticism [78], low self-esteem [85, 86], and longer duration of epilepsy [81] have been identified. Psychological and social factors may have a more profound impact on the quality of life compared with clinical manifestations [83]. Many epileptic patients also have depression which can contribute to TTH [87].

Comorbid psychiatric disorders and quality of life associated with concomitant headache in patients with epilepsy have not been investigated. The side effects of AEDs used by patients with epilepsy for many years or for life are another poorly investigated issue.

Conclusion. Thus, many patients with epilepsy report headaches which may occur in the interictal period or have various temporal relationships with epileptic seizures, occurring before, during or after a seizure. Clinical types of headache associated with epilepsy are included in the ICHD, but not in the classification of epileptic seizures and types of epilepsy. Interictal headache is the most common type of headache associated with epilepsy.

In most studies, migraine and migraine-type headache were most common in patients with epilepsy and were followed by TTH. The comorbidity and shared pathophysiological mechanisms of migraine and epilepsy are well studied and considered proven. Migraine-type headache may precede and trigger an epileptic seizure. Less understood forms of headache, primarily TTH, are more frequent in epilepsy than is commonly thought and significantly impair the quality of life. Possible causes of TTH include emotional stress of having such severe chronic disease as epilepsy, comorbid psychiatric disorders, and stigmatization. The presence of comorbid headache and its clinical phenotype should be taken into account by clinicians treating epileptic patients.

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