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# Headache and Epilepsy

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Headache, especially migraine, has long been associated with epilepsy, based on the common clinical features of these disorders. Both migraine and epilepsy have a genetic predisposition and share common pathophysiological mechanisms including an imbalance between excitatory and inhibitory factors that result in spells of altered brain function and autonomic symptoms. There are well-documented reports on the headache as a sole manifestation of epileptic seizure and headache is commonly associated with as preictal, ictal, and postictal symptoms in epilepsy patients. In addition, migraine and epilepsy are frequently described as highly comorbid conditions and several antiepileptic drugs are used for the patients with migraine as well as epilepsy. In the present review, we briefly discuss the connection between headache and epilepsy in various aspects, including classification, clinical features, epidemiology, genetics, pathophysiology, and treatment. **(2017;7:7-15)**

**Key words:** Headache, Migraine, Epilepsy, Epidemiology, Genetics, Treatment

## Introduction

The association of headache and epilepsy has long been recognized, even before the introduction of electroencephalography (EEG) in clinical practice.[1] Headache, especially migraine, shares several interesting features with epilepsy. Both migraine and epilepsy are typical episodic neurological disorders and have a genetic predisposition. Several genetic mutations, such as CACNA1A and ATP1A2, are found both in families with migraine and epilepsy, and the concept of 'channelopathy' can be applied to patients with these genetic mutations,[2] which means that mutations in ion channels can alter the channel function that cause homeostasis cannot be maintained in the presence of usually not harmful stimuli.[3] Both disorders have similar pathophysiologic mechanisms including an imbalance between excitatory and inhibitory factors that result in spells of altered brain function and autonomic symptoms.[4,5] In addition, both have similar clinical features and follow usually reliable preictal, ictal and postictal manifestations arising from the cortex with the modulation by subcortical connection.[6] Accordingly, it is not surprising that several anti-epileptic drugs (AEDs) are effective and widely used for the prevention of migraine.[7]

However, there are only a few cases of clear co-occurrence of headache and epilepsy, such as migraine aura-triggered epilepsy (i.e., migralepsy) and headache as a sole manifestation of epileptic seizure (i.e., ictal epileptic headache). Clinically, headache occurs more frequently with various temporal relationships with epileptic seizure such as headache as an epileptic aura, ictal headache with the features of migraine or tension-type headache, and most commonly, postictal headache. In the present review, we briefly discuss the connection of headache and epilepsy in various aspect, including classification, clinical features, epidemiology, genetics, pathophysiology, and treatment.

## Classification

According to the International Classification of Headache Disorders (ICHD) classification, only three specific entities of headache were described in association with epilepsy; hemicrania epileptica, postictal headache, and migraine aura-triggered seizure (Table 1).[8] Headache attributed to epileptic seizure includes hemicrania epileptica, in which headache occurs during a partial epileptic seizure ipsilateral to the epileptic discharge, and postictal headache, in which headache is caused by, and occurs within 3 h after, an epileptic seizure. Hemicrania epileptica is relatively rare, with only several well-described patients. Although hemicrania epileptica is still accepted in the recent version of ICHD classification,[8] the clinical use-

**Table 1.** Headache Associated Epileptic Seizure in International Classification of Headache Disorders

| | Complication of migraine | Headache attributed to epileptic seizure | |
|---|---|---|---|
| Criteria | Migraine aura-triggered seizure | Hemicrania epileptica | Postictal headache |
| A | A seizure fulfilling diagnostic criteria for one type of epileptic attack, and criterion B below | Any headache fulfilling criterion C | Any headache fulfilling criterion C |
| B | Occurring in a patient with migraine with aura, and during, or within 1 hour after, an attack of migraine with aura | The patient is having a partial epileptic seizure | The patient has recently had a partial or generalized epileptic seizure |
| C | Not better account for by another diagnosis | Evidence of causation demonstrated by both of the following:<br>1. Headahce has developed simultaneously with onset of the partial seizure<br>2. Either or both of the following:<br>a) headache has significantly improved immediately after the partial seizure has terminated<br>b) headache is ipsilateral to the ictal discharge | Evidence of causation demonstrated by both of the following:<br>1. Headahce has developed within 3 hours after the epileptic seizure has terminated<br>2. Headache has resolved within 72 hours after the epileptic seizure has terminated |
| D | | Not better accounted for by another diagnosis | Not better accounted for by another diagnosis |

fulness of hemicrania epileptica as a separate disease entity is often questioned, and it has been suggested that hemicrania epileptica should be classified as a type of ictal epileptic headache.[9] Although the accurate pathophysiology of hemicrania epileptica is uncertain, it has been suggested that the increased cerebral blood flow observed during the preictal or ictal period may trigger trigeminovascular activation, resulting in headache.[10-12] Postictal headache is relatively common, and the reported prevalence of postictal headache varied from 24 to 60% depending on the characteristics of studied patients and diagnostic criteria of postictal headache.[10,13-16] Migraine aura-triggered seizure, a seizure that is triggered by an attack of migraine with aura, is classified as a complication of migraine. As in hemicrania epileptica, migraine aura-triggered seizure is a rare condition in which a migraine with aura attack is followed, within an hour, by an epileptic seizure. Although migraine aura-triggered seizure is introduced in the classification of migraine as a complication of migraine, only a few cases are reported, and the majority of them have been criticized by the other authors,[17] because most of the cases of migraine aura-triggered seizure are complex cases that do not provide clear evidence of an association between migraine and epilepsy. Without a concomitant EEG study, it would be difficult to ascertain whether the migraine with aura preceded the epileptic seizure (preictal migraine) or triggered the epileptic seizure (migraine aura-triggered seizure). In addition, the presence of ictal or interictal epileptiform discharges on EEG may be indicative of the diagnosis of epilepsy (especially occipital lobe seizures), and the lack of EEG abnormality could not rule out the diagnosis of epilepsy in patients with deep epileptic focus or patients with epileptogenic areas or tangential dipole. There are also reports that migraine-triggered seizure was triggered by migraine without aura attacks or occurred later than 1 hour post-aural time frame stipulated by the definition of classification.[18]

Classification of seizures and epilepsies by International League Against Epilepsy (ILAE), focusing on the networks and etiologies of seizures and epilepsies, is very concise and did not consider individual features of ictal or postictal semiology into the classification.[19] In this classification, hemicrania epileptica and migraine-triggered seizure can be classified as just 'focal seizure' with structural or unknown etiology based on the results of genetic and radiological evaluations. Semiological seizure classification, first introduced nearly 20 years ago, describes the patients' aura and ictal semiology regardless of the results of EEG and neuroimaging (Table 2).[20,21]This classification has merits in that it conveys the key features of aura and ictal semiology in temporal order, but postictal symptoms including postictal headache were not significantly considered even in this classification, possibly because the presence or characteristics of postictal symptoms rarely have localizing or lateralizing value in individual patient. In this classification, headache as an aura and hemicrania epileptica can be classified as somatosensory aura, but it can be also classified as autonomic aura when the pathophysiology of autonomic involvement in migraine is emphasized.

**Table 2.** Semiological seizure classification

| | |
|---|---|
| Aura | |
| Somatosensory aura | Visual aura |
| Auditory aura | Gustatory aura |
| Olfactory aura | Autonomic aura |
| Abdominal aura | Psychic aura |
| Autonomic seizure | |
| Dialeptic seizure | |
| Typical dialeptic seizure | |
| Motor seizure | |
| Simple Motor Seizure | |
| Myoclonic seizure | Tonic seizure |
| Epileptic spasm | Clonic seizure |
| Tonic-clonic seizure | Versive seizure |
| Complex Motor Seizure | |
| Hypermotor seizure | Gelastic seizure |
| Automotor seizure | |
| Special seizure | |
| Atonic seizure | Astatic seizure |
| Hypomotor seizure | Akinetic seizure |
| Negative motor seizure | Aphasic seizure |

## Ictal epileptic headache

Recently, several well-described cases of headache as sole manifestation of an epileptic seizure has been documented, and the term 'ictal epileptic headache' has been proposed to identify the patients with an EEG-recorded epileptic seizure with migraine/headache-like features.[1,22,23] Although ictal epileptic headache has not been introduced to the ICHD classification, the suggested definition includes headache "as sole ictal manifestation" and without presenting "specific picture of migraine, migraine with aura or tension-type headache", lasting from seconds to days, with evidence of ictal epileptiform EEG discharges, which immediately resolves after intravenous AED administration. Aside from the feature of sole ictal manifestation, ictal epileptic headache is different from hemicrania epileptica, because it necessitates the presence of ictal epileptiform EEG discharges and response to intravenous AED administration.[1,22,23] In hemicrania continua, headache should occur ipsilateral to the epileptic discharge, but headache can be present in the ipsilateral and contralateral side of epileptiform discharge in ictal epileptic headache.[8]

There have been only a few reports on ictal epileptic headaches that have been confirmed by ictal epileptiform EEG discharges and these cases vary considerably with respect to their patterns of headache and underlying epilepsy syndrome. Diverse patterns of EEG findings were found, including rhythmic focal spikes over posterior cortex, or bilateral continuous spike and wave discharges. Clinically, it is easily conceivable that it would be very difficult to demonstrate the ictal EEG changes and response to intravenous AED administration in patients with ictal epileptic headache who experience short lasting headache. Therefore, epileptic activity in reported cases with ictal epileptic headache was sufficiently prolonged and sustained to meet the diagnostic criteria of nonconvulsive status epilepticus. One interesting finding in patients with ictal epileptic headache is that many of them have the feature of photosensitivity.[17,24] They usually present a personal or familial history of epilepsy and migraine and a photoparoxysmal EEG response. In addition, it is noteworthy that complete remission of the headache and of epileptic abnormality in most of these ictal epileptic headache patients was not achieved by means of specific antimigraine drugs, but following intravenous administration of AED such as diazepam or phenytoin.

### Epidemiology

Headache, including migraine, is a common neurological disease. In general population, the life-time prevalence of severe headache is about 46% and that of migraine is 10-22%.[5,25] In an epidemiologic study in South Korea, the 1-year prevalence of all types of headache was 61.4% and that of migraine was 6.1%,[26] and another telephone survey study documented that 22.3% of adults fulfilled the diagnostic criteria of migraine.[27] The prevalence of active epilepsy in the general population is 0.3-0.7%, and the prevalence of treated epilepsy in South Korea was 0.4%.[28]

The first hypothesis on the comorbidity of headache and epilepsy in adults is mainly based on a large cohort study that reported a 2.4-fold increased risk of migraine in almost 2000 patients with epilepsy compared with their relatives without epilepsy.[29,30] Studies with epilepsy patients confirmed that epilepsy patients suffered from various types of headaches, most commonly postictal headache,[16,31,32] and the presence of headache significantly added the burden of disease in epilepsy patients.[31,32] However, recent studies raise some doubts on the widely held concept of comorbidity of the two conditions,[23,33,34] because headache during the interictal period, in particular migraine, was not encountered more often in patients with epilepsy than expected in the general population.[15,35] One recent study showed that only periictal headache, not comorbid migraine and tension-type headache, is more common and occurs in more than one-third of patients with epilepsy.[36] These conflicting findings can be explained by the co-occurrence of confounding factors according to the different sampling methods and study designs.[34] In an epidemiologic study in South Korea, the prevalence of migraine in ep-

ilepsy patients at their first visit was 12.4% (74 of 597). It was suggested that the prevalence of migraine in South Korea (12.4%) was higher than the prevalence of migraine in the general Korean population (6.1-6.5%).[13,26] However, the prevalence of migraine in epilepsy patients in that study (12.4%) was similar with prevalence of migraine in other countries (10-22%). Therefore, there is no conclusive evidence of a real-relationship between the two disorders.

When looking at individual attacks, it is clear that there is a time-dependent relationship between headache and epilepsy. Headache in epilepsy patients can occur as an interictal, periictal, ictal or postictal symptoms with diverse clinical features, making it difficult to differentiate migraine from epilepsy in some patients. The reported incidence of prodromal, ictal and postictal headache was 4.4%, 1.5% and 24.5% respectively in Korean epilepsy patients at their first visit, and the features of migraine were found in 46.2% of patients with prodromal seizure-related headache and in 36.3% of patients with postictal seizure-related headache.[13] The incidence of headache in more than 800 patients with refractory epilepsy with video-EEG conformation as an aura, preictal and postictal headache in Korea was 0.7, 6.3%, and 30.9% respectively.[14] Although the reported incidence of headache associated with epileptic seizures was quite different among studies, all studies consistently show that postictal headache is the most common type of headache, with the incidence from 24 to 60%. In one study, headache was the most frequently encountered postictal symptom in patients with epilepsy (38%) followed by dizziness and confusion, and the presence of postictal headache was very useful in differentiating patients with epileptic seizures from patients with non-epileptic seizures.[37]

## Headache in childhood epilepsy

Headache and epilepsy are common complaints in the neurology outpatient clinic, perhaps even more so in child neurology with a relatively higher prevalence of these disorders in this population. Actually, the early reports on the connection of headache and epilepsy were based on the clinical observation of pediatric patients who experienced recurrent episodes of 'intermediate' in type between migraine and epilepsy.[6,38] In practice, it is often difficult to clinically distinguish migraine from epilepsy, and this effort is complicated in children because they are frequently not good at describe their symptoms and the attacks of both migraine and epilepsy are characterized by abrupt, paroxysmal changes in mood and behavior, sometimes consciousness and may be accompanied by changes in visual, motor, sensory, or speech function.[7,39] Children are more likely to have autonomic symptoms both in headache and epilepsy attacks, and they can have isolated, long-lasting ictal autonomic manifestations, while ictal autonomic manifestations (both in headache and epilepsy) in adults are usually associated, simultaneously or sequentially, with other motor or sensory ictal signs and symptoms both in headache and epilepsy attacks.[40,41]

Compared to adult patients, there are only few reports on the comorbidity of headache and epilepsy in childhood. One retrospective case-control study showed that children with migraine had 3.2-fold increased risk of epilepsy compared with tension-type headache, while children with epilepsy had a 4.5-fold risk of developing migraine over tension-type headache.[42] In a cross-sectional study including 400 children with epilepsy who were seen in a tertiary neurologic clinic, overall migraine prevalence was 25%. Migraine was more common in children older than 10 years and with benign epilepsy with centrotemporal spikes.[43] The prevalence of migraine was even higher in a South Korea study, since 86 of 229 patients (37.6%) epilepsy patients were also diagnosed as migraine.[44]

The most notable association of migraine and epilepsy is found in patients with idiopathic childhood occipital epilepsy of Gastaut type. This epilepsy syndrome is usually self-limiting disorder affecting boys and girls equally with peak incidence between 8-9 years of age.[45] It is a very rare condition, with an estimated prevalence of 0.3% in children with newly diagnosed nonfebrile seizures.[46] Elementary visual hallucinations are the most common ictal manifestation at onset and are often the sole ictal semiology, developing within seconds and generally lasting under 1-3 minutes. The most common nonvisual symptom is horizontal deviation of the eyes, followed by hemiconvulsion or generalized tonic-clonic seizure.[45] Compared to the short duration of visual hallucination of idiopathic childhood occipital epilepsy of Gastaut type, the visual phenomena caused by migraine with aura generally develop slowly within minutes with longer durations (up to 60 minutes by definition)[8] and tonic deviation of the eyes are also not seen in migraine.[6] Benign childhood occipital epilepsy of Panayiopoulos type typically presents between 3 and 5 years of age with rare prolonged and nocturnal seizures, marked autonomic features, followed by clonic motor symptoms. Although migraine is uncommon in this syndrome, poistictal migrainous headache is very common in these patients.[47,48] Aside from these idiopathic childhood occipital epilepsy syndromes, headache in children with symptomatic occipital epilepsy have also been described, and misdiagnosis of occipital seizures with migraine and vice versa is common, especially in pediatric age.[49]

Benign epilepsy with centrotemporal spikes is the most common focal epilepsy of childhood and account for 13-23% of all childhood epilepsy.[50] Children with this syndrome most commonly present between 7 and 10 years, with focal seizures either in wakefulness or in sleep involving unilateral sensorimotor function of the face, speech arrest, and hypersalivation. Higher prevalence of migraine was also documented patients in this syndrome.[50]

## Pathophysiology

Most studies on the possible common pathophysiology underlying headache and epilepsy support the hypothesis of excessive neocortical cellular excitability as the main pathological mechanism underlying the onset of both disorders. In epilepsy, neocortical hyperexcitability is thought to transition to abnormal hypersynchronous electrical discharges in neuronal cells, and subsequent alterations of ion membrane permeability or ion exchange activity leading to recurrent seizures.[39,51,52] In migraine, however, neocortical hyperexcitability is believed to transition to cortical spreading depression (CDS) rather the hypersynchronous activity in epilepsy. Although CSD is recently recognized as an epiphenomenon of spreading depolarization due to a depolarization block of neuronal activity in migraine,[53] CSD is accepted as the basic mechanism for migraine aura and the trigger for headache pain. CSD is characterized by a self-propagating wave of strong, sustained neuronal depolarization with massive efflux of $K^+$ from intracellular to extracellular compartments. This is followed by neural suppression, which may last for minutes. In migraine, CSD causes activation of trigeminal nociceptive system, resulting in the release of multiple neuroinflammatory molecules. The relation between CSD and epileptic activity was investigated in subjects with subarachnoid hemorrhage (SAH) using intracranial recordings that were implanted for monitoring purposes. In this study, spreading convulsions are defined as a spreading depolarization with ictal epileptic field potentials riding on the final shoulder of the slow potential change where, normally, depression of spontaneous activity is observed, and two of the twenty-five patients with SAH showed spreading convulsions.[54] Depression period per day and number of spreading depolarization per day peaked on the day of SAH and on the day 7 after the events, when the risk of seizure and delayed vasospasm is increased after SAH.[55] Co-occurrence of CSD with epileptic activity was observed in patients with acute brain injury,[56] and repeated CSD appears to increase epileptic activity in experimental studies, due to suppression of inhibitory GABA function.[57,58] It is well documented that the occipital lobe is the brain structure most responsible for both development of migraine and epilepsy,[22] and the occipital cortex is uniquely vulnerable to CSD, further strengthening the hypothesis that a pathologically low threshold for activation of cortical hyperexcitability may be implicated in both migraine and epilepsy.[59] In epilepsy, ictal discharge originating in the occipital cortex may remain localized or spread to adjacent areas. When the ictal discharge remains localized, it can cause various visual symptoms mimicking migraine aura, and one of the most frequent ictal pattern is a sequence of epigastric discomfort, unresponsiveness and vomiting when the discharge spreads outside the occipital cortex. Therefore, the symptom cluster of visual aura, abdominal discomfort, vomiting and headache can make clinical differentiation between occipital seizures and migraine particularly difficult.[22] The previously divisive issue of vascular changes in migraine has now largely been identified as an epi-phenomenon of migraine,[60] and similarly, no significant vascular changes are thought to occur in epilepsy.

There are other evidences that migraine and epilepsy share common pathophysiologic mechanism. Both disorders are episodic neurological disorders and most patients experience relative periods of interictal symptom freedom. Mutations in ion channels, specifically involving translocating transmembrane proteins such as $Na^+$-$K^+$ ATPase, can account for these episodic neurological symptoms.[3,61] In normal conditions high extracellular $K^+$ concentration increases glial $Na^+$-$K^+$ ATPase activity; this promotes removal of $K^+$ that accumulates in the extracellular space during repetitive neuronal finding. $Na^+$-$K^+$ ATPase pump plays in the regulation of both seizure onset, by acting on membrane depolarization (due to inhibitory potential post-synaptic modulation), and CSD, by modifying the local $K^+$ concentration.[10,39] This experimental finding linked both epilepsy and migraine to the ability of the $Na^+$-$K^+$ pump to regulate $K^+$ extracellular concentrations. Interestingly, this experimental finding was confirmed in humans by a novel mutation in ATP1A2, which encodes the $\alpha 2$ submit of $Na^+$-$K^+$ ATPase, associated with two phenotypically different pictures: familial hemiplegic migraine and benign familial infantile convulsions. While it is likely that the dysfunction of $Na^+$-$K^+$ ATPase is not the only pathological mechanism, the recent concept of channelopathy supports this ion channel dysfunction as a strong contributor to both episodic disorders.

## Genetics

It is well documented that both migraine and epilepsy have genetic predisposition. Familial hemiplegic migraine (FHM) is a

well-known, but rare subtype of migraine with aura that is inherited in an autosomal dominant manner. Interestingly, mutations in all three FHM genes [CACNA1A (FHM1), ATP1A2 (FHM2) and SCN1A (FHM3)] can also cause epileptic seizures. All three genes in FHM are involved in the function of ion channels, and genetically determined dysfunction of these ion channels and associated proteins can cause changes in neuronal ion concentration, which can alter cortical excitability. Imbalance between inhibitory and excitatory factors is hypothesized to play a central role in both epilepsy and migraine.[62] CACNA1A (FHM1) gene, for example, encodes α subunit of neuronal voltage-gate calcium channel 2.1. Mutations in this gene are recently shown to alter the affinity of the associated inhibitory G-protein (gain of function), thus potentially lead to reduced inhibition, which can cause neurons to become hyper-excitable. Mutation in the CACNA1A gene can cause hemiplegic migraine, epilepsy and episodic ataxia.[5,62] Pathophysiological implications of mutation in ATP1A2 (FMH2) were previously described, and genetic dysfunction of ATP1A2 is not only associated with FHM but also benign familial infantile convulsions. Aside from a genetic cause of FHM3, SCN1A mutation is famous for the most important cause of Dravet syndrome. Dravet syndrome is also known as severe myoclonic epilepsy of infancy, which is characterized by a rare, catastrophic, lifelong form of epilepsy that usually begins in the first year of life with frequent and prolonged seizures. SCN1A provide instructions for making α subunit of a sodium channel called Nav1.1, and a recent study suggested that milder phenotypes of SCN1A mutation can cause lesser impairment of $Na^+$ channel function leading to reduced $Na^+$ currents in GABAergic inhibitory interneuron or electrical network hyperexcitability in patients with these mutations.[63,64]

Mutations in the proline-rich transmembrane protein (PRRT2) gene have been associated with paroxysmal kinesigenic dyskinesia, benign familial infantile seizures, and the infantile convulsion-choreoathetosis syndrome. PRRT2 encodes a protein that is expressed in the central nervous system and is thought to be involved in the modulation of synaptic neurotransmitter release. Reduced PRRT2 protein may lead to altered synaptic neurotransmitter release and dysregulated neuronal excitability, resulting in paroxysmal movement disorders and seizure.[65] Mutations in this gene are also hypothesized to be involved in hemiplegic and 'normal' migraine. However, the association of mutations in the gene with migraine could also be explained by chance due to the high prevalence of migraine in the general population.[5]

Mutations in FHM and PRRT2 genes are a very rare and only account for a small number of patients with migraine and/or epilepsy. More important is the real genetic contribution on 'normal' migraine and epilepsy. Recent genome-wide association studies in migraine and epilepsy have given important results, but they can only explain a small genetic contribution to these syndromes. In an epilepsy genetic study including 730 participants with non-acquired focal epilepsy or generalized epilepsy, 32% of women and 15% of men reported migraine. The prevalence of migraine with aura was significantly increased when other family members were affected by a seizure disorder, however, this was not the case for migraine without aura and failed to find significant genetic factor affecting both migraine and epilepsy in 'normal' patients,[5,66] so genetic linkage of migraine and epilepsy has so far only been demonstrated in specific and invariably rare syndromes. Non-syndromal migraine and epilepsy, on the other hand, are probably the result of a complex interplay between multiple genes and environmental factors and influences, and more advanced genetic analysis technique, such as next generation sequencing or other more accurate and precise phenotyping strategies are expected to further increase understanding of genetic association of migraine and epilepsy.[64]

## Treatment

Several classes of medications are used for the prevention of migraine, including tricyclic antidepressants, beta blockers, calcium channel blockers and AEDs. It seems to rational to use AEDs for the prevention of migraine because both migraine and epilepsy share the same pathophysiology of imbalance between excitatory and inhibitory factors and mechanisms of many AEDs include blockage of ionic gradient which is suggested to be involved in the CSD. Valproic acid (VPA) and topiramate (TPM) are approved AED for the preventive use of migraine, and many other drugs including gabapentin, acetazolamide, carbamazepine, oxcarbazepine, and zonisamide were suggested to have the preventive role for migraine.[7]

VPA is an antagonist of voltage-dependent sodium channels, therefore suppressing repetitive neuronal firing. VPA also reduces excitatory transmission by increasing brain gamma-aminobutyric acid (GABA) concentrations. The action of VPA on GABA likely confers the ability to reduce cortical events and neuronal activity in the nucleus caudalis of trigeminal nerve. This is achieved by the activation of glutamic acid decarboxylase and by inhibition of GABA degradative enzymes. From the several clinical studies confirmed that the ability to reduce the attack rate of migraine, questions remain on its ability

to decrease duration and severity of the residual attacks.[67,68]

The specific mechanism of action of TPM in migraine remains not fully elucidated. It is likely that several chemical properties, some of which are shared with VPA, contribute to its antimigraine effects. TPM blocks both sodium and calcium channels, thereby likely affecting the neuronal component of the migraine attack. TPM also augments GABA concentrations, and inhibits cortical spreading in animal models. TPM also inhibits glutamate receptors and carbnonic anhydrase, although the exact implications of these chemical properties on migraine are still obscure. Evidence of efficacy of TPM in preventing migraine attacks is confirmed in four class I studies and seven class II studies. The effect observed in meta-analyses suggests that the patients treated with PM are twice as likely to experience more than 50% reduction in the frequency of headache compared with patients treated with placebo. By reducing headache, TPM has also significantly improved patients' quality of life.[68,69]

A recent Cochrane review concluded that at the moment there is no evidence on the efficacy of other AEDs migraine including levetiracetam, zonisamide, carisbamate, clonazepam, and perampanel, although there is one study documented the similar efficacy of topirmate and zonisamide in migraine patients.[68]

### Why migraine is not a common cause of epilepsy?

In the central nervous system, there appears to be a hierarchial organization based on "neuronal networks" (cortical and subcortical) that may be more or less prone to CSD (migraine) and epileptic focal discharges (seizures). Onset and propagation are triggered when these neurophysiological events reach a certain threshold ("all or-none events"), which is lower for the onset of CSD than that of the seizure. The onset of CSD and of the epileptic seizure may facilitate each other. The underlying neurophysiological causes may be the same, with two phenomena displaying the "all-or-none" characteristic, which may be triggered by more than one pathway converging upon the same destination. However, it has been suggested that the threshold required for the onset of CSD is likely to be lower than that required for the epileptic seizure; therefore the onset of the epileptic seizure facilitates the onset of CSD to a greater degree than the onset CSD facilitates the onset of epileptic seizure.[70] Migraine without aura is thought to be the result of a CSD that starts and propagates from silent cortical areas following trigemino-vascular activation, without any additional signs/symptoms. Similarly, an epileptic seizure, whose onset and propagation occur along silent/non-eloquent cortical areas, may produce trigemino-vascular activation, which results in a migraine attack without any additional epileptic signs/symptoms. The latter condition is understandably very rare, when we consider the higher threshold required for the onset of epilepsy. This observation is supported by the fact that periictal headaches associated with other signs/symptoms during an epileptic seizure are very common, which in turn confirms that the threshold for migraine onset is lower than that of seizure onset.[70]

## Conclusion

Headache and epilepsy are comorbid, episodic disorders sharing common pathophysiological mechanisms of CSD leading to neuronal hyperexcitability that explains the use of AEDs in both disorders. Their overlap is further supported by the presence of common genetic mutations and shared clinical features of migraine and epilepsy especially in patients with occipital lobe seizures. Although there is no conclusive evidence of a real causal relationship between headache and epilepsy, the association of these episodic neurological disorders is an interesting issue, and further laboratory and clinical studies would demonstrate the real connection of headache and epilepsy.[34]

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