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CLINICAL AND NEUROLOGICAL MANIFESTATIONS OF HEADACHES IN EPILEPSY

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A R T I C L E I N F O.

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Abstract

The association between headache and epilepsy has long been recognized even before the introduction of electroencephalography (EEG) into clinical practice. So, like headaches, it shares several interesting features with epilepsy. In particular, migraine and epilepsy are typical episodic neurological disorders and have a genetic predisposition.

Headache, especially migraine, shares several interesting features with epilepsy. [1]. Migraine and epilepsy are typical episodic neurological disorders and have a genetic predisposition. Several genetic mutations, such as CACNA1A and ATP1A2, are found in families with both migraine and epilepsy. According to Spillane J., Kullmann DM, the concept of " channelopathy " can be applied to patients with these genetic mutations [2], which means that mutations in ion channels can alter channel function which disrupt homeostasis.[3] Rogawski MA and colleagues confirmed that both diseases have similar pathophysiological mechanisms, including an imbalance between excitatory and inhibitory factors that lead to periods of altered brain function and autonomic symptoms.[4,5] In addition, both have similar clinical features and follow generally reliable prectal findings. , ictal and postpical manifestations arising from the cortex with modulation by subcortical connections.[6] Accordingly, it is not surprising that several antiepileptic drugs (AEDs) are effective and widely used for migraine prevention.

However, there are only a few cases of clear overlap between headache and epilepsy, such as migraine epilepsy caused by aura and headache as the sole manifestation of an epileptic seizure (eg, ictal epileptic headache). Clinically, headache is more common with various temporal associations with an epileptic seizure, such as headache as an epileptic aura, ictal headache with features of migraine or tension headache, and most commonly postictal headache. In this review, we will briefly discuss the association of headache and epilepsy in various aspects, including clinical features, epidemiology, pathophysiology and treatment.

Belcastro V. and Parisi P. describe several well-described cases of headache as the only manifestation of an epileptic seizure, and in order to verify the diagnosis of ictal epileptic headache, EEG signs must coincide with epileptic seizures and migraine symptoms.[1,22,33] Although ictal epileptic headache pain was not included in the classification of ICHD, the proposed definition includes headache "as the only manifestation" and without presenting "a specific picture of migraine, migraine with aura, or tension-type headache" lasting from a few seconds to several days, with confirmation of the presence of ictal epileptiform discharges on EEGs, which are immediately eliminated after intravenous administration of anticonvulsants. In addition to the features of presentation, ictal epileptic headache

differs from hemicranial epilepsy in that it requires the presence of ictal epileptiform EEG discharges and a response to intravenous administration of anticonvulsants. [1,2,,23]. There have been only a few reports of ictal epileptic headaches that were confirmed by ictal epileptiform EEG discharges, and these cases vary considerably depending on their headache patterns and epilepsy syndrome. A variety of patterns of EEG findings were found, including rhythmic focal spikes across the posterior cortex or bilateral continuous bursts and waves. Clinically, it is easy to imagine that it would be very difficult to demonstrate ictal EEG changes and response to intravenous anticonvulsant in patients with ictal epileptic headache who experience transient headache. Thus, the epileptic activity in the reported cases with ictal epileptic headache was sufficiently prolonged and persistent to meet the diagnostic criteria for nonconvulsive status epilepticus. Verrotti A., Coppola G. found that patients with ictal epileptic headache have increased photosensitivity.[17,24] In addition, it should be noted that complete remission of headache and epileptic abnormality in the majority of these patients with ictal epileptic headache was not achieved with the help of specific antimigraine drugs, but on the contrary, complete cure occurred after intravenous administration of anticonvulsants, such as diazepam or phenytoin.

Headache, including migraine, is a common neurological disorder. In the general population, the lifetime prevalence of severe headache is about 46%, and migraine is 10-22%. [5,25] In a worldwide epidemiological study, the 1 -year prevalence of all headache types was 61.4% and migraine 6.1%, 26 and another telephone survey study reported that 22.3% of adults completed diagnostic criteria for migraine. The prevalence of active epilepsy in the general population is 0.3-0.7%.

A large cohort study conducted in 2004 reported a 2.4-fold increase in the risk of migraine in nearly 2000 patients with epilepsy compared with their relatives without epilepsy.[29,30] Other researchers (M. Syvertsen, R Mameniskiene) confirmed that patients with epilepsy suffered from various types of headaches, most often postictal headache, [31,32], in addition, the presence of headache significantly increased the burden of disease in patients with epilepsy. [31,32], However recent studies P. Kwan and colleagues question the prevalence of comorbidity between the two conditions because interictal headache, particularly migraine, is no more significantly different than expected in the general population[15,35]. B. Duchaczek and his colleagues found that only Periictal headache, rather than concomitant migraine or tension-type headache, is more common in more than a third of patients with epilepsy[36]. According to V. Belcastro these conflicting results may be explained by the co-occurrence of precipitating factors depending on different sampling methods. [34] In 2012, BK Kim An epidemiological study was conducted in South Korea on the prevalence of migraine in patients with epilepsy and the study showed that during the initial examination of patients, the prevalence of migraine was 12.4% (74 out of 597). It was suggested that the prevalence of migraine in South Korea (12.4%) was two times higher than the prevalence of migraine in the general Korean population (6.1–6.5%). [13,26] However, the prevalence of migraine in patients with epilepsy in this study (12.4%) was similar to the prevalence of migraine in other countries (10–22%). Therefore, there is no convincing evidence of a real relationship between these two disorders.

When looking at individual attacks, it is clear that there is a time relationship between headache and epilepsy. Headache in patients with epilepsy may occur as interictal, periictal, ictal, or postpical symptoms with varying clinical features, making it difficult to differentiate migraine from epilepsy in some patients. The reported incidence of prodromal, ictal and post-epital headache was 4.4%, 1.5% and 24.5%, respectively, in patients with epilepsy at their first visit, and migraine features were found in 46.2% of patients with headache associated with with a prodromal attack, and in 36.3% of patients with headache caused by a postictal seizure.[13] According to a study by Lee SK, the incidence of headache in more than 800 patients with refractory epilepsy with video-EEG conformation in the form of aura, preictal and postictal headache in China was 0.7, 6.3% and 30.9%, respectively.[8, 9,14] 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 an incidence ranging from 24 to 60%. In one study, headache was the most common 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 those with non-epileptic seizures.

Headache and epilepsy are common complaints in outpatient clinics, even more so in pediatric neurology with a relatively higher prevalence of these disorders in this population. In fact, early reports of an association between headache and epilepsy were based on the clinical observation of pediatric patients who experienced recurrent episodes of an "intermediate" type between migraine and epilepsy.[6,34] In practice, it is often difficult to clinically distinguish migraine from epilepsy, and this is complicated in children because they often do not describe their symptoms very well, and attacks of migraine and epilepsy are characterized by sudden, paroxysmal changes in mood and behavior, sometimes consciousness, and may be accompanied by changes in visual, motor, sensory or speech functions.[7,13] Children are more likely to have autonomic symptoms in both headaches and epilepsy, and may have isolated, long-lasting ictal autonomic manifestations, whereas ictal autonomic manifestations (in both headache and epilepsy) in adults are usually associated, concurrently or consistently with other motor or sensory ictal signs and symptoms in both headaches and epilepsies.

Compared with adult patients, there are only a few reports of comorbid headache and epilepsy in childhood. One retrospective study found that children with migraine had a 3.2-fold increased risk of epilepsy compared with tension-type headache, while children with epilepsy had a 4.5-fold increased risk of developing migraine in older patients [14, 32]. A cross-sectional study found that among 400 children with epilepsy who were seen in a neurology clinic, the overall prevalence of migraine was 25%. Migraine was more common in children over 10 years of age and with benign epilepsy with centrotemporal spikes.[34] The prevalence of migraine was even higher in the Asian population, as 86 of 229 patients (37.6%) with epilepsy were also diagnosed with migraine.

The most prominent association between migraine and epilepsy occurs in patients with idiopathic childhood occipital epilepsy. It is a very rare condition with an estimated prevalence of 0.3% in children with newly diagnosed nonfebrile seizures. Elementary visual hallucinations are the most common ictal presentation at onset and are often the only ictal semiology, developing within seconds and usually lasting less than 1–3 minutes. The most common asymmetric symptom is horizontal deviation of the eyes, accompanied by a hemi -convulsive or generalized tonic-clonic seizure. Compared to the short duration of visual hallucinations of idiopathic childhood occipital epilepsy of the Gastaut type, the visual phenomena caused by migraine with aura usually develop slowly over several minutes with a longer duration (up to 60 minutes by definition) [8] and tonic deviation of the eyes is also not observed with migraine. [6,17,18]. Although migraine is rare in this syndrome, migraine headaches are very common in these patients.

[19,20,23] noted that benign epilepsy with centrotemporal spikes is the most common focal epilepsy of childhood and accounts for 13-23% of all childhood epilepsy. Children with this syndrome most often occur between 7 and 10 years of age, with focal attacks either while awake or during sleep with unilateral sensorimotor facial function, speech delay and hypersalivation. A higher prevalence of migraine has also been reported in patients with this syndrome.

Most studies of the possible common pathophysiology underlying headache and epilepsy support the hypothesis of excessive neocortical cellular excitability as the main pathological mechanism underlying the occurrence of both disorders. In epilepsy, it is believed that the neocortical hyperexcitability progresses to abnormal hypersynchronous electrical discharges in neuronal cells and subsequent changes in ionic membrane permeability or ion exchange activity leading to recurrent seizures.[32,33,34] However, in migraine, the neocortical hyperexcitability is associated with the transition to widespread cortical depression (C ortical spreading depression, C SD), which is most likely hypersynchronous activity in epilepsy. Although Dreier JP and colleagues recently revealed that CSD is recognized as an epiphenomenon of propagation depolarization due to a block in depolarization of

neuronal activity in migraine, CSD is accepted as the underlying mechanism of migraine aura and pain trigger in headaches. CSD is characterized by a self-propagating wave of strong, sustained neuronal depolarization with massive K+ efflux from intracellular to extracellular compartments. In migraine, CSD causes activation of the trigeminal nociceptive system, resulting in the release of several neuroinflammatory mediators. According to Belcastro V., the occipital lobe is the brain structure that is most often responsible for the development of both migraine and epilepsy, and the occipital cortex is vulnerable to CSD, which further strengthens the hypothesis that pathology and activation of the occipital lobe may be related to both with migraine and epilepsy. There is other evidence that migraine and epilepsy share a common pathophysiological mechanism. Both diseases are episodic neurological disorders, and most patients experience relative periods of freedom from interictal symptoms. Mutations in ion channels, particularly those associated with transmembrane proteins such as Na+-K+ ATPase, may explain these episodic neurological symptoms. Under normal conditions, high extracellular K+ concentration increases glial Na+-K+ ATPase activity ; this promotes the removal of K+, which accumulates in the extracellular space. The Na + -K + ATPase pump plays a role in regulating both the onset of uptake, acting on membrane depolarization, and the CSD, by changing the local K + concentration. This experimental study links both epilepsy and migraine to the ability of the Na + -K + pump to regulate extracellular K + concentrations. Interestingly, this experimental finding was confirmed in humans by a novel mutation in ATP1A2, which encodes the α2-feeding Na+-K+ ATPase, associated with two phenotypically distinct patterns: familial hemiplegic migraine and benign familial migraines. infantile seizures. Although it is likely that Na+-K+ ATPase dysfunction is not the only pathological mechanism, the recent concept of channelopathy supports this ion channel dysfunction as a strong contributor to both episodic disorders.[27,28,31]

Several classes of medications are used to prevent migraines, including tricyclic antidepressants, beta blockers, calcium channel blockers, and AEDs. It appears rational to use AEDs for migraine prevention because both migraine and epilepsy share the same pathophysiology of an imbalance between excitatory and inhibitory factors and the mechanisms of many AEDs involve blocking the ion gradient that is involved in CSD. Valproic acid (VPA) and topiramate are approved AEDs for migraine prophylaxis, and many other drugs, including gabapentin, acetazolamide, carbamazepine, oxcarbazepine, and zonisamide, have been proposed for migraine prophylaxis [7,20,25].

Vvalproic acid is a sodium channel antagonist and therefore inhibits neuronal re -firing. Valproic acid also reduces excitatory transmission by increasing brain gamma-aminobutyric acid (GABA) concentrations. The effect of valproic acid on GABA appears to reduce cortical events and neuronal activity in the caudal trigeminal nucleus. This is achieved by activating glutamic acid decarboxylase and inhibiting GABA degrading enzymes. [18,19]. The specific mechanism of action of topiramate in migraine remains incompletely understood. It is likely that certain chemical properties, some of which are similar to valproic acid, contribute to its antimigraine effects. By reducing headaches, topiramate also significantly improved patients' quality of life. A recent Cochrane review concluded that there is currently no evidence of the effectiveness of other migraine AEDs, including levetiracetam, zonisamide, carisbamate, clonazepam and peripanel, although one study confirmed similar effectiveness of verbamate and zonisamide in patients with migraine.[20, 21.29]

Thus, headache and epilepsy are comorbid, episodic disorders that share common pathophysiological mechanisms leading to neuronal hyperexcitability. Their overlap is also supported by the presence of common genetic mutations and common clinical features of migraine and epilepsy, especially in patients with convulsive occipital seizures.[31,32,34] Although there is no convincing evidence of a real cause-and-effect relationship between headache and epilepsy, the association of these episodic neurological disorders is an interesting problem, and further laboratory and clinical studies would demonstrate a real connection between headaches and epilepsy.

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