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REVIEW ARTICLE

Epilepsy and migraine—Are they comorbidity?

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Abstract Epilepsy and migraine often co-occur. From the clinical symptoms, they often have some signs of symptoms before onset; from the pathogenesis of epilepsy and migraine, both of them have a high degree of neuronal excitement and ion channel abnormalities; in terms of treatment, many antiepileptic drugs are work in migraine. All of this indicates that they interact with each other. But it is undeniable that there are interactions and relationships between them, and there are also some differences such as the different clinical episodes, the different ways of neuronal haperexcitability and the different drug treatment programs. And are they comorbidity? If we can better understand the correlation between seizures and migraines, then this will help develop better guidelines for clinical diagnosis and treatment.

Introduction

Epilepsy and migraine are both recurrent common diseases. Gowers firstly put forward a clinical hypothesis there was a relationship between epilepsy and migraine in the last century.[1] As time goes, the two disorders have more and more same typical clinical features, pathophysiology and therapy.[2] Especially in familial hemiplegic migraine syndromes (FHM) where different mutations can cause epilepsy or migraine, maybe the comorbidity, seizures and migraine may have a sort of common genetic basis. Although some wider manifestations are caused by the multiple pathogenic mechanisms, the two diseases are derived from the electrical disorder in the brain at present. In epilepsy, overactivity of neuron leads to the agglomeration of a great many of neurons to discharge in a rhythmic way which manifested as seizures. In migraine, neuronal overactivity results in cortical spreading depression (CSD)

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and aura, along with the assembly of the trigeminal nucleus causing central sensitization and pain. Seizures frequently occur accompanied with preictal, ictal and postictal migraines. Vice verse migraine aura and headaches may cause seizures. Also, seizures and migraine both have ion channel dysfunction and various ionic channel blockers are found to be effective for both epilepsy and migraine, demonstrating a fact that there is commonality and overlap exist in the two disorders once again.

Here, we will review recent research of the relation between epilepsy and migraine, especially the studies which are published in 2016. Research is quite detailed about the overlap of clinical aura and symptoms of the two diseases at present. Therefore we will not talk too much about it. This article mainly discusses about the overlap of epilepsy and migraine in genetic, ion channels and CSD from the pathogenesis, expecting to find out the commonness of the two diseases, which can help the clinical diagnosis and treatment.

Common genetic mechanisms

Epilepsy and migraine are both highly heritable diseases, especially idiopathic epilepsy and migraine with aura.[3] The risk of patients who have idiopathic epilepsy getting migraine with aura is roughly double. Accordingly, patients with migraine also increased the risk of getting epilepsy.[4,5] And we will focus mainly on the condition of the patients who get epilepsy and migraine at the same time and their heredity which is related to comorbidity with epilepsy and migraine.

Hemiplegic migraine is a sporadic or familiar disorder which genetics has made us discover the links between epilepsy and migraine. At present, in FHM, a total of three genetic mutations [CACNA1A (FHM1), ATP1A2 (FHM2) and SCN1A (FHM3)] are associated with epilepsy.[6] Among them, the most clear genetic connection between epilepsy and migraine is SCN1A gene, which maps to chromosome 2, encoding for the alpha1 subunit of the voltage-gated sodium channel. Protein of the sodium channel is mostly located in the spinal cord and cerebral cortex which is closely related to the regulation of action potential. The SCN1A gene mutations can lead to seizures and FHM3 occurrences.[7–9] The SCN1A gene mutations are common in all types of epilepsy. Among them, patients with Dravet syndrome (DS) and infant idiopathic comprehensive seizures and generalized seizures with febrile seizures plus (GEFS+) and partial seizures with febrile seizures plus (PEFS+) have been found to exist mutations in SCN1A gene.[10–12,14–17] In DS patients with about 650 heterozygous SCN1A mutations, there was an average mutation rate of about 85%.[13] About half of these mutations were nonsense mutations and half were missense mutations, which can either increase or decrease sodium channel function.[8] However, SCN1A mutations are also associated with FHM3, until now, reported that there are nine SCN1A missense mutation caused FHM3. Some of these mutations (Q1489K, L1649Q,I1498M, F1661L and L1624P) caused FHM3 but did not cause seizures.[18–21] Whereas others were described to be associated with both FHM and epilepsy (L263Q, T1174S, Q1489H and L263V) or be associated with elicited repetitive daily blindness (ERDB) (Q1489H and F1499L).[22–24] Difference in SCN1A mutations types can lead to different effects of channel function. The L1649Q and Q1489K mutations only lead to pure FHM3 and can inhibit neuronal function, especially the GABA intermediate neurons.[25–27] In contrast, some studies found that some Portuguese family members who had a L263V mutation in FHM had generalized seizures or complex partial seizures.[23,25] The L263V mutation leads to the enhancement of channel function that is to accelerate recovery of sodium channel inactivation, thus prolonging the duration of action and increasing the excitability of neurons. As a result, in the same individual, the gene mutation may lead to epilepsy and FHM3.[28]

Another gene, CACNA1A which is located on chromosome 19, encodes for the alpha1 subunit of the voltage-dependent P/Q calcium channel. The P/Q calcium channel regulates the release of neurotransmitter, associating with the release of serotonin and glutamate by increasing the flow of calcium to stimulate the presynaptic membrane. CACNA1A gene mutations may impair calcium channel function, causing generalized epilepsy.[29,30] Sometimes, CACNA1Agene mutations occur either in epileptics, or FHM, but sometimes at the same time.[31–33] CACNA1Amutations may also lead to FHM1 by affecting CSD in which the cortical neurons of R192Q mutant mice are the imbalance of excitation and inhibition, thereby reducing the threshold for CSD and accelerating its propagation.[34] The S218L mutant mice is more sensitive to CSD.[35–37] The I170T mutant young girl underwent seizures during a FHM attack.[38]

However, there is ATP1A2 gene which maps to chromosome 1 and codes for alpha2 subunit of a Na+/K+ ATPase. As we all know, alpha2 subunit is highly expressed in neurons and astrocytes. Na+/K+ ATPase is able to control the K+ extracellular concentration in astrocytes, while increasing K+ concentration is associated with CSD.[39,40] Thus, this regulation enhances the excitability of the neuron and results in a threshold that can trigger CSD.[41,42] In conclusion, abnormal function of Na+/K+ ATPase system caused by ATP1A2 gene mutations, resulting in a destruction of the K+ gradient and influencing glutamate clearance, which may cause CSD, FHM, and seizures. Just like FHM1, all kinds of mutations in ATP1A2 genes can also cause epilepsy.[43] For example, There were 5 patients with a ATP1A2 mutation who had epilepsy and FHM at the same time in two Italian families.[42,44] Two mutations of the ATP1A2 gene -The M721T and R689Q -were discovered in two Dutch families who had FHM2. Patients who had the R689Q mutation also suffered from benign familial infantile convulsions, while patients with the M721T mutation did not have epilepsy.[45] The D718N and P979L mutations have been found in some studies that they could raise the risk of seizures and mental retardation.[46] At the same time, the R1007W mutation could be a susceptible factor increasing epileptic seizures.[47]

There is a similar situation in mitochondrial disease. As we all know, MELAS syndrome includes mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes, but these patients are also vulnerable to epilepsy and migraine with aura. Among them, the vast majority of patients had a unique mitochondrial gene mutation (3234 A > G) and pathological researches had found that these patients had