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REVIEW ARTICLE

Epilepsy and migraine—Are they comorbidity?

Jin Liao [a], Xin Tian [a], Hao Wang [a], Zheng Xiao [b,*]

[a] Neurology Department at Chongqing Medical University, Chongqing, China
[b] Neurology Department at the First Affiliated Hospital of Chongqing Medical University, No. 1 Youyi Street, Yuanjiagang, Yuzhong District, Chongqing, China

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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)

* Corresponding author.
E-mail address: xiaozhenghf@126.com (Z. Xiao).
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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

cytochrome oxidase deficiency. Whether these patients have abnormal CSD and that happens to be their pathogenesis is not certain.[48]

In addition, structural and metabolic disorders can also demonstrate that gene mutations play a major role in epilepsy and migraine-related pathophysiological mechanisms. Notch mutations in the drosophila lead to jaggy wings and other developmental disorders.[49] In humans, Notch locus can control the development of smooth muscle cells and their mutations are linked with the early development of vascular disease, strokes, migraine with aura and epilepsy.[50,51] Gene mutations can contribute to development of CSD,[52] but it is unknown that whether the susceptibility to epilepsy is just because of the structural lesions of stroke, or whether there is an additional and specific effect of the mutated gene.

Russo L et al found a link between migraine and GABA-A receptor gene mutations.[53] However, other studies did not find this link.[54–56] On the other hand, mutation in the GABA-A receptor gene are always existed in various forms of epilepsy.[57–59]

In summary, the current genetic linkage of epilepsy and migraine is only confirmed on some specific and rare syndromes. Non-syndromic epilepsy and migraine may have complex interactions with multiple genes and environmental factors. When controversial issues are existed in clinic, it is necessary to adopt the genetic testing of seizures or migraine. For example, patient with epilepsy at night who is always mistaken for a sleep disease, due to genetic testing may make a diagnosis of autosomal dominant nocturnal frontal lobe epilepsy.[60] In FHM, the relevant genetic testing is definitely valuable and could have much therapeutic significance, just as calcium channel blockers and antiepileptic medicines are ideal drugs for migraine prevention.

Common channel mechanism

Epilepsy and migraine both are abnormal neuronal excitatory diseases. Epileptic seizures are the clinical manifestations which are the abnormal paroxysmal hypersynchronous activity in brain neurons. Epileptiform discharge is the pathophysiological basis of epileptic seizures, which are accompanied by a large number of out flow of potassium ions and abnormal calcium influx as well as the abnormal movement of sodium and chloride ions. About genetics in recent years, some studies found that an ion channel dysfunction caused by a genetic defect, which closely related to the onset of two diseases and provided new evidence for the inner link of these two disease (see genetic mechanisms). As we all know, epilepsy is a typical ion channel disease, and all brain activity including epilepsy, is regulated by action potentials happening in neurons. The appearance of action potentials in a neuron or a group of neurons relies on a balance of synaptic excitation and inhibition.[61] Breaking the balance can be achieved by GABA (which may be the principal inhibitor neurotransmitter) or glutamate (which may be the core of an excitatory neurotransmitter) anomalies.[60,62] Many common idiopathic epilepsy is hereditary and this can happen due to various types of mutations in the GABA receptor-encoding genes or mutations in other channels, like calcium channels, which regulate abnormal synchronization between thalamus and cortex, leading to generalized spike-wave discharges.[63] Furthermore, the ultimate common pathway of action potentials is the necessity of repeatedly open and close the voltage-gated sodium channel, so some idiopathic seizures generally contain mutations in the sodium channel. The most common mechanism of antiepileptic medicines such as phenytoin and carbamazepineis to suppress the quick opening and closure of sodium channels.[64] In addition, topiramate, which is antagonist at the AMPA-type glutamate receptor and weakens carbonic anhydrase inhibitor, enhances GABA activity on chloride channels and reduces the opening of L-type calcium channels.[65] At the same time, these antiepileptic drugs are also effective for migraine and this may indicate that migraine also have some kind of ion channel changes.

Dysfunction determined by genetic mutation of ion channels and relevant proteins can lead to variation in ion concentration of neuron, which can change cortical excitability.[66] The hypothesis that imbalance between inhibitory and excitatory factors plays a key role in both seizures and migraine.[61,67] Is there a hyperirritability which is similar to seizures and associates with change of ion channel in migraine? First of all, we know that the more generally recognized pathophysiology of migraine is the CSD and trigeminal vascular system (TVS) activation theory. Massive evidence at present has manifested that the trigeminovascular system is triggered by CSD, which roots in neocortical hyperexcitability. Pain in migraine roots in the activation of trigeminovascular afferents from the meninges, which become sensitized in a way analogous to their sensitization in other neurogenic pain states.[68] Mechanisms of the cortical hyperexcitability are unclear, but it may be associated with superabundant excitatory transmitter release, rooting in changes of function in calcium channel, just like what happened in FHM.[69] The above mentioned CACNA1A gene encodes the alpha subunit of a neuronal voltage-gate calcium channel. Mutations of this gene changes the affinity of the relevant inhibitory G-protein, which may lead to a reduction in inhibition that caused neurons to become overly excited leading to the occurrence of migraine.[70]

Above all, epilepsy and migraine are comorbidity in the sense of ion channels. Therefore, in the future, we need to study if a patient suffers from epilepsy and migraine at the same time, whether or not the existence of the same ion channel dysfunction and factors that affect its function. The challenge for future researches is to illuminate the factors that a patient cortical over-excitement caused a seizure and another patient caused a migraine. Of course, there are some of very important questions. If epilepsy and migraine have some of the same pathophysiology, why their performance is so different? Why is 'migralepsy' so rare? Whether under these two conditions cortical hyperexcitability have unlike approaches or reactions to environmental factors?

Common CSD mechanism

The excitability of neocortical cells, which was the major pathological mechanism, associated with the occurrence of

epilepsy and migraine.[71] In epilepsy, hyperexcitability is turned into the hypersynchronous activity. In migraine, however, hyperexcitability is turned into CSD rather than into the hypersynchronous activity that characterizes seizures. CSD seems to be the linkage between epilepsy and migraine.[72–75] In 1951, Laeo first put forward the theory of CSD. He observed in animal experiments with cortical EEG when the cortex encountered adverse stimulus, it would appear after occipital EEG activity decreased to about 2–6 mm/min speed slow forward and expand accompanied by a large number of ions transfer called CSD. Animal studies have shown that at the beginning of CSD, neurons and glial cells are depolarized with a sudden occurrence of a few seconds of high spike wave activity (representing a potential local epileptic discharge event), followed by a resting state of nerve cells for several minutes.[76] These high spike waves are different from epileptic seizures, but they have potential properties that prompt synchronization of the neural network and promote seizures and spread under certain conditions. However, it is necessary to be further research to clarify the connection between the epileptiform issue and the high spike wave. Classical electrical stimulation, mechanical stimulation, increased extracellular K+ concentration, the inhibition of Na +/K+ ATPase, all can trigger CSD. In addition, animal studies had confirmed that calcium signal in astrocytes can increase to release neurotransmitter of glutamate, linked with the release and spread of the above-mentioned spike wave, which related to the CSD.[35,77] Cerebral cortex after sudden excitement occurring transient suppression (CSD) caused the activation of TVS, including the release of many inflammatory molecules and neurotransmitter cascade, which may be the basis for the occurrence of aura or neurological deficits.[78]

CSD is widely known in epilepsy animal models, along with the characteristics by quick and complete depolarization of plenty of cortical neurons with a large number of potassium ions out flow. Its spread is the pathological mechanism of migraine aura symptoms, and symptoms such as soma to sensory, visual and auditory are often a sign of epilepsy. The results of the study on the excitability of CSD on human cerebral cortex in patients with epilepsy showed that CSD significantly increased the amplitude-induced long-term potentiation of excitatory postsynaptic potential after transient suppression indicating that CSD could facilitate the human brain cortical tissue synaptic excitability and efficacy which is also considered the cause of cortical excitability in patients with migraine.[74] Therefore, we infer that the pathophysiology of CSD and epileptic seizure is the same. Both phenomena show "all or none" which are determined or triggered by the respective environment or genetic factors but attributed to the same end: depolarization and hypersynchronization, just the threshold that triggers CSD is less than the threshold for triggering seizures.[74,75,79–82] A "migraleptic" occurrence is very infrequent because the threshold for triggering seizures is higher than the triggering threshold for CSD. Moreover, recurrent seizures may also cause the patient to tend to CSD, hence augmenting the incidence of a peri-ictal migraine-type headache; accordingly, a post-ictal headache in patients with epilepsy is more ordinary than any other types.[75,79,80,82]

In humans, CSD can occur simultaneously with epileptic activity in acute brain injury.[83] Reiterant CSD seems to add the activity of epilepsy in vitro because of impaired GABA inhibitory function.[84,85] However, in chronic epilepsy, there may be an inherent protective mechanism against CSD since brain slices in chronic epilepsy subjects showed a sharply increasing threshold for CSD.[86] This finding is consistent with the results of an earlier in vitro study, in which the threshold for CSD of neocortical slices from human subjects and rats with chronic refractory seizures was higher than the CSD threshold of age-matched and younger rats without seizures.[87] However, as we all know the application of GABA antagonist is equivalent to lowering the CSD threshold, so a higher threshold for CSD in epilepsy may not be due to altered GABA-ergic effects.[87] We suggest that the presence of high thresholds for CSD in chronic epilepsy is not associated with GBAB. There may be other mechanisms. Dreier et al conclude that migraine aura would happen more continually in chronic seizures if the "inherent protective mechanism" of this higher threshold did not exist.[86]

CSD appears to be the main pathophysiological mechanism of migraine, and is closely related to epilepsy, but currently connection of the few seconds of spike wave activity in CSD and epileptiform discharge are not clear. It is possible that both CSD and other mechanisms like different environmental or individual factors (genetic or otherwise), associated with epilepsy and migraine.

Conclusion

Epilepsy and migraine are both diseases where electrical transmembrane gradients play an important role. More and more evidence direct to a connection between seizures and migraine that possibly includes function changes of membrane channels and neurotransmitters effecting cortical excitability, linking by CSD.[88,89] Imbalance between excitatory (glutamate) and inhibitory (GABA) factors seems to play a key role in epilepsy and migraine. Thus, different mutations in ion channel and neurotransmitter receptor gene can cause overlapping seizures and migraine syndromes, which are particularly evident in FHM. Drugs that can treat both diseases also help to find out their potential commonalities and differences. If we can further understand the molecular mechanisms included in the link between seizure and migraine and thus identify the target of drug action which is critical to improve the efficacy. Gene detection in patients with seizures and migraine so as to find a common target for drug action may create a different treatment in the future. From the genetic mechanism and ion channels and CSD, they seem to be the comorbidities. However, the relationship between these diseases still has a lot of questions that cannot be dealt with. They are the consequence of an intricate interaction between multiple genes and environmental factors and individual factors. If more noninvasive techniques in the future could be utilized to research the intricate connection between seizures and migraine, these problems may be elucidated.

Conflict of interest

We have no conflict of interest.

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