The Pathogenesis of Epilepsy and its Diagnosis and Treatment

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Abstract. Epilepsy is one of the most prevalent, chronic, and severe seizure-related disorder of the nervous system, affecting seventy million individuals globally. The risk factors and pathogenesis of epilepsy are also diverse. Nevertheless, there have been mature treatments for epilepsy, among which antiepileptic drug treatment is the most common treatment around the world. Almost 70% of patients have their seizures controlled after drug treatment, but some drug-resistant epilepsies still need to be treated by some other supplemental treatment. In order to take appropriate treatments, we must first fully understand the pathogenesis of epilepsy. As a result, this paper introduced three kinds of pathogenesis in detail, namely abnormal ion channels, abnormal neurotransmitters, and abnormal neuroglial cells. In addition, the diagnosis of epilepsy was also introduced. Last but not least, we highly summarized the treatment except for drug treatment, namely surgical treatment and neuromodulation. Furthermore, this paper also proposed a new treatment, CRISPR-Cas9 gene editing technology, that may be used to treat epilepsy in the future.

Keywords: Epilepsy, Pathogenesis, Diagnosis, Treatment, CRISPR-Cas9.

1. Introduction

1.1. A basic overview of epilepsy

A chronic neurological illness called epilepsy will cause transitory brain malfunction as a result of sudden abnormal neuron discharge in the brain. In terms of neurological diseases, epilepsy has become the most common and serious disease which is second only to headache. Currently, it influences more than seventy million individuals worldwide, covering all ages, ethnicities, social groups, and regions.[1] According to international researches, the prevalence and incidence of epilepsy vary due to different factors such as income level, age, gender, epilepsy syndrome, classification of seizures, risk factors of epilepsy and so on. For example, poor people in middle- and low-income nations and those people who have unknown etiology have higher prevalence and incidence. And epilepsy's prevalence rate and incidence rate are higher in children than in adults, and then they decrease with age. However, they are higher in elderly people (over 65 years old) due to the increase of cerebrovascular disease, Alzheimer's and so on. Also, epilepsy is more common in males than females.[2]

Generally, epilepsy could be divided into 3 categories according to the seizures it causes and its etiology. There are focal seizures, generalized seizures, and some unclassifiable types of seizures due to unknown start. Focal seizures start in only one hemisphere, so in some focal seizures, the person is conscious. But a focal seizure may propagate to the opposite hemisphere and give rise to a generalized seizure, in which case the focal onset acts as a warning. Unlike focal seizures, generalized seizures occur when the abnormal electrical activity involves both hemispheres, which always involve loss of consciousness. In 2010, the ILAE (International League Against Epilepsy) put up a latest seizure classification system which further classified and supplemented the original seizure classification at different levels. In addition, the classification of epilepsy syndromes is often divided into idiopathic epilepsy syndromes (which have unknown causes and may relate to genetics), symptomatic epilepsy syndromes (which have known causes), and possible symptomatic epilepsy syndromes (which have unknown causes and may relate to the lesion) according to the causes of epilepsy.[3]

Epilepsy risk factors are complex and diverse. It can be approximately divided into three causes, namely genetic factors, brain diseases, and systematic diseases. Firstly, genetic mutations constitute

a significant factor of epilepsy, particularly in idiopathic ones. There are many related genes, such as SCN1A, SCN1B, GABRB1, GABRB3, UNC13B and so on. Research shows that seventy to eighty percent of epilepsy happen due to genetic factors, even higher in children.[4] A person having a genetic makeup is more susceptible to getting epilepsy. Ion channels or associated molecules have some changes in structure or function, which may result in inherited epilepsy, according to several molecular genetics research. Secondly, epilepsy could be caused by bad brain conditions, such as brain tumours, head trauma, and maldevelopment before birth due to an infection in mom or poor nutrition or lack of oxygen, brain or head trauma which sometimes leads to epilepsy after many years after injury, and degenerative diseases such as Alzheimer's. Last but not least, some systematic diseases can also cause epilepsy, such as hypoxia (e.g. asphyxia), metabolic diseases (e.g. hypoglycemia), cardiovascular diseases (e.g. hypertensive encephalopathy), and some toxic diseases.

Symptoms of epilepsy vary depending on the type of seizures but common signs include repetitive jerking and bizarre postures, stiff or limp muscles and limbs, dizziness, confusion, loss of consciousness, and changes in taste, smell, sight, hearing, touch and so on. The clinical symptoms of different types of seizures are complicated and varied because of the differences in the origin of abnormal discharges and how the discharges propagate. For example, according to seizure classification, some focal seizures could be identified by motor onset symptoms: clonic, atonic, epileptic spasms, myoclonic, or hyperkinetic. And also, nonmotor onset could show as a dysfunction of cognition, emotion, sense and so on. For another thing, motor onset symptoms of generalized seizure include clonic, atonic, myoclonic, epileptic spasms, tonic, myoclonic–atonic, or myoclonic–tonic–clonic. Nonmotor onset manifests prominent myoclonic seizures or eyelid myoclonia and so on.[5]

1.2. Current status and significance of the research on epilepsy

Epilepsy has become a common neurological disorder in people's daily life, and it has some impact on the brain development, psychological state, social interaction, work and life of patients. Nevertheless, studies show that approximately seventy percent of patients' seizures could be effectively treated or even cured after regular treatment such as drug therapy, surgery, etc. Furthermore, the treatment of epilepsy is closely related to its diagnosis and the identification of its pathogenesis. Only after the diagnosis and specific pathogenesis are clarified, suitable treatment can be taken. Therefore, this study will elaborate on the following three aspects, namely the pathogenesis, diagnosis, and treatment of epilepsy.

2. The pathogenesis of epilepsy

Epilepsy has an extremely complicated pathogenesis that has not been completely clarified yet. At present, it is mainly believed that the central nervous system's imbalance between excitement and inhibition is the root cause of epilepsy. This imbalance is mainly associated with abnormal ion channels, abnormal neurotransmitters, or abnormal neuroglial cells.

2.1. Abnormal ion channels

Since the structural foundation for controlling the excitation of excitable cells in vivo is related to ion channels, related researches have also shown that ion channels may be a factor in the occurrence of certain genetic diseases, such as epilepsy, by causing abnormal changes in the excitability of nervous tissues. Early research suggested that idiopathic epilepsy which may relate to genetic factors is a member of channelopathies.[6] With the development of time and technology, there are sufficient literatures to clarify the mechanism of abnormal ion channels causing hereditary epilepsy, which also provides the basis for the disease-targeted therapy of epilepsy. Currently, among all abnormal ion channels, the researches on Na^+ channels, K^+ channels, and Ca^{2+} channels are relatively comprehensive.

2.1.1. Na^+ channels

The beginning and spread of cell action potentials depend heavily on voltage-gated Na^+ channels.[7] The α-subunits are functional subunits that regulate Na^+ channels and are encoded by nine genes of one family, of which SCN1A, SCN2A, and SCN8A are expressed most in the CNS (central nervous system). In addition, the β-subunits, as auxiliary units of α-subunits, can regulate the expression and function of α-subunits, and the corresponding encoding genes are SCN1B, SCN2B, SCN3B, and SCN4B. $GEFS^+$ (Genetic epilepsy with febrile seizures plus) is a kind of GGE (genetic generalized epilepsy).[8] Studies have shown that $GEFS^+$ results from a point mutation in SCN1B that changes how the β-subunits regulate the α-subunits, resulting in the repeated opening of Na^+ channels, causing persistent overexcitation of neurons. In addition, missense mutations in the SCN1A gene can also result in abnormal changes in nervous system excitability and cause $GEFS^+$.[9]

2.1.2. K^+ channels

The most various set of ion channels, K+ channels, come in a wide range of types. They are crucial in controlling cell membrane resting potential and the repolarization of action potential.[7] Therefore, epilepsy can also result from the mutations in the genes that encode K+ channels. 2 α-subunits and 2 β-subunits make up voltage-gated K^+ channels. Current studies have shown that the genes encoding K^+ channels mainly include KCNQ1, KCNQ2, KCNQ3, and KCNQ4. The α-subunits are encoded by gene KCNA1-6, and the β-subunits are encoded by gene KCNB1-3. BNFC (benign familial neonatal convulsions) is also a GEE. It has been reported that BFNC is caused by the mutation in one of the genes KCNQ2 or KCNQ3, resulting in abnormally increased excitability in nerves.[9]

2.1.3. Ca^{2+} channels

Ca^{2+} channels widely exist in different tissues and cells of the body and participate in the physiological processes of nerves, muscles, and other systems. Some researches have detected neuron participation in epileptic seizures with calcium imaging, suggesting that rapid calcium influx is associated with cellular depolarization, so abnormal Ca^{2+} channels in the nervous system can lead to abnormal depolarization of nerve cells to cause epilepsy.[10] The two main categories of Ca^{2+} channels are voltage-gated and ligand-gated Ca^{2+} channels. Voltage-gated Ca^{2+} channels are the main pathway of calcium influx and are involved in the intracellular excitatory effect, including six types: L-, N-, P-, Q-, R-, and T-type.[11] There are two categories of them, namely high voltage-activated and low voltage-activated $Ca2^+$ channels. At present, the research on gene mutation of T-type ones in humans is relatively limited compared to mice. Current studies point out that gene CACNA1A encodes a subunit of the P- or Q-type ones, and loss-of-function mutations of CACNA1A can cause GGE. For example, severe epileptic encephalopathies can be brought on by its deletion mutations and de novo missense mutations. On the other hand, various neurotransmitters are the primary activators of ligand-gated Ca^{2+} channels, which will be mentioned below.[9]

2.2. Abnormal neurotransmitters

The abnormal neuron discharge when seizures occur is mainly linked with abnormal neurotransmitters. Excitatory neurotransmitters are normally in balance with inhibitory neurotransmitters so that neuronal membranes are stable. But when neurotransmitters are abnormal, the membrane could be out of balance, making the membrane unstable and having abnormal discharge. Related neurotransmitters can be mainly divided into amino acids, and monoamines and acetylcholine.

2.2.1. Amino acids

At present, the amino acids which are known to be closely related to epilepsy mainly include glutamate, GABA (gamma-aminobutyric acid), glycine and so on.

In the brain, glutamate is the most significant excitatory neurotransmitter. Relevant studies have shown that epileptic seizures caused by glutamate may resulted from the increased intracellular

synthesis of glutamate in the early stage and a large amount of extracellular release in the later stage. Its receptors are coupled to ion channels and induce epilepsy by regulating the activity of ion channels.

The primary inhibitory transmitter in the CNS is thought to be GABA. At present, there are three receptors GABAA, GABAB, and GABAC having been found. One of the most prevalent inhibitory transmitter receptors in the brain, receptor GABAA, is most closely related to epilepsy. Various genes encode different receptors, and gene GABRB3 encodes the β3-subunit of GABAA. Studies have found that GABRB3 gene mutation will reduce the inhibitory action of GABAA receptors and cause the aggregation of β3-subunits to produce toxic effects at the same time, finally resulting in severe epileptic encephalopathy LGS.[12]

2.2.2. Monoamines and acetylcholine

Monoamines such as dopamine and 5-HT can inhibit epileptic seizures, while acetylcholine promotes seizures. Mutations in those genes which encode these neurotransmitter receptors can also cause epilepsy. For example, mutations in gene CHRNA4 and CHRNB2, which encode subunits of neuronal nAChRs (nicotinic acetylcholine receptors), are related to the rare monogenic form of idiopathic epilepsy known as ADNFLE (autosomal dominant nocturnal frontal lobe epilepsy).[13]

2.3. Abnormal neuroglial cells

The maintenance of neurons' normal excitability is largely dependent on neuroglial cells. For example, seizures may result from changes in the glutamate or GABA uptake capacity of astrocytes. Furthermore, neuroinflammation, one of the mechanisms involved in epilepsy, is associated with the rapid activation of microglia. When microglia are activated, the generation of inflammatory molecules and reactive oxygen species (ROS) can cause tissue damage and neurotoxicity, which will induce seizures.[14]

3. The diagnosis of epilepsy

3.1. Whether epilepsy or not

After the first seizure, the specialist should ask the patient and his family in detail to get the patient's seizure situation and use EEG (electroencephalogram) to diagnose whether the patient has developed an epileptic seizure as soon as possible. If the results of a routine EEG do not show anything abnormal, a sleep-deprived EEG or a 48-hour ambulatory EEG can be used, combined with MRI, CT, and other checkups to identify the specific risk factors.[15] In addition, video-EEG monitoring is also important for distinguishing epileptic seizures from non-epileptic seizures such as syncope, sleep disturbance, migraine and so on.

3.2. Which type of epilepsy

After an epileptic seizure is identified, the specialist should ask the patient and his family about his epilepsy history and seizure type. Different types of epilepsy have different abnormal waves on the EEG. Therefore, when the type is unclear, it can be distinguished by combining its symptoms and different types of normal EEG samples**.** In addition, patients may suffer from seizures many times a day. And in some cases, drug treatment fails to control seizures, threatening the patients' life. Therefore, predicting seizures and treating patients with preventive medicines in advance can greatly reduce the risk and damage. In this regard, some studies have proposed that the scalp EEG signals can be combined with the automated features using CNN, and then epilepsy can be classified with an LSTM classifier to predict the type of seizures.[16]

4. The treatment of epilepsy

Currently, drug treatment, surgical treatment, and neuromodulation are used to treat epilepsy. A new method for treating epilepsy using CRISPR-Cas9 gene editing technology will also be proposed here.

4.1. Antiepileptic drug treatment

At present, drug treatment is the most common treatment for epilepsy worldwide. About 70% of patients will have seizures controlled after antiepileptic drug treatment and can be cured in two to five years. Drug therapy principles and some AEDs (antiepileptic drugs) will be introduced below.

4.1.1. Principles of drug treatment

Monotherapy is the main measure of drug treatment for epilepsy, and when monotherapy does not work, a combination of AEDs is taken.[17] The patient ought to keep medication and not to stop AEDs at will. The specific category of seizure or epilepsy syndrome ought to be taken into consideration while selecting drugs. In addition, the patient's gender, age, and some side effects of the drug also need to be taken into account. For example, when taking drugs for children, tablets should be replaced by syrup that is easier to take. When taking drugs for the elderly, the side effects of drugs and the interaction between drugs should be considered because the elderly are more likely to be sick and take more drugs.

4.1.2. some antiepileptic drugs

Studies have shown that valproic acid, benzodiazepines, phenobarbital, and other drugs are effective for focal epilepsy as well as most generalized epilepsy. At present, some new drugs such as lamotrigine and topiramate have better effects and fewer side effects than some traditional drugs.[18]

4.2. Surgical treatment

Almost 30% of patients with antiepileptic drug therapy still have drug-resistant epilepsy. At this time, surgical treatment plays an important role. The patient's condition can be controlled or even cured through surgery. However, only focal epilepsy with a clear focus or a single focal epileptogenic zone is suitable for surgical treatment.[19] Also, the surgery needs to be performed under the condition that other functions of the human body are not damaged. For example, Rasmussen syndrome which causes inflammation of the unilateral cerebral cortex and severely affects brain development can be treated with functional hemispherectomy.[20] However, on the other hand, surgical treatment is not suitable for Dravet syndrome caused by mutations in the gene SCN1A.[21]

4.3. Neuromodulation

Neuromodulation therapy is a new technology in clinical neuroscience. At present, neuromodulation has become the most promising method for the treatment of epilepsy. Neuromodulation, which uses the electro-circuit model of neuronal function, stimulates the brain to modulate network activity with direct or induced electrical currents so that abnormal brain discharge can be improved and brain damage caused by epilepsy can be repaired. Currently, epilepsy can be treated with rTMS (repetitive transcranial magnetic stimulation), DBS (deep brain stimulation), VNS (vagus nerve stimulation) and so on.[22]

4.4. CRISPR-Cas9

Currently, CRISPR-Cas9 gene editing technology can treat a variety of diseases through gene splicing. As mentioned above, in terms of pathogenesis, many types of epilepsy are caused by mutations in related coding genes. Therefore, it may be possible to use CRISPR-Cas9 technology to combine targeted disease-causing genes and correct them so as to treat many types of idiopathic epilepsy effectively. For example, for the epilepsy induced by mutations in GABRB3, CRISPR-Cas9 technology can be used to design suitable gRNA sequences to better bind the mistaken DNA

sequences and edit them correctly. In addition, current studies have shown that applying CRISPR-Cas9 technology to iPSC (induced pluripotent stem cell)-based-disease models can effectively reveal the process by which SCN1A loss-of-function mutation causes epilepsy.[23]

5. Conclusion

To summarize, the pathogenesis, diagnosis, and treatment of epilepsy have been basically clarified above. The pathogenesis of epilepsy mainly includes abnormal ion channels, abnormal neurotransmitters, and abnormal neuroglial cells. The diagnosis of epilepsy mainly makes use of different kinds of EEG combined with specialists' inquiry to diagnose whether the seizure is epilepsy and which type of epilepsy it is. In terms of the treatment, the etiology, seizure type, and pathogenesis of epilepsy and patients' age and some other factors should be considered comprehensively. It is mainly divided into antiepileptic drug treatment, surgical treatment, and neuromodulation. This paper also suggested that a new technology, CRISPR-Cas9 gene editing technology, may be used for targeted gene therapy for epilepsy. However, it still needs to be verified by further experiments. Moreover, at present, the pathogenesis, diagnosis, and treatment of epilepsy have not been completely discovered, which needs to be further studied with the development of science and technology.

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