Research Progress on the Effect of Epilepsy on Cognitive Function in Patients under Slow-wave Sleep

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Abstract

Slow-wave sleep (SWS) exerts great influence on cognitive functions such as sensation, perception, attention, memory, thinking, language, etc. Previous evidence has demonstrated that sleep disturbance itself has a negative impact on the cognitive function of healthy body to some extent; At the same time, cognitive dysfunctions are always observed in epilepsy patients, which is related to various factors. It is speculated that the cognitive dysfunction of epileptic patients, especially those who have seizures under SWS, has a close connection with sleep disorder. Based on the facts and unsubstantiated speculations described above, this article will review the research progress on the impact of cognitive function of epileptic patients with SWS caused by sleep disturbance and the relationship between epilepsy and SWS disorder in combination with relevant literature. Through the in-depth analysis of the mechanisms of sleep disorder and the pathophysiological changes of the body after seizures, it is finally concluded that there may be a considerable degree of commonality between sleep disorders and large seizures under SWS, which is conducive to revealing the mechanism of specific large seizures under SWS.

Keywords

Review, Epilepsy, Cognition, Slow-wave sleep

Background: Epilepsy is a group of chronic recurrent transient central nervous system dysfunction, which is characterized by recurrent epilepsy caused by abnormal discharge of brain neurons. Because of the different origin of central lesion and discharge, epileptic seizures can be manifested as abnormalities of motor, sensory, consciousness, memory, learning, etc. According to the former epidemiological statistics, the current prevalence of epilepsy in China is 7‰ [1], of which people under 18 accounts for more than 60%. There are many cognitive and learning defects in these adolescents and children, which affect the learning and life of patients seriously. At present, due to the important role of slow-wave sleep in teenagers' life and learning process, many studies believe that the slow wave sleep durable time of epileptic patients is reduced, and the normal sleep physiological function has different degrees of disorder, which in turn causes high-frequency seizures in a feedback manner. Accordingly, sleep disorders caused by different types of epilepsy may be related to changes in cognitive function. This article will mainly discuss the relationship between epilepsy and SWS in terms of secondary changes.

1. Changes of cognitive function under sleep disorder

The disorder of sleep, especially slow wave sleep, has a great impact on cognitive function, and its mechanisms
are mainly as follows.

1.1 Adrenaline stress activation

Slow-wave sleep process can inhibit the secretion of epinephrine in the hypothalamus-pituitary epinephrine axis. When sleep disorder occurs, a large amount of adrenaline is released from the adrenal cortex, resulting in that the advantages and disadvantages of adrenergic receptor function are changed, leading to the decline of cognitive function [2-4].

1.2 Electrical activity in the hippocampus

In the research of Johnson et al, information from the hippocampus reaches the cortex in the form of electrical shocks during sleep, and the way of changing the structure of synapses may strengthen the specific pathways of the cerebral cortex, so that the newly acquired information can be stored in cortex over a long period of time [5]. Therefore, sleep disorders may affect long-term memory and other cognitive functions through this pathway.

1.3 Abnormal secretion of neurotransmitter

Decreased levels of adrenergic transmitters can lead to certain cognitive impairment, which is related to age [6-7]. Glutamate, an excitatory amino acid, is another neurotransmitter closely related to slow-wave sleep. Some studies have shown that glutamate can indirectly promote quality of slow-wave sleep by increasing the content of cyclic adenosine monophosphate. The effect of glutamate in different brain regions is different. Glutamatergic nerve fibers in the striatum can inhibit the sensory impulse from the thalamus to the cerebral cortex. When the glutamate neurotransmitter decreases, these impulse increases and the monoamine activity in the cerebral cortex increases, causing cognitive impairment.

2. Effect of epilepsy on cognitive function

2.1 Effects of secondary changes of epilepsy on cognitive function under sleep disturbance

2.1.1 The influence of structure on cognitive function

Many studies have shown the destruction of hippocampus formation will affect cognitive function, and its structural destruction contains various complex mechanisms. First, the loss or dysfunction of GABA intermediate neurons in the hippocampus will cause spontaneous recurrent seizures (SRS) in chronic temporal lobe epilepsy (TLE) [8]. The latest research shows that GABA synaptic inhibition is enhanced before excitatory synaptic plasticity in specific scenarios, and the faster plasticity of inhibitory synapse may allow encoding memory in scenarios preventing cognitive dysfunction in various hippocampal lesions [9]. Therefore, it is hopeful that using the most advanced CRISPR/Cas9 technology to transplant GABA intermediate neurons can improve SWS and cognitive function. In the latest research done by He, R, et al, the changes of Nogo-66 receptor 1 (NgR1) pathway and the interaction protein 1 (Lingo-1) of Nogo receptor rich in leucine repeats and Ig-like domains have potential inhibitory effects on rats during epilepsy [10]. This may be related to Lingo-1's inhibition of myelin-promoting sheath formation and neuroprotective effect, as well as to the change of synaptic structure and enhancement of specific brain pathways, resulting in the improvement of the structure of the limbic system, thus restoring long-term memory and other functions. Therefore, further study of the structure and function of NgR1 and its action protein becomes a key point to improve the cognitive and sleep disorders caused by epilepsy. In terms of frontal lobe function, research shows that the frontal lobe function of juvenile myoclonic epilepsy patients is affected, which may be caused by the injury of frontal lobe related nerve tissue [11]. However, it was also found that there was no significant correlation between the results of focal EEG and frontal lobe cognitive function, which also suggested that cognitive function could not be obtained only from focal EEG but must be considered from clinical manifestations and other comprehensive results.

The above studies all remind that the loss of normal structure in different parts may affect the cognitive function after epilepsy, so the study of brain structure and its physiological function is still the breakthrough to solve the pathophysiological process of central nervous system diseases.

2.1.2 Effects of some chemicals on cognitive function

In addition to the influence of brain structure on cognitive function, a large number of studies have shown that many chemicals also have significant effects on cognitive function. The lower expression ratio of SynGAP- α 1/2C terminal splicing variants was found in mice during the study of functional loss variants in SYNGAP1 will
lead to serious learning disabilities and can also lead to shorter latency of epilepsy [12-13]. What is more, something else was found that the up regulation of α1/2 expression improved learning and memory impairment and increased the latency of epilepsy. This evidence shows that endogenous SynGAP isoforms with α1/2 splicing sequence can promote cognitive function and give epilepsy protection, which means regulating SynGAP-α1/2C expression provides a feasible therapeutic strategy for improving cognitive function or prolonging the latency of epilepsy. In addition, Oraby, A.M. et al. used enzyme-linked immunosorbent assay to detect the content of serum heat shock protein 70 in children with temporal lobe epilepsy and compared it with normal children [14]. The experiment found that the level of heat shock protein in the blood of children with temporal lobe epilepsy was significantly higher than that of the control group, while the cognitive function score of epilepsy group was lower than that of normal children. Previous studies also found that the level of serum heat shock protein 70 was significantly negatively correlated with short-term memory and comprehensive score, which largely proves that epileptic lesions can affect cognitive function through heat shock protein 70 [15]. In recent years, studies have found that the cognitive function of epileptic patients is significantly lower than that of healthy people while the activity of serum ATPase and the content of many chemicals such as S100B, NES and Bcl-2 have a great relationship with the time and frequency of seizures and the cognitive function after seizures [16]. Therefore, the changes of the above chemicals to some extent may affect the synthesis of neurotransmitters, resulting in sleep disorder and then reduce the cognitive function after seizures.

2.2 The effect of epileptogenic process itself on cognitive function

In previous studies, it has been found that epileptic encephalopathy (EE) activity itself can lead to cognitive adverse consequences and it will deteriorate over time [17]. The following conclusions are drawn medial temporal lobe epilepsy (MTLE) and EE itself will lead to exacerbation of seizure dependence, but not limited to the above two types; In addition, clinical trial data show that status epilepticus (SE) may be an independent state leading to seizures. The results also suggest that there is no direct causal relationship between the high frequency of seizures and cognitive impairment, but more attention should be paid to the way of the epileptic process, especially the aggressive epileptic process may be one of the important factors leading to cognitive impairment. Therefore, whether there is a correlation between the secondary changes of epilepsy and the epileptogenic process under molecular mechanism, the solution of this problem will help to understand the root cause of low cognitive function and explore the improvement measures.

2.3 The relationship between related cognitive dysfunction and cognitive impairment caused by epilepsy

Bipolar affective disorder (BD) and TLE have been found many similarities in temporal lobe pathology, epidemiology, treatment process and clinical response, so exploring BD-mediated temporal lobe process has become the core issue in this study [18]. In this experiment, 27 BD-I and 29 TLE patients were tested in neurophysiology. The results showed that the main defects of BD-I were executive function, attention span and language memory; The defects of TLE are executive function and memory. The conclusion is that both frontal and temporal lobes are involved in both diseases. However, TLE was not controlled before baseline surgery, but measured before and after surgery. Therefore, it is necessary to make a head-to-head comparison between the two diseases in the neurophysiological test to explain the nature and extent of their cognitive defects and potential overlap.

3. Relationship between convulsion patients and sleep disorder under slow wave sleep

According to the above existing mechanisms of sleep disorders on cognitive function, secondary changes of epilepsy and other factors on cognitive learning function, the relationship between cognitive function changes and sleep disorders in epileptic patients under slow wave sleep is relatively complex, involving multiple aspects and angles. The structure, protein and other secondary changes of epilepsy caused by epileptic seizures (grand seizures) under slow wave sleep will lead to the grand seizures or SE under slow wave sleep; During this type of convulsion, it will affect the electrical activity, epinephrine secretion and the release of neurotransmitters (glutamate, etc.) in the hippocampus. At the same time, according to the above research, the seizures of epileptic patients at different locations (frontal or temporal lobe) have certain similarities with those of non-specific epileptic patients at corresponding time periods in many aspects, which means that there may be many similarities in the pathogenesis of epilepsy between them; However, the difference between them is likely to be caused by factors related to sleep disorders, which may also imply that seizures under slow-wave sleep may have a greater relationship with many factors causing sleep disorders. Through further research on the mechanism of sleep disorders, it is possible to
reveal the causes of cognitive dysfunction in patients with slow-wave sleep or non-specific epilepsy and take further measures against sleep disorders so that exploring new therapies to improve patients’ cognitive dysfunction. In addition, different mechanisms of sleep disorders can be explored through the impact of mental illness (BD) on cognitive function.

References


