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EPILEPSY: PATHOPHYSIOLOGY AND THERAPY

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ABSTRACT

Epilepsy is a brain disease that is characterized by seizures and associated comorbidities and afflicts 50 million individuals worldwide. The epileptic seizure, which can be of various degrees, involves neurons that emit abnormal signals, causing the pathological state characteristic of the disease consisting of convulsions and loss of consciousness. Epilepsy involves various brain pathologies such as neuroinflammation with the release of mediators such as cytokines, chemokines, and the products of arachidonic acid cascade. Epileptic seizures and neuronal loss can be triggered by various agents, including infectious ones (e. g. bacteria and viruses), which can induce or aggravate the situation by acting on toll-like receptor 4 (TLR4). Memory T cells, which are activated after an infection, may also participate in epileptic disease. Microglial cell activation leads to the generation of inflammatory cytokines IL-1, tumor necrosis factor (TNF), IL-6, interferon (IFN)-γ and transforming growth factor (TGF)-β. Endothelial cells are also implicated in epileptic seizures, through the overexpression of adhesion molecules such as P-selectin, E-selectin, and intercellular adhesion molecule 1 (ICAM). Therapy involves the use of anti-epileptic drugs which are not always effective. Therapy with steroids and non-steroidal anti-inflammatory drugs may help in some cases. The use of surgery can be an extreme remedy to be decided with great caution. Here we report an update of the status of epileptic syndrome with related seizures, and therapeutic approaches.

KEYWORDS: *epilepsy, seizure, neuroinflammation, therapy, immune*

INTRODUCTION

From Napoleon Bonaparte (1769-1821) to Margaux Hemingway (1954-1996), many famous subjects have been diagnosed with or are presumed to have had epilepsy. Epilepsy is a brain disease with emotional and cognitive dysfunction, characterized by an enduring predisposition to generate seizures and associated comorbidities, which affects approximately 50 million individuals worldwide. (Vezzani- The role of inflammation in epilepsy (1).

An epileptic seizure occurs as a result of an “electrical storm” in the brain, with neurons firing waves of abnormal signals (2). The consequences of this abnormal electrical activity lead to seizures, impaired loss of consciousness, and sensory changes (3). Seizures are a serious health problem, and the symptoms depend on which part of the brain is affected, how fast the abnormal electrical activity spreads through the brain, and the patient's overall health (4).

Individuals with epilepsy may have partial seizures and generalized seizures. Partial seizures involve only a small part of the brain, can be complex or simple, and can affect consciousness; while generalized seizures affect both hemispheres of the brain and usually cause more serious changes (5). The reason why an epileptic seizure occurs is still unclear and under study. Several mechanisms are implicated in the genesis of epilepsy including neuroinflammatory ones, neuronal

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death, and dysfunction of glycine concentrations (6). Some authors have reported that low concentrations of glycine may mediate seizures, while high concentrations inhibit seizure frequency Activation of glycine receptors modulates spontaneous epileptiform activity in the immature rat hippocampus (7).

The etiology of epilepsy can be structural, immune, infectious, metabolic, genetic, or unknown. In the etiology of epilepsy, there is cross-talk between astrocytes and neurons (8). Astrocytes are important in the modulation of synapse excitation and the homeostasis of neurons which may be implicated in the excitability and persistence of firings. Astrocytes, involved in the formation and regulation of synapses, are responsible for the control of cerebral potassium, but also for the concentrations of glutamate which increase in epilepsy and can be released following dysfunction of calcium flows, a phenomenon involving neuronal discharges (9). Thus, calcium may represent a pharmacological therapeutic target against epileptic seizures, even though the calcium blockade could cause adverse effects to the patient. Since glycine levels are altered during an epileptic crisis, it could also represent a therapeutic target, a hypothesis that future studies will clarify (10). Inherited systemic metabolic errors can also cause neurological changes, including epilepsy. The electro encephalogram (EEG) can be a valid diagnostic analysis, but it is a non-specific examination and therefore is considered only partially helpful. Thus, a thorough metabolic examination could detect a more targeted treatment for the etiology and would allow for early diagnosis and prompt intervention (11).

Epilepsy and inflammation

Temporal lobe epilepsy is the form that occurs most in adult patients and, therefore, is the most studied. The epileptic acute phase is followed by a latency period with activation of microglia, resulting in the generation of inflammatory mediators. Clinical studies have revealed that a seizure can often be triggered by stressful events, low blood sugar, bright lights, loud sounds, and poor sleep. In epilepsy, like many other inflammatory brain disorders, microglia, blood-brain barrier (BBB) endothelial cells, astrocytes, and peripheral immune system cells are activated (12). The activation of these cells leads to the generation of pro-inflammatory compounds including cytokines, arachidonic acid compounds, and inducible nitric oxide synthase (iNOS), amongst others. Thus, it can be inferred that brain inflammation in epilepsy can be both the cause and the consequence. it is known that in epilepsy, an inflammatory process takes place with aggravation of seizures and their frequency (13).

Infections with Gram negative bacteria and the induction of lipopolysaccharide (LPS) in mouse models, by binding to toll-like receptor 4 (TLR4), can exacerbate seizures. Peripheral circulating cytokines produced in the inflammatory process can activate afferent nerves to the brain by stimulating microglia and other brain cells to produce inflammatory proteins (14). In seizures, there can be loss of cells which often contributes to inflammation in the brain. Inflammatory pathologies of the central nervous system (CNS) may constitute a predisposition to epileptic convulsive phenomena. Inflammation is a defensive response to external insults and consists in the release of a cascade of chemical and biological mediators, but also of anti-inflammatory compounds (15). Inflammation is mediated by products released by both innate and adaptive immune cell responses implicated in several brain pathologies, including epilepsy. The activation of cerebral microglia leads to the secretion of inflammatory cytokines of innate immunity, such as IL-1, tumor necrosis factor (TNF), IL-6, interferon (IFN) and transforming growth factor (TGF)-β, which represent those that are the most studied in brain pathologies (16). After a brain injury, chemokines can be released as well. They are chemoattractant proteins that recruit immune cells that cross the BBB after an external insult (17).

Pro-inflammatory cytokines can trigger the release of chemokines that promote angiogenesis, microglia motility, and neural stem cell migration. Epileptic effects can occur more frequently in subjects suffering from autoimmune diseases, such as multiple sclerosis, systemic lupus erythematosus, vasculitis, encephalitis, etc. Severe epilepsy can lead to seizures with severe brain damage, hemiparesis, hemisphere atrophy, effects that may also be mediated by the presence of autoantibodies (18). In the brain regions where seizures are generated, there is a rapid release of inflammatory molecules and the involvement of different immune populations, with the upregulation of pro-inflammatory cytokine genes. During seizures, endothelial cells are also activated with overexpression of adhesion molecules such as P-selectin, E-selectin, and intercellular adhesion molecule 1 (ICAM) (19).

Therapy

The clinical spectrum in epilepsy and the mechanisms of immune system failure can be different in various individuals. The disease can arise acutely and for a limited time, while other times it can represent a first episode of a chronic disease. Epilepsy can be induced by the activation of memory T lymphocytes after an infection resulting in systemic inflammation, which can also reactivate an already existing pathology. In these cases, immunotherapy may be indicated (20).

Anti-epileptic drugs, while they are only 30-40% effective, inhibit the hyperexcitability of neurons to the benefit of epileptic seizures. However, it has been seen in clinical experiments that biochemical manipulations can prevent epileptic

seizures (21). Today, a wide range of anti-epileptic drugs are commercially available, although the most commonly used are carbamazepine and phenytoin, which reduce the abnormal firing of neurons in the cerebral cortex. Therapy with steroids and other anti-inflammatories (non-steroidal anti-inflammatory drugs) has shown anticonvulsant activity and, in some cases, may be helpful since pro-inflammatory compounds are released in epileptic seizures. These drugs are particularly effective in febrile seizures mediated by arachidonic acid products such as prostaglandins and leukotrienes that are inhibited by nonsteroidal anti-inflammatory drugs (NSAID) and steroidal anti-inflammatory drugs (corticosteroids), respectively. In the most serious cases, when these drugs are not effective, the surgical technique can be used by removing the part of the brain where the seizure starts (22). Corticosteroid or immunoglobulin therapy (or in combination) should be performed at intervals of time (about a month, and for a few years). Another surgical technique involves the removal of the corpus callosum to prevent the spread of the abnormal signals from one side of the brain to the other (23).

CONCLUSIONS

When drug treatment fails, surgical treatment to remove seizures could be considered, but this procedure should be decided by the surgeon in consultation with the family. In light of the above results, we can classify epilepsy, as not only a neurological dysfunction but also a neuro-inflammatory disease (24). These observations may help to find new and appropriate therapy.

Conflict of interest

The author declares that they have no conflict of interest.

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