Connections Between Infections and Seizures

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Introduction

About 5% of patients with an infection of the central nervous system will experience a seizure. A seizure may be the presenting symptom, or only one manifestation, of the infection. Common infections of the central nervous system that may present with seizures include: herpes simplex, cytomegalovirus, arbovirus, human immunodeficiency virus, neurocysticercosis, malaria, toxoplasmosis, bacterial meningitis and brain abscess. The seizures may be due to direct invasion of brain tissue by the infecting organism, production of toxins by the organism or production of inflammatory mediators by the brain. Infectious processes in the brain can lead to breakdown of the blood–brain barrier and brain edema. Severe systemic infections can also be associated with seizures, even if the infection is not present in the central nervous system. In this instance the seizures are most likely due to hypoxia or other severe metabolic changes, such as hyponatremia, that are the result of the overwhelming infection. In all cases, treatment for the seizures associated with infection usually involves treatment of the underlying infection.

Bacterial infections in the central nervous system are less likely to cause seizures than viral infections. However, generalized convulsions may occur with bacterial meningitis. Compared to other bacteria, infections with Haemophilus influenzae are more commonly associated with seizures. The mechanism of the seizures is not known. As with other infectious processes, it has been postulated that the seizures are either a result of the primary infection or due to the inflammatory response to the bacterial infection. To date there is not much data for either possibility.

Encephalitis due to a viral infection of the brain can be associated with both focal and generalized seizures. Viral encephalitis is characterized by neuronal and glial degeneration, inflammatory infiltrate, edema, and tissue necrosis. Herpes simplex virus is the most common pathogen associated with seizures in cases of viral encephalitis. But, seizures occur in approximately 85% of children infected with Japanese encephalitis and up to 10% of adults with West Nile virus. Equine encephalitis, St. Louis encephalitis, cytomegalovirus and rabies have also been reported to cause seizures. Finally, it has been estimated that 2–5% of HIV-infected patients have seizures due to the primary infection of the brain by the virus.

The issues surrounding the relationship between herpes virus infections of the central nervous system and seizures is a bit more complicated. Infection with herpes virus, particularly herpesvirus 6B (HHV-6B) is quite common. Recently, it has been questioned whether the association between acute infection with HHV-6B and seizures in infants less that 1 month old is a causal relationship. It could be that the infection is causing the seizures, but it is also possible that infants susceptible to the infection are those most likely to have seizures. The evidence is not clear one way or the other. Herpesviruses can also result in a latent or persistent infection. This persistent infection has been implicated in febrile seizures and some forms of epilepsy – in the absence of symptomatic encephalitis. HHV-6B has been found in resected tissue from a substantial proportion of patients with temporal lobe epilepsy. The virus is found in astrocytes in this tissue. The current hypothesis is that the presence of the virus is a result of an early infection and its continued presence somehow lowers the seizure threshold or likelihood of developing epilepsy. Herpes is easily reactivated, particularly by other viral infections. It is possible that reactivation of the virus results in a series of consequences that result in a lowering of the seizure threshold. One hypothesis is that reactivation of HHV-6 alters gene expression in astrocytes, which in turn alters glutamate pathways. Thus the seizures could be due to an action of the reactivated virus or a secondary action initiated by the presence of the virus in the latent form. There is not enough data to state definitively one way or the other.

Other infections that involve the central nervous system have been reported to cause seizures. Neurocysticercosis, infection of the central nervous system with the cyst form of tapeworms, is the most common parasitic infection of the brain. In developing countries, up to 50% of adult-onset epilepsy is due to neurocysticercosis. Malaria is estimated to spread into the central nervous system in approximately one third of the cases and cerebral malaria can present with seizures. The incidence of acute seizures in neurosyphilis is 14–60%. Infectious diseases in which seizures have been reported, but are not typically the presenting feature, include: rubeola, schistosomiasis, trichinosis, paragonimiasis, echinococcosis, trypanosomiasis, typhus and amebiasis.

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In summary, infections of the central nervous system are clearly associated with seizures, either during the acute infection or as a delayed response. The mechanism underlying these seizures is not understood and are most likely dependent on the infectious agent and time course of the infection. In addition, inflammatory processes in the brain have been implicated in a number of cases and could be the underlying cause of seizures in some, if not all, infections.

**Background**

Studies of infectious causes of seizures have been limited by a number of significant issues. Seizures are most commonly studied in the laboratory in rodents – rats or mice. However, infectious processes are quite different in rodents than in humans. Rodents are generally resistant to a number of organisms that commonly infect humans. Conversely agents infectious to rodents may not be infectious in humans. When a common agent infects both species, the infection may follow a different course making comparisons difficult. Host responses to the infecting organism can also be different. Finally, there is the need to work with infectious agents in the laboratory and the constraints that brings. Some pathogens are difficult to grow and maintain in the laboratory. Two infectious agents that have been studied in animal models are Herpes simplex type 1 and neurocysticercosis.

Herpes simplex type 1 (HSV-1) is a neurotropic virus that can travel through the central nervous system by retrograde axonal transport and has been shown to have an affinity for the temporal region. In patients with encephalitis due by HSV-1, 38% will have seizures. The symptoms associated with HSV-1 infection are thought to be due to both viral and host factors. As a herpes virus, HSV-1 also has the ability to become latent. In order to study the mechanism of the seizures in HSV-1 infection, attempts have been made to produce an animal model of HSV-1 infection with adequate reflection of both the acute and chronic characteristics of the infection.

Mice, rats, and rabbits have since been used in generating models of HSV-1 infection. The virus has to be grown in cultured monkey kidney or baby hamster kidney cells. Mice have been infected corneal scarification, rats by intranasal inoculation and rabbits by injection into the olfactory bulb. In most publications, animals are reported to have symptoms of a systemic viral infection. The severity of the symptoms is relative to the dose and route of administration of the virus. There is a significant mortality rate in all of these approaches and viral shedding has been measured in ocular and nasal secretions from the infected rats.

Seizures have been documented by observation and electrical recording. Both generalized and partial seizures have been reported. The severity of the seizures seems to correspond to the severity of the viral infection as determined by the systemic symptoms. Brain slices have also been obtained from infected animals and recordings have demonstrated abnormal excitability with depolarized membrane potentials and a lower threshold for burst generation. In one study using rats, in animals with seizure activity, inflammatory infiltrates and hemorrhagic lesions were detected in the trigeminal ganglia, olfactory bulb, amygdala, hippocampus, piriform cortex, entorhinal cortex and the spinal trigeminal ganglia. Astrocytic hypertrophy has also been demonstrated. Thus rodent models have successfully modeled human infection with herpes. The models have evidence of inflammation and neuronal death, hyperexcitability and seizures. However, these models have considerable mortality and have not yet yielded answers to the questions about mechanisms underlying the seizures.

Hippocampal slice cultures have also been infected with HSV-1 by adding the virus directly to the culture medium. Acute infection can induce epileptiform activity and neuron loss suggesting that this model could be used to examine the mechanisms by which the virus causes cell loss and hyperexcitability. Whether any mechanism determined in this model would relate to the human infection remains to be determined.

Another infection that has been studied in animals is neurocysticercosis, an infection of the human central nervous system by the helminth Taenia solium. Since pigs serve as the intermediate host, humans become infected with the tapeworm form (taeniasis) by eating undercooked pork that is infected with the egg form. The larvae hatch and cross the intestinal mucosa to enter the bloodstream. They exit the bloodstream and migrate to tissues, including the brain, where they mature into cysts called cysticerci. These cysticerci are viable parasites, which modulate and inhibit the host immune response. The presence of cysticerci in the brain does not always produce symptoms. Individuals who died of other causes have been found to have viable cysticerci in the brain. When cysts begin to degenerate an inflammatory response is elicited in the brain and seizures can occur. However, the inflammation itself does not invariably produce seizures. Why some inflamed cysts produced seizures and others do not is not understood. It is not known what causes the seizures in neurocysticercosis, but it has been postulated that one, or more, epileptogenic substance is released by the dying parasite or produced by the surrounding inflammatory cells (Fig. 1).

Calcification commonly occurs with degeneration of the cysts – most likely late in the degeneration process. About 10–20% of patients show calcification on CT scans, but only a small number of these people have epilepsy. Of the people with epilepsy, the calcification correlates with the seizure focus in about 50% of cases. Calcified cysts can be associated with surrounding edema, most likely due to inflammation. Thus, another unresolved issue is the relationship between calcification and development of epilepsy.

**Methods**

There are a number of possible animal models of the T. solium infection. Taenia solium, the human tapeworm, is not infectious in rodents, but a closely related helminth Taenia crassiceps can produce cysticercosis in mice. However, it will not produce infection of the brain. Taenia crassiceps or granulomas associated with T. crassiceps can be injected directly into the cranium of rodents or pigs.
*Taenia solium* will infect pigs, either naturally, orally or by injection. The naturally infected pigs most closely mimic the human experience, but cerebral infection only occurs with heavy infestation. Direct injection of invasive larvae into the brains of rats and mice is easier to control and monitor. All of these models are technically demanding and require months for cyst maturation.

Cysts from *T. crassiceps* can be produced in the peritoneal cavity of mice, by inoculation. In the peritoneal cavity, the parasites eventually begin to die and host responses result in the formation of granulomas around the cysts. These granulomas mature through a series of defined stages (1–4) depending on the amount of intact organism remaining. By stage 4 only host cells and debris remain, without clearly identifiable parasite elements.

To test whether a substance in the granuloma could cause seizures, granulomas were harvested from mice infected with *T. crassiceps*. A portion of the granuloma was saved for histological analysis and the remainder was homogenized in phosphate buffered saline. The extract prepared from the granulomas was then injected into the brain of an adult to mimic the presence of these substances in neurocysticercosis. Preliminary data showed that injection of the extract into either the hippocampus or the amygdala could produce electrographic seizures. With the animals under low levels of anesthesia, no behavioral seizures were observed after injection of extract. The hippocampus and amygdala were chosen because of their relatively low seizure threshold. A single injection of 10 μL extract (containing 25 μg total protein), or control substance, was administered and the animals were monitored continuously for at least 1 h. Control experiments with known convulsants determined that the recorded electrical activity had to reach at least twice the amplitude of the baseline activity to be defined as epileptiform and the onset of the epileptiform activity should occur within 3 min to be considered a direct effect of the injected material. After termination of each experiment, the brain was examined to confirm accuracy of the injection and recording sites.

**Recent Results**

Initial experiments determined that injection of 10 μL of phosphate buffered saline had no effect on the recorded electrical activity. Each extract prepared from each granuloma was tested in at least two animals. Extracts from stage 1 and 2 granulomas consistently produced an epileptiform discharge in the hippocampus that started within 1 min of injection and lasted 44 s (range of 25–76 s). Extracts from granulomas in stage 3 or 4 did not reliably produce seizures. Once the epileptiform activity had stopped it did not recur. Injections of extracts from non-stimulated host cells prepared from spleen of uninfected mice and homogenized viable parasites did not produce epileptiform activity. The results suggest that a substance in the granulomas may produce epileptiform activity.

**Future Goals**

To really understand the relationship between seizures and infections of the central nervous system, there is need for better animal models. This will require a thorough understanding of the pathophysiology of the infectious process in both humans and whatever experimental animal model. For the case of neurocysticercosis, how does the cyst suppress the immune response? What leads to death of the organism, stimulation of the immune response and formation of the granuloma? What is the role of the inflammatory response in the genesis of the seizures? For herpes infections, what is the direct effect of an acute infection on neuronal and glial function? Are there changes in cellular function when the virus is latent? How is the virus re-activated in the brain and is the effect of a re-activated virus different from a new infection? There is still much that needs to be learned about infections in the brain and how they lead to seizures.

In addition, the infecting organism needs to be clearly defined and a means to grow it reproducibly is necessary. Some questions could be answered in *in vitro* systems, such as slice cultures or acute cultures of dissociated cells, but not all. Where there are questions about the role of the blood–brain barrier or inflammatory processes the experiments will need to be done in an *in vivo* system.
The idea that the inflammation is a major contributor to the seizures recurs with a number of the infectious processes. Inflammation is a host response to injury. Local and sustained inflammatory responses have benefits in infectious disease, generally limiting bacterial replication and spread. Sustained or inappropriate inflammation is the cause of a number of human diseases. Until recently, the brain was considered to be resistant to inflammation or immune activation. This is not true, but the immune responses in the brain are somewhat different than those peripherally. The brain does exhibit a number of key features of inflammation, including glial activation, edema, an acute phase response, and synthesis of cytokines, free radical, adhesion molecules and other markers of the inflammatory response. Finally, immune cells do invade brain tissue. Most inflammatory mediators are expressed at very low (or undetectable) levels in the normal brain, but can be rapidly induced. For example, infection will stimulate microglia to transform into macrophages, which will move to the site of infection. Activated microglia produce cytokines and trophic factors that can either damage or protect surrounding cells.

Another goal of research in the link between seizures and infection is to develop better treatment strategies for these seizures. Clearly the primary treatment is aggressive management of the underlying infection, especially for bacterial infections. With viral infections of the central nervous system, will aggressive antiviral therapy reduce the incidence of later seizures? Should there be an attempt to treat a latent infection? Can re-activation of herpes be detected before seizures begin? Finally, can understanding how infectious process lead to seizures improve the treatment of idiopathic seizures?

Further Reading