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CNS Inflammation and Epileptogenesis

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Abstract – An association between acute CNS infections and seizures is reported in the literature. The etiology of these seizures is, in some cases, precipitated by epileptogenic pathogenesis of the infectious agent in the brain parenchyma. A different etiology of seizures as a consequence of infections, independent of the infectious agent, relates to the inflammatory reaction. Thirdly, the febrile response to infections may predispose the CNS to seizures due to the metabolic aberrations of fever. Febrile states have also been implicated in some cases of mesial temporal lobe epilepsy. Current attempts to control seizures with anti-inflammatory treatments have shown contrasting result, therefore specific agents need to be developed and tested.

Index Terms – CNS Infections, Epileptogenesis, Fever, Immune Modulators, Inflammation, Mesial Temporal Lobe Epilepsy, Seizures

Introduction

The central nervous system (CNS) is considered an immuno-privileged site because of the presence of a blood–brain barrier, a lack of a conventional lymphatic drainage, and an apparently low traffic of monocytes and lymphocytes. It is, however, becoming clear that immune and inflammatory reactions do occur in the CNS. The pathogenesis of infections which precipitate these inflammatory reactions, along with the physiological response to infections have both been implicated in the genesis and promotion of seizures (Vezzani and Granata, 2010). Epilepsy is a disabling neurological disorder characterized by recurring, unprovoked seizures. It affects about 1% of the population of all ages and often requires lifelong medication. In about 30% of affected individuals, epilepsy is refractory to pharmacological treatment, and surgical removal of the epileptic focus is suitable only for a minority of such patients (Johnston, 2007). Understanding the etiology underlying the occurrence of seizures is necessary for devising novel therapeutic approaches.

Epileptogenic Infections

Seizures may occur as a direct consequence of the activity of pathogens in the CNS. Pathological and physiological aberrations in CNS functions that can lead to epileptogenesis may result from one of the following: morphological changes during life cycle of the pathogen that affect normal signaling in brain parenchyma; or the effect of the pathogen on the circulation of nutrients and other essential factors necessary for normal CNS functions.

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Neurocysticercosis

Cysticerci often live asymptomatically in the host for years, evading the immune system. Once in the CNS, the parasite goes through a series of stages as it develops in a fluid-filled cyst. The mature vesicular lesions are also asymptomatic, and initially, are capable of suppressing the host inflammatory response. The lesions later become inflamed as the host's response gradually clears the parasite. This phase is frequently complicated by seizures. In some instances, the lesions will resolve completely. However in other cases, resolution is incomplete, leaving a residual calcified lesion, which may be associated with chronic epilepsy (White, 2010).

Cerebral malaria

The parasite *P. falciparum* is the causative organism of cerebral malaria. 70% of malaria cases occur in sub-Saharan Africa, where children are most commonly affected (Guerra et al, 2005), such that malaria may account for 40% of pediatric admissions to some hospitals, 10% of which may be due to cerebral malaria (Foster et al, 2005). The incidence of cerebral malaria in malaria-endemic areas of sub-Saharan Africa is 1.12 cases per/1000 children per year, with a mortality of 18.6% (Krishna and Newton, 1998).

The sequestration of infected and non-infected erythrocytes within cerebral vessels predisposes the CNS to epileptogenic lesions. Adherence of *P. falciparum* in blood vessels reduces the micro-vascular flow, and leads to hypoperfusion of the CNS. In addition, the presence of parasites inside erythrocytes decreases the ability of the cell to deform to facilitate its passage through the microvasculature. Sequestration might happen as a consequence of cyto-adherence of infected erythrocytes to endothelial cells via *P. falciparum* derived proteins on the infected erythrocyte surface attaching to ligands in the venules (Idro et al., 2005).

In addition to the examples above, the literature reports other epileptogenic infectious agents. These include: *Echinococcus, Angiostrongylus cantonensis, Toxacara sp. Schistosoma sp.* and various *HHV* species (Newton and Wagner, 2009).

Inflammatory reactions and seizures

A different etiology of seizures as a consequence of infections relates to the inflammatory reaction, independent of the infectious agent. Two main possibilities may explain the initiation of inflammatory responses within the CNS (Vezzani and Granata, 2010): the immune inflammatory process is initiated within the CNS, and the infiltration of blood-borne immune cells or circulating inflammatory mediators is a consequent response to this intrinsic event; or the CNS is the target of an inflammatory response that originates within peripheral lymphoid tissues. The evolving theory of inflammation-driven epileptogenesis as a result of pro-inflammatory cytokines in the CNS has been described with data from animal models and clinical observation.

Evidence from human specimens

An increased IL-1α expression in microglia cells has been documented by immunohistochemistry in brain specimens obtained from patients who have undergone temporal lobectomy as treatment for mesial temporal lobe epilepsy (MTLE) (Sheng et al., 1994). A subsequent study described the presence of reactive astrocytes in hippocampal specimens surgically removed from patients with MTLE who had a history of febrile convulsions. The expression of NF-κB, a transcription factor that regulates expression of inflammation genes, specifically in lesioned hippocampi indicates the activation of an inflammatory cascade in brain parenchyma (Crespel et al., 2002). The studies in human epilepsy specimens from MTLE patients support the existence of an inflammatory state sustained epileptic focus in the brain parenchymal cells.

Evidence from Animal Models

Studies conducted in experimental animal models have identified several cytokines including, IL-1β, IL-1Ra, TNF-α, IL-6, as critical factors in sensitizing the CNS to seizures (Scantlebury and Heida, 2010). Elevated levels of IL-1β in CSF have been shown to reduce the seizure threshold in rats, making them more susceptible to seizures after minimal induction by LPS-mediated pathways. Conversely, IL-1β receptor-deficient rats are resistant to seizures induced by LPS (Heida et al., 2004). The role of TNF-α in seizure sensitization have been investigated in rat models of pneumococcal meningitis. By administering TNF-α-converting enzyme inhibitors to these rats, CSF levels of TNF-α were markedly decreased, along with seizures associated with the bacterial infection (Meli et al., 2004). Finally, in transgenic mice primed to be in a chronic CNS inflammatory state by over-expressing IL-6 or TNF-α, there was an observed increase in sensitivity to seizures induced by glutamatergic agonist, along with a loss of GABA neurons in the hippocampus (Smaland et al., 2003). These data suggest that pro-inflammatory cytokines in the CNS contribute to the propensity of seizure development.

Febrile Response to infections

A third etiology of seizures in the setting of CNS infections stems from the acute metabolic disturbance associated with febrile states. A febrile seizure is a convulsion in a child triggered by a fever. These convulsions occur without any brain or spinal cord infection or other nervous system cause. Febrile seizures are usually triggered by fevers from ear infections, roseola infantum, upper respiratory infections and meningitis (Johnston, 2007).

Clinical Studies

Febrile seizures occur in ~5% of children <5 years old who develop an acute infection. A fundamental question about febrile seizures that remains unanswered is why they develop in some children with a febrile illness but not others. It does not appear to be the magnitude of fever which plays a role. Children with a lower fever at the time of seizure have an increased risk for subsequent convulsion with another febrile illness, perhaps because they have a lower threshold for seizures in the first place (El-Rhadhi, 1998). While fever is defined as a temperature of at least 38.4°C, some clinical studies of febrile seizures have accepted temperature values as low as 38°C, as high enough to precipitate central nervous system (CNS) dysfunction (Al-Eissa, 1995). Clinically, it is difficult to determine the exact temperature at seizure onset, and, sometimes, febrile seizures can occur as the presenting sign of febrile illness.

Although most febrile seizures do no harm and two-thirds of initial cases have no witnessed recurrence, in rare cases they are the first evidence of important epilepsy syndromes. Furthermore, febrile seizures in early childhood have been implicated in the development of epilepsy with mesial temporal sclerosis in later life (Cendes, 2004).

Observations by Falconer, based on a series of 100 patients who had surgery for intractable temporal lobe epilepsy

(TLE) in the 1960s showed that many of these patients had mesial temporal sclerosis as an underlying pathology. Additionally, a significant proportion of the patient population had episodes of prolonged febrile seizures in their early childhood (30% in the MTS group compared with 6% in the group without MTS) (Falconer et al., 1964). With this data, a causal relationship was suggested between prolonged febrile seizures and MTS.

Animal Model of Febrile Seizures

To study the etiology of febrile seizures, animal models have been developed — an inflammatory dose of the bacterial endotoxin, lipopolysaccharide (LPS), which evokes an immune reaction and a fever response (about 1-1.5°C) is coupled with what is normally a sub-convulsant dose of kainic acid (KA), in immature rats (P14) (Heida et al., 2004). This model mimics the most essential features of febrile seizures: the immune response and the fever. Hyperthermia (>38.3°C) can decrease gamma-aminobutyric acid A ($GABA_A$) receptor-mediated inhibition to a greater extent than it decreases excitation, which may shift the balance towards excitation and contribute to seizure generation (Leung et al., 2007). While this phenomenon has only been studied in hyperthermic models, it is proposed to occur when temperature is increased from physiologic fever (Scantlebury and Heida, 2010).

Evidence from Animal Models

There is now evidence from animal models of febrile seizures that supports a link between prolonged febrile seizures and the development of epilepsy. In one study, prolonged (30 min) hyperthermic seizures maintained in rats (P10), by exposure to heated dry air, resulted recurrent seizures in 35% of animals in adulthood. The seizures were brief, non-convulsive and of focal limbic origin. The adult rats with recurrent seizures also had mild to moderate learning and memory deficits (Dube et al., 2009). Although, this model does not capture the main features of the most severe form of MTLE, which include secondarily generalized seizures and overt MTS, it has provided some insights into the mechanisms that lead to recurrent seizures following prolonged febrile seizures.

Prolonged hyperthermic seizures results in an early upregulation in alpha-amino-3- hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors lacking the GluR2 subunit in the hippocampus (Richichi et al., 2008). This type of AMPA receptor is calcium permeable, and, when activated, can lead to pathological increases in intracellular calcium. This affects many processes leading to the abnormal function or expression of specific ion channels or receptors resulting in the creation of seizure generating networks (Chen et al., 2001).

Another known metabolic disturbance of fever in children is an increase in the respiratory rate. It is unclear however, whether this effect leads to a respiratory alkalosis. This is of importance since alkalosis increases neuronal excitability (Reid et al., 2009). Animal models of febrile seizures exhibit respiratory alkalosis, and administration of CO_2 brings an abrupt end to the seizures (Schuchmann et al., 2006). There is still uncertainty as to whether alkalosis plays a remarkable role in the etiology of febrile seizures in children.

Therapeutics

Anti-COX Agents

The use of anti-inflammatory drugs to treat epilepsy has shown varied results. Anti-inflammatory drugs with anti-COX activities have been shown to either reduce or exacerbate seizures induced by kainic acid. For example, aspirin decreases kainite seizures, and has been shown to modulate the anticonvulsant activity of sodium valproate (Bing et al, 2000). However, in different studies, pretreatment of rats with indomethacin, aspirin, nimesulide, or selective COX-2 inhibitors augmented kainate-induced seizures (Baik et al, 1999). These apparent dual effects of COX inhibitors likely depend on their specific actions on the basal production of the various prostaglandins, and on the different profiles of prostaglandins produced during seizures in the various experimental models (Baik et al, 1999). Post-seizure administration of COX-2 inhibitors protects hippocampal neurons from damage induced by seizures and enhances functional recovery of cognitive functions after kainate seizures (Benveniste et al, 2004). The above evidence supports a relevant role of prostaglandins in the mechanisms of neuronal hyperexcitablity.

IV Immunoglobulin

Intravenous administration of high doses of immunoglobulins has an anticonvulsive effect. IV injections of human globulin-N protected cats against generalized seizures induced by electrical stimulation of the amygdala (Hirayama et al, 1986). Immunoglobulins have been shown to inhibit NF-κB activation induced by TNF-α in endothelial cells and macrophages (Ichiyama et al, 2004). The evidence therefore suggests that their anticonvulsant effect may be at least in part mediated by anti-inflammatory mechanisms.

Steroids

The use of steroids in various forms is common for more severe, treatment-resistant forms of childhood epilepsy. Adrenocorticotrophic hormone (ACTH) — a peptide that releases endogenous steroids — has been used successfully as a treatment for infantile spasms, a severe form of childhood epilepsy that is resistant to conventional anti-epileptic drugs (Avishai-Eliner et al, 2002). The success of ACTH have been shown empirically and confirmed in randomized controlled trials. Consequently, ACTH remains a mainstay of therapy for this condition (Baram and Hatalski, 1998).

Conclusions

There is preclinical evidence that suggests brain inflammation promotes neuronal hyperexcitablity and seizures. The role played by cytokines in epileptogenesis, and the effect of metabolic derangements associated with fever on the CNS have been investigated in some detail. Although these studies highlight several novel mechanisms that might be utilized as therapeutic targets, clinical evidence has shown inconsistent results. Data from animal models suggest that targeting specific cytokines might be warranted. Several important questions remain, such as: how acute febrile seizures become prolonged, or why epilepsy occurs in some and not all children with febrile epilepsy; whether inflammatory mechanisms are important at all stages of epileptogenesis and epilepsy; whether patients all have a similar degree of inflammation; whether various epilepsy etiologies are associated with inflammation that can be targeted therapeutically. A clinical trial of an IL-1β synthesis inhibitor was initiated in 2010 because this mechanism could contribute to different types of seizures. If this and other trials are successful, assessment of which patients are responding to anti-inflammatory therapy might become possible and, hence, the underlying epilepsy pathologies in which inflammation is important might be determined.

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