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# Focal Epilepsies: Immunologic and Inflammatory Mechanisms

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**There is increasing evidence documenting activation of inflammatory processes in focal epilepsies. This review article summarizes current data regarding immune mediated inflammatory processes in patients with symptomatic partial epilepsies such as mesial temporal sclerosis, focal cortical dysplasia, and Rasmussen's encephalitis. We have also reviewed several neuronal surface antibody–associated syndromes, which have been recently described with focal seizures as an important part of clinical presentation, such as antibody-associated limbic encephalitis and N-methyl-D-aspartic acid receptor antibody syndrome. An autoimmune mechanism may be one pathogenic factor in some symptomatic epilepsies acting as a triggering event in the process leading to the development of epilepsy.**
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## Introduction

There is increasing evidence that activation of immune and inflammatory processes occurs in a variety of focal epilepsies.[1]

Innate immunity refers to an acute reaction of neuronal tissue to a particular stimulus, such as injury or seizures. This reaction includes a release of interleukins (ILs), complement proteins, prostaglandins, chemokines, and adhesion molecules and activation of intracellular signaling pathways such as nuclear factor kappa B. Cell types involved in innate immunity are mainly microglial cells, astrocytes, neurons, and potentially, infiltrating granulocytes and macrophages. Adaptive immunity refers to a more selective reaction against specific antigens by infiltrating T and B lymphocytes or microglial cells.[4]

There is information to suggest that there is activation of the innate and adaptive immune systems in human epilepsy and that this inflammatory response contributes both to the generation and recurrence of seizures and to seizure-related neuronal damage.[2,3] This article reviews the data regarding immune mediated inflammatory processes in patients with symptomatic partial epilepsies such as mesial temporal sclerosis and focal cortical dysplasia (FCD). In addition, although immune activation has been shown in prototypic inflammatory epilepsies, such as Rasmussen's encephalitis (RE) and limbic encephalitis (LE), antibodies against neuronal surface proteins are increasingly recognized in diverse central nervous system (CNS) disorders in which seizures are an important presenting symptom. There are well-defined syndromes with neuronal surface antibodies in which focal seizures are a relevant part of the presentation such as antibody-associated LE and N-methyl-D-aspartic acid (NMDA) receptor antibody syndrome; however, seizures with autoimmune etiology exist beyond the spectrum of these syndromes, and it is increasingly important to recognize them because they are potentially treatable with immune modulation therapies.

## Symptomatic Partial Epilepsies

### Mesial Temporal Lobe Epilepsy With Hippocampal Sclerosis

Mesial temporal lobe epilepsy (MTLE) is the most common type of localization-related epilepsy. Patients often have a history of early risk factors such as febrile seizures, status epilepticus, and infection. A seizure-free period may be present before uncontrolled partial seizures begin. There are some progressive features such as increasing seizure frequency and cognitive decline.

In patients with temporal lobe epilepsy (TLE), there is evidence of microglial activation within the hippocampus, providing evidence of an activated immune response.[5-8] Nuclear factor kappa B overexpression has been shown in reactive astrocytes and surviving neurons in human hippocampal sclerosis specimens.[9]

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There is prominent and persistent activation of the IL-1B system involving both activated glial cells and neuronal cells. In contrast, only a few cells of adaptive immunity (CD3/CD8-positive T lymphocytes) have been detected in human MTLE specimens.[8]

Table 1 summarizes clinical studies on the role of cytokines in temporal lobe seizures.[4]

In patients with refractory focal epilepsy, a video electroencephalogram study showed a rapid postictal increase in plasma IL-6 levels in patients with TLE.[11] The same authors also showed higher levels of C-reactive protein at baseline in patients with epilepsy compared with healthy controls, further emphasizing the association between inflammation and refractory epilepsy.[13]

Studies on the effects of vagus nerve stimulation in patients with intractable epilepsy revealed a shift from a proinflammatory to an anti-inflammatory profile in blood. Responders had higher IL-6 levels, which decreased following placement of vagus nerve stimulation; however, in nonresponders, IL-6 increased.[14]

The activation of inflammatory pathways in human TLE is also supported by gene expression profile analysis.[7] A recent study by Pernhorst et al[15] demonstrated differential correlation of key inflammatory factor expression and seizure frequency in patients with pharmacoresistant MTLE. Toll-like receptor 4 (TLR4—a key trigger of inflammation previously shown to induce the transcription of several cytokines in a TLE animal model) gene expression correlated directly, whereas activating transcription factor 3 (a negative regulator of TLR4) and IL-8 expressions correlated inversely with seizure frequency.

Interactions between dysregulated persistent inflammation, blood-brain barrier damage, and uncontrolled seizures can create a self-perpetuating cycle causing uncontrolled inflammation that triggers progression of MTLE. This was elegantly reviewed by Yang et al.[16] Once the process is initiated, a cycle of seizure-induced inflammation and inflammation-mediated stimulation amplifies the initial effects[4] (Fig.).

A recent review article by Devinsky et al[17] highlights the role of glia-induced hyperexcitability and inflammation in the pathophysiology of epilepsy. This raises the question of glial targets for epilepsy therapy.

Roseti et al[18]also recently have demonstrated that the chemokine fractalkine or CX3CL1, an important modulator of inflammation, which is widely expressed in brain tissues, plays a role in the decreased gamma amino butyric acid (GABA)ergic function in human TLE specimens, further supporting the relevance of brain inflammation in human focal epilepsy. Meador et al[19] described the effect cortical resections can have on the systemic immune system. They found that resections of the dominant hemisphere on patients with epilepsy reduced lymphocytes, total T cells, and helper T cells, whereas resections on the nondominant hemisphere increased the same components. Flare skin responses were reduced or increased by left or right cerebral resections, respectively.

## Focal Cortical Dysplasia

These are focal cytoarchitectural malformations of the cerebral cortex and a major cause of medically intractable epilepsy in children and young adults. Activation of astrocytes and microglia-macrophage lineage has been described in FCD specimens from adult and pediatric populations.[2,20,21]

Boer et al[20]demonstrated in a study of a cohort of patients with FCD that the density of activated human leukocyte antigen-DR (HLA-DR)-positive microglial cells correlated with the duration of epilepsy and the frequency of seizures before surgical resection. The number of HLA-DR-positive cells was higher in FCD type II compared with FCD type I despite no significant difference in seizure frequency and duration,[21] suggesting a different nature of activation in FCD type II. Regarding adaptive immunity, the presence of T lymphocytes was greater in FCD type II specimens.

Increased levels of proinflammatory cytokines have been shown in pediatric FCD cases,[2] and there is activation of tissue plasminogen,[21] TLR,[22] and vascular endothelial growth factor signaling.[23] All these contribute to glial activation and associated inflammatory responses.

Eeg-Olofsson et al[24] have found that defects in the antigen-presenting HLA system might lead to persistent virus infection resulting in a neuronal membrane defect and seizures in a subgroup of patients with focal epilepsy. More recently, Chen et al[25] described an association between human papilloma virus (HPV) and FCD IIB and were able to demonstrate for the first time HPV16 E6 in the human brain, leading to a possible novel etiology for FCD IIB based on HPV16 E6 expression during fetal brain development.

In a study of surgical specimens from pediatric patients with refractory epilepsy due to diverse causes including

**Table 1** The Presence of Cytokine Activation in Clinical Studies of Patients With TLE

| Cytokines | Patient Population | Findings | Reference |
|---|---|---|---|
| IL-1 and -amyloid precursor protein | Epilepsy surgery patients with TLE | Increased levels of both | Sheng et al[5] |
| IL-1 | 12 TLE + HS surgery patients | Activation of IL-B | Ravizza et al[8] |
| NFB | 18 Patients with TLE + HS | Increased | Crespel et al[9] |
| IL-6 | 25 Patients with TLE | Postictal increase | Bauer, 2009[10] |
| IL-6 | 20 Patients | Postictal increase in TLE but not in extra-TLE | Alapirtti et al[11] |
| IL-6 | 91 Patients | Chronic increase in TLE but not in extra-TLE | Liimatainen, 2009[12] |

HS, hippocampal sclerosis; NFB, nuclear factor kappa B.