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Immunomodulatory Treatments in Epilepsy

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The role of immunity and inflammation appears to be an integral part of the pathogenic processes associated with some seizures, particularly with refractory epilepsy. Prompt treatment with immunotherapy may lead to better outcomes. Immune treatment options for treatment of epilepsy include therapies such as corticosteroids, immunoglobulins, plasmapheresis, or steroid-sparing drugs such as azathioprine. Recent alternatives have included even more aggressive treatment with cyclophosphamide, anti–pre-B-lymphocyte monoclonal antibody rituximab, and monoclonal antibodies such as efalizumab or natalizumab, which are presently used for other inflammatory disorders. Randomized controlled trials of immunotherapy in presumed autoimmune epilepsy are needed to provide further support for the rapid use of immunotherapy in patients with immune mediated epilepsy.
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Introduction

Epilepsy affects approximately 50 million people worldwide and is one of the most common disabling neurologic disorders. Pharmacotherapy continues to be the major approach to antiepileptic therapy. However, despite the introduction of a variety of new antiepileptic medications over the past decades, approximately 20%-30% of patients with epilepsy continue to have pharmacoresistant seizures.[1,2] Structural lesions and genetic disorders are often associated with refractory epilepsy. The pathogenic role of immunity and inflammation in epilepsy and particularly in refractory epilepsy has long been suspected, based on case observations regarding the effectiveness of immunomodulating therapies in the management of certain epilepsies. Subsequent findings of inflammatory markers, including autoantibodies in patients with a variety of epileptic disorders, have given further credence to the role of inflammation in epilepsy.[3]

Central nervous system (CNS) insults such as trauma, stroke, viral infection, febrile seizures, and status epilepticus (SE) are considered risk factors in the development of epilepsy. CNS inflammation develops immediately after these events, suggesting that a proinflammatory state in the brain might play a role in the development of epilepsy. Evidence for increased synthesis of inflammatory mediators in the brain during epileptogenesis has been corroborated by microarray analysis of transcripts of various classes of genes, showing prominently upregulated inflammatory genes.[4] Pharmacologic studies in experimental models of acute or chronic seizures and assessment of seizure susceptibility in genetically modified mice demonstrated that proinflammatory mediators released from activated glia and neurons contribute to the mechanisms of ictogenesis.[5]

Experimental and clinical data suggest that both native and adaptive immunity may be involved in epilepsy. Native immunity results in an immediate, nonspecific response against pathogens via activation of immune cells and inflammatory mediators. This is thought to contribute to seizures and epileptogenesis. Adaptive immunity activates antigen-specific B and T lymphocytes or antibodies in the context of infections and autoimmune disorders. In the brain, native immunity cell types consisting of microglia, astrocytes, and neurons produce mediators of inflammation.

The full spectrum of inflammatory and autoantibody-associated epilepsies has not yet been determined. However, the association between autoantibodies and CNS disease is being increasingly recognized. Serum and cerebrospinal fluid (CSF) antibodies that bind to neuronal cell surface proteins including channels and receptors have the potential to be pathogenic and cause CNS disease. Recently, antibodies that bind extracellularly and are associated with CNS disorders have been called "neuronal surface antibodies" (NSAbs), and the disorders associated with these NSAbs are called "neuronal surface antibody syndromes".[6] The identification of specific and potentially pathogenic NSAbs is increasing, and the spectrum of the clinical syndromes associated with NSAbs is widening. There are well-defined CNS syndromes associated with NSAbs where seizures are

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an important feature. Examples include the epilepsies related with N-methyl-D-aspartate receptor (NMDAR), voltage gated potassium channel (VGKC) complex, and contactin-associated protein–like 2 antibodies.[3] In addition, there are other epileptic conditions where an immune-mediated mechanism is suspected, such as febrile infection–related epilepsy syndrome in school-aged children.[7]

Evidence that the immune system and inflammation are involved in the pathophysiology of epilepsy has raised the prospect of new therapeutic approaches to treat epilepsy. The mounting evidence that inflammatory mediators contribute to the onset and recurrence of seizures in experimental seizure models, as well as the presence of inflammatory molecules in human epileptogenic tissue, gives rise to the possibility of targeting inflammation-related pathways with immunotherapies to control seizures that are resistant to available antiepileptic drugs (AEDs).[8]

Immunotherapies in Epilepsy

Immunotherapy options for treatment of epilepsy include medications such as corticosteroids, intravenous immunoglobulins (IVIg), plasmapheresis, and steroid-sparing drugs such as azathioprine. Recent options have included even more aggressive treatment with cyclophosphamide, the anti–pre-B-lymphocyte monoclonal antibody rituximab, or monoclonal antibodies such as efalizumab or natalizumab, which are presently employed for other inflammatory disorders.

Glucocorticoids and Associated Drugs

Glucocorticoids and adrenocorticotropic hormone (ACTH) act as anti-inflammatory mediators, suppressing immune responses and having endocrine and neuromodulatory properties.[9] It is generally thought that steroids act on neurotransmitters such as γ-aminobutyric acid (GABA) and glutamate and thus inhibit seizures, but the exact therapeutic mechanism remains unknown.[10] Steroid hormones have been shown to have an effect on membrane stabilization and neuronal excitability in the mammalian brain.[11] Some of the changes seen in neuroactive steroids appear to be mediated via the GABA A receptor function that acts to modulate neuronal excitability via inhibitory and excitatory input, thus altering seizure susceptibility.[12]

ACTH is used as therapy for diverse neurologic disorders. ACTH promotes the release of adrenal steroids (glucocorticoids), and most ACTH effects on the CNS have been attributed to activation of glucocorticoid receptors. However, in several human disorders, ACTH has therapeutic actions that differ qualitatively or quantitatively from those of steroids. ACTH may directly influence limbic neurons by reducing the expression of corticotropin-releasing hormone (CRH) in amygdala neurons and by activating melanocortin receptors.[13] This supports that steroid-independent actions of ACTH may account for some of its established clinical effects on the CNS. It is generally accepted that ACTH is useful for the treatment of infantile spasms or West syndrome. The practice parameter of the American Academy of Neurology and the Child Neurology Society reported that ACTH is probably effective for the short-term treatment of infantile spasms.[14] In addition, ACTH has been reported as effective for patients with intractable epilepsy other than West syndrome.[15] Thus, ACTH and glucocorticoids have been successfully used in the treatment of some types of epilepsy, including Lennox-Gastaut syndrome, myoclonic seizures, Parry Romberg syndrome, and West syndrome.[16] Steroids have been found to be of some benefit in VGKC complex and NMDAR-antibody encephalitis for seizure control in children and for reduction of cognitive deficits.[17] There was also a case report in 2011 of a 2-year-old girl with early-onset epileptic encephalopathy, epileptic spasms, with elevated level of CSF neopterin, oligoclonal bands, and elevated level of VGKC complex antibodies who demonstrated a partial response to prednisolone administered orally at 40 mg daily.[17]

Methylprednisolone is a synthetic steroid of intermediate activity with poor mineralocorticoid action. Methylprednisolone inhibits phospholipase A2 activity and prostaglandin synthesis, thus dampening the inflammatory cytokine cascade, inhibiting the action of T cells, and decreasing the extravasation of immune cells into the CNS. It facilitates the apoptosis of activated immune cells and indirectly decreases the cytotoxic effects of nitric oxide and tumor necrosis factor α.[18] The mechanism by which methylprednisolone controls seizures is not known but may be related to inhibition of the CRH peptide gene. CRH itself has been related to eliciting epileptic seizures and its inhibition could be a mechanism of steroid action.[13] The effect of methylprednisolone was assessed in 14 children with drug-resistant epilepsy.[19] Decreased seizure frequency ($\geq$50%) or interruption of SE was observed in most subjects, regardless of the underlying pathology.

The antibiotics minocycline and tetracycline have also shown anti-inflammatory effects with inhibition of apoptosis by attenuating tumor necrosis factor α and downregulation of proinflammatory cytokines.[20] Minocycline also has anti-inflammatory actions by inhibiting microglial activation and transmigration of T lymphocytes. These treatments offer some degree of anticonvulsant effect and reduce the risk of epilepsy in patients with arteriovenous malformations.[20,21]

Intravenous Immunoglobulin

IVIg is a purified blood product pooled from more than 1000 human blood donors. It is composed mainly of immunoglobulin G (IgG) (95%) and the remainder is IgA with negligible concentrations of IgM.[22] It has multiple mechanisms of action, though no single mode has been identified as the primary one. The mechanisms can be broadly categorized into immunomodulatory and neuromodulating effects. Despite numerous studies demonstrating efficacy in autoimmune disease, the precise mode of action of IVIg remains unclear. IgG can exert both proinflammatory and anti-inflammatory activities, depending on its