Epilepsy and the Immune System

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Objective: To discuss evidence that immune mechanisms are involved in the pathogenesis of some forms of epilepsy.

Data Sources: Computerized data sources and published indexes and articles.

Study Selection: Published reports showing disorders of the immune system in patients with epilepsy and in animals with experimental epilepsy.

Data Synthesis: Rasmussen encephalitis is an example of an autoimmune disorder of the central nervous system. Serum samples of patients with this disease contain antibodies to the glutamate receptor GluR3, and immunization of animals with GluR3 induces a disorder resembling the human disease. There are still few data to prove that immune mechanisms are involved in the pathogenesis of intractable childhood epilepsies other than Rasmussen encephalitis. Epilepsy is more common in patients with systemic lupus erythematosus who have antiphospholipid antibodies, and it is possible that these antibodies can lead to immune-mediated cortical damage. Immune defects in patients with epilepsy may occur as a consequence of long-term antiepileptic treatment or may represent a genetic coupling to the convulsive disorder.

Conclusion: The finding of an immunological basis may offer new modalities for the treatment of selected cases of intractable partial epilepsies.

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The finding of immune system activation in patients with a seizure disorder has lead to the suggestion that immune mechanisms may play a role in the pathogenesis of some forms of epilepsy.¹ For a long time, such theories lacked an experimental basis. The results of recent studies, especially in patients with Rasmussen encephalitis, have given new information about the possible relation between epileptic disorders and the immune system.

RASMUSSEN ENCEPHALITIS—AN AUTOIMMUNE DISORDER?

The clinical setting in Rasmussen encephalitis is an apparently healthy child or young adult developing focal seizures that initially appear to be benign, but that gradually develop into epilepsia partialis continua with hemiparesis and mental retardation. A neuropathological examination reveals the typical picture of encephalitis with perivascular lymphocyte cuffs and scattered microglial nodules.² Rogers and coworkers³ demonstrated in 1994 that immunization of rabbits with the glutamate receptor GluR3 produces a condition resembling Rasmussen encephalitis. They also showed that serum samples of patients with this disease indeed contain antibodies to GluR3 and postulated that Rasmussen encephalitis is an autoimmune disorder.³

To establish that a disease has an autoimmune etiology, Witebsky postulates require that an autoimmune response be recognized in the form of an autoantibody or cell-mediated immunity, that the corresponding antigen be identified, and that an analogous autoimmune response be induced in experimental animals. Finally, the immunized animals must develop a similar disease.⁴

The most straightforward evidence for an autoimmune etiology of a disease is to reproduce it in a normal recipient by direct transfer of autoantibodies or sensitized cells. This is seen as nature’s own experiment in neonatal myasthenia gravis, where placental transfer of maternal IgG anti–acetylcholine receptor anti-
bodies produces muscular weakness in the newborn. However, the blood-brain barrier represents an impediment for antibodies to reach target antigens in the central nervous system. Opportunities for direct transfer of autoimmune central nervous system disease are, therefore, limited.

The classic strategy for documenting an autoimmune etiology has been to identify and isolate the offending antigen and reproduce the essential features of the disease by experimental immunization. This has been accomplished with Rasmussen encephalitis. In raising antibodies to glutamate receptors, Rogers et al demonstrated that 2 animals immunized with GluR3 developed behavior typical of seizures and histopathological features mimicking Rasmussen encephalitis. This observation has since been confirmed in other species. 

Additional support that the autoantibodies are pathogenic comes from the demonstration that IgG from rabbit antiserum to GluR3 binds to and activates a subpopulation of fetal murine cortical neurons in culture and that this binding could be blocked by a competitive antagonist, CNQX.

The experimental disease in these animals mirrors several features of the human disease, such as the epileptic seizures, the histopathological findings, and the selectivity of the immune response to GluR3. It differs, however, from Rasmussen encephalitis in humans in that the latter is unilateral while the experimental disease involves both hemispheres.

The neuronal cell death observed in vitro appears not to be caused by excitotoxicity. IgG antibodies to GluR3 isolated from immunized animals (both ill and healthy) promote death of cultured cortical cells by a complement-dependent mechanism. IgG and complement factors of the membrane attack complex were found on neurons and their processes in the cortex of brains from patients with Rasmussen encephalitis. Antibodies seem, therefore, to gain access to the central nervous system and trigger complement-mediated neuronal damage. This process may be of special importance in the initial, active phase of the disease.

Genetic and species differences may exist, as Levite et al recently reported that murine GluR3 antibodies can mimic excess glutamate effect and induce neuronal death via activation of the receptor ion channel, apparently independent of complement.

There is additional circumstantial evidence that autoimmune mechanisms operate in Rasmussen encephalitis. Li et al have demonstrated restricted T-lymphocyte populations in the brains of patients with Rasmussen encephalitis. Removal of antibodies by plasma exchange transiently reduces the seizure frequency and improves the neurologic function as the serum concentrations of GluR3 antibodies decrease. As antibodies to GluR3 are found in serum samples from immunized animals without apparent disease, a focal or a general disruption of the blood-brain barrier is essential for serum antibodies to reach the brain.

The finding of an immunological background for an intractable epilepsy offers new modalities for treatment. For example, Rogers et al demonstrated the effect, albeit transient, of plasma exchange. This has since been confirmed by other groups. Corticosteroids also have some effect. Surprisingly, intraventricular infusion of interferon alfa reduced the seizure frequency dramatically in a child with intractable Rasmussen encephalitis. This, however, may relate to the demonstration that GluR3 antibodies exhibit greater immunoreactivity toward the interferon alfa receptor than toward GluR3.

These new data on Rasmussen encephalitis confirm that immune factors may be central in the pathogenesis of an epileptic disorder and may lead to an increased understanding of the basis of other seizure disorders with immunological concomitants.

**EPILEPSY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)**

Between 10% and 20% of patients with SLE develop epileptic seizures at some stage of their disease. This is nearly 8 times the prevalence of epilepsy in the general population; epilepsy is, therefore, much more common in patients with SLE than would be expected. Between 5% and 10% have onset of seizures several years before the clinical onset of SLE. This may mean that long-term treatment with antiepileptic drugs may precipitate SLE, or that epilepsy and SLE occur together as manifestations of a genetically determined predisposition. According to Mackworth-Young and Hughes, epilepsy developing in patients before the other manifestations of SLE differs from that developing after the other manifestations of SLE. Epileptic seizures occurring before the onset of other manifestations of SLE were more often primary generalized, but seizures that occurred after the clinical onset of SLE were either focal or generalized- tonic.

Seizures may occur in patients with SLE based on immune-mediated neuronal damage, because of thrombotic events in cortical blood vessels, or they may be secondary to hypertensive encephalopathy or renal failure. Antibodies to transmitter receptors such as GluR3 have never been convincingly demonstrated in patients with SLE. Epilepsy in patients with SLE is significantly associated with antiphospholipid antibodies (aPLs). Chapman et al reported recently that purified IgG containing aPLs depolarized synaptoneurosomes from rat brainstem and suggested this as an additional mechanism in nonthromboembolic central nervous system manifestations.

Patients with aPLs are at risk of thromboembolic manifestations, intrauterine fetal loss, and thrombocytopenia (antiphospholipid syndrome). Such antibodies are commonly found in serum samples of patients with SLE and are generally heterogeneous, and the different specificities may play causal roles in different clinical manifestations. For example, anti-β2-glycoprotein I antibodies may have a direct pathogenic role in thrombosis. They recognize a β2-glycoprotein I structure on cellular structures and are also significantly elevated in patients with epilepsy. IgG antibodies to cardiolipin have been found in 30% to 60% of unselected patients with SLE. Liou et al found that epilepsy was 3.7 times as frequent among patients with SLE who had antibodies to cardiolipin than among patients with SLE who did not have antibodies to cardiolipin.
Using magnetic resonance imaging and spectroscopy, Sabet-Arman and coworkers\(^24\) found that epilepsy (and stroke) was more common in patients with SLE and aPLs and suggested that these antibodies exacerbate SLE, resulting in increased thrombotic and nonthrombotic brain injuries. Angelini and coworkers\(^25\) studied 23 children with partial epileptic seizures and no clinical or serological evidence of SLE. None of them had magnetic resonance imaging evidence of focal ischemic lesions, but 3 of them, all with frontal lobe epilepsies, had aPLs. These researchers\(^25\) speculated that the antibodies could lead to immune-mediated damage, which could be a pathogenic mechanism for partial epilepsy.

**OTHER CHILDHOOD EPILEPSIES**

There are few data that indicate that immune mechanisms are involved in the pathogenesis of intractable childhood epilepsies other than Rasmussen encephalitis. Most interest has been focused on infantile spasms (West syndrome) and the Lennox-Gastaut syndrome. These are heterogeneous conditions with uncertain pathophysiological characteristics and can be precipitated by various causes. Corticotropin and corticosteroids are widely used in their treatment, and some researchers\(^25\) speculated that the antibodies could lead to immune-mediated damage, which could be a pathogenic mechanism for partial epilepsy.

**IMMUNOGLOBULIN TREATMENT IN PATIENTS WITH EPILEPSY**

In 1977, Pechadre et al\(^30\) reported that children with epilepsy who were treated with intramuscular injections of immunoglobulin for recurrent upper respiratory tract infections had a decrease in the frequency and severity of their seizures. This has been supported by several reports, but only one has been double-blind and placebo-controlled. That study\(^31\) gave a positive trend in favor of intravenous immunoglobulin treatment, but the difference was not statistically significant.

A direct effect of immunoglobulin on the brain is possible only if the blood-brain barrier is abnormal. It has been demonstrated in experimental animals that the blood-brain barrier opens transitorily during seizures. Since the effect of immunoglobulin treatment is seen only with intact IgG and not with F(ab')\(_2\) fragments, the effect requires an intact Fc part of the molecule.\(^32\)

**IMMUNOLOGICAL CONSEQUENCES OF LONG-TERM TREATMENT WITH ANTIEPILEPTIC DRUGS**

Phenytoin treatment may induce a reversible IgA deficiency involving serum and secretory IgA.\(^1\) This has been demonstrated by monitoring IgA levels before and during initiation of phenytoin treatment and measuring IgA levels after withdrawal of the drug.

Carbamazepine may also induce a reduction of serum IgA levels, but never as low as with phenytoin. Another antiepileptic drug, zonisamide, has recently been reported to induce IgA and IgG2 deficiency.\(^33\)

Some cases of epilepsy are, however, associated with primary IgA deficiency. This is the most common immune defect in humans. Most subjects with primary IgA deficiency are healthy, but patients with selective IgA deficiency often have an increased susceptibility to upper respiratory tract infections.\(^34\) Seizures may also occur in patients with ataxia telangiectasia, which is associated with IgA (and occasionally IgG) deficiency. While primary IgA deficiency is associated with the haplotype HLA–A1–B8 and DR3, patients with drug-induced defect are haplotype HLA–A2. The mechanisms responsible for depression of humoral and cellular immunity by phenytoin are unknown, but studies in mice indicate a CD8\(^+\) cell–mediated inhibitory effect.\(^35\)

**REFERENCES**


