

Reactions of the immune system in epilepsy

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ABSTRACT

Epilepsy may present as a symptom of many neurological disorders and often an etiological explanation cannot be identified. There is growing evidence that autoimmune mechanisms might have a role in some patients. The evidence for immunological mechanisms in epilepsy can be examined within the following three main areas: the childhood epilepsy syndromes, epilepsy associated with other immunologically mediated diseases, and the more common unselected groups of patients with epilepsy. Autoimmunity was recently suspected to be involved in the pathology of certain human epilepsies. This includes numerous reports of the detection of theoretically relevant serum autoantibodies, experimental data showing that antibodies can be epileptogenic, and a response of some epilepsy syndromes to immunomodulation. The high prevalence of epilepsies in specific immune diseases suggests that immune system may play a role in the pathogenesis of epilepsy or might be associated with it. There is some evidence that immune mechanisms play a role in the pathogenesis of some epilepsy syndromes.

Key words: autoimmunity, autoantibodies, epilepsy

Epilepsy is one of the most common neurological disorders, but in the majority of cases the cause of the seizures is unknown. There is an association between epilepsy and certain autoimmune diseases such as systemic lupus erythematosus (SLE), antiphospholipid syndrome and stiff person syndrome. The autoimmune nature

of some epilepsies came from the presence of antibodies to a major excitatory neurotransmitter in the CNS. For a disorder to be defined as autoimmune, ideally it should fulfil a number of criteria; the simple presence of circulating antibodies is not enough, as such antibodies can be generated during tissue destruction. Although a number of different antibodies have

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been detected in the sera of patients with epilepsy, it is probably only those antibodies directed against membrane proteins such as ion channels and receptor proteins, which have the potential to be pathogenic. An autoimmune aetiology may be suggested by a family history of autoimmunity and an HLA association; the presence of antibodies to a defined cell-surface antigen relevant to the disease process; a clinical response to specific immunomodulatory therapy; and transmission of the disease to experimental animals by passive transfer with immunoglobulins (1-3).

Some cases of epilepsy are, however, associated with primary IgA (and occasionally IgG) deficiency. The IgA deficiency state was apparently reversible, since normalization of serum levels occurred after withdrawal of phenytoin. Mean serum IgG was lower in epileptic patients who had taken phenytoin for less than 1 year and had a low IgA, than in patients who had taken phenytoin for 19 years or more. Recently, nervous system disorders have been shown to be associated with autoantibodies. It is well recognized that patients producing one autoantibody have an increased likelihood of having other autoantibodies. It is possible that the epilepsy represents the first manifestation of the syndrome itself. The antibodies themselves may be directly implicated in causing epilepsy. (4-7).

Increased prevalence of anticardiolipin antibodies (aCL) and antinuclear antibodies (ANA) and changes in serum immunoglobulin concentrations have been reported in patients with epilepsy. An elevated percentage of IgG anticardiolipin (aCL)-positive patients in a cohort of unselected epilepsy patients compared to control sera. A pathogenic role for these antibodies cannot be excluded. Possible mechanisms might be microinfarcts secondary to ischemic events or immune-mediated processes directed against endothelial or neuronal cells. There is a relationship between epilepsy and aCL. The prevalence of IgM aCL antibodies was significantly higher than that of IgG in all epilepsy subgroups. These results suggest that immune dysregulation may be associated with epilepsy (8-10).

An increased incidence of antiphospholipid antibodies (aPL) has been reported in consecutive patients with epilepsy of unexplained cause without the antiphospholipid syndrome or SLE. Lupus anticoagulant (LA) was also found in pa-

tients with epilepsy admitted to hospital. Increased prevalence of aCL, anti- β 2 glycoprotein I (anti- β 2 GPI) and anti-protrombin antibodies in young patients with epilepsy, and antinuclear antibodies (ANA) and changes in serum immunoglobulin concentrations have been reported in patients with epilepsy. Antinuclear antibody was also significantly more prevalent in localization related epilepsy and in newly diagnosed epileptics. aCL were associated with long duration of epilepsy and poor seizure control. Low serum concentrations were more common in patients with epilepsy, particularly those using phenytoin. Unspecific antimitochondrial antibodies (AMA) were more common among the epilepsy patients. IgA class antigliadin antibodies (AGAbA) were associated with primary generalized epilepsy (11-14).

Between 1% 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 (15).

Epilepsy developing in patients before the older manifestations of SLE differs from that developing after the other manifestations of SLE. Epilepsy in patients with SLE is significantly associated with aPL. Epilepsy (and stroke) was more common in patients with SLE and aPL and suggested that these antibodies exacerbate SLE, resulting in increased thrombotic and non-thrombotic brain injuries. Antibodies could lead to immune-mediated damage, which could be a pathogenic mechanism for partial epilepsy.

The presence of autoantibodies in the serum was not statistically dependent on the type of epilepsy, the kind of antiepileptic drug, or the age or sex of the patients. Large prospective studies are needed to define the role of the aCL and ANA in pathophysiology of epilepsy. A relationship between epilepsy and aCL and ANA suggesting a possible role of such antibodies in pathophysiology of epilepsy. The presence of antiphospholipid (APL) and anti-nuclear antibody (ANA) in some patients with epilepsy or

new-onset seizures was regarded initially as a consequence of anti-epileptic drugs (13).

A recent study describes that a newly diagnosed subgroup of patients not on antiepileptic drugs were found to have a higher prevalence of IgG anticardiolipin antibodies and that this was higher in localization-related epileptic patients in comparison to those with generalized epilepsy. There were no consistent associations between autoantibodies and specific antiepileptic medications. Large prospective studies are needed to define the role of the aCL antibodies and ANA in pathophysiology of epilepsy (14).

Antiphospholipid antibodies were also found to be highly prevalent in children with epilepsy and especially in those with early-onset and high-frequency seizures (12).

The increased prevalence of autoantibodies in patients with epilepsy has been traditionally regarded to be a consequence of antiepileptic drugs. The prevalence of autoantibodies is greater in patients with epilepsy, including newly diagnosed seizure disorder. The increased prevalence of autoantibodies is more strongly associated with epilepsy than with antiepileptic drugs, perhaps indicating that immune dysregulation may be commonly associated with epilepsy (14).

Rasmussen's encephalitis (RE), a rare progressive disorder of unilateral brain dysfunction, is characterized by intractable focal seizure and inflammatory histopathology with perivascular lymphocytes cuffing and scattered microglial nodules.

Antibodies against GluR3 have been observed in some patients with RE (16) but also in focal epilepsy (17).

The antibodies could activate cortical neurons and induce cytotoxicity (18-20)

There are patients with RE without antibodies to GluR3 (21).

In patients with Landau-Kleffner syndrome, characterized by aphasia, behavioral problems, and seizures, were observed autoantibodies directed against brain endothelial cells and neuronal nuclear proteins; intravenous immunoglobulins (IVIg) may have a beneficial effect in this syndrome (22-26).

Although West's syndrome and Lennox-Gastaut syndromes have different clinical phenotypes, both respond to IVIg therapy (24).

Hashimoto's encephalopathy is often associated with seizures, confusion, and hallucina-

tions. Antithyroid antibodies are always present. Corticosteroids represent the therapy. The syndrome may be explained by a common brain/thyroid antibody (27-29).

Patients with paraneoplastic encephalomyelitis and focal encephalitis may present seizures, which are usually associated with small cell lung cancer (SCLC) and other cancers. Patients with SCLC and these syndromes usually have anti-Hu antibodies in serum and CLS (30).

There were identified N-methyl-aspartate receptor antibodies in patients with paraneoplastic encephalitis (31-33) or potassium channel antibodies (34).

In one study of unselected patients with epilepsy, 6.25% had increased serum antiganglioside (anti-GM1) antibodies. Gangliosides are important components of synaptic membranes and anti-GM1 have been shown to be epileptogenic in experimental animal models (35).

The amount of serum antiglutamate receptor (anti-GluR1) antibodies correlated positively with the duration of epilepsy and seizure frequency (36).

Over the last few years, antibodies to intracellular proteins such as glutamic acid decarboxylase (GAD) or specific ribonuclear proteins, have been detected in the serum and cerebrospinal fluid of patients with certain forms of epilepsy. Some of these patients respond to immunotherapies, suggesting that the antibodies are pathogenic. Antiglutamic acid decarboxylase (anti-GAD) antibodies in serum and cerebrospinal fluid (CSF) have been reported in patients with drug-resistant epilepsy. Some patients with drug-resistant localization-related epilepsy have evidence of GAD autoimmunity (14, 36).

Ion channels represent good candidate antigens for autoimmune epilepsy. The possibility that some epilepsy syndromes may be secondary to an ion channel disorder requires further research (37-39).

The presence of autoantibodies to brain endothelial cells suggesting that autoimmunity may be important in the pathogenesis of epilepsy (40,41).

Antibodies to GAD have also been found in patients with drug-resistant temporal lobe epilepsy, as well as in other neurological disorders such as stiff person syndrome and cerebellar ataxia, but the relevance of these antibodies is

still to be determined. The presence of autoantibodies to voltage-gated potassium channels and glutamic acid decarboxylase suggests that the immune system may contribute to certain forms of epilepsy or seizure-associated disorders. Although a number of different antibodies have been detected in the sera of patients with epilepsy, it is probably only those antibodies directed against membrane proteins such as ion channels and receptor proteins, which have the potential to be pathogenic.

Some channelopathies are also related to epilepsy.

The sodium channelopathies, include familial generalized epilepsies with febrile seizures. The nicotinic acetylcholine receptor channelopathies cause the autosomal dominant nocturnal frontal lobe epilepsy syndrome (ADNFL) (42).

Antibodies to subtypes of the Shaker family of voltage-gated potassium channels (VGKC) have been detected in patients with a variety of seizure-associated conditions.

Voltage gated potassium channelopathies are responsible for benign familial neonatal convulsions and episodic ataxia type I.

Some causes of limbic encephalitis are also with the presence of antibodies to (VGKC) (43-45).

The possible role of autoantibodies in epilepsy was recently pursued. A statistically significant difference was found only in two assays. Increased titers for anti-voltage gated potassium channels were found in 11% of patients compared to only 0.5% of controls. High

levels of anti-glutamic acid decarboxylase were detected in 3.6% of epilepsy patients but in none of the controls (6).

Autoantibodies against glutamate receptor β 2-subunit were detected in some patients with reversible autoimmune limbic encephalitis (46).

In patients with chronic forms of epilepsy partialis continua were identified antibodies to NMDA receptors (47).

A summary of antibodies reported in epileptic patients is presented in table I. (16)

Patients with Alzheimer's disease develop frequently epileptic seizures. It is well known that in Alzheimer's disease there is an inflammatory neurotoxic process (48, 49).

In patients with multiple sclerosis epileptic seizures are often partial epilepsies with focal onset with or without generalization. Seizures may be caused by cortical or subcortical lesions and the surrounding edema (50, 51). □

CONCLUSION

It is difficult to confirm or refute scientifically that autoimmune attack and circulating autoantibodies are the cause of the epilepsy syndrome. The antibodies may simply be an epiphenomenon of the vascular damage present in epilepsy. The evidence that serum autoantibodies may associate with some forms of epilepsy is beginning to strengthen. Currently there are no autoantibodies found specifically in epilepsy.

Disorder	Antibody target	Immunotherapy
Rasmussen's encephalitis	GluR ₃	Plasma exchange or immunoadsorption
Epilepsia partialis		
Drug resistant		
Systemic lupus erythematosus	Phospholipid	Not reported
Primary generalized before	Cardiolipin	
SLE onset	β ₂ -glycoprotein I	
Focal or generalize-tonic		
During SLE		
Therapy-resistant localization related epilepsy	Cardiolipin, nuclear, β ₂ -glycoprotein I GAD	Not reported
Newly diagnosed seizure	cardiolipin, nuclear, β ₂ -glycoprotein I	Not reported
Generalised epilepsy syndromes	Cardiolipin	Not reported
West's syndrome		Corticosteroids intravenous therapy
Cryptogenic Lennox- Gastaut	Haemocyanin	Intravenous therapy
Completely controlled epilepsy	GAD	Not reported

TABLE 1. Neurological diseases characterized by epilepsy and autoantibodies

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