Epilepsy: an autoimmune disease?

Epilepsy may present as a symptom of many neurological disorders and often an aetiological explanation cannot be identified. There is growing evidence that autoimmune mechanisms might have a role in some patients. 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 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.

**Childhood epilepsy syndromes**

**RASMUSSEN’S ENCEPHALITIS**

Rasmussen’s encephalitis is a rare progressive disorder of unilateral brain dysfunction, focal seizures, and inflammatory histopathology. It usually presents in middle childhood with intractable seizures and progressive neurological deficits culminating in hemiparesis. The seizures are often resistant to antiepileptic drugs. Treatment with corticosteroids, intravenous immunoglobulins (IVIg), or plasmapheresis has been reported to be beneficial in some. However, no blinded placebo controlled trials have been undertaken to confirm the efficacy of such treatments. In many children with Rasmussen’s encephalitis control of their epilepsy may only be obtained by hemispherectomy.

The serendipitous finding that rabbits immunised with a fusion protein of glutamate receptor (GluR) 3 (but not GluR 1, 2, 5, or 6) developed seizures and histopathological changes that mimicked Rasmussen’s encephalitis initiated the Rasmussen’s encephalitis autoimmune hypothesis. However, mice immunised with GluR3, which developed high concentrations of anti-GluR3 antibodies and brain pathology reminiscent of the disease did not go on to develop epilepsy. Antibodies against GluR3 (and GluR2 at low concentrations) have been detected in the serum of some patients with Rasmussen’s encephalitis; however, confirmatory reports from other groups and studies determining the frequency of these antibodies in consecutive series of patients with the disease are notable for their absence. Similarly, a systematic search for other autoantibodies in patients with Rasmussen’s encephalitis has not been performed. A pathogenic role for these anti-GluR3 antibodies has been postulated with experimental data indicating their ability to activate cortical neurons and induce complement dependent and independent cytotoxicity.

**LANDAU-KLEFFNER SYNDROME**

This childhood syndrome, first described in 1957, is characterised by aphasia, behavioural problems, and seizures (often of partial motor in type). The EEG recorded during sleep is diagnostic and shows focal and multifocal spikes and spike wave discharges predominantly in the temporal and parietal regions. In many cases onset can be temporally related to a previous infection. Autoantibodies directed against brain endothelial cells and neuronal nuclear proteins have been reported. Case reports of successful treatment with IVIg treatment exist, although this is not an invariable finding.

**WEST’S SYNDROME (INFANTILE SPASMS) AND LENNOX-GASTAUT SYNDROME**

Although both West’s syndrome and Lennox-Gastaut syndrome have very different clinical phenotypes, both syndromes have been reported to respond well to IVIg therapy. Among the numerous unblinded studies published most have reported a positive response to treatment. Van Engelen et al have reviewed the use of IVIg treatment in childhood epilepsies and concluded that although there was no formal evidence of efficacy due to lack of controlled trials, some patients benefited greatly from this treatment. In one series of children with West’s syndrome 33% showed a positive response, with a rapid and permanent resolution in 21% of those treated. One placebo controlled (single blind crossover) study of 10 patients with Lennox-Gastaut syndrome reported a reduction in seizures in 20% of patients.

Reports of an activated but functionally impaired immune system, increased serum immunoglobulins and a HLA DR5 association in Lennox-Gastaut syndrome further supports immunological involvement.

**Epilepsy associated with autoimmune diseases**

Seizures occur in association with some antibody mediated autoimmune diseases affecting the CNS—namely, systemic lupus erythematosus, stiff man syndrome, and Hashimoto’s encephalopathy.

**SYSTEMIC LUPUS ERYTHEMATOSUS**

The incidence of epilepsy in patients with systemic lupus erythematosus is raised to between 5.4%-10%. The seizures tend to respond to anticonvulsant drugs, and can take any form, with various EEG abnormalities reported. Epilepsy is particularly common in association with the presence of anticardiolipin antibodies, especially in high titre; the lupus anticoagulant; and the
antiphospholipid syndrome. However, these findings are not universal. Brain MRI tends to be normal in those with epilepsy alone but abnormal in those with clinical features of the antiphospholipid syndrome. In another study of patients with systemic lupus erythematosus admitted to hospital, an association of epilepsy with stroke (clinical or on imaging) was reported.

The role of these antiphospholipid antibodies in causing epilepsy has been open to debate. Possible mechanisms include a direct effect of antibodies causing seizures, the trapping of immune complexes within vessels resulting in seizures, and antiphospholipid antibodies causing microvascular lesions. The direct effect of antibodies in provoking epilepsy is supported by studies showing that antibrain antibodies can directly cause seizures; that serum from patients with systemic lupus erythematosus with epilepsy and antiphospholip antibodies can inhibit Cl currents through the GABA receptor complex; and that the presence of antiphospholip antibodies in the CSF is longitudinally associated with clinical symptoms. The finding that antiphospholip antibodies react directly with CNS tissue does not rule out secondary damage as a mechanism for seizures. Ischaemia induced seizures secondary to a hypercoagulable state is backed by reports of abnormal imaging and an association with stroke in some groups of patients. Even in the presence of normal imaging postmortem has disclosed cerebral microinfarctions. Many patients with systemic lupus erythematosus and epilepsy have no detectable antiphospholip antibodies in the serum or the CSF, so other processes such as infection, metabolic abnormalities, or as yet unidentified antibodies could be responsible. It is of interest that anti-GM1 antibodies, reported to be epileptogenic, have been identified in 15.5% of patients with systemic lupus erythematosus.

STIFF MAN SYNDROME

The stiff man syndrome is a rare CNS disease characterised by progressive rigidity and painful spasms of the muscles. Serum antibodies to glutamic acid decarboxylase (GAD), the cytoplasmic enzyme that catalyses the conversion of glutamate to GABA, have been detected in 63% of patients with stiff man syndrome. This enzyme is concentrated within GABA-ergic nerve terminals and pancreatic β cells. Serum containing such anti-GAD antibodies binds to pancreatic β cells in 95% of patients, whereas CSF antibodies are detectable in 80% of patients. “Antibody positive” stiff man syndrome is associated with other organ specific autoantibodies and autoimmune diseases, most often insulin dependent diabetes. Reports suggest an increased prevalence of epilepsy in stiff man syndrome at around 12%. Interestingly, in a study of 33 patients with the syndrome, all those with epilepsy had anti-GAD antibodies. Theoretically, seizures as well as the other neurological manifestations of stiff man syndrome can be explained by interference with the inhibitory neurotransmitter GABA. Reports of a clinical response to GABA-ergic agonists such as benzodiazepines, sodium valproate, and baclofen, and in some cases, to corticosteroids and plasmapheresis, suggest a possible pathogenic role for these anti-GAD antibodies. The few cases that have come for postmortem examination have shown little in the way of pathological changes suggesting a functional disturbance as could occur by a direct antibody effect.

HASHIMOTO’S ENCEPHALOPATHY

This rare encephalopathy is often associated with seizures, confusion, and hallucinations. Antithyroid antibodies are invariably present although thyroid function can be normal. Its autoimmune nature is supported by the presence of intrathecal antibodies and a response to corticosteroids. Within a series of seven such patients one had complex partial epilepsy and recurrent status epilepticus without other clinical features. The CSF may contain increased protein concentrations, a pleocytosis, and oligoclonal bands, and MRI may be normal although atrophy, white matter lesions, and ischaemic changes have all been reported. Cerebral oedema, immune complex cerebral vasculitis, acute disseminated encephalomyelitis, and a direct antibody effect possibly due to a common “brain/thyroid” antigen are possible mechanisms to explain the syndrome.

Antibodies associated with unselected patients with epilepsy

Raised concentrations of serum antibodies, which recognise brain antigens, have been detected in groups of patients with isolated epilepsy. A dramatic response to IV Ig has been reported in a group of children with refractory seizures. In addition more specific antibodies have been detected in such patients with epilepsy alone.

ANTIPHOSPHOLIPID AND ANTINUCLEAR ANTIBODIES

An increased incidence of antiphospholipid antibodies has been reported in consecutive patients with epilepsy of unexplained cause without the antiphospholipid syndrome or systemic lupus erythematosus. One series found lupus anticoagulant in 6% of patients with epilepsy admitted to hospital, all of whom were men in their sixth to eighth decade. In patients seen at an epilepsy centre there was an increase in the incidence of antiphospholip IgG and antinuclear antibody positivity, a sixfold and 2.5-fold risk respectively. All types of epilepsy were seen and the seizures were generally well controlled with antiepileptic drugs. In a series of children with cryptogenic partial epilepsy 13% had high titres of antiphospholip antibodies, all with frontal lobe seizures and normal imaging, whereas none were found in the control groups. One case had refractory seizures, which resolved with the temporary addition of corticosteroids. There are possible explanations for this reported increase in the occurrence of antibodies normally found in systemic lupus erythematosus and the antiphospholipid syndrome. Firstly as already discussed, the antibodies themselves may be directly implicated in causing epilepsy. Secondly, it is possible that the epilepsy represents the first manifestation of the syndrome itself. An eightfold increase in the expected incidence of idiopathic epilepsy (petit mal and grand mal) was noted in the patients who subsequently developed systemic lupus erythematosus with a mean interval of 15.4 years. Although antiphospholipid antibodies were positive in 67% of patients at the time of onset of systemic lupus erythematosus symptoms it is not known whether they were present earlier on. Thirdly there is some evidence that antiepileptic drugs may induce systemic lupus erythematosus, antinuclear antibodies, or antiphospholipid antibodies, with reversal with drug withdrawal. Antiepileptic treatment was not withdrawn in the patients whose epilepsy predated onset of systemic lupus erythematosus to investigate this possibility. Against the theory of autoantibodies induced by anticonvulsant drugs are the findings that no significant difference existed in the drug regimes used in a group of patients that were antibody positive compared to the negative group; that two of four patients with epilepsy and the lupus anticoagulant developed the antibody before starting antiepileptic drugs; and that reversibility does not always occur with drug withdrawal. In those patients whose antibodies and disease resolves with drug withdrawal there has been no
Summary of the epilepsies with possible immune mediated mechanisms

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Putative antibody/target</th>
<th>Immunomodulatory treatment response</th>
<th>Epileptogenic effect of antibodies</th>
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<tr>
<td>Rasmussen's encephalitis</td>
<td>GluR3</td>
<td>Corticosteroids, IVlg, PP</td>
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<td>Landau-Kleffner syndrome</td>
<td>Brain endothelial cells/neuronal nuclear proteins</td>
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<tr>
<td>West's syndrome and Lennox-Gastaut syndrome</td>
<td>PL, CL, LAC</td>
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<td>Stiff man syndrome</td>
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<td>NR</td>
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<tr>
<td>Hashimoto's encephalopathy</td>
<td>?</td>
<td>Syndrome generally</td>
<td>NR</td>
</tr>
<tr>
<td>General epilepsies</td>
<td>CL, PL, ANA, GM1, GluR1, GAD</td>
<td>Positive in one case report</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IVlg, cytotoxic agents</td>
<td>+</td>
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<td></td>
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<td>NR</td>
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</table>

NR=Not reported; PP=plasmapheresis; ANA=antinuclear antibody; LAC=lupus anticoagulant; CL=cardiolipin; PL=phospholipid.

long term follow up to investigate the possibility that they have a predisposition to develop autoimmune disease which antiepileptic drugs unmask.

ANTIGANGLIOSIDE ANTIBODIES

In one study of unselected patients with epilepsy, 6.25% had increased serum anti-GM1 antibodies. All had complex partial epilepsy with secondary generalisation, drug resistance, psychiatric disorders, and normal hippocampi on MRI (the clinical picture was consistent with involvement of temporal and frontal lobe convexitities). Neither anti-GM1 antibodies nor oligoclonal bands were detected in the CSF of the two patients tested. In two patients three to four courses of IVlg were instituted and this resulted in a 3.5-fold and 24-fold reduction in seizure frequency. A further case of anticonvulsant drug resistant epilepsy associated with anti-GM1 reported the responsible IgM antibody as causing Waldenstrom's macroglobulinaemia. In this case the patient who presented with partial motor status had antibody in the CSF but, as in the previously reported patients, a normal MRI. The seizures resolved after institution of aggressive immunosuppressive chemotherapy only, which also resulted in a reduction but not disappearance of the antiglycolipid antibodies. None of the patients in these studies had evidence of a peripheral neuropathy or motor neuron disease and the ganglioside antibodies had different specificities to those found in these peripheral disorders.

Gangliosides are important components of synaptic membranes and anti-GM1 antibodies have been shown to be epileptogenic in experimental animal models. Such antibodies have been reported to increase release of neuronal GABA after depolarisation, possibly exerting a convulsant effect by interfering with kindling or inhibiting the interaction of GABA with synaptic receptors and/or transport sites. Anti-GM1 antibodies in peripheral neuropathies are thought to interfere with conduction by their action on voltage gated Na+ and possibly K+ channels of myelinated nerve fibres; however, this mechanism of action has not been investigated in the CNS.

ANTIGLUTAMATE RECEPTOR ANTIBODIES

Further to the reports of an association between anti-GluR3 antibodies and Rasmussen's encephalitis, serum from 150 patients with refractory epilepsy was tested for antibodies to different subregions of the glutamate receptors 1, 2, 3, and 4. The amount of antibodies to GluR1 and to a lesser extent GluR 3 and 4 were significantly increased in the patients with epilepsy compared with either the neurological or healthy control groups. There were methodological problems with this study and thus these findings need further investigation. The CSF in the serum anti-GluR1 antibody correlated positively with the duration of epilepsy and seizure frequency. This finding may add strength to a report of reduced GluR1 concentrations in the hippocampus and temporal pole cortex of patients with epilepsy with a lesser decrease of GluR4 present in the hippocampus only.

ANTIGLUTAMIC ACID DECARBOXYLASE ANTIBODIES

Anti-GAD antibodies have been reported in a patient with anticonvulsant resistant temporal lobe epilepsy in whom the MRI and CSF were consistent with acute encephalitis but in whom viral screen was negative. The seizures responded to corticosteroids.

Conclusions

It seems likely that serum autoantibodies may be associated with some forms of epilepsy (table). However, epilepsy itself and antiepileptic drugs are reported to alter immune responses and it is not clear which autoantibodies arise as a consequence and which are causative. Furthermore, the mechanisms of action of the putative pathogenic antibodies are not well understood. Immunotherapies seem to have efficacy above standard antiepileptic treatment in some groups of patients. The studies of immunotherapy to date have involved few patients, almost invariably in open labelled designs, mainly due to the rarity of the epilepsy syndromes. Clearly larger placebo controlled trials are needed. Corticosteroid responsiveness does not necessarily indicate immune mediated pathology but could result from a direct inhibitory action on GABA receptors by such treatment. Conversely, irreparable CNS damage resulting from autoimmune mechanisms could result in a lack of response to immunomodulation. Thus predicting the underlying pathogenesis from the response to treatment can be misleading.

It is well recognised that patients producing one autoantibody have an increased likelihood of having other autoantibodies. It is possible, therefore, that as yet undiscovered epilepsy antibodies coexist with irrelevant identified ones. The logic for investigating the same target protein for genetic and autoimmune disease is well illustrated in the peripheral nervous system where mutations and autoantibodies targeted to the muscle acetylcholine receptor cause similar symptoms and signs. The recent identification of mutations involving K+ channels in benign familial neonatal epilepsy, neuronal nicotinic acetylcholine receptor in autosomal dominant nocturnal frontal lobe epilepsy, and Na+ channels in generalised epilepsy with febrile convulsions suggest that autoimmune attack of ion channels could similarly underlie some epileptic disorders. The effects of anticonvulsant drugs, which act on ion channels either to reduce excitatory neurotransmitter release or enhance inhibitory activity, support a role for ion channels in producing epilepsy. In addition, some ion channel drugs (for example 4-aminopyridine, which inhibits K+ channels responsible for terminating the nerve action potential and thus prolongs the activation state) may precipitate seizures. Thus, for many reasons ion channels represent good candidate antigens for autoimmune epilepsy and a more
widespread and systematic search for anti-ion channel autoantibodies is indicated.

The resolution of these issues could help to select the subgroup of patients who are most likely to benefit from immune modulatory treatments in the future and identification of pathogenic autoantibodies may allow early intervention and removal before damage ensues.

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