AUTOIMMUNITY IN EPILEPSY

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SUMMARY

Autoimmunity is a contributory factor in the aetiology of some of the epilepsy syndromes. The central nervous system (CNS), previously considered an immune-privileged site, can also become vulnerable to immunological attack. Certain syndromes remain obscure as to their primary aetiology, such as Rasmussen's encephalitis; despite the systemic presence of a potentially causative antibody, the inflammation remains confined to one hemisphere of the brain. Other epilepsies, termed 'malignant' because they present aggressively at a young age and are often progressive, are not clearly inflammatory in origin, although some do respond to immunomodulatory treatments. The presence of certain antibodies also characterises specific neurological syndromes that may be associated with seizures: their presence does not confirm that they are causative and they could merely be secondary to the primary pathology and/or to the uncontrolled electrical activity in the brain. The field of channelopathies is ever-growing, and dysfunction of specific membrane channels characterises certain epilepsy syndromes and postulates them as potential autoantigenic targets. It is often difficult to confirm or refute scientifically that autoimmune attack and circulating autoantibodies are the cause of the epilepsy syndrome, and further studies including the use of animal models would be necessary in order to investigate this hypothesis thoroughly. The aim of this review is to highlight some of the mechanisms that may be responsible for causing epilepsy as well as emphasising the gaps in our understanding of certain other more obscure areas.

INTRODUCTION

Epilepsy is the most common neurological condition, with an incidence of about 50–70 new cases per 100,000 population per year, with slightly higher incidence rates in developing countries. While most are idiopathic, autoimmunity may play a role in the aetiology of some cases. In some autoimmune conditions, epilepsy coexists at a rate that is higher than that predicted by chance, as for example in myasthenia gravis. The same applies to multiple sclerosis (MS) (in which a CNS inflammatory cascade leads to the breakdown of myelin) and Alzheimer's disease (a neurodegenerative condition, albeit with less evidence of an auto-inflammatory process). In rarer conditions, such as Rasmussen's encephalitis and the malignant epilepsies of childhood, epilepsy is a main feature but the causative agent is dubious. The aim of this review, as in others already in print,[1] is to discuss the evidence supporting the hypothesis that immune mechanisms play a role in the epileptic manifestations associated with some uncommon neurological conditions and whether immunomodulatory treatments have a role to play in the management of epilepsy and the primary underlying pathology.

Epilepsy is characterised by synchronous and excessive propagation of electrical activity in the brain that can be either localised to a specific territory or propagated in an uncontrolled and generalised fashion. Autoimmunity is a process resulting from failure of self-tolerance, in which the body's own immune system attacks itself, as though it were a foreign antigen.[2] Until recently, the CNS was considered to be an immune-privileged organ, invincible in its mechanisms to counteract autoimmunity. The blood–brain barrier was believed to be the architecture that helped maintain this characteristic by its lack of lymphatic drainage, although this is now known to be false.

The immune system recognises foreign antigen and aims to destroy it with minimal damage to self. It facilitates this by:

1. recruiting lymphocytes and antigen-presenting cells to the area of antigen localisation;
2. recognition of antigen by humoral and cellular immunity with B and T-cell involvement and macrophages;
3. amplification of response by various components, e.g. cytokines and the complement system; and
4. phagocytic destruction and cytotoxic mechanisms.

Autoimmune disease is the result of immune attack against self by antibodies and specific effector T cells that recognise self peptides. Sometimes normal T and B-cell response is mounted towards a foreign-peptide/organism, cross-reacting with self antigens by a process of molecular mimicry, as occurs in systemic lupus erythematosus (SLE) and myasthenia gravis. Genetic factors play a role in contributing towards a tendency for autoantibody formation, inherent B-cell hyperreactivity or the predisposition towards an anti-self response (associations with HLA and/or DR types).

THE POLICEMAN OF THE CNS

The blood–brain barrier acts as an efficient boundary between the CNS and blood, and has an important role in immune surveillance. Its protagonists include endothelial cells, smooth muscle cells, perivascular

microglia and astroglial foot processes. Access of systemic immune mediators into the CNS probably takes place by a rolling movement through the microvasculature. Loose binding to the endothelial cells is mediated by the selectin family of adhesion molecules; firmer adhesion takes place by the activity of the integrin molecules. Various other adhesion molecules, such as VCAM-1 (vascular cell adhesion molecule), E-selectin and ICAM-1 (intercellular adhesion molecule), allow the transendothelial passage of other cells. There is an upregulation of these molecules in CNS lesions from MS patients.[3] The unfenestrated endothelial cells and the epithelial cell layer bear specialised tight junctions that maintain the integrity of the blood–brain barrier. The barriers are anatomical and physiological, and are responsible for the different chemical compositions of blood, cerebrospinal fluid (CSF) and brain tissue.

The barrier's integrity is broken down when exposed to inflammation, infection, oxidative stress and neoplasia. This is shown by endothelial cell dysfunction, loss of viability and a decline in trans-endothelial electrical resistance.[4] During an inflammatory process, cytokines and/or oxidative stress promote breakdown of the blood–brain barrier and may mediate cell damage and death in the CNS. Cytokines mediate and orchestrate inflammatory responses in various contexts, for example, in autoimmune disorders, MS and ischaemia. Integration of their effects with those of T cells in promoting or abating inflammation will determine the clinical course, i.e. promoting neurotoxicity or neuroprotection.[5,6] The CNS has been shown to have a potential for regeneration, supporting growth and limiting the spread of damage. It also supplies immune cells to this effect: microglia that promote repair and regrowth, and regulatory T cells that maintain a harmonious system.[7]

THE CNS IMMUNE SYSTEM

Immune privilege is the result of the restriction of major histocompatibility complex (MHC) antigen expression in the CNS to microglia and astroglia, thus promoting these cells to initiate and orchestrate immune responses. Neuronal and myelin antigens are thus protected from T-cell activity, since neurons and oligodendrocytes lack MHC molecules. Myelin in the form of myelin basic protein and proteolipid protein is thus normally sequestered away from lymphocytes.[8] These chemicals may be exposed if there is pathological myelin breakdown leading to phagocytosis by microglial cells, as may occur in the process of inflammation or infection, and by the activation of autoreactive T cells that switch into autoaggressive T cells. Despite the security maintained by the blood–brain barrier, it may allow activated lymphocytes to pass through the endothelial blood–brain barrier and migrate through the brain tissue.[9] This breakdown contributes to the pathophysiology of MS and the animal model of experimental autoimmune encephalomyelitis (EAE). Table 1 highlights the main contributory features taking place during immune reactivity in the CNS, while Table 2 points out the main effector mechanisms.

TABLE 1
Regulation of immune activity in the CNS.

- Microglial and astroglial cells have antigen-presenting capacity.
- Perivascular microglia are fully functional antigen-presenting cells. Central nervous system parenchymal microglia and astroglia have immune regulatory potential.
- Parenchymal microglial cells appear to have more competent antigen-presenting capacity than astrocytes.
- Expression of MHC class II on microglia is upregulated during injury/inflammation.
- Costimulatory molecules such as CD80 and CD86 are important for efficient antigen presentation and are present in lesions in EAE and MS.
- Microglia produce cytokines that are proinflammatory or inhibitory of the immune response. Cytokines may have a paracrine effect to regulate the functional responses of T cells or an autocrine effect to regulate the activity of the microglial cell itself.
- There is evidence of leakage of CNS-derived antigen into the systemic circulation, implying that immune reactivity may also occur at a systemic level.

TABLE 2
CNS immune-mediated injury.

- Neurons and oligodendroglia are the target cell population.
- Humoral-mediated injury via cell-membrane damage secondary to antibody binding to the cell surface, fixation and activation of complement.
- Cell-mediated injury consisting of T cell/macrophage responses and CNS endogenous cells (microglia and astroglia).
- Cytokine mechanisms:
  - CD8 T cell lethality mediated via calcium-dependent release of perforins (mediating apoptotic events) and granzymes (inflicting damage by punching holes in cell membranes); and
  - CD4 T cells mediate a lethal mechanism via ligand binding to Fas molecules on target cells leading to apoptosis (Fas and TNF receptors belong to the same receptor superfamily).
- Cytokines TNF α and β induce apoptosis in target cells.
- CNS protective mechanisms to elicit a yin–yang state – astroglia and microglia also produce molecules that protect, e.g. from free radical mediated injury, or promote recovery from CNS injury.

The hypothalamo-pituitary adrenal axis may also play a

role in the maintenance of immune integrity in the CNS.[10] The increase in IL-1 in septic shock, for example, mediates the increase in adrenocorticotrophic hormone (ACTH) and glucocorticoid release from the adrenal glands. The same mechanism operates in experimental models of tumours, with associated rises in glucocorticoids in response to lymphoma mediated by immune-derived products and therefore a counterregulatory mechanism that aims to prevent an inflammatory response. A breakdown in the hypothalamo-pitutitary adrenal axis may therefore lead to autoimmunity, and this is supported in animal models of lupus-like disease.

RASMUSSEN'S ENCEPHALITIS

The GluR system

L-glutamate is the major excitatory neurotransmitter in the mammalian CNS. It acts through both ligand-gated ion channels (ionotropic receptors) and G protein-coupled (metabotropic) receptors. Activation of these receptors mediates basal excitatory synaptic transmission and is responsible for memory and learning. When activated, brain cells communicate together electrically, resulting in calcium influx and the release of glutamate. This neurotransmitter diffuses through the synaptic cleft and communicates with other cells by interacting with receptor proteins.

The ionotropic glutamate receptors are subdivided pharmacologically into three groups:
1. AMPA (GluR1-4);
2. NMDA (NR1, NR2A-D, NR3A); and
3. Kainate (GluR5-7, KA1-2) receptors.

The metabotropic glutamate receptors are G protein-coupled receptors that are also divided into three groups, based on pharmacological similarity:
1. group I-mGlu1, mGlu5;
2. group II-mGlu2, mGlu3; and
3. group III-mGlu4, mGlu6, mGlu7, mGlu8.

Some physiologically active autoantibodies are directed towards excitatory glutamate receptors (GluR) of the brain. Examples of these occur in rare forms of childhood epilepsy and in Rasmussen's encephalitis; in the latter, antibodies to GluR3 have been described. This rare disease of the CNS is characterised by progressive degeneration of a single cerebral hemisphere and autoimmunity directed against the glutamate receptor subunit where GluR3 appears to be the autoantigen. It is a progressive disease of childhood characterised by severe intractable epilepsy, hemiplegia, dementia and inflammation of one hemisphere of the brain.[11]

GluR3B-immunised mice exhibit multiple brain abnormalities, partly resembling those observed in Rasmussen's encephalitis, suggesting that this results from autoimmunity to the GluR3B epitope. However, the mouse model fails to explain why patients with Rasmussen's encephalitis have seizures: the mice do not exhibit epilepsy, even upon facilitating entry of the autoreactive antibodies into the brain by weakening the blood–brain barrier.[12] Therefore, one cannot but debate whether the presence of antibody is the causative agent in Rasmussen's or is purely a secondary effect of an aggressively inflammatory condition of the brain that is undergoing damage and immunological breakdown and in which primary aetiological agent is as yet unrecognised.

Treatment of Rasmussen's encephalitis

The epilepsy associated with Rasmussen's often proves to be refractory to treatment. However, immuno-modulatory treatments do offer some success.[13, 14] Treatment of adult patients consists of intravenous high-dose steroids, or intravenous immunoglobulins, or both. Patients often respond to this regime with improvement of their epilepsy and minor improvement of their hemiparesis. Regimes consisting of monthly cycles of intravenous immunoglobulins at 0·4 g/kg/day for five days followed by single monthly 0·4 g/kg maintenance doses, when their condition appears to begin to improve, have also been used. This has also been described as a successful regime in the long-term treatment for adult-onset Rasmussen's encephalitis and is advisable prior to any radical surgical procedures. Plasmapheresis has also been used as adjunctive treatment and may aid assessment of residual function in the diseased hemisphere preoperatively.[15, 16] Studies with single positron emission computed tomography (SPECT) scanning (^{99}Tc HMPAO) confirm hypoperfusion in the diseased hemisphere. The response to immunomodulatory treatment, which is often an improvement in physical and cognitive function, can be monitored using the same technique. Magnetic resonance spectroscopy can be applied in the same manner to measure the metabolic impairment occurring in the involved hemisphere and to monitor progress.[17, 18]

Surgical intervention is considered in those patients whose epilepsy remains intractable despite attempts to treat with immunomodulation. Early surgical resection has been known to provide effective seizure control. Preoperative assessment should include detailed imaging of the brain with magnetic resonance imaging and SPECT where available, as well as Wada testing together with long-term video electroencephalogram monitoring.

GLuR ANTIBODIES IN TUMOURS

Glioneural tumours are an important cause of pharmacoresistant epilepsy. Their neurochemical profile reveals high expression of specific GluR subtypes. These lesions are intrinsically epileptogenic and this probably relates to the presence of GluR on their surface, thus supporting the central role of glutamatergic and therefore excitotoxic transmission by these lesions. Antibodies to various glutamate receptor subtypes have

been demonstrated in gangliomas and dysembryoplastic neuroepithelial tumours from patients with intractable pharmacoresistant epilepsy. Increased expression of particular glutamate receptor subtypes has been noted in reactive astrocytes in the perilesional zone in comparison to normal cortex, particularly GluR2-3, GluR5 and GluR5-7. The neurochemical profile of glioneuronal tumours with high expression of specific GluR subtypes supports the central role of glutamatergic transmission in the mechanisms underlying the intrinsic and high epileptogenicity of these tumours.[19]

MALIGNANT EPILEPSIES OF CHILDHOOD

Paediatric literature is supportive of immunological factors contributing to epilepsy in some of the different varieties of malignant epilepsies of childhood, which are associated with developmental arrest or regression after the onset of seizures. Immunosuppressive drugs such as ACTH or corticosteroids appear to have an anti-convulsant effect in some of these syndromes. Table 3 highlights some of the salient clinical features of three such conditions. As always, it is difficult to elicit whether these patients were born with a genetic predisposition to suffer from severe epilepsy, which then exposes CNS antigens to the immune system and triggers immunological dysregulation, or whether these children have an inborn error of immune dysregulation that leads subsequently to epilepsy.

In 1977, Pechadre reported that children with epilepsy who received intramuscular immunoglobulins for recurrent upper respiratory throat infections experienced an improvement in their epilepsy.[20] Female children responded better than males, especially if they suffered from idiopathic epilepsy syndromes rather than the symptomatic type. Their behaviour and psychomotor development also improved.[21]

In the early 1980s, small numbers of children with West and Lennox-Gastaut syndromes were found to have cell-mediated deficiencies or immunoglobulin deficiencies or disturbances.[22–4] Some children with idiopathic Lennox-Gastaut syndrome have a functionally impaired humoral immune response to a primary antigen – haemocyanin but there is also evidence of a stimulated immune system with elevated IgG levels. This is reminiscent of conditions such as SLE – where autoimmunity is accompanied by a degree of anergy to extrinsic stimuli.[25] HLA-DR5 antigen has been commonly described in Lennox-Gastaut syndrome with a decreased frequency of HLA-DR4.

The number of cases of West and Lennox-Gastaut syndromes treated successfully with intravenous immunoglobulin is indeed small. However, up to 75% of treated cases may experience an improvement in behaviour, while only one-fifth achieve seizure remission. An add-on pilot study of intravenous immunoglobulins administered to 15 children with West or Lennox-Gastaut syndromes was carried out in the presence of continuing conventional anti-epileptic medication. There was a 70% reduction in clinical seizure frequency and an improvement in psychomotor development.[21]

Some disorders of language and social development have been reported to improve in patients treated with immunomodulatory treatment. An example of such a disorder is Landau-Kleffner syndrome. Children with this disorder appear to have a greater frequency of serum autoantibodies to brain endothelial cells and to nuclei (anti-nuclear antibodies) than children with non-neurological illnesses or healthy children, suggesting that autoimmunity may be important in the pathogenesis of language and social development abnormalities in a subgroup of these children.[26]

TABLE 3
Malignant epilepsies of childhood.

1. West syndrome
Incidence 1 in 4,000–6,000 births.
Cryptogenic in 40% of cases; the rest may be due to pre-, peri- or post-natal causes.
Onset before age of one.
Developmental arrest occurs at onset of spasms.
Clinical triad: infantile spasms, psychomotor retardation and hypssarrythmia on EEG with disorganised high-voltage slow waves, spikes and sharp waves occurring diffusely with posterior predominance.

2. Lennox-Gastaut syndrome
Onset is typically between one and seven years of age.
Several seizure types and diffuse cognitive dysfunction.
Cerbral malformations are less common than in West syndrome.
EEG typically slow background with 1·5 to 2·5 Hz slow and spike and wave interictal discharges.

3. Landau-Kleffner syndrome
An acquired aphasia developing between three and nine years of age.
A variety of seizure types, the severity of the seizure disorder being unrelated to the language loss.
EEG often shows spike wave activity over both temporo-central lobes.

Experience in the management of such patients with immunomodulatory treatment is limited, and the success rates more so. However, it appears that intravenous immunoglobulin is effective in a subgroup of patients with severe and intractable epilepsy.[27]

SLE AND BEHCET'S

Systemic lupus erythematosus and Behcet's syndrome are the most common connective tissue disorders to be complicated by serious, sometimes fatal, neurological involvement.[28] Neurological manifestations of SLE include epileptic seizures, encephalopathy, cerebral vasculitis and neuropsychiatric manifestations. Anticardiolipin and anti-beta 2 glycoprotein I antibodies in the serum often correlate with the clinical picture of seizures, whereas the presence and deposition of immune complexes on choroid plexuses is not necessarily associated with neurological disease in SLE.[29] As many as 75% of patients with SLE may have some form of neurological manifestation of disease.

Behcet's syndrome is a vascular multisystem inflammatory disease of unknown origin. Pathophysiologically there is neutrophil hyperactivity, endothelial injury with vasculitis and autoimmune responses. Neurological manifestations are not found in more than 10% of cases and are more common in men. Acute neuro-Behcet's may present as meningoencephalitis, often responding to steroids, while the chronic progressive form is often more intractable and may lead to dementia and psychosis. This form is associated with persistent elevation of Interleukin-6 (IL-6) in the cerebrospinal fluid and is resistant to steroid treatment but may respond to methotrexate.[30, 31] Chlorambucil can be effective in treating meningoencephalitis, while other such immunosuppressive agents – azathioprine, cyclosporin and cyclophosphamide, used alone or in combination – and intravenous immunoglobulins have limited or no role at all in the treatment of neuro-Behcet's. Seizures in neuro-Behcet's syndrome that are due to the syndrome *per se* are probably rare and may simply be provoked by other interventions or drugs. However, the occurrence of seizures in neuro-Behcet's carries a high mortality.[32]

APL, ANA AND GAD ANTIBODIES IN 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.[33] A recent study describes that a newly diagnosed subgroup of patients not on anti-epileptic drugs were found to have a higher prevalence of IgG anticardiolipin antibodies and that this was higher in localisation-related epileptic patients in comparison to those with generalised epilepsy. The prevalence of IgM anticardiolipin antibodies was significantly higher than that of IgG in all epilepsy subgroups.

Anti-nuclear antibody was also significantly more prevalent in localisation-related epilepsy and in newly diagnosed epileptics.[34] These results suggest that immune dysregulation may be associated with epilepsy. Antiphospholipid antibodies were also found to be highly prevalent in children with epilepsy and especially in those with early-onset and high-frequency seizures.[35]

Some patients with drug-resistant localisation-related epilepsy have evidence of glutamic acid decarboxylase (GAD) autoimmunity.[36] Glutamic acid decarboxylase is the enzyme that catalyses the production of gamma aminobutyric acid (GABA), a major inhibitory neurotransmitter. Antibodies to GAD lead to disruption of inhibitory pathways resulting in a hyperexcitable system and are found typically in patients with Type I insulin-dependent diabetes mellitus, 'stiff-person' syndrome, chronic cerebellar ataxia and myoclonus. The 'stiff-person' syndrome is characterised by axial and proximal muscle rigidity with painful muscle spasms and some response to treatment with steroids and intravenous immunoglobulins. It is associated commonly with insulin-dependent diabetes mellitus and in some cases may be associated with an underlying malignancy (commonly in the breast or ovary); epilepsy may occur in some patients.[37, 38]

A pilot study of patients with idiopathic and symptomatic epilepsy was tested for GAD antibodies. No absolute differences in titres were noted between those patients whose epilepsy was well-controlled and those whose condition was uncontrolled. However, four female patients with uncontrolled seizures had levels three times the highest detected in the seizure-free group.[39] It would be important and interesting to test larger numbers of patients for GAD antibodies to study this further and to match their titres with clinical presentations and seizure control.

CHANNELOPATHIES

Our understanding of 'channelopathies' has revolutionised our practice in various subspecialties of neurology, especially in epilepsy, migraine and neuromuscular disorders.[40] 'Channels' refers to the transmembrane pores that allow specific ions to flow and polarise, depolarise or hyperpolarise the cell and thus allow the intra and extracellular environment to be maintained in a stable equilibrium. The important ions are voltage-gated sodium, potassium, calcium, chloride and ligand-gated acetylcholine, GABA and glycine channels. The channels are embedded within the lipid bilayer, and are divided into several subunits, each with separate functions and encoded by a separate gene. Pathology affecting these channels may lead to membrane hypo or hyperexcitability. Disturbance of channel function may be genetic, iatrogenic, toxic or autoimmune.

The sodium channelopathies include familial generalised

epilepsies with febrile seizures, as well as other neurological conditions. Calcium channelopathies are responsible, among other conditions, for familial hemiplegic migraine. The nicotinic acetylcholine receptor channelopathies cause the autosomal dominant nocturnal frontal lobe epilepsy syndrome (ADNFL).[41] Voltage-gated potassium channelopathies are responsible for benign familial neonatal convulsions and episodic ataxia type I. Antibodies to the potassium channel, on the other hand, are associated clearly with generalised peripheral autoimmune-mediated nerve hyperexcitability (e.g. neuromyotonia, cramp-fasciculation syndrome, Isaac's syndrome).[42] Some cases of limbic encephalitides and Morvan's syndrome are also associated with the presence of antibodies to voltage-gated potassium channels.[43]

The possibility that some epilepsy syndromes may be secondary to an ion channel disorder requires further research, as the resulting implications for treatment would be of great importance.[44–6] There is substantial supporting evidence: conventional anti-epileptic drugs are known to act across and inhibit particular ion channels; there is age dependence in the onset of particular epilepsy syndromes; neuronal hyperexcitability may be due to ion channel dysfunction and some perhaps result from dominant mutations with variable penetrance. Improved molecular techniques should provide further insight into our understanding of channelopathies in epilepsy and in developing more suitable treatment modalities.

COULD AUTOIMMUNITY PLAY A ROLE IN THE CAUSATION OF EPILEPSY IN ALZHEIMER'S DISEASE OR MS?

Alzheimer's disease is a recognised risk factor for developing epileptic seizures, often partial epilepsy, but there is little evidence for any underlying causative inflammation.[47, 48]

Dementia, including Alzheimer's, can be a result of immune ageing, whereby a population of activated autoreactive T cells may cross the blood–brain barrier and activate brain microglia sufficiently to initiate an inflammatory neurotoxic process. Identification of the primary trigger that stimulates T cells in the initial phase may lead to therapy to arrest the process or even prevent this.

Epileptic seizures are more common in patients with MS than those predicted by chance; often, these are partial epilepsies with focal onset with or without generalisation. There seems to be a correlation between the paroxysmal phenomena and plaque formation, and seizures may be caused by cortical and subcortical lesions and the surrounding oedema. Indeed, epilepsy may present as an initial symptom of MS or as the single clinical manifestation of a relapse.[49,50] It is beyond the scope of this review to dwell on the details of the various models of experimental allergic encephalo-myelitis (EAE) or the genetic models of CNS inflammation that are alleged to simulate the clinical scenario of MS. There are clinical and histological differences, and similarities between the EAE model and MS have been addressed in a recent paper.[51] The aetiology of MS is unknown, but is likely to be multifactorial and to include genetic, environmental and infectious causes. Whether these in turn contribute towards the development of a lower seizure threshold is unknown.

CONCLUSION

There is some evidence that immune mechanisms play a role in the pathogenesis of some epilepsy syndromes. When immune and autoimmune pathogenesis is suspected in disease, further study using an animal model with either passive transfer of the underlying antibody or by active immunisation with the culprit antigen is often done. However, it would be challenging to produce a good animal model in all the conditions mentioned above. This review has addressed the issue that in some cases different strategies in managing intractable epilepsy syndromes have to be adopted and calls for a deeper understanding of neuroimmunology and the relevant immuno-modulatory treatments. It is necessary to improve understanding as to how damage to the CNS can be arrested and neutralise mediators of toxicity and encourage post-traumatic repair. The development of immune-cell therapy may be the next horizon that our attention ought to be focused on in order to manage such patients.

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