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Seizures in autoimmune encephalitis: Kindling the fire

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Summary

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Epilepsy is a common neurological disorder that increases the risk of morbidity and mortality. Autoimmune epilepsy is a subset of epilepsy that occurs in the setting of autoimmunity, such as in autoimmune encephalitis (AIE). AIE is autoimmune disorder characterized by immune mediated neuroinflammation resulting in variety of neurological symptoms including psychiatric disturbance, cognitive dysfunction and seizures.

Seizures in AIE are thought to be a result of antibodies directed against neuronal cell-surface proteins involved in synaptic transmission. The role of blood brain barrier dysfunction, myeloid cell infiltrate and the initiation of pro-inflammatory cascades in epileptogenesis has been shown to be important in animal models and human patients with epilepsy.

Epileptogenesis in AIE is likely to arise from the synergistic effect of both innate driven neuroinflammation and antibody induced hyperexcitability. Together these processes produce persistent drug resistant seizures that contribute to the morbidity seen in AIE. Understanding the pro-inflammatory pathways involved in this process may improve diagnostics and provide alternative treatment targets in AIE.

Keywords: autoimmune epilepsy, neuroinflammation, innate immunity

Key points

- Autoimmune encephalitis (AIE) is a rare but important cause of seizures, epilepsy and drug resistant epilepsy.
- Seizures in AIE may respond to immunomodulation, suggesting an important role for the immune system and neuroinflammation.
- Neuroinflammation is a key process involving immune cell activation and release of various bio active molecules that can exert effects on nearby neurons.
- In AIE autoantibodies can also exert direct effects on pre and post synaptic channels leading to neuronal excitability.
- Understanding the mechanisms of how neuroinflammation contributes to seizure generation is critical in devising anti-seizure therapies in AIE

Introduction

Epilepsy affects at least 45.9 million adults worldwide, and hence poses an enormous global socioeconomic burden¹. Poorly controlled or uncontrolled seizures in the setting of epilepsy can have important implications for the individual, including cognitive, psychiatric, and physical morbidity, with an overall poor quality of life and associated increased risk of mortality, including sudden death². Autoimmune diseases of the central nervous system (CNS) are increasing in prevalence in the community³. Seizures can be a common presentation of autoimmune encephalitis⁴. Termed 'Autoimmune Seizures' or 'Autoimmune Epilepsy' these disorders are thought to be immune mediated⁴. Recognition of the importance of autoimmune seizures has provided impetus to understand their biological basis. The interaction between the immune system, neuroinflammation and epileptogenesis likely holds the key to unlocking the pathogenesis of autoimmune seizures.

1 Autoimmune Encephalitis

1.1 Overview

The autoimmune encephalitides (AIE) are a collection of immune mediated disorders targeting the CNS⁵. These disorders can present with a broad range of neurological symptoms, particularly seizures, cognitive impairment, and neuropsychiatric disturbance⁵. Diagnosis relies on identification of the symptom complex, supported by evidence of auto antibodies as well as inflammatory changes in cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI)⁶. AIE are a relatively rare group of disorders, with an estimated incidence of 1-2/100,00 per year and a prevalence of 13.7/100,000⁷. AIE can be further divided into three subtypes based on the identification of antibodies: a subtype defined by antibodies directed at intracellular targets, a subtype defined by antibodies directed at cell surface antigens, and a further subtype without identifiable antibodies ('seronegative' AIE)^{8, 9}.

The subtype defined by antibodies directed against intracellular antigens are predominately paraneoplastic disorders. This group typically requires identification and treatment of the underlying neoplastic process for the neurological symptoms to improve¹⁰. The cell surface antibody associated AIE subtype are associated antibodies against a number of important

trans-membrane channels, receptors, and docking proteins involved in synaptic transmission. These include N-methyl D-aspartate Receptor (NMDAR), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), Voltage Gated Potassium Channel (VGKC) complex (most notably Leucine-rich Glioma-inactivated-1 or LGI-1) and the gamma amino-butyric acid (GABA) receptors.

The final subtype is associated with similar clinical, CSF and radiological findings as above but without an identifiable auto antibody, termed as 'seronegative' AIE⁸. All three subtypes of AIE can have seizures as a significant component of the disease.

2 Autoimmune encephalitis and Seizures

2.1 Definitions

Seizures are a common manifestation of AIE and up to 70% of individuals with AIE will experience seizures at some time during course of their illness¹¹. Seizures occurring in the setting of AIE can be classified as autoimmune epilepsy.

Autoimmune epilepsy may present as status epilepticus (SE). In some cases these seizures may not respond to anti-epileptic medications (AEDs). Failure of adequate trials of two tolerated, and appropriately prescribed AEDs to achieve sustained seizure freedom is defined as drug refractory or resistant epilepsy (DRE)¹². Patients with AIE can suffer persistent neurological sequelae after the acute disease has subsided, including DRE.

2.2 Prevalence

In a review of patients with a diagnosis of AIE, 79.5% of patients developed seizures¹¹. 20% of patients had seizures as the predominant symptom¹³. Another study of 52 patients with AIE who presented with seizures examined the prevalence of the different types of seizures¹¹. Focal onset motor seizures were the most common (50%), with the temporal lobe being the most common seizure onset location (73.5%)¹¹. A mesial temporal lobe (MTL) lesion was diagnosed in 62.1%. SE was seen in 28.9%¹¹. 37.2% had persistent seizures past the acute period, and 11% of these were drug resistant seizures¹¹.

AIE is also being recognised as an important cause of seizures, particularly in the geriatric population. In one Chinese cohort of 103 patients with geriatric new onset epilepsy (onset age >60) the most common cause was autoimmune (41.7%)¹⁴. A similar theme is seen in new onset refractory status epilepticus (NORSE), in which autoimmune mechanisms such as AIE are believed to be the most common cause^{15, 16}.

2.3 Clinical Presentation

Many of the individual AIE subtypes have a high incidence of seizures (**See Table 1**). In GABA_B antibody associated AIE, 80-100% of patients present with seizures which have a broad spectrum of semiology, from focal onset seizures with impaired awareness to status epilepticus¹⁷. Similar phenotypes are seen in anti GABA_A antibody associated AIE and anti AMPAR antibody associated AIE¹⁸⁻²⁰. Patients with LGI-1 antibody associated AIE can demonstrate characteristic facio-brachial dystonic seizures (FBDS) or mesial temporal lobe epilepsy (MTLE) or both^{21, 22}. In NMDAR antibody associated AIE one study reported 80.7% of patients had clinical seizures during the acute phase of the illness²³.

In a cross-sectional study of 198 adult patients with acute encephalitis, and of the 44 patients who had a clear autoimmune etiology (10 NMDAR, 10 VGKC), 54.5% of this group had seizures as part of their acute illness²⁴. Recurrence of seizures after recovery from initial illness (post-encephalitic epilepsy or PE) was present in 29.9% of patients²⁴. Predictors of PE were symptomatic seizures during the acute phase and Fluid attenuated inversion recovery (FLAIR) abnormalities on MRI²⁴. In another study CSF from patients with PE were compared with patients with drug resistant seizures from other causes, and were demonstrated to have chronic dysfunction of the blood brain barrier (BBB) based on an increased CSF to serum albumin ratio²⁵.

AIE will commonly present with additional symptoms and signs including sub-acute onset of cognitive impairment, neuropsychiatric disturbance such as mania or psychosis, movement disorders (dyskinesia/dystonia/parkinsonism), sleep-wake cycle disturbance, autonomic dysfunction or a viral illness-like prodrome⁵. Presence of any of these in a patient with new-onset seizures raises the suspicion of AIE.

2.4 Treatment

Response to immune modulating treatment in AIE patients strongly supports an inflammatory/immune mechanism for the seizures. In a systematic review performed by Feyissa and colleagues, 36% of patients with seizures responded to immunotherapy alone, whilst only 10% responded to AEDs alone and 8% to the combination of AEDs and immunotherapy²⁶. Similarly, in another systematic review of patients with epilepsy due to autoimmune aetiologies only 10% of patients respond to AEDs alone, and those treated with sodium channel blockers (carbamazepine, lamotrigine and sodium valproate) comprised 73% of responders²⁷.

There is additional evidence for second-line immunotherapy in the management of AIE related seizures. In a study of 41 patients with seropositive disease treated with immunotherapy for seizures 51.2% were seizure free within two to four weeks, while 73.2% had responded by six months²⁸. Of the remaining patients 66.6% responded to second-line immunotherapy (anti-CD20 monoclonal antibody; rituximab)²⁸. Specific inflammatory pathways are highly likely to be involved. Targeted immunotherapy with an interleukin-6 (IL-6) receptor antagonist (tocilizumab) has been shown to be effective in terminating seizure activity in a small group of patients with NORSE who were refractory to B cell depletion therapy²⁹. Cytokine analysis in these patients prior to therapy demonstrated elevated IL-6, interleukin-2 (IL-2) and tumor necrosis factor α (TNF- α) levels in both serum and CSF, elevated interleukin-10 (IL-10), interleukin-4 (IL-4) in CSF only, and elevated interleukin-12 (IL-12) in serum only²⁹. Only one patient had cytokine analysis post tocilizumab performed, which demonstrated suppression of IL-6²⁹.

As a rare disease evidence for treatment paradigms in AIE is scarce. However, accumulation of expert opinion, case reports and case series, cohort studies and rare randomised clinical trials have created widely accepted lines of treatment. A potential treatment algorithm is shown in **Figure 1**.

Intravenous corticosteroid therapy (1 g methylprednisolone IV for 3-5 days) and intravenous immunoglobulin (IVIg, total dose of 2g/kg given over 2-5 days) either individually or in

combination are considered first-line therapy^{30, 31}. A recent randomised placebo-controlled trial of IVIg in VGKC antibody associated AIE demonstrated superiority in reduction of seizures as compared with placebo³². In instances where the patient is in being cared for in high dependency unit (HDU), plasma exchange (5-10 cycles) may also be used as a first-line therapy, or may be reserved as second-line therapy^{30, 31}.

Should there be minimal to no improvement after first-line treatment, second-line treatment is considered. Second-line treatment consists of either cyclophosphamide (15mg/kg every 3 weeks for 4-6 months) or rituximab (2 x 1000 mg doses 14 days apart OR 375mg/m³ weekly for 4 weeks)³³ alone or in combination^{30, 31}. Patients refractory to second-line therapy may be treated with either tocilizumab³⁴ or the proteasome inhibitor bortezomib³⁵. Given tocilizumab's (an interleukin 6 receptor monoclonal antibody) mechanism of action and limited evidence for its use in NORSE²⁹, tocilizumab may be preferentially used for patients with drug resistant seizures. Bortezomib (a proteasome inhibitor with apoptotic effects on antibody producing plasma cells) has been shown to be effective in small number of case reports of anti NMDA antibody mediated AIE.³⁵ Hence, it may preferentially be used in refractory cases of seropositive AIE patients. It would be recommended that sub-specialty advice be sought before proceeding with third-line therapy. It is also important to ensure pre-immunosuppression screening is performed prior to initiating immunotherapy.

With regards to maintenance therapy, the evidence is scant. Commonly used therapies include a slow weaning dose of oral corticosteroids, azathioprine, mycophenolate, regular IVIg, maintenance rituximab (either 6 monthly or as per CD19/20 counts), or combinations of these therapies. Duration of these therapies remains unclear and are often tailored on a case-by-case basis. Finally, it is also important to screen for neoplastic lesions and treat if identified³⁶. Immunotherapy alone in patients with an associated neoplasm is unlikely to be successful¹⁰.

2.5 Outcomes

Recurrent seizures may persist following recovery from the acute encephalitic illness (chronic epilepsy), and may be drug resistant. A study evaluating patients with seropositive

AIE and seizures examined AED use and risk factors for developing chronic drug resistant seizures³⁷. Seizure relapse (a new seizure during the remission period) occurred in 5.8% of individuals and was not associated with early withdrawal of AED (less than three month use). A limitation of this study was the relatively short one year follow-up, which may not be long enough to capture delayed seizure activity³⁷. Drug resistant seizures were associated with SE and cortical FLAIR abnormalities on imaging³⁷.

In another study of 33 patients with AIE (seropositive and seronegative), 39.3% had chronic epilepsy at final follow up (mean 19 months)³⁸. Predictive factors for developing chronic epilepsy included delayed immunotherapy and a low frequency of clinical and electrophysiological seizures (potentially due to delay in diagnosis and treatment)³⁸.

Another study looked at 17 patients with SE caused by AIE compared with patients with SE caused by viral encephalitis³⁹. Those with AIE had worse cognitive (on the modified telephone interview for Cognitive Status or TICS-M) and functional outcomes (modified Rankin Scale or mRS) compared to those with viral encephalitis³⁹.

3 Antibody effects

There is growing evidence for the pathogenicity of the identifiable antibodies in a number of subtypes of AIE, and that the antibodies may play a role in the generation of seizures in these disorders. This may occur either by directly interfering with the normal physiological activity of the antibody target (ion channel or receptor), or alternatively by causing reduced surface expression of the target.

LGI-1 antibody associated AIE provides an example of the direct action of the antibody on the antigen/receptor, disrupting its normal function. In physiological conditions LGI-1 acts as a ligand for ADAM22 to positively regulate AMPA receptors⁴⁰. In vitro LGI-1 antibodies from the CSF of patients with LGI-1 antibody associated AIE has been shown to disrupt the interaction between LGI-1 and ADAM22 within synapses, which reduces clustering of AMPA receptors in the hippocampal synapses⁴⁰. Intraventricular injection of human derived CSF containing LGI-1 antibody into mouse ventricles was shown to induce facilitation of

hippocampal neuronal glutamate release⁴¹. In vitro patch clamping of hippocampal slices derived from the same animals revealed neuronal hyper-excitability⁴¹.

An analogous situation occurs in a genetic condition called autosomal dominant temporal lobe epilepsy secondary to mutations in the LGI-1 gene. Disruption of the ADAM22-LGI-1 interaction due to the mutation results in a seizure disorder⁴², with mesial temporal lobe seizures⁴², mimicking what is observed in LGI-1 antibody associated AIE.

The seizure predominant phenotype, GABA_B receptor antibody associated AIE, has demonstrated similar direct antibody effects. The serum from patients with GABA_B AIE can abolish the response of GABA_B receptors to baclofen, an agonist of this receptor⁴³. These antibodies have also been shown to decrease excitability of GABAergic pyramidal neurons in mouse neuronal cultures⁴³. This potentially reduces neuronal hypoexcitability in the entorhinal cortex⁴³, creating a base level of hyperexcitability and increasing the risk of seizures.

Other antibody-receptor interactions appear to result in decreased expression or internalisation of the receptor. Antibodies to the GluR2 subunit of AMPA receptors decreased the number of these receptors in post synaptic terminals in rat hippocampal cultures⁴⁴. This has been demonstrated to decrease inhibitory synaptic transmission and increase intrinsic excitability in rat hippocampal cultures as measured by single cell voltage clamp recordings⁴⁵. Similarly, antibodies to GABA_A receptors led to a reduction of these receptors at synaptic terminals in rat neuronal cultures¹⁸.

NMDAR antibody associated AIE has been extensively studied with regard to pathogenicity. Serum from patients with NMDAR antibody associated AIE applied to rat hippocampi causes internalisation of the NMDA receptors⁴⁶. This selectively decreases NMDA neuronal currents as measured by whole-cell voltage patch clamp recordings⁴⁶. The same changes are seen when using recombinant NMDAR antibodies in primary mouse hippocampal cultures⁴⁷ suggesting a direct antibody effect. Rats that are infused intraventricularly with CSF from individuals with NMDAR antibody associated AIE develop behavioural and memory problems, similar to that seen in humans with NMDAR antibody associated AIE⁴⁸.

4 Seizures and Inflammation

4.1 Proinflammatory pathways

There is mounting evidence that neuroinflammation can foster epileptogenesis and that seizures themselves can induce a pro-inflammatory state. It has been demonstrated that potentially pro-inflammatory cytokines interleukin-1 β (IL-1 β), IL-6, TNF- α can modulate susceptibility to limbic seizures in rat models of temporal lobe epilepsy⁴⁹. These cytokines are also upregulated in the human CNS during seizures⁵⁰. Other upregulated molecules during limbic seizures include cell-surface proteins associated with monocyte activation (CD86, Human Leukocyte Antigen-DR (HLA-DR), CD14⁺CD16⁻) and T cell activation (CD25, CD69, CTLA-4 and HLA-DR)⁵⁰.

Rat models of chronic temporal lobe epilepsy (TLE) resulting from SE induced by kainic acid (KA), a commonly used molecule for inducing seizures in animal models, has shown infiltration of T cells and macrophages into the CNS after induction of seizures⁵¹.

Interestingly in rats that are genetically modified to be lymphocyte deplete, seizure frequency / propensity is demonstrated to be higher compared to control rats post SE⁵¹.

These studies suggest that while the innate cell infiltration may play a role in perpetuating inflammation, the role of the lymphocytic infiltration may be one of immune regulation.

One study examining KA induced SE in rats demonstrated specific infiltration of blood derived monocytes expressing C-C motif chemokine receptor 2 (CCR2)⁵². These cells interact with resident microglia and increase levels of IL-1 β ⁵². Preventing monocyte infiltration in this study diminished IL-1 β levels and reduced neuronal damage⁵².

Across other animal models of epilepsy, these CNS homing CCR2 monocytes/macrophages are consistently observed. In a pilocarpine induced rat model of SE there is also upregulation of CCR2 and C-C motif chemokine ligand 2 (CCL2) within glial and neuronal cells in the hippocampus⁵³. In a Theiler's murine encephalomyelitis virus mouse model of encephalitis, there is presence of hippocampal sclerosis (HS) with microgliosis⁵⁴.

Hippocampal histology sections from seizing mice demonstrated predominately macrophage infiltration and neurodegeneration with minimal T lymphocyte infiltration⁵⁴.

Immune cell infiltration and inflammation can also be seen *in vivo* in humans⁵⁴. In patients with DRE with HS who underwent temporal lobectomy, 41% had evidence on histology of lymphocytic infiltration indicating chronic inflammation⁵⁵. Interestingly these cases were more likely to have post-operative seizure reoccurrence⁵⁵, suggestive of a predominately functional rather than purely structural lesion resulting in seizures.

4.2 Blood Brain Barrier Dysfunction

Neuroinflammation can be associated with increased BBB permeability and innate and adaptive cell infiltration into the CNS. This has been demonstrated in a rat model of electrically induced SE⁵⁶, where Van Vliet and colleagues used an albumin bound fluorescent tracer to measure BBB permeability⁵⁶. The amount of the tracer was greatest in the hippocampus immediately after induction of the first seizure and persisted at moderate levels in rats with chronic ongoing seizures⁵⁶. In addition, further disturbing the BBB with the hyper-osmotic agent mannitol resulted in worsening frequency of seizures within these animals⁵⁶. This same study demonstrated a similar pattern of albumin deposition with immunohistochemistry in the resected portion of the hippocampus of patients with drug resistant temporal lobe seizures⁵⁶.

Pre-existing BBB dysfunction may also be able to contribute to seizure generation. Osmotic disruption of BBB with mannitol in patients with CNS lymphoma followed by intraarterial methotrexate resulted in an increased likelihood of seizures as compared with patients who did not receive BBB disruption⁵⁷. There are indications in animal studies that the effect of BBB breakdown may also be long-lasting. A 'two-hit' hypothesis has been described in a rat model of epilepsy where KA induced seizures at age 15 days lead to activation of microglia and pro-inflammatory cytokine production (such as IL-1 β and CCL2) in the hippocampus⁵⁸. When these rats were exposed to a second insult of KA at age 45 days they had a greater susceptibility to seizures, greater microglial activation and pro-inflammatory cytokine production in the hippocampus than those rats who did not experience the initial insult⁵⁸.

4.3 Interleukin-1 β

Whilst there are a number of pro-inflammatory cytokines that play a role in this process, IL-1 β has been implicated as a key mediator. In a rat model of KA induced seizures there was increased production of IL-6 and IL-1 β mRNA levels in the CNS, both at the site of seizure generation as well the rest of the cortex⁵⁹. In other studies application of IL-1 β prolonged KA induced seizures⁶⁰. Even in rat models of genetic absence epilepsy IL-1 β is upregulated in the CNS, as measured by immunostaining of cortical sections, and corresponds to increased prevalence and duration of cortical spike-wave discharges⁶¹. Removing or blocking IL-1 β had the opposite effect, leading to a reduction in seizures. IL-1 β receptor deficient mice are resistant to experimentally induced febrile seizures⁶², while IL-1 β and IL-1 receptor antagonism in acute and chronic epileptic mouse models decreases seizure frequency⁶³⁻⁶⁵.

Microglia and infiltrating myeloid cells appear to play a key role in IL-1 β production. In KA rat models IL-1 β localizes to activated microglia⁶⁶. In another study microglia expressed TNF- α but not IL-1 β or MHC-II, as opposed to infiltrating myeloid cells which expressed IL-1 β and MHC-II⁶⁷. In a KA SE rat model increased microglial/macrophage activation was observed both on immune staining of hippocampal sections, and via increased translocator protein (TSPO) binding on positron emission tomography (PET) imaging⁶⁸. Rats with higher TSPO signal early on in epileptogenesis had more recurrent seizures and poorer cognitive outcomes⁶⁸.

How IL-1 β mediates seizure propensity is not clear. IL-1 β has been shown to inhibit voltage gated sodium channels in rat cultures of cortical neurons, leading to decreased sodium currents and action potential⁶⁹. This would cause hypoexcitability within those neurons. This would appear unlikely to increase seizure propensity, unless it predominately affects inhibitory pathways. CSF containing IL-1 β , from patients with active MS, inhibits GABAergic transmission in mouse corticostriatal slices^{70, 71}. This suggests that IL-1 β may indeed affect inhibitory neuronal pathways preferentially.

4.4 Potential Effector Pathway: P2X7 Receptor

One potential key effector pathway is that of the ubiquitously expressed purinergic receptor P2X7R, which belongs to the P2X family, found on immune cells. It is found predominately on macrophages, antigen presenting cells (APCs) and monocytes, but is also expressed on T and B cells, as well as microglia and astrocytes⁷². When the physiological ligand, ATP, binds the receptor it can activate one of two different conductance states; channel function or pore function⁷³. Brief agonist binding leads to the opening of a non-selective cation channel, whilst prolonged stimulation leads to opening of a pore permeable to moieties of up to 900Da⁷³.

Activation of P2X7R acts as a co-stimulus for the formation of the nucleotide-binding domain, leucine-rich repeat, pyrin domain containing 3 (NLRP3) inflammasome and secretion of pro-inflammatory cytokines IL-1 β and IL-18⁷⁴. It can also form a membrane complex with non-muscle myosin heavy chain to regulate phagocytosis in the absence of opsonins⁷⁵. The pore conductance appears to be an important component in the innate response as loss of pore function via polymorphisms result in decreased inflammasome activation and decreased pro-inflammatory cytokine secretion⁷⁶. Activation of P2X7R in monocytes⁷⁷ can also be induced via stimulation of Toll-like receptor 2 (TLR2).

In a coriaria lactone induced rat model of SE P2X7R was found to be up-regulated in the hippocampus during status epilepticus as shown by western blot analysis⁷⁸, along with IL-1 β and IL-6⁷⁸. Seizures in this model could be ameliorated by intraventricular infusion of Brilliant Blue G, a P2X7R antagonist⁷⁸. In a pilocarpine model of temporal lobe epilepsy, Dona and colleagues demonstrated P2X7R upregulation in rat hippocampi using immunohistochemistry and western blot analysis⁷⁹. In another rat model of SE using KA, P2X7R was found to be upregulated on microglia using western blot analysis⁸⁰. Infiltration of myeloid immune cells has been seen in association with up-regulation of P2X7R in the CNS⁸¹. A rat model of SE induced by pilocarpine demonstrated increased numbers of neutrophils and monocytes in the fronto-parietal cortex when given BzATP, a P2X7R agonist, compared with saline⁸¹. There was also upregulation of CCL-2 in the fronto-parietal cortex of these rats⁸¹. Multiple studies using the KA induced SE rat models have shown that treatment with a specific P2X7R antagonist reduces electrographic seizures, clinical seizure

severity and neuronal death^{82, 83}. This has been replicated in the pentylenetetrazol (PTZ) kindling model of epilepsy in rats^{84, 85}.

Changes in P2X7R expression has also been seen in humans⁸⁶. A study by Barros-Barbosa and colleagues examined cortical samples of human patients with mesial temporal lobe epilepsy, patients with non-mesial temporal lobe epilepsy and control patients using immunofluorescent confocal microscopy⁸⁶. Both epilepsy patient groups demonstrated increased expression of P2X7R as compared with the control group⁸⁶.

5 Two-Stage Hypothesis: Generation of Seizures in AIE

Neuroinflammation appears to play a role in epileptogenesis in animal models and select patient populations. It has also been shown that antibodies in AIE alter neuronal excitability. It is likely that these two processes work synergistically in patients with AIE resulting in drug resistant seizure disorders.

The importance of neuroinflammation and BBB dysfunction in AIE has been suggested in imaging studies. Fluorodeoxyglucose positron emission tomography (FDG-PET) neuroimaging in various subtypes of AIE demonstrate areas of both hypermetabolism and hypometabolism⁸⁷⁻⁹¹. While the areas of hypometabolism may be related to neuronal signalling changes due to antibody effects, the areas of hypermetabolism could indicate excitotoxicity due to seizures, neuroinflammation or early BBB dysfunction.

BBB dysfunction is a precursor for neuroinflammation in this setting. Molecular studies evaluating cytokine profiles in these patients suggests contribution from the pro-inflammatory cascade, implicating pathways that have been shown to be important in immune mediated epileptogenesis in animal models. A recent study identified higher levels of IL-6, pentraxin-3 (part of an innate pro-inflammatory cascade, produced after TLR activation), CD40L and IL-17A in the CSF of patients with NMDAR antibody associated AIE⁹². As described earlier, a study examining patients with autoimmune epilepsy (presenting with

NORSE) found elevated levels of IL-6, TNF- α , IL-2 and IL-4 in the CSF, and elevated levels of IL-6 and TNF- α in the periphery²⁹.

Multiple small immunopathological biopsy and autopsy studies from patients with AIE⁹³⁻¹⁰⁰ have demonstrated a variety of pathological changes. Across these studies there is a predominance of perivascular lymphocyte infiltration with antibody or complement deposition. There is also prominent proliferation of innate cells (microglia and macrophages). Phenotypic activation markers of these cells were not examined in these studies.

In AIE the seizures are likely driven by the combination of ongoing neuroinflammation as well as alterations in neuronal excitability set points due to antibody effects on receptors. This is reflected in the attempts to produce animal models of NMDAR antibody associated AIE. In a study by Wright et al. purified NMDAR antibodies from patients injected into the ventricles of mice were able to lower seizure threshold, but spontaneous seizures were not seen on continuous EEG recordings¹⁰¹. A more recent study by Taraschenko et al. demonstrated the generation of spontaneous non-convulsive seizures on continuous EEG monitoring in mice injected with rabbit Anti-NMDAR IgG or CSF from patients with NMDAR antibody associated AIE, compared with a control group¹⁰². However in this second study the mice injected with patient CSF had 4-5 fold more seizures than the group injected with rabbit Anti-NMDAR IgG¹⁰². It is plausible that the addition of pro-inflammatory compounds present in the CSF, such as IL-1 β , in the setting of antibody mediated AIE lower excitability thresholds, could drive epileptogenesis in AIE.

This two stage process of neuroinflammatory pathways driving seizures in the setting of antibody mediated neuronal remodelling is a potential model of immune mediated epileptogenesis (A plausible mode of seizure generation is shown in **Figure 2**). However this requires further investigation into pro-inflammatory pathways, such as the role of P2X7R and IL-1 β , in AIE to delineate the process, and in particular why seizures persist beyond the initial acute phase of the illness once the antibody producing cells have been suppressed.

Conclusion

AIE is an immune mediated neuroinflammatory condition in which seizures are a common reported symptom. Neuroinflammation can be a significant driver of epileptogenesis in animal models of epilepsy, particularly the infiltration of peripheral innate cells, their interaction with microglia, and the production of pro-inflammatory molecules such as IL-1 β . AIE provides a unique human model of neuroinflammatory epileptogenesis in which two components likely work synergistically. First, BBB dysfunction and the proinflammatory cascade mediates cellular infiltration, immune cell activation, and gliosis. Second, neuronal specific antibodies mediate neuronal excitability. Together these two processes produce often difficult to treat seizures that contribute to the morbidity associated with this disease. There remains a paucity of data delineating this process which may provide further insight into epileptogenesis, improved diagnostics and potential treatment targets for this disorder.

Author Contributions

RW performed the literature search and wrote the manuscript. MM, TO, HB, DT and KB oversaw preparation of the manuscript, and contributed to writing and editing of the manuscript. All co-authors have been substantially involved in the preparation of the manuscript, have seen and approved this version of the manuscript, and accept responsibility for its content. No undisclosed groups or persons have had a primary role in manuscript preparation.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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AIE Subtype	Seizure prevalence?	Seizure presentation	Other clinical features	Tumor association	References
GABAB	80-100%	Focal onset seizures with impaired awareness, Status epilepticus	Limbic Encephalitis	Lung Carcinoma	16
GABAA	88%	Focal onset seizures with impaired awareness, Status	-	Thymoma	17, 18

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		epilepticus			
AMPAR	30%	Focal onset seizures with impaired awareness, Status epilepticus	Limbic Encephalitis, amnestic syndrome	Thymoma, Lung Carcinoma	19
LGI-1	66% (focal seizures), 47% (Facio-brachial dystonic seizures)	Facio-brachial dystonic seizures, Mesial temporal lobe epilepsy	Limbic Encephalitis, rapid onset dementia, memory impairment,	-	20, 21
NMDAR	81%	Focal onset seizures with impaired awareness, Status epilepticus	Dyskinetic movements (esp. orofacial), psychiatric symptoms, dysautonomia, catatonia	Ovarian Teratoma	22

Table 1: Clinical Seizure Characteristics of Common Antibody-mediated Autoimmune Encephalitis

(Abbreviations: Gamma-Aminobutyric acid B (GABAB); Gamma-Aminobutyric acid A (GABAA); α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPAR); Leucine-rich, Glioma Inactivated 1 (LGI-1); N-methyl-D-aspartate Receptor (NMDAR))

Figure 1: Treatment Algorithm for Autoimmune Encephalitis (AIE)

**As per 2016 Lancet Consensus Diagnostic Criteria⁶*

***For Paraneoplastic Autoimmune Encephalitis treatment for malignancy is also required*

Figure 2: Two-Stage Hypothesis, Generation of Seizures in Autoimmune Encephalitis

Innate cell infiltrate into the central nervous system, activating microglia, resulting in neuroinflammation (A). Lymphocytes produce antibodies that bind to cell surface proteins in neuronal synapses (B). These act synergistically to produce excessive, synchronous neuronal discharges seen clinically as seizures (C).

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