

Review Article

Autoimmune Encephalitis and Epilepsies in Children: A Review of Clinical Approach, Management and Treatment

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Received: July 30, 2017; **Accepted:** September 20, 2017; **Published:** September 27, 2017

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Citation: Thusang K, Luat AF (2017) Autoimmune Encephalitis and Epilepsies in Children: A Review of Clinical Approach, Management and Treatment. Front Neuroinflamm Neurodegener Dis 1(1): 100003.

Abstract

Epilepsy affects up to 1% of children and a third of them may develop drug resistant epilepsy. There has been a growing body of evidence suggesting the involvement of the immune system in epilepsy. Autoimmune encephalitis and epilepsies are increasingly recognized. Its early recognition and identification is vital for it is potentially treatable with immunotherapy. Rasmussen encephalitis is a rare form of chronic focal encephalitis usually with childhood onset manifesting with triad of medically uncontrolled focal seizures, hemiplegia, and progressive encephalopathy, associated with inflammation and progressive unilateral hemispheric atrophy. Hemispherectomy remains to be the only treatment for this condition. In this review, we discussed the common forms of childhood onset-autoimmune encephalitis and epilepsies as well as their clinical features, diagnostics and management approach.

Keywords: epilepsy, rasmussen encephalitis, autoimmune encephalitis

Introduction

Epilepsy is a common chronic childhood neurologic disorder affecting 0.5 to 1% of children [1]. Although majority of epilepsy can be controlled with one or two anti-epileptic drugs (AED's), in 30%, seizures continue and become drug-resistant [2]. Drug resistant epilepsy or DRE is defined by the International League Against Epilepsy (ILAE) as failure of adequate trials of 2 tolerated and appropriately chosen and used AEDs whether used as monotherapies or in combination to achieve sustained seizure freedom [3]. The reported incidence of DRE in children ranges between 6 to 24% [4-7].

There is a growing body of evidence suggesting the autoimmune basis of seizures and some forms of epilepsy. For example, the prevalence of detecting serum neurological antibodies in individuals with epilepsy and DRE is 9 to 20% [8-10]. In children with new onset seizure, 10% have been found to be positive for one or more autoantibodies [11]. Several studies have shown the efficacy of immunotherapy in certain autoimmune encephalitis and in some severe epilepsy syndromes [12]. The role of inflammation in epilepsy is further supported by evidence from basic science studies [13,14]. Hence, the concept of autoimmune epilepsy is rapidly emerging.

ILAE recognizes autoimmune epilepsy as epilepsy with evidence of autoimmune mediated central nervous system (CNS) inflammation [15]. Suleiman and Dale use the term autoimmune epilepsy in conditions where the

'specific' or adaptive immune system is involved in the pathogenesis of epilepsy [16]. Britton defines it as immunologically mediated disorders in which recurrent seizures are its primary and persistent clinical feature [17]. The distinction between autoimmune encephalitis and autoimmune epilepsy is not clear but it could be construed that there may be absence of manifestations of and encephalopathy and encephalitis (like lethargy and confusion) in autoimmune epilepsies. Wright and Lim [18] suggested that the acute seizures associated with autoimmune encephalitis would be considered as "provoked" or "acute symptomatic" whereas the patients who develop seizures following an episode of autoimmune encephalitis may have an enduring risk for unprovoked seizure and may be considered to fulfil the recently revised ILAE criteria for definition of epilepsy by Fisher et al. [19]. Seizures in autoimmune encephalitis and autoimmune epilepsy are usually refractory to conventional AEDs but maybe responsive to immunotherapy [20]. In children, just like in adults, the clinical features of autoimmune encephalitis include acute to sub-acute onset of focal seizures (with and without secondary generalization) and seizure clustering associated with other clinical features including encephalopathy, neuropsychiatric symptoms, movement disorder and neurocognitive impairment; cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) findings indicative of neuroinflammation; electroencephalography (EEG) findings of slowing and/or epileptiform discharges involving the temporal lobe (s), histopathological findings compatible with inflammation, positive cell-surface neuronal antibodies (serum or CSF), anti-epileptic drug resistance and positive immunotherapy response and no other explanation for the cause [16]. However, there are clinical features in adults that are not present in children. Furthermore, there are autoimmune epilepsies like Rasmussen encephalitis that are typically seen in children and are not common in adults.

In the evaluation of DRE, one of the goals of every epilepsy center is the early identification of resectable seizure focus. Similarly, the early recognition of autoimmune encephalitis and epilepsy is necessary for immunotherapy may provide seizure control and better outcome. This review focuses on the clinical features of common childhood onset encephalitis and epilepsy with autoimmune and inflammatory basis as well as the diagnostic and management approach.

Rasmussen Encephalitis

Clinical features

Rasmussen encephalitis [21] is a rare form of chronic focal encephalitis characterized by intractable focal seizures, hemiplegia, and progressive encephalopathy, associated with progressive unilateral hemispheric inflammation and atrophy. The cause of Rasmussen encephalitis is unknown but autoimmune and inflammatory etiology is suspected [17]. Its' histopathologic findings closely mimic that of viral encephalitis although no specific infectious pathogen has been noted. Its pathologic features including microglial and lymphocytic nodules, perivascular cuffing, neuronal death and neuronophagia and end stage features like cortical cavitation, marked astrogliosis and neuronal cell loss support an immunologic cause [22]. Rasmussen encephalitis is very rare and affects mostly children and young adults with median age of onset of 6 years (range: infancy to young adulthood). An estimated German-wide incidence of 2.4 cases per 10 million of ≤ 18 years of age per year have been reported [23]. The diagnostic criteria proposed by the European Consensus in 2005 (also called Bien Diagnostic Criteria for Rasmussen Encephalitis) using clinical, EEG and MRI findings have high sensitivity and specificity and it remains to be a useful guideline in its diagnosis (Table 1) [24,25]. However, the Bien criteria may have poor sensitivity for the diagnosis if MRI is negative for atrophy [26]. Three disease stages of the disease have been identified [22]. *Prodromal stage* is characterized by non-specific symptoms, low seizure frequency and mild hemiplegia; *acute stage* is marked by frequent seizures, often with *epilepsia partialis continua* (EPC), progressive hemiplegia, cognitive decline and aphasia, if dominant hemisphere is involved. Although EPC is the most common seizure type reported in Rasmussen

encephalitis, there have been cases of temporal lobe epilepsy reported in older patients and adults [27]. *Residual stage* is characterized by permanent and stable neurological deficits yet continuing seizure activities.

Table 1: Diagnostic criteria for Rasmussen Encephalitis (RE)

Part A	
Clinical	Focal seizures (with or without Epilepsia partialis continua (EPC) and unilateral cortical deficit(s))
EEG	Unihemispheric slowing with or without epileptiform activity and unilateral seizure onset.
MRI	Unihemispheric focal cortical atrophy and at least one of the following: • Grey or white matter T2/ Fluid Attenuation Inversion Recovery (FLAIR) hyperintense signal • Hyperintense signal or atrophy of the ipsilateral caudate head
Part B	
Clinical	EPC or Progressive* unilateral cortical deficit (s)
MRI	Progressive* unihemispheric focal cortical atrophy
Histopathology	T cell dominated encephalitis with activated microglial cells (typically, but not necessarily forming nodules) and reactive astrogliosis. Numerous parenchymal macrophages, B cells or plasma cells or viral inclusion bodies exclude the diagnosis of RE.

Rasmussen encephalitis can be diagnosed if either all of the three criteria of Part A or two out of the three criteria of Part B are present. If no biopsy is performed, MRI with administration of gadolinium and cranial CT need to be performed to document the absence of gadolinium contrast enhancement and calcifications to exclude the differential diagnosis of unhemispheric vasculitis.

Diagnostic evaluation and treatment

CSF analysis in Rasmussen encephalitis is usually normal. Antibodies to glutamate receptor (GluR) 3 were initially thought as a disease biomarker [28]. However, further studies indicated that GluR3 autoantibodies are non-specific for Rasmussen encephalitis [29]. The evolution of EEG findings in Rasmussen encephalitis has been thoroughly studied by Longaretti et al. [30]. In less than 3 months after seizure onset, 50% would show background abnormalities in the affected hemisphere including high amplitude delta slowing; by 3-6 months after seizure onset, independent interictal spikes may be seen in the non-affected hemisphere in 25% and in 62% by 3-5 years and the appearance of contralateral interictal discharges was noted to be associated with cognitive decline. Of note, its EEG findings could not be distinguished from that of focal cortical dysplasia.

Progressive, lateralized cerebral hemiatrophy demonstrated by neuroimaging (computed tomography (CT) and MRI) is the characteristic finding (Figure 1). However, during the early stages of the disease, structural imaging may be normal and functional neuroimaging using single photon emission computed tomography (SPECT)[31] or 2-deoxy-2-[¹⁸F] fluoro-D-glucose (FDG) positron emission tomography positron emission tomography (PET) scanning can detect functional abnormalities [32]. Typically, FDG PET scan shows unilateral lobar or hemispheric hypometabolism, but within the hypometabolic zone, focal areas of hypermetabolism may be found which represent sites of epileptic activity (Figure 2). Lee et al. [32] has demonstrated the progression of the cerebral glucose metabolism abnormalities during the early and late stages of the disease in children with biopsy proven Rasmussen encephalitis. During the early stages (< 1 year from seizure onset), abnormal glucose metabolism is typically seen in the frontal and temporal regions and less frequently in parietal areas, whereas the posterior cortex is preserved. In the later stages of the disease (> 1 year after onset of seizures), glucose PET studies show more extensive hemispheric

involvement including the occipital cortex, but the functional abnormalities remained lateralized suggesting that identification of the most involved areas by PET even during the early stage of disease when MRI could be normal may guide the site of brain biopsy and may, therefore, facilitate early diagnosis and treatment of the disease.

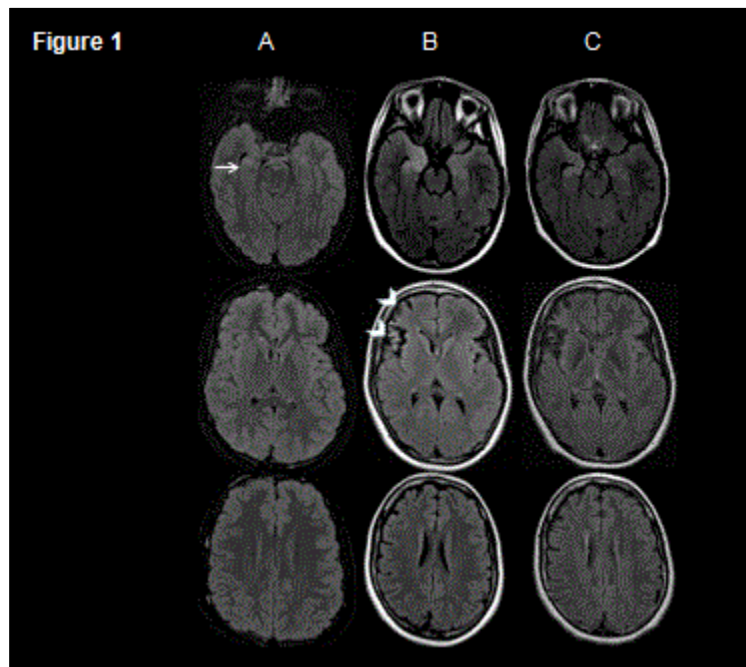


Figure 1: Sequential Fluid attenuation inversion recovery (FLAIR) magnetic resonance imaging (MRI) of a 14-year old boy with suspected Rasmussen encephalitis. **(A)** His first MRI showed subtle area of increased FLAIR signal in the right medial temporal region including the hippocampus (white arrow). **(B)** Second MRI done a year later showed evidence of progression of the lesions characterized by increased FLAIR signal in the medial temporal region associated with atrophy of the right insular and inferior frontal cortex (arrow heads). **(C)** Six months after the second MRI, progression of the atrophy of the right medial-temporal, insular and inferior frontal cortex could be seen.

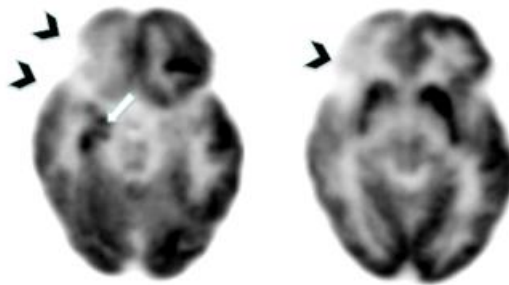


Figure 2: The 2-deoxy-2- ^{18}F fluoro-D-glucose (FDG) positron emission tomography (PET) of the same patient showing severe glucose hypometabolism in the right frontal cortex particularly the right inferior frontal aspect and the rest of the right hemisphere (black arrowheads). Glucose hypermetabolism is seen in the right medial temporal cortex (white arrow) [31].

Rasmussen encephalitis tends to be a progressive and its associated seizures especially EPC are not typically responsive to conventional AEDs. Surgical hemispherectomy is currently the mainstay of treatment. Due to the functional deficits associated with hemispherectomy, the ideal candidates are patients in the residual stage of the disease, with dense hemiparesis and with language not lateralized in the affected hemisphere [23]. To preserve function, small resections have been done. However, there have been no reports of sustained seizure-freedom or a halt in cognitive decline following limited resection. Due to the hypothesis that Rasmussen encephalitis is immune-mediated, immunotherapy has been utilized including the use of intravenous immunoglobulin and corticosteroids in case reports and small series. In most cases, the effect of immunotherapy is only temporizing [17]. A randomized trial of tacrolimus and intravenous immunoglobulin has shown lengthening of survival with either treatment and slow down tissue and function loss and prevent the development of intractable epilepsy. The authors suggested that such therapies may arrest the neurologic decline in patients in a dilemma state of pharmacoresistant epilepsy who are too functional to be offered functional hemispherectomy [23].

Antibody-associated Autoimmune Encephalitis and Epilepsies

For the past decade, there have been continuous discoveries of several autoimmune antibodies implicated in autoimmune encephalitis and epilepsies. Most of these antibodies target cell surface antigens such as anti-N-methyl-D-aspartate (anti-NMDA) receptor. Some targets intracellular antigens like glutamic acid decarboxylase (GAD). Conversely, there are antibodies against protein complexes associated with certain channels such as the voltage gated potassium channel complex (VGKC) proteins. The common feature of these target antigens is their pivotal role in synaptic transmission and plasticity. Investigators have shown that these autoantibodies alter the structure and function of the antigen and may be directly pathogenic [33]. For example, in anti-NMDA receptor encephalitis, patients' antibodies target the extracellular epitope located in the N-terminal domain of the NR1 subunit of the NMDA receptor reducing the number of cell-surface NMDA-receptors and NMDA-receptor clusters in post-synaptic dendrites [34]. Using in-vivo and in-vitro techniques, it has been shown that anti-NMDA receptor autoantibodies decrease the surface density and surface localization of NMDA receptor clusters via antibody mediated capping and internalization of the receptors with resultant selective decrease of NMDA receptor mediated synaptic currents resulting to synaptic dysfunction [35]. Similarly, antibodies against α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) target extracellular epitopes of glutamate receptors type 1 or type 2 subunits by receptor cross-linking and internalization with resultant reduction of AMPA receptor clusters at the synapse [36].

Disease may occur at any age and the onset is usually acute to sub-acute. The clinical presentation may be diffuse such as in anti-NMDA receptor encephalitis, which is typically multiphasic, associated with prominent behavioral and psychiatric manifestations, movement disorder and dysautonomia suggesting diffuse central nervous system involvement or it may be more focal manifesting as limbic encephalitis associated with various autoantibodies like leucine-rich glioma inactivated 1 (LGI1) and gamma-aminobutyric acid_B (GABA_B) receptor antibodies marked by prominent seizures, confusion and memory loss [16]. The clinical manifestations however are broad and significant overlap may be seen [16,37]. The seizure onset is variable but usually explosive evolving into status epilepticus or seizure clusters. Seizures are usually focal and may be temporal or extratemporal but the common feature is its' poor response to AEDs [20,38]. However, most are responsive to immunotherapy. In addition, early recognition is also necessary for underlying tumor may be present and its removal may lead to recovery.

The mechanism of AED pharmacoresistance of seizures in autoimmune encephalitis and epilepsies can be explained by the link between epilepsy and inflammation [39-41]. Experimental and clinical evidence showed that specific chemokines and their receptors are up-regulated in epileptic brain tissues [42]. Recently, more attention has

been given to the role of pro-inflammatory cytokines interleukin-1 β (IL- 1 β) and the danger signals (also called “damage-associated molecule patterns”, e.g. high-mobility group box 1 (HMGB1)) [43]. These endogenous molecules are released by microglia, astrocytes and neurons in the presence of inciting event (e.g. seizures, infection, stress, trauma) that leads to the activation of a cascade of inflammatory events in the target cells (neurons and glia) by activation of the interleukin 1 receptor/ Toll-like receptor (IL-1R/TLR) signaling pathway leading to neuronal hyperexcitability, long term decrease in seizure threshold resulting from rapid post-translational changes in voltage and ligand-gated ion channels that increase excitability, transcription changes in the genes involved in neurotransmission and synaptic plasticity. Seizure recurrence further activates inflammation leading to a vicious cycle that contributes to the development of epilepsy [44]. The overexpression of proinflammatory cytokines also affect blood-brain-barrier (BBB) integrity directly by cytokine-mediated activation of metalloproteinases, tight junction disruption or indirectly by promoting the transmigration of leucocytes and may promote excitability in the surrounding neurons by permitting the entry into the brain of unwanted peripheral immune cells or molecules [39,41]. Indeed, using a mouse model of epilepsy, Fabene et al. has shown that seizures induced increase expression of vascular cell adhesion molecules and enhanced leucocyte rolling and arrest in the BBB vessels and leucocyte-vascular interactions inhibition either by antibody blockade of these adhesion molecules or by genetic interference, suppressed the leucocyte migration and decreases spontaneous seizure frequency[45]. Taken together, these processes could lead to pharmacoresistance to conventional AEDs in autoimmune encephalitis and epilepsy. At the same time, these findings raise the possibility of exploring new therapeutic strategies targeting these inflammatory pathways for the prevention and treatment of epilepsy. Recently, successful response to anakinra, a recombinant version of human IL1 receptor antagonist in super-refractory status epilepticus has been shown [46].

In the subsequent sections, we will discuss the autoimmune antibody associated encephalitis and epilepsies reported in children.

Clinical features

Anti-NMDA receptor: The autoimmune encephalitis most frequently reported in children is the anti-NMDA receptor encephalitis. According to the California Encephalitis Project, anti-NMDA receptor encephalitis was the leading cause of all the cases with identified etiologies and 65% of cases occurred in patients <18 years of age [47]. The syndrome was first described by Dalmau et al. in young women with ovarian teratoma who developed acute psychiatric syndrome; seizures, lethargy, dyskinesia, autonomic instability and hypoventilation associated with serum/CSF antibodies against NR1-NR2 heteromers of anti-NMDA receptors [48]. Subsequently, cases of non-paraneoplastic syndromes associated anti-NMDA receptor encephalitis have also been reported and in 41% of cases, clinically detectable tumor could not be identified [34]. The non-paraneoplastic form of the syndrome is more common in younger children and in males [34].

A staged clinical presentation of the syndrome has been noted [49-51]. The first stage, *prodromal phase*, noted in majority of patients, consists of headaches, fever, and other systemic symptoms like nausea, vomiting diarrhea and upper respiratory tract symptoms. Within few days (less than 2 weeks), the *psychotic phase* follows consisting of broad psychiatric manifestations including delusions, perceptual disturbances, disorganized thoughts and behavior including fear, anxiety along with agitation, paranoia, labile mood, bizarre behavior and personality changes. While psychotic features are common in adults, children often manifest with manic symptoms such as behavioral outburst, irritability and hyperactivity [52]. Initial symptoms may be temper tantrums that may easily be overlooked [53]. The *unresponsive phase* consisting of neurologic complications then ensue and are manifested as global alterations of consciousness ranging from decreased responsiveness and akinetic mutism with eyes open mimicking catatonia [54] to increased agitation [49]. Alternating periods of catatonia and agitation may occur.

Abnormal movements, specifically, oral-lingual-facial dyskinesias then occur. The movement disorder associated with ovarian-tumor associated-anti-NMDAR encephalitis is distinctive, consisting of repetitive, semirhythmic ocular, jaw, facial, lingual, limb and trunk movements, with oculogyric deviation, opisthotonus, and dystonic limb posturing that persist during episodes of diminished responsiveness, and diminishes when consciousness returns. These movements have been proposed to be due to anti-NMDA receptor antibodies-mediated interruption of forebrain corticostriatal inputs removing the tonic inhibition of brainstem pattern generators leading to release of primitive patterns of bulbar and limb movements [55]. Some of these involuntary movements mimic seizures. Although the autonomic features in children is less severe compared to adults, other signs of dysautonomia are more common including erratic sleep patterns (insomnia or hypersomnia), urinary incontinence as well as hypertension and tachycardia, that are correlated with agitation, similar to autonomic storming [53].

Anti-LGI1 and anti-contactin-associated protein-like 2 (CASPR2): VGKCs are transmembrane potassium channels responsible for resetting the depolarized cell to its resting state following each nerve impulse [56]. VGKC's dysfunction leads to delay in the repolarization phase of an action potential leading to cellular hyperexcitability. Traditionally, it was thought that the VGKC autoantibodies were antibodies against the channel itself but further study showed that these antibodies actually bind to the VGKC-complex proteins namely LGI1 and CASPR2 [57]. Furthermore, the significance of positive VGKC-antibodies in the absence of LGI1 and CASPR2 antibodies has been questioned and some investigators believe that is not a clear marker for autoimmune inflammation [58] and in children, it appears to be a non-specific biomarker of neuroinflammation [59]. Hence, a recent review article proposes avoiding the use of the term VGKC-antibody associated encephalitis and to redefine it into 3 subgroups: anti-LGI1 and anti-CASPR2 encephalitis and VGKC-positive patients lacking LGI1/CASPR2 [60].

LGI1 is a soluble glycoprotein that is regionally distributed in the hippocampus and temporal cortex forming a complex with VGKC through its interaction with the epilepsy-related ADAM22/23 transmembrane proteins [61,62]. ADAM22/23 are members of the A Disintegrin And Metalloproteinase family of transmembrane proteins and by forming a complex with the LGI1, it regulates AMPA receptor-mediated synaptic transmission by coordinating the maturation of excitatory synapse through the regulation of the functional incorporation of post-synaptic densities (PSD)-95 family proteins which serve as central scaffolds of excitatory synapse, thus controlling normal synaptic development [63,64]. Dysfunction of this interaction in the presence of LGI1 antibodies may cause AMPA receptor overstimulation [65]. Similarly, mutation affecting the LGI1-ADAM 22 complex has been implicated in a syndrome that is associated with progressive encephalopathy and epilepsy [66]. It should be noted that LGI1 is also the gene involved in autosomal-dominant lateral temporal lobe epilepsy [67]. CASPR2, a member of the neuroligin family present both in the CNS and peripheral nervous system (PNS) functions to ensure proper localization of VGKC in the juxtaparanodal regions of myelinated axons in both the peripheral nervous system (PNS) and CNS [68].

In adults, LGI1 antibodies are most commonly found in non-paraneoplastic limbic encephalitis usually associated with hyponatremia and faciobrachial dystonic seizure, its specific seizure-phenotype that usually appears before the cognitive and psychiatric manifestations of limbic encephalitis [69]. Anti-LGI1 encephalitis is rarely associated with tumor. There have been no reported children with positive LGI1 antibodies. However, there were 4 children who tested positive for VGKC antibodies not directed against LGI1 and CASPR2 who presented with encephalitis and status epilepticus suggesting that the encephalitis syndrome of these children is different from the limbic encephalitis associated with adult cases of LGI1 encephalitis [70]. CASPR2 antibodies have been frequently associated with peripheral nerve hyperexcitability and Morvan syndrome, manifested with neuromyotonia, dysautonomia, encephalopathy and insomnia [71]. Cases of anti-CASPR2 encephalitis have also been reported but it is less frequent than LGI1 encephalitis and its clinical presentation is more diverse consisting of signs and symptoms

of CNS and PNS involvement including limbic encephalitis, neuromyotonia, cerebellar ataxia and Morvan syndrome [60]. Unlike in adults, in children, the clinical presentation associated with VGKC antibodies is less specific and identification of positive VGKC antibodies represent a nonspecific biomarker of neuroinflammation without specific diagnostic significance [59].

Glutamic acid decarboxylase 65 (GAD-65)-antibody: GAD is the enzyme involved in the decarboxylation of excitatory neurotransmitter glutamic acid into the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and is selectively present in GABA-ergic neurons and pancreatic beta cells. Unlike NMDA receptors, it is an intracellular protein but it could be exposed on the cell surface during exocytosis from GABA-ergic neurons thereby allowing pathogenic antibody-antigen interaction to occur [72]. Two GAD isoforms have been identified: namely GAD65 and GAD67 [73]. GAD 65 is highly expressed in CA1 and hippocampal dentate gyrus [74]. GAD-antibodies have been considered as a biomarker of autoimmunity and it has been reported in a spectrum of neurological syndromes including stiff person syndrome, limbic encephalitis, cerebellar ataxia and paraneoplastic neurologic syndromes and are often times also associated with type 1 diabetes mellitus [75]. Lilleker et al. identified high titers of serum GAD-antibodies (>1,000 u/ml) and positive CSF GAD-antibodies in 5% of adult onset epilepsy of unknown etiology but treatment with immunotherapy failed to improve seizure control [76]. The authors concluded that the significance of anti-GAD antibodies in epilepsy is still unclear and they speculated that in some patients, its presence could be regarded as an epiphenomenon acting as a biomarker for an immune mediated process rather than pathogenic. Alternatively, the poor response of anti-GAD associated seizures or encephalitis to immunotherapies directed at depleting the antibodies or antibody-producing cells, may also suggest that anti-GAD cytotoxic T-cell mechanisms are also pathogenically involved [77].

Similar to adults, GAD-antibodies have been reported in children with limbic encephalitis [72,78,79]. One child presented with transient global amnesia which is a rare phenomenon in children [72].

Gamma-aminobutyric acid_A (GABA_A) and Gamma-aminobutyric acid_B (GABA_B)- receptor antibody

Two general classes of GABA receptor are known: GABA_A is a ligand-gated ionotropic channel complex that mediates fast inhibitory synaptic transmission in the CNS, whereas GABA_B receptor is metabotropic G protein-coupled receptors. Both function to modulate the GABA inhibition of the CNS. The pathogenic role of GABA receptor antibodies associated with autoimmune encephalitis and epilepsies may be related to down regulation of GABA receptor function [80].

GABA_A receptor antibody: Encephalitis associated with GABA_A receptor antibody (>1:160 titer) can present with status epilepticus and EPC refractory to AEDs requiring pharmacologically induced coma [81,82]. Other core symptoms noted included cognitive impairment, decrease level of consciousness, altered behavior or movement disorder. According to the report of Spatola et al., children are more likely to have generalized seizure, movement disorder and viral-related symptoms and are less likely to have underlying tumor compared to adults and the authors suggested that the age-related symptoms noted in GABA_A receptor associated encephalitis may result from the combination of specific antibody effects on synaptic circuits (e.g. antibody-mediated decrease of receptors) and increased vulnerability of some areas of the developing brain (hippocampus, basal ganglia) to inflammatory disorders [82].

GABA_B receptor antibody: The first case series of patients with limbic encephalitis and GABA_B receptor antibodies was reported in adults and some were associated with small cell lung carcinoma [83]. In children, encephalitis associated with GABA_B receptor antibodies is not usually a result of a paraneoplastic process [84]. It may present with aggressive course including acute encephalopathy, opsoclonus, chorea, lingual dystonia and refractory

seizures [84] and some may present with clinical features compatible with limbic encephalitis presenting with seizures, confusion and memory loss as well as ataxia and opsoclonus-myoclonus syndrome [85].

Glycine receptor (GlyR) antibody : Following the discovery of anti-NMDA receptor antibodies in 2007, GlyR antibody, first described in adults with clinical phenotype of progressive encephalomyelitis with rigidity and myoclonus (PERM) [86] was discovered. PERM is similar to stiff person syndrome with rigidity, stimulus sensitive spasms, myoclonus, hyperekplexia, autonomic disturbance, with additional brainstem defects. Further studies have shown that GlyR antibodies are associated with broader neurologic phenotypes including stiff person syndrome, limbic encephalitis and demyelinating optic neuropathies [87]. In children, GlyR antibodies have been associated with encephalitis and focal seizures [88], focal status epilepticus with progressive dyskinesia [89] and explosive seizure with ataxia [90].

Diagnostic evaluation and treatment

The diagnosis of antibody associated-encephalitis and epilepsy in children should be suspected in the presence of acute to sub-acute onset of severe, explosive seizures (status epilepticus and seizure clusters) of unknown cause associated with other clinical manifestations including lethargy, movement disorder and dysautonomia supported by evidence of neuroinflammation from CSF studies and MRI and confirmed by the presence of positivity to neuronal surface antibodies. A guideline for the diagnosis of autoimmune epilepsy in children has been proposed (Table 2) [11] which was modified from the guideline in adults [91].

Table 2: Criteria and supportive features to suspect autoimmune epilepsy in children with seizures

The following two clinical criteria are used to suspect autoimmune epilepsy associated with neuronal surface antibodies and glutamic acid decarboxylase antibodies (both are needed)	
1.	Acute or subacute (<12 weeks) onset of symptoms
2.	Exclusion of other causes (CNS infection, trauma, toxic, tumor, metabolic, previous CNS disease)
The following supportive features would strengthen the suspicion of autoimmune epilepsy (patients should have at least 1 of the following):	
1.	The presence of a well-defined clinical syndrome such as NMDA receptor encephalitis or limbic encephalitis.
2.	CNS inflammation manifested by at least one of :
a.	CSF pleocytosis (defined as >5 white cells/mm ³) or presence of oligoclonal bands, elevated IgG index, or elevated neopterin (defined as >30nM).
b.	MRI abnormality compatible with an inflammatory or autoimmune encephalitis including increased signal in the mesiotemporal lobe (LE-like syndrome).
c.	Inflammatory neuropathology on biopsy
3.	History of other antibody mediated condition (e.g. myasthenia gravis), organ specific autoimmunity or other autoimmune disorders.
4.	Response to immunotherapy

In general, all patients with suspected autoimmune encephalitis should undergo lumbar puncture, MRI, EEG and serologic testing for autoantibodies to confirm the diagnosis and exclude alternative diagnosis. Lumbar puncture is typically done with measurement of the opening pressure. CSF studies should include cell count with differential count, protein, oligoclonal bands and sugar as well as viral and bacterial studies. Majority of the patients with anti-NMDA receptor encephalitis have CSF pleocytosis (>5 white blood cells per mm³) and have positive CSF

oligoclonal band although in some, it may be normal initially [49]. Similarly, the CSF in GABA_A and GABA_B receptor antibody encephalitis as well as in GAD-antibody and GlyR-antibody encephalitis show lymphocytic pleocytosis with high protein [85,87,92]. It has been suggested that CSF pleocytosis and oligoclonal bands can be a useful CSF markers in the diagnostic evaluation of anti-NMDA receptor and GAD-antibody associated autoimmune encephalitis as well as paraneoplastic encephalitis [92]. Conversely, the CSF in anti-LGI1 and anti-CASPR2 encephalitis may be normal or may only show oligoclonal bands [93].

In the appropriate clinical setting, the definitive diagnosis of autoimmune encephalitis is confirmed by the identification of specific neuronal autoantibodies but not all patients with autoimmune encephalitis have antibodies, and the absence of antibodies does not rule out an autoimmune etiology. Antibody testing should be performed both in serum and CSF. In anti-NMDA receptor encephalitis, diagnosis is confirmed by the detection of IgG antibodies to NR1 subunit of the NMDA receptor in serum or CSF [94]. However, the sensitivity is higher with CSF [95] and the CSF titer change is most closely associated with relapse [95]. The detection of anti-LGI1 and anti-CASPR2 offers a high specificity for an antibody-mediated neurological syndrome. The significance of VGKC antibodies positivity without anti-LGI1 and anti-CASPR2 is controversial and should be interpreted with caution [96]. The characteristic MRI findings in autoimmune encephalitis include fluid-attenuated inversion recovery (FLAIR) or T2-weighted signal hyperintensities in medial temporal lobes (Figure 3A and B) and/or brainstem while the subcortical regions and the cerebellum are sometimes affected as well [97]. However, in anti-NMDA receptor encephalitis, MRI may be normal or non-specific is as many as 40-50% [34]. Despite normal MRI, glucose metabolism PET scan in anti-NMDA receptor encephalitis may show distinctive pattern of extensive, symmetric cortical hypometabolism especially in posterior areas; asymmetric anterior focus of hypermetabolism; and basal ganglia hypermetabolism [98]. In anti-LGI1 encephalitis, in addition to the findings consistent with limbic encephalitis, MRI may show motor cortex involvement which correlates with the tonic-dystonic seizures associated with the syndrome [99]. In GABA_A receptor antibody encephalitis, MRI often shows multifocal cortical/subcortical and widespread FLAIR and T2 signal abnormalities that can serve as a clue in the diagnosis [82].

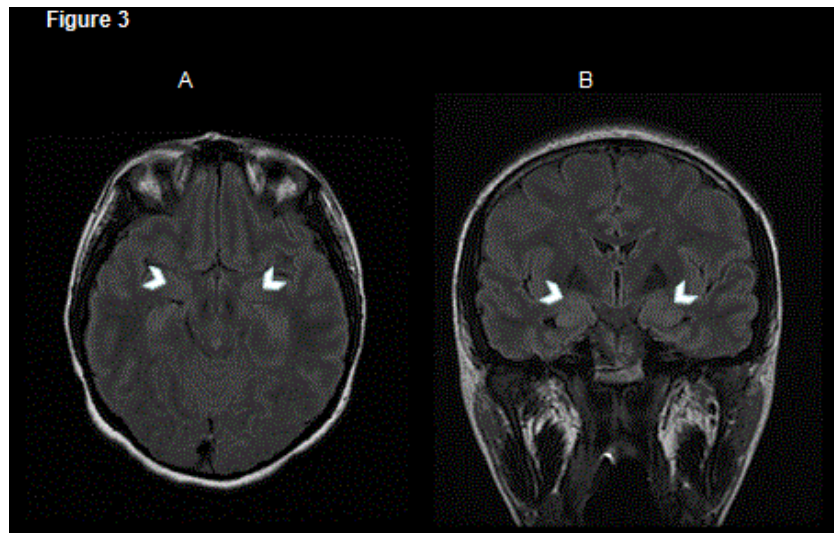


Figure 3: Brain MRI of a previously healthy 14-year old girl who presented with acute onset of encephalopathy and explosive seizures. Serum antibody testing was positive for glutamate decarboxylase (GAD) antibody. (A) Axial (B) Coronal FLAIR MRIs show bilateral and symmetric areas of subtle hyperintensity in the bilateral hippocampus (white arrowheads).

EEG should be performed to exclude subclinical seizures. EEG abnormalities are frequently seen and include focal or generalized slowing, epileptiform activity, and periodic lateralized epileptiform discharges. Extreme delta brushes have been found in 30% of patients with anti-NMDA receptor encephalitis [100]. In addition to delta brushes, Frontal intermittent rhythmic delta (FIRDA) and continuous slowing have been reported [101].

Depending on the nature of the antibody and clinical syndrome, screening for occult tumor should also be done especially in children with anti-NMDA receptor encephalitis. If tumors are not found in anti-NMDA receptor encephalitis, it is recommended that tumor screening be done every 6 months for some years [16]. In general, the search for occult tumor includes imaging of the neck, chest, abdomen, and pelvis, including testes in boys [102]. Imaging modalities used include ultrasound, MRI and glucose PET scan.

Currently, there are limited guidelines for the selection of first line treatment for childhood autoimmune encephalitis and epilepsies and most recommendations and treatment algorithms are based on retrospective cohort, and observational studies [103]. However, it has been shown that treatment with immunotherapy is associated with better outcome than without treatment.

Patients are usually treated initially with first-line immunotherapies including pulse intravenous (IV) methylprednisolone dose of 30 mg/kg per day for 3 to 5 days, IV immunoglobulin (IVIG) at 2 gram per kilogram given in 2 doses over 2 days or 0.4 gram/kg/day for 5 days and plasma exchange (as an alternative to IVIG) with 5 to 7 exchanges of 50 ml/kg on alternate days [16]. Some investigators prefer IVIG over plasma exchange in young children with anti-NMDA receptor encephalitis due to their young age, presence of disease-associated limitations like psychosis, severe agitation, autonomic instability and nosocomial infection [33]. When culprit tumors are present, it should be removed. In paraneoplastic-associated anti-NMDA receptor antibody cases, limited data suggested that early tumor removal leads to better outcome [34].

Investigators have shown that although there was no difference between the proportions of patients with and without tumor who eventually recovered and patients with tumor responded to first line therapy (tumor removal and immunotherapy) more frequently than those without tumor and many of those without tumor required second line immunotherapy (rituximab or cyclophosphamide or both) [49].

Second line therapy are reserved for refractory cases with partial or no response to first-line agents and includes rituximab (375 mg/m² weekly, four doses) and cyclophosphamide 750 mg/m² given on monthly basis for 3-6 months or until recovery is achieved [16]. In contrast to anti-NMDA receptor encephalitis, treatment response to immunotherapy in GAD-antibody encephalitis is variable and in general more resistant to therapy [16]. Encephalitis associated with GABA_A and GABA_B antibody encephalitis usually shows response to immunotherapy. Among the 12 patients with GABA_A antibody encephalitis, reported by Petit-Pedrol et al., 3 had full recovery, 9 had partial recovery whereas 3 died [16]. Similarly, among the 19 patients with GABA_B receptor associated encephalitis reported by Hoftberger et al., majority showed response to immunotherapy [85]. The few cases of GlyR antibody encephalitis reported showed immunotherapy responsiveness [89, 90]. There have been few reports on the long-term outcome of children with autoimmune encephalitis and epilepsy. Hachon et al. [104] reported that among patients who received immunotherapy, 53% had complete recovery. Conversely, among those who did not receive immunotherapy, 29% had complete recovery. However, the difference did not reach statistical significance. Medium term outcome (12-16 months from the onset; mean of 24 months) of the patients in their series showed that 42% had complete recovery; but 50% still have behavioral and cognitive problems and 33% continue to have seizures.

Childhood Onset Encephalopathy with Inflammatory Mediated Status Epilepticus Febrile Infection-Related Epilepsy Syndrome (FIRES)

FIRES, is a rare and severe childhood epilepsy syndrome characterized by the development of seizures in a healthy child between age 4 years to adolescence during or a few days following a non-specific febrile illness [105]. Different names have been used to refer to the clinical entity including febrile infection responsive epileptic encephalopathies of school age [105], new onset refractory status epilepticus [106], devastating epilepsy in school age children (DESC) [107], acute encephalitis with refractory, repetitive partial seizures (AERRPS) [108] and most recently, fulminant inflammatory response epilepsy syndrome [109] but the unifying features of these clinical entities is the presence of known febrile infection preceding the onset of refractory status epilepticus and the absence of identified etiology. Staged clinical presentation has been described by van Baalen et al. as follows [110]: *initial phase* marked by febrile illness; few days later, the *acute phase* consisting of recurrent seizures or refractory status epilepticus with no more fever. Seizure semiology has been described to have focal features including automatisms and head deviation and some has features of temporal lobe seizures [111]. The last phase defined as a *chronic phase* characterized by drug-resistant epilepsy and neuropsychological impairment. Extensive workup for the underlying etiology is usually negative including infectious, autoimmune, metabolic and genetic workup. However, chronological evolution of the MRI findings have been described and serial MRI studies have been reported to show evolution from normal MRI findings to progressive cytotoxic edema in the bilateral medial temporal lobe structures in one to three weeks then severe cerebral atrophy after 6 to 12 months [112]. The underlying mechanism of FIRES is unclear but some authors proposed immunologic etiology and inflammatory process [110,113,114]. Genetic predisposition was also proposed [115]. However, further studies did not identify pathogenic mutations to candidate genes including protocadherin 19 (PCDH19), sodium channel protein type 1 subunit alpha (SCN1A), DNA polymerase subunit gamma-1 (POLG) mutation and rare copy number variants (CNV) [116]. The failure of antibody-detection against the known neuronal antigens as well as its lack of response to immunotherapy question the role of autoantibodies in the epileptogenesis of FIRES [117].

Idiopathic hemiconvulsion hemiplegia and epilepsy syndrome (IHHE)

IHHE was first described by Gastaut in 1960 [118]. The syndrome occurs in previously normal young children (<4 years of age) and is characterized by the combination of unilateral convulsive status epilepticus (mainly clonic), followed by transient or permanent hemiplegia. Similar to FIRES, the neurologic syndrome is preceded by non-specific febrile illness. During the acute stage, seizures start with either unilateral rhythmic 2-3 Hz jerk or head and eye version and may last for several hours (up to 24 hours) [114]. MRI typically shows diffusion restriction on one side (mainly in the perisylvian and parieto-occipital regions) suggestive of cytotoxic edema followed by unilateral atrophy during the chronic stage [119]. The minimum duration of hemiplegia is one week which differentiates it from the Todd's paralysis that may occur with complex febrile seizure [120]. During the chronic phase, majority of patients develop epilepsy and majority develop temporal lobe seizures [114]. Subsequently, in addition to epilepsy, affected children develop hemispheric brain atrophy with contralateral hemiplegia, and variable cognitive deficits. The underlying etiology of IHHE is unknown. However, similar to FIRES, the role of inflammation has been speculated [111]. Based on clinical features and experimental models, Nabbout et al. proposed that the vicious cycle of the synergy of inflammation and seizure activity contributes to the pathogenesis of IHHE and FIRES and suggested that both syndromes should be grouped under the concept of acute encephalopathy with inflammation-mediated status epilepticus (AEIMSE) with difference in clinical presentation related to the stage of brain maturation [114].

Diagnostic evaluation and treatment

Diagnostic evaluation of every infant and child who presents with new onset status epilepticus following febrile illness should include lumbar puncture and CSF analysis to exclude treatable causes including infectious etiology. In the presence of focal features like in IHHE and signs and symptoms raising concern for increased intracranial pressure, neuroimaging with MRI is always done prior to lumbar puncture. Admission to an intensive care unit is warranted for thorough monitoring. Most patients with FIRES fail to respond to conventional AEDs and immunotherapy [117]. However, ketogenic diet has been found to be beneficial not only for seizure control but also for the improvement of cognitive outcome [121].

In the study of Nabbout et al., nine patients with FIRES received ketogenic diet at 4:1 of fat to combined protein and carbohydrate ratio and out of the 8 patients who developed ketonuria, seizures stopped in 7 patients within 2 to 4 days following the onset of ketonuria and within 4 to 6 days following the ketogenic diet initiation [121]. The efficacy of ketogenic diet in inflammatory-mediated epileptic encephalopathies like FIRES is related to its anti-inflammatory properties mediated by various mechanisms as demonstrated in several studies [122-124]. Systemic polyunsaturated fatty acids (PUFAs) levels reportedly rise in response to ketogenic diet and PUFAs have been shown to block epileptiform discharges in rat models of epilepsy and decrease the production of inflammatory eicosanoids, cytokines and reactive oxygen species and adhesion molecules expression [123]. More recently, in a lipopolysaccharide (LPS)-induced fever rat models, rats on ketogenic diet have been shown to have less fever and lower pro-inflammatory cytokines including IL-1 β in the plasma and the brain compared to controls [124].

During the acute phase of IHHE, treatment is primarily supportive and in the short term, most children do well after the initial status epilepticus [125]. The use of NMDA-type glutamate receptor antagonist during the acute stage to counteract cytotoxic edema has been proposed [126]. Rarely, cerebral edema in IHHE can be severe and may present with space-occupying lesion warranting decompressive hemicraniectomy [127]. After some period of time (months to years), two-thirds of patients with IHHE develop epilepsy and seizures can be medically intractable with the majority of those with mesial temporal lobe epilepsy benefiting from surgical treatment [128].

Conclusion

Several childhood onset encephalitis and epilepsy with autoimmune etiology and immunologic basis have been increasingly recognized. Although the signs and symptoms of antibody associated autoimmune encephalitis and epilepsy may overlap, there are associated unique neurologic phenotypes that permit early recognition and diagnosis thereby leading to early initiation of immunotherapy. Surgical hemispherectomy continues to be the only treatment option for Rasmussen encephalitis whereas ketogenic diet may be a viable treatment option for children who present with acute encephalopathy with inflammation-mediated status epilepticus.

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