The Immune System in Pediatric Seizures and Epilepsies

Christian M. Korff, MD,[a] Russell C. Dale, MD, PhD[b]

The relation between the immune system and epilepsy has been studied for a long time. Immune activation may precede or follow the appearance of seizures. Depending on the situation, the innate and acquired immunity may be involved to various degrees. The intense, ongoing research has opened encouraging management and therapeutic perspectives for a significant number of patients suffering from seizures. These include the use of various drugs and less conventional approaches with anti-inflammatory or immunomodulatory properties. Data for children remain scarce, however, and the practical implications of recent discoveries in the field remain to be identified formally. The aim of this review is to present current knowledge of the role of immunity in relation to seizures, with a particular emphasis on clinical data available in childhood. More specifically, various autoantibodies involved in autoimmune encephalitis and epilepsy and general pathophysiological hypotheses on the role of immunity in seizure genesis are discussed, specific epilepsy syndromes in which autoimmune components have been studied are summarized, workup recommendations and therapeutic options are suggested, and finally, open questions and future needs are presented.

The risk of new onset seizures is particularly high during childhood. The average prevalence of nonfebrile recurrent seizures in developed countries is between 3.5 and 5 per 1000 children,[1,2] and the cumulative incidence rate of epilepsy by age 15 years old is ~0.8%. Despite huge advances in the field of imaging and genetics that have improved the understanding of underlying pathophysiological mechanisms, > 60% of seizure disorders remain without an identifiable cause.[3]

In a recent, large population-based study (N = 2 518 034), children with autoimmune diseases had an overall 5 times higher risk of epilepsy when compared with age-matched controls.[4] This risk was consistently heightened in all of the 12 autoimmune diseases considered, including some not known to affect central nervous system (CNS) function such as myasthenia gravis or psoriasis.[4] In some of these situations, specific autoantibodies (auto-ABs) have been involved in the development of neurologic signs and symptoms, yet precise pathophysiological mechanisms remain to be identified.

In addition, immune function has been intensively studied in numerous primary neurologic diseases, which include the common epilepsies for which an underlying etiology remains to be discovered.[5] The acknowledgment of the importance of immunity in the pathophysiology of the epilepsies is illustrated by the current intention of the International League Against Epilepsy to include a new immune etiological category in its proposal for an Organization of the Epilepsies.[6] Overall, the ongoing research in that field opens encouraging management and therapeutic perspectives for a significant number of adults with

abstract

[a]*Pediatric Neurology Unit, University Hospitals of Geneva, Geneva, Switzerland; and* [b]*The Children's Hospital at Westmead Clinical School, University of Sydney, Sydney, New South Wales, Australia*

Drs Korff and Dale conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted.

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Address correspondence to Christian M. Korff, MD, Pediatric Neurology Unit, Child and Adolescent Department, University Hospitals of Geneva, 6 Rue Willy-Donzé, CH 1211 Geneva 14, Switzerland. E-mail: christian.korff@hcuge.ch

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TABLE 1 Auto-ABs Against Neuronal Antigenic Targets Reported in Children With Seizures

	Intracellular Antigens		Surface Antigens							
	GAD	Onconeural	VGKC-complex (including Caspr-2)	NMDA-R	AMPA-R	Folate-R	$GABA_A$-R	$GABA_B$-R	Glycine-R	DPPX-6
Suggestive associated features	LE, ataxia, type-1 diabetes	LE, ataxia (limited data in children)	LE, focal seizures, neuromyotonia	Psychiatric disturbance, movement disorder, sleep difficulties, dysautonomia	LE (limited data in children)	Early-onset refractory seizures, developmental delay and/or regression, microcephaly	LE, multifocal encephalitis (limited data in children)	LE (limited data in children)	Stiff-person syndrome, PERM, LE, focal encephalitis	Prodromal weight loss, gastrointestinal dysmotility, psychiatric manifestations, brainstem involvement
Prognosis in children	Unfavorable	Unknown	Favorable with immune therapy or associated-tumor removal	Favorable with immune therapy or associated-tumor (often ovarian) removal	Unknown	Unknown, may improve with folinic acid	Unknown	Unknown	Favorable with immune therapy	Favorable with immune therapy
Important pediatric references	12–15	16	17–23	24–29	38	30–32	11	33	34–36	

Auto-ABs found predominantly in adults are not presented. ABs against leucine-rich glioma inactivated protein have not yet been reported in children with seizures. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; DPPX-6, dipeptidyl-peptidase-like protein-6; GABA, γ aminobutyric acid; PERM, progressive encephalomyelitis with rigidity and myoclonus; R, receptor; VGKC, voltage-gated potassium channels.

seizures, but data in children remain scarce.[7] Because early identification and intervention is increasingly shown to improve the general outcome, alerting pediatricians about this specific topic is important.

Accordingly, this article presents an overview of the current state of knowledge of the involvement of innate and adaptive immunity in epilepsies with an emphasis on available pediatric data.

IMMUNITY AND EPILEPSIES: RECENT PROGRESS IN THE UNDERSTANDING OF A COMPLEX RELATIONSHIP

An explosion of the number of scientific studies on the relation between autoimmunity and epilepsy has occurred since the early 1990s. In some circumstances, immune activation precedes and provokes the appearance of seizures. Animal research data indicate that contrarily, in other situations, the inflammatory cascade may be activated by the seizures themselves. It is generally accepted that a certain degree of immune reaction is favorable and contributes to the protection of the brain from permanent damage after seizures; in certain circumstances, however, these immune processes may be deleterious.[8] In addition, various auto-ABs have been associated with acute or chronic conditions in which seizures are a hallmark, but it is often unclear whether they are pathogenic or if they simply represent markers of an underlying disease.

Auto-ABs Related to Seizures in Childhood

Numerous auto-ABs have been the subjects of study in epilepsy in past years.[9] Two main categories of auto-ABs are usually identified based on the location of their target antigens: intracellular (unlikely to be pathogenic) or neuronal surface (likely to be pathogenic). Their presence has been demonstrated in the serum or cerebrospinal fluid (CSF) of many patients with seizures, but the precise roles of many auto-ABs remains to be fully understood, especially in children. A recent review article covers this subject extensively.[10] Current knowledge[11–38] is summarized in Table 1.

Autoimmune encephalitis syndromes are increasingly being defined by their associated auto-AB biomarker, such as N-methyl D-aspartate glutamate receptor (NMDA-R) AB. However, many patients with suspected autoimmune encephalitis do not have an associated biomarker, and so clinical syndromes remain important, the most important of which being limbic encephalitis (LE). LE is an inflammatory encephalitis that predominantly affects the limbic region with clinical memory change, temporal lobe seizures, and psychiatric symptoms, and it is more common in adults than in children. MRIs typically show restricted inflammation and swelling in the bilateral limbic regions, EEGs can show localizing features, and CSF may show features of inflammation. A set of diagnostic criteria for LE has been recently proposed by Graus et al.[39] Unlike in adults, when LE is often associated with paraneoplastic auto-ABs, LE in children is often

TABLE 2 Pediatric Epilepsies or Epileptic Conditions in Which Dysimmune Features Have Been Reported

Disease	Disease Characteristics	Underlying Cause	Major Elements Indicating Immune Activation	Ref. No(s).
Rasmussen encephalitis	Refractory focal epilepsy, progressive hemispheric atrophy, and contralateral neurologic dysfunction	Unknown	1. Peripheral T cells stimulated by GluRε2 2. Predominance of T-cell infiltration of the CNS 3. Granzyme-B-mediated T-cell cytotoxic reaction	40–59
West syndrome	Epileptic spasms, hypsarhythmia, developmental delay or regression	Multiple reported (mostly structural, metabolic, or genetic defects)	1. Positive effect of steroid treatment 2. Auto-AB detected in some patients	21,23,30,60,61
Landau-Kleffner syndrome	Acquired aphasia, CSWS in bilateral temporal regions	Unknown	1. Positive effect of steroid treatment 2. Auto-AB or changes in levels of various circulating cytokines detected in some patients	62–69
AEIMSE	A group of likely related acute encephalopathies that present in childhood with status epilepticus, including HHE, FIRES	Unknown	1. Auto-AB rarely detected in patients 2. Positive effect of IL-1 receptor antagonist (anakinra) treatment in some FIRES patients	13,22,70–84
Mesial temporal sclerosis linked with previous prolonged febrile seizures	Prolonged febrile seizures in infancy, subsequent identification of mesial temporal lobe sclerosis	Unknown	1. Various cytokines detected in serum or CSF of some patients after febrile seizures 2. Involvement of genes coding for innate immune-response proteins	85–90

AEIMSE, acute encephalopathy with immune-mediated status epilepticus; CSWS, continuous spike-waves during sleep; FIRES, febrile infection-related epilepsy syndrome; GluR, glutamate receptor; HHE, hemiconvulsion-hemiplegia-epilepsy syndrome.

seronegative (although it can be associated with glutamic acid decarboxylase [GAD] auto-ABs).[17]

Specific Pediatric Epilepsies or Conditions in Which Auto-ABs or Dysimmune Features Have Been Reported

A majority of children who have seizures share certain clinical features that likely reflect a participation of the immune system in their diseases.[9] These include a change (mostly an increase or, more rarely, a decrease) in seizure frequency during periods of infectious illnesses or a favorable response to certain immunotherapeutic approaches. Some of the previously described auto-ABs (as well as additional auto-ABs not primarily directed against CNS targets), elevated cytokinesm, and other nonspecific markers of an immune activation have been found in children with certain well-delineated epilepsy syndromes, such as Rasmussen encephalitis,[40–59] West syndrome,[21,23,30,60,61] Landau-Kleffner syndrome,[62–69] acute encephalopathy with immune-mediated status epilepticus,[13,22,70–84] and mesial temporal sclerosis linked with previous prolonged febrile seizures[85–90] (Table 2). Detailed pathophysiological mechanisms remain to be understood.

VARIOUS MECHANISMS LINK IMMUNE ACTIVATION AND SEIZURES

It is generally accepted that the activation of the immune system can be both the consequence and the cause of seizures, which in both cases can induce permanent functional changes in the CNS. These may themselves contribute to generate epileptic seizures.[91–93] Various pathways link the immune response and seizures. These include adaptive systemic responses, such as T- and B-cell activation and auto-AB production, and innate mechanisms of the CNS, like the increased production of cytokines by activated glial cells observed in response to various stimuli such as seizures. The latter mechanism is a recently identified process named neurogenic neuroinflammation, in which innate and adaptive inflammatory reactions and vascular cell activation within the CNS are triggered by activity in primary afferent nerve fibers or higher-order neurons.[94] On the basis of 5 recent overview articles,[91,94–97] one can attempt to summarize the most important steps that link the immune system and seizures with the following:

1. An initial injury occurs, in the CNS or in the periphery, and provokes an activation of the immune system in one or both compartments (systemic or neuroinflammatory). Various

events have been identified as being able to play such a role, including peripheral infections, autoimmune diseases, CNS vascular disease (thrombosis, emboli, and hemorrhage), vasculitis, neurotrauma, metabolic disorders, CNS infections, seizures, and status epilepticus.

2. Inflammatory mediators are released in either compartment, or in both, depending on the nature of the initial injury. These mediators include various cytokines (such as interleukin [IL]-1β, IL-6, and tumor necrosis factor-α), complement proteins, so-called danger signals (molecules that alert the microenvironment to an ongoing injury, such as high-mobility-group box-1 and its activation of toll-like receptor 4 in neurons and glial cells), cell-adhesion molecules, prostaglandins produced by the activation of the cyclooxygenase-2 signaling pathway, and chemokines. The upregulation of these mediators and their release by lymphocytes in the periphery, or by activated glial and neuronal cells, may in turn provoke blood-brain barrier (BBB) breakdown, adhesion and penetration of activated peripheral lymphocytes, immunoglobulins and albumin into the brain (and, for the latter, subsequent activation of the transforming growth factor-β signaling pathway), increasing extracellular potassium concentration, as well as functional changes in neurons, glial cells, and astrocytes.

3. Neuronal functional changes occur, which increase seizure susceptibility. Examples of these functional changes include the increased expression of IL-1R1 (the target and mediator of the biological response to IL-1β) in neurons; the activation of various intracellular kinase families, such as inducing phosphorylation of a subunit of glutamatergic NMDA-R; the inhibition of the glutamate reuptake or the increase of glutamate release in the extracellular space by astrocytes; the promotion of synaptic reorganization; and the dysfunction of ion channels. Animal research studies also showed that certain genes that code for mediators of the inflammatory response, such as IL-1, IL-6 (and its receptor), and IL-1β are upregulated in the acute phase that follows status epilepticus or traumatic brain injury.[8,98]

All of these mechanisms increase neuronal excitability and lower the seizure threshold, which creates a vicious cycle of increased seizure susceptibility. Animal research has provided details regarding the various mechanisms for inflammation-induced epileptogenesis. These include the abovementioned increased adhesion of activated peripheral leukocytes to endothelial cells followed by their infiltration into the CNS through cytoskeletal reorganization.[99] These cells generate free radicals and cytotoxic enzymes, which, in addition to further production and secretion of cytokines and chemokines, participate in neuronal dysfunction or degeneration that contribute to the appearance of a subsequent chronic susceptibility to seizures.[95]

On the other hand, a neuroprotective role of $CD3^+$ T cells of counterbalancing the innate inflammation has been shown in mice that suffer from kainic-acid–induced seizures and lesioned hippocampi,[100] thus leaving the question of the exact role of the adaptive response open.

From another standpoint, the relation between the BBB and the occurrence of epilepsy has been studied extensively for years,[101–105] but the way in which BBB disruption may provoke chronic epilepsy remains incompletely understood. It has been hypothesized, for example, that acute BBB disruption after initial seizures cause prolonged or permanent changes in brain permeability, which forms the basis of chronic surrounding neuronal excitability and further seizure genesis.[106–108] Recent advances in the BBB disruption theory will likely help our understanding of the process. Bargerstock et al[109] showed that S100B, an astrocytic protein, is released in the systemic circulation when the BBB endothelial tight-junctions are disrupted, for instance, during seizures. This release may in turn induce a systemic autoimmune reaction against the brain, which underlies the development of chronic conditions in the CNS, such as epilepsy and Alzheimer disease. These results need confirmation.

THERAPEUTIC APPROACHES AND PROGNOSIS

Various drugs and molecules with anti-inflammatory or immunomodulatory properties have been shown to decrease the occurrence of additional seizures in acute clinical or experimental situations and to prevent kindling and epilepsy development in animals.[98,110–117] Their mechanisms of action are summarized in Table 3. As a general rule, situations in which neuronal auto-ABs are found and target surface antigens (eg, NMDA-R) have a much higher therapeutic response rate than those in which antigens are intracellular, such as GAD.[118] Potential immune approaches for children in various epileptic conditions include steroids,[119,120] intravenous immunoglobulin (IvIg),[121–123] plasma exchanges,[124,125] rituximab (RTX), cyclophosphamide, and alternative approaches such as the ketogenic

TABLE 3 Examples of Drugs and Treatments With Anti-Inflammatory or Immunomodulatory Properties That Have Shown Experimental or Clinical Efficacy in Seizure Treatment or Prevention of Epilepsy Development

Mechanism of Action	Examples of Drugs, Treatments
BBB homeostasis control	Steroids, ketogenic diet, hypothermia, vagal nerve stimulation, erythropoietin, magnesium sulfate, rapamycin
Decreased leukocyte adhesion to BBB	Natalizumab (integrin α-4 specific monoclonal AB), steroids, IL-R antagonists
Immunosuppression	
Inhibition of auto-AB production	Steroids, cyclophosphamide, RTX
Inhibition of T cell response	Tacrolimus, diazepam
Inhibition of cytokine production and signaling	Minozac, ICE-inhibitor (eg, VX-765, anakinra), levetiracetam
Via NF-κB inhibition	Valproate, propofol, thiopental, ketamine
Removal of auto-AB	IvIg, plasma exchanges
PTGS2 inhibition	NSAIDs: celecoxib, parecoxib
Microglia inactivation	Erythropoietin, minocycline

ICE, interleukin converting enzyme; NF, nuclear transcription factor; NSAID, nonsteroidal anti-inflammatory drug; PTGS2, prostaglandin G/H synthase 2 (formerly COX-2, cyclooxygenase 2); R, receptor.

diet, in which anti-inflammatory and neuroprotective properties are likely to be major players in its mechanisms of action.[70,97,126–128]

Two meta-analyses on the use of IvIg or immunomodulatory interventions overall in epilepsy concluded that, on the basis of available data, their efficacy could not be demonstrated.[129,130] Thus, the question of whether anti-inflammatory or immunomodulatory therapies should be added to classic antiepileptic drugs in autoimmune or even in all types of epilepsies remains open.

In a recent study, Irani et al[131] reported a rapid decrease and progressive total disappearance of faciobrachial dystonic seizures in the 9 patients with ABs against leucine-rich glioma inactivated 1 protein who were treated with steroids in addition to the initial antiepileptic drugs to which seizures were refractory.

Similarly, Toledano et al[132] selected 29 of 110 patients at their neuroimmunology clinic who presented with seizures as a major complaint. Children as young as 2 years old were included. These patients were suspected of having seizures of an autoimmune etiology on the basis of the presence of at least 1 neural AB, personal or family history or physical stigmata of autoimmune disorders, and frequent or refractory seizures. Treatment with daily infusions of 1 g of intravenous methylprednisolone or 0.4 g/kg IvIg for 3 to 5 days followed by weekly infusions for 6 to 12 weeks at the same dose (alone or in combination) was administered. Eighteen patients responded with a decrease in seizure frequency, which was sustained in the majority of cases. The study brought class IV evidence that these therapeutic options improved seizure control.[132]

The role of agents that modify the innate immune system function and attenuate neuroinflammation, such as melatonin, minocycline, or interferon β-secreting mesenchymal stem cells,[133–136] is emerging. In a recent study, minocycline was shown to improve adaptive behaviors of certain children with Angelman syndrome, although the exact mechanism of action could be multifactorial.[137] Whether these molecules have a role to play in the management of certain forms of epilepsy remains to be evaluated. Another major, current theme in neuroimmunology is that early therapy is more likely to be effective than later treatment in autoimmune encephalitis, which has been recently demonstrated in a thorough review of the literature.[138]

PRACTICAL IMPLICATIONS OF AVAILABLE DATA AND CURRENT UNDERSTANDING IN THE MANAGEMENT OF CHILDREN WITH SEIZURES

When Should One Clinically Suspect a Child With Seizures of Immune Etiology?

Suleiman et al[139] proposed a flowchart to approach children with suspected autoimmune seizures. Likewise, Bien[118] proposed a detailed table of clinical and paraclinical features that should prompt the search for auto-ABs in patients with epilepsy. More recently, Graus et al[39] proposed a clinical approach to the diagnosis of autoimmune encephalitis, which emphasized that clinical suspicion should result in first-line immune therapy rather than wait for auto-AB results. Based on these proposals, we propose that immune function analyses should be specifically considered in children if 3 of these 5 criteria are present (Fig 1): (1) unusually high frequency of seizures from onset, with early refractoriness to classic antiepileptic drugs; (2) additional clinical signs of acute or subacute onset, which are suggestive of diffuse CNS involvement (such as psychiatric or behavioral troubles, disturbance of consciousness, abnormal movements, or sleep problems); (3) the clinical presentation clearly orients to a syndrome associated with the presence of specific auto-ABs; (4) presence of a personal or family history of autoimmune disease; and (5) the clinical presentation does not orient to well-circumscribed and rapidly identifiable epilepsy syndromes, and structural lesions, and infectious, metabolic, or toxic diseases are excluded by history and initial investigation.

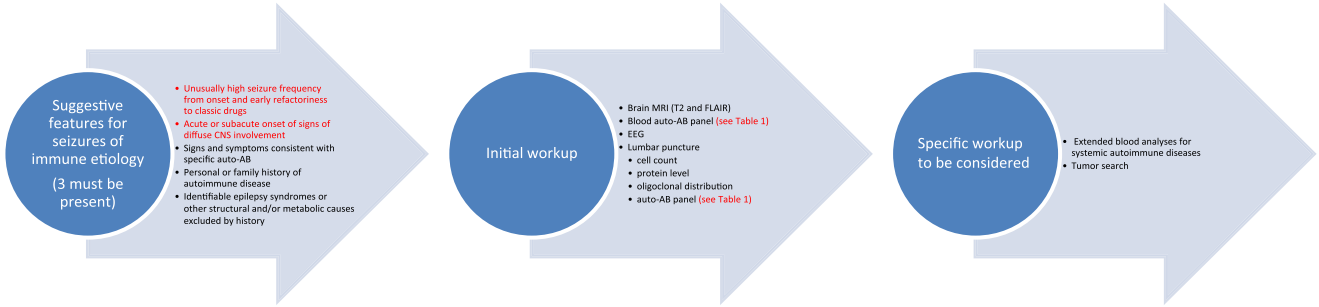

FIGURE 1
Children with seizures of suspected immune etiology: suggestive clinical features and proposed stepwise diagnostic approach. FLAIR, fluid attenuation inversion recovery; T2, transverse relaxation time.

In addition, certain infections are known to trigger encephalitis and epilepsy in children. Some of them directly infect the brain and cause a primary viral encephalitis; on the other hand, certain micro-organisms can induce a secondary autoimmune encephalitis, such as herpes simplex or varicella zoster-induced anti-NMDA-R encephalitis.[140–142] In some of these infectious or postinfectious encephalitis syndromes, there is evidence of autoimmunity and specific biomarkers (such as NMDA-R AB), whereas in other syndromes, there is no specific biomarker, and the exact inflammatory mechanism is unclear. Studies of postencephalitic epilepsy showed that herpes simplex and mycoplasma have the highest potential to result in ongoing epilepsy.[143,144] In these studies, severe clinical indicators such as status epilepticus were risk factors for subsequent drug-resistant epilepsy. Recently, auto-AB against leimodin-1, an intracellular protein that is expressed in smooth muscle tissue and the thyroid but also in the cytoplasm of neurons, have been found in the serum and CSF of certain children from eastern Africa with nodding syndrome, a thus far unexplained and epidemic epileptic disorder that is associated with the parasitic worm *Onchocerca volvulus*.[145]

Responsiveness to immune therapy is indicative of autoimmune epilepsy, but this is only possible to determine in retrospect. Intraindividual seizure variability or multifocality and history of neoplasia have been related to autoimmune epilepsy in adults, and they should also be considered as suggestive features in children. It is important to note that the absence of these features cannot definitively rule out autoimmune epilepsy.

Also, certain patients with autoimmune encephalitis do not exhibit any clinical symptoms besides the seizures.[146] These observations are likely to be rare, particularly in childhood, and we do not believe all children presenting with seizures should be investigated for an immune etiology in the absence of other clinical or investigational features that are suggestive of inflammation.

These limitations emphasize the fact that the spectrum of autoimmune epilepsy is yet to be defined, and novel CSF or blood biomarkers are needed.

How Should a Child With Seizures of a Suspected Immune Etiology Be Investigated?

There have been major advances in our understanding of the roles of auto-ABs as mediators and biomarkers in autoimmune epilepsy, but it is likely that many syndromes have dominant cellular or innate-immune mechanisms that are poorly recognized. Broader biomarker profiles including cytokine and/or chemokine, molecular techniques, and ligand imaging studies will certainly improve our ability to identify CNS inflammation in the future.

We suggest that targeted blood analyses for the most likely auto-ABs according to clinical presentation, the use of biochips (mosaics of cells that display various antigens, such as those described in Table 1),[118] and a cerebral MRI with transverse relaxation time and fluid attenuation inversion recovery sequences should be the minimal procedures performed initially in children with seizures of a suspected immune etiology. Because blood investigations may bring nonspecific (positive or negative) results, a lumbar puncture should be performed to look for increased protein or cell counts, oligoclonal bands, and intrathecal production of auto-ABs. A standard EEG may bring forward additional clues in specific situations, such as when NMDA-R encephalitis is suspected and a pattern of extreme δ brush is present (although this feature has low sensitivity).[26,147] An extended blood, CSF, and urine workup for systemic autoimmune diseases should also be considered, especially in those with multiorgan involvement (Table 4). This workup includes liver- and kidney-function markers, erythrocyte sedimentation rates, complement proteins, various auto-ABs encountered in systemic lupus erythematosus or vasculitides, as well as auto-ABs associated with autoimmune thyroid disease (which one has to remember represents

TABLE 4 Proposed Investigation of Seizures and Epilepsy of Suspected Immune Etiology

Test Grouping	Specific Tests
Specific auto-ABs associated with autoimmune epilepsy (see Table 1)	Cell-based assay, such as Eurimmun biochip Anti-NMDA-R AB Anti-$GABA_A$-R AB Anti-MOG AB (if CNS demyelination) Anti-GAD Other auto-ABs rarely found in children: LGI-1, Caspr2, $GABA_B$-R, DPPX-6, neurexin 3a, AMPA-R
Evidence of peripheral inflammation or immune dysregulation	Complete blood cell count Erythrocyte sedimentation rate CRP IgG, IgM, IgA C3, C4, CH50
Evidence of systemic autoimmunity or vulnerability to autoimmunity	Antinuclear AB Rheumatoid factor Antiphospholipid AB Antineutrophil cytoplasmic AB Anti-DNA AB AB to extractable nuclear antigens: Anti-Sm, Anti-Jo1, antihistones, anti-scl70, anti-SSA/SSB, antiribonucleoproteins, antithyroid peroxidase AB, anti-TSH receptor AB
Evidence of (nonspecific) immune activation, inflammation, or CNS infection	Microscopy, protein count, CSF oligoclonal bands, neopterin

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; anti-SSA, anti–Sjögren's-syndrome-related antigen A; anti-SSB, anti-Sjögren's syndrome type B; anti-TSH, antithyrotropin receptor Caspr2, contactin-associated protein; CRP, c-reactive protein; DPPX-6, dipeptidyl-peptidase-like protein-6; GABA, γ aminobutyric acid; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; LGI, leucine-rich glioma inactivated 1 protein; MOG, myelin oligodendrocyte glycoprotein; NMDA-R, N-methyl D-aspartate glutamate receptor.

a predisposition to autoimmunity and autoimmune thyroid disease rather than a pathogenic marker of autoimmune epilepsy). Tumor searches should be performed according to the potential finding of auto-ABs specifically associated with malignancies, such as ovarian teratomas in girls with the NMDA-R auto-AB. Searching for nonspecific markers of immune activation in the CNS, such as CSF neopterin or oligoclonal bands, may also be helpful.[148,149]

There is an urgent need to develop reliable markers of CNS immune activation, which are currently lacking or not broadly available. These will likely include CSF cytokines and chemokines and EEG or imaging features. An example of the latter was provided recently by an ^{11}c-acetate positron emission tomography scan study of 23 adult patients with epilepsy arising from the temporal lobe in which increased binding of one of these markers, translocator protein 18 kDa, was demonstrated ipsilaterally and contralaterally to seizure foci, which suggests ongoing diffuse inflammation.[150] In another study, the attempt to detect specific EEG features in patients with epilepsy and various antineuronal ABs failed to define discriminating features.[151] However, there are acute EEG indicators of poor outcome in children with encephalitis.[152] Thus, EEG can also be useful in terms of prognosis.

How Should a Child With Seizures of Demonstrated (or Strongly Suspected) Immune Etiology be Treated?

The classic treatment schemes used in other autoimmune neurologic diseases may also be applied to seizures and epilepsy of immune etiology. Current recommendations for autoimmune encephalitis, such as NMDA-R AB encephalitis, include intravenous methylprednisolone at 30 mg/kg per day for 3 to 5 days (≤1 g) followed by ongoing, monthly pulsed steroids, oral prednisone, or prednisolone at 1 to 2 mg/kg per day for 2 to 4 weeks and a slow taper.[118,139,153] This approach should be considered as soon as suspicion of autoimmune etiology arises, be it in chronic or acute situations.[39] As specifically demonstrated in conditions like NMDA-R encephalitis,[153–155] aggressive treatment including ≥4 to 10 plasma exchanges[118] followed by IvIg at 2 g/kg divided by 2 to 5 doses (or IvIg followed by plasma exchanges after a minimal 2-week interval)[156] and various combinations of immunosuppressive drugs (including intravenous RTX at 375 mg/m^2 every week, 2–4 times; and intravenous cyclophosphamide at 750 mg/m^2 monthly for 3–6 months)[118] should be rapidly considered in conjunction with steroids in severe disease.

Importantly, this treatment scheme has been proposed for autoimmune epilepsy and/or encephalitis and may not be effective in other dysimmune epilepsy syndromes. Given the fact that immune activation in the CNS can be protective, the best therapeutic approach for patients with suspected but not confirmed immune-mediated epilepsy remains uncertain. In Fig 2, we propose an immune-therapy trial scheme that could be followed in future prospective studies of suspected immune or autoimmune epilepsy.[138,157]

CONCLUSIONS

It is now clear that inflammation and autoimmunity play important roles in childhood seizures and epilepsies. These immune reactions can be the cause of seizures, such as when auto-ABs against various CNS targets involved in neuronal activation are produced. On the other hand, various CNS and peripheral immune responses are activated after seizures. The latter mechanisms are encompassed in the recently described concept of neurogenic neuroinflammation, which can result in the activation of an anti-inflammatory cascade

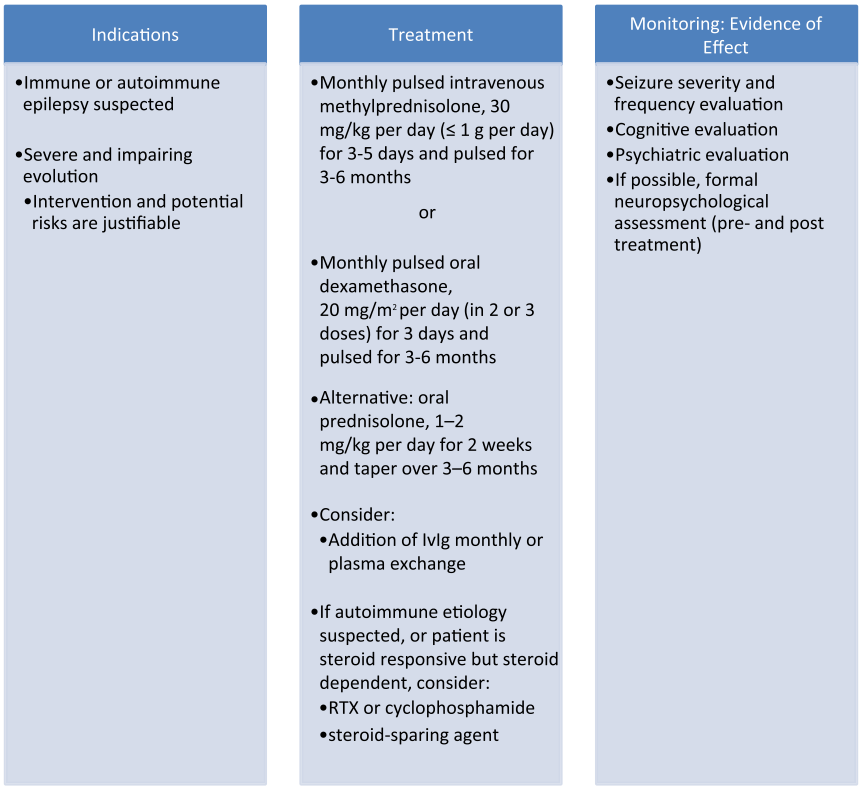

FIGURE 2

A guide to immune therapy trial. The duration of the immune trial is dependent on the clinical scenario. In general, the therapeutic trial needs to be long enough to determine effect, and in more severe conditions, the trial should be sustained or even redosed.[138,157] Steroids should be considered for all patients with suspected autoimmune epilepsy. In strongly suspected cases or cases with proven steroid responsiveness and/or dependence, other immune therapies such as IvIg, RTX, cyclophosphamide, and steroid-sparing agents like mycophenolate mofetil should be considered.

and homeostatic mechanisms with subsequent neuroprotection and interruption of seizures or the perpetuation of a maladaptive and neurotoxic immune response as the basis of further epilepsy genesis.[94] Important questions that remain open include the understanding of the precise timing and sequence of elements of the immune response to seizures, the detection of reliable diagnostic biomarkers of CNS inflammation in children with epilepsies, the identification of specific clinical, radiologic, and electrophysiological features that may allow early suspicion of immune epilepsy, and the development of optimal therapeutic strategies and molecules targeted against the various inflammatory mediators described above through prospective-controlled studies.

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ABBREVIATIONS

auto-AB: autoantibody
BBB: blood-brain barrier
CNS: central nervous system
CSF: cerebrospinal fluid
GAD: glutamic acid decarboxylase
IL: interleukin
IvIg: intravenous immunoglobulin
LE: limbic encephalitis
NMDA-R: N-methyl D-aspartate glutamate receptor
RTX: rituximab

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