Autoimmune encephalitis in children: clinical phenomenology, therapeutics, and emerging challenges

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Purpose of review
Auto-antibodies that bind to conformational extracellular epitopes of neuronal receptors or synaptic proteins have provided clinicians with essential biomarkers in acute neurology. This review summarizes the current status and challenges in the field.

Recent findings
In children, anti-N-methyl-D-aspartate receptor encephalitis remains the most identifiable autoimmune encephalitis, although many patients have a clinical syndrome of brain inflammation in which no antibodies are identified. Anti-myelin oligodendrocyte glycoprotein antibody associated demyelination is now recognized as a major cause of monophasic and relapsing demyelination, often presenting with encephalopathy. We discuss the importance of auto-antibody detection methodology and the possible influence of intrathecal antibody synthesis on the speed of recovery and response to immune therapy. The current, often pragmatic rather than evidence-based therapeutic pathway will be discussed, highlighting key challenges such as the timing of second-line therapy, monitoring of disease activity, and identifying the patient who is responding poorly to treatment.

Summary
Although there have been significant developments, future priorities include the need for paediatric-specific consensus definitions for seronegative suspected autoimmune encephalitis, novel tools for monitoring patients with autoimmune encephalitis, consensus treatment recommendations, and neuroprotective strategies.

Keywords
auto-antibody, autoimmune, encephalitis, therapy

INTRODUCTION

The discovery of pathogenic auto-antibodies in children with acquired autoimmune central nervous system (CNS) disorders has improved the diagnosis and treatment of children with encephalitis and acquired neurological deficits [1]. Although auto-antibody biomarkers have changed the field of paediatric neurology, a large proportion of children with suspected immune-mediated CNS disease do not have detectable auto-antibodies, and many diagnostic and therapeutic challenges remain. This review will update the reader on the current status of autoimmune encephalitis in children, and discuss future priorities and challenges.

THE DIAGNOSTIC CHALLENGE AND THE DIFFERENTIAL DIAGNOSIS

A 'neurological deterioration' in childhood presents a major concern to the family, and a diagnostic conundrum to the clinician. The presence of preceding or concurrent infection and clinical encephalopathy with focal neurological deficits raises the possibility of an immune-mediated process affecting the brain, amongst a large differential diagnosis of childhood encephalopathy [2]. A number of terminologies are often used to describe

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KEY POINTS

- Autoimmune encephalitides with cell surface auto-antibodies are a group of treatable acquired CNS disorders affecting children and young people.
- The tenets of treatment that improve outcomes are: immune therapy is better than none, early treatment is better than late, and if a patient fails first line therapy second line therapy should be considered.
- However, treatment guidelines are based on mostly retrospective cohort studies, and there are no randomized controlled trials.
- New consensus definitions of autoimmune encephalitis have improved the field, but the proposed criteria, particularly for 'seronegative suspected autoimmune encephalitis', needs testing in children.
- Despite the major advances in the field, a large proportion of children with suspected autoimmune encephalitis are seronegative, and these patients may have unidentified auto-antibodies or more likely other immune mechanisms.

'suspected immune CNS disease', which have differing meanings, including the following:

(1) Autoimmune: Acquired immune process involving autoreactive lymphocytes (T or B cells) or auto-antibodies that target the CNS.
(2) Auto-antibody-associated or mediated: Presence of an auto-antibody biomarker that may be pathogenic, which may cause or contribute to CNS disease.
(3) 'Immune-mediated': Broader, more non-specific term, used when the immune system is suspected to be involved, but the exact immunopathogenic mechanism is unclear.
(4) Innate immune activation: When the innate immune system is activated peripherally and/or centrally, associated with CNS dysfunction. Biomarkers to define innate immune activation are lacking. Innate immune activation and acquired autoimmunity probably often co-exist.

The clinical phenotype, and MRI neuroimaging and Cerebrospinal fluid (CSF) testing are important when considering the differential diagnosis of 'immune encephalopathy', which is explored in Table 1.

THE PATHOGENIC AUTO-ANTIBODY 'CELL SURFACE' PARADIGM AND AUTO-ANTIBODY ASSAYS

Pathogenic auto-antibodies bind to conformational extracellular epitopes of cell surface proteins such as neuronal receptors, ion channels or synaptic proteins. The conformation and shape of the epitope is likely to be important, and for this reason, cell-based assays with live or fixed eukaryotic cells to express the protein at the cell surface in its 'physiological' state are used (Table 2 [3–18]). A recent example of the importance of auto-antibody methodology is the case of the Voltage Gated Potassium Channel (VGKC)-complex antibody radioimmunoassay, which precipitates pathogenic target antigens Leucine-rich, glioma inactivated 1 (LGI-1) and Contactin associated Protein 2 (CASPR2) [19,20], alongside a host of other intracellular antigens [21]. For these reasons, VGKC-complex antibody findings should be interpreted with caution, and other observers go further and suggest VGKC-complex Radioimmunoassay should no longer be used in clinical practice (instead LGI1 and CASPR2 antibodies using cell-based assay) [22]. For anti-N-Methyl D-Aspartate Receptor (NMDAR) encephalitis, CSF testing is considered more sensitive and specific [23], although this is not true for myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease when serum testing is more sensitive [24]. Testing both CSF and serum samples is generally recommended when possible.

THE AUTOIMMUNE ENCEPHALITIS SYNDROMES: CLINICAL PHENOTYPES

The more common auto-antibody associated encephalitis syndromes described in children are presented in Table 2. Other auto-antibodies described in adults that are very rare or unreported in children (LGI-1, Caspr2, Gamma-aminobutyric acid B receptor, Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, DPPX (Dipeptidyl-peptidase-like protein-6), IgLON family member 5) are not discussed further, but can be reviewed elsewhere [25].

Anti-NMDAR encephalitis (NMDARE) is the prototypic autoimmune encephalitis, and in its established form is clinically recognizable with psychosis, agitation, dyskinesias, sleep disturbance, mutism, seizures, dysautonomia and encephalopathy [3]. The presence of movement disorder, psychosis and agitation is suggestive of the diagnosis of anti-NMDAR encephalitis in children [26], and these and other clinical characteristics have formed the recent consensus criteria for a 'suspected diagnosis of anti-NMDAR encephalitis', which encourages clinicians to start first-line immune therapy whilst awaiting auto-antibody testing (Fig. 1) [1]. The vast majority of children with NMDARE have polysymptomatic disease, and in the largest cohort of 577 patients, only 1% of patients had monosymptomatic disease during the first month of illness [3]. For this

Table 1. The child with acquired encephalopathy with focal neurological deficits of infectious/immune origin (subgroups, pathogenesis and immunotherapeutics)

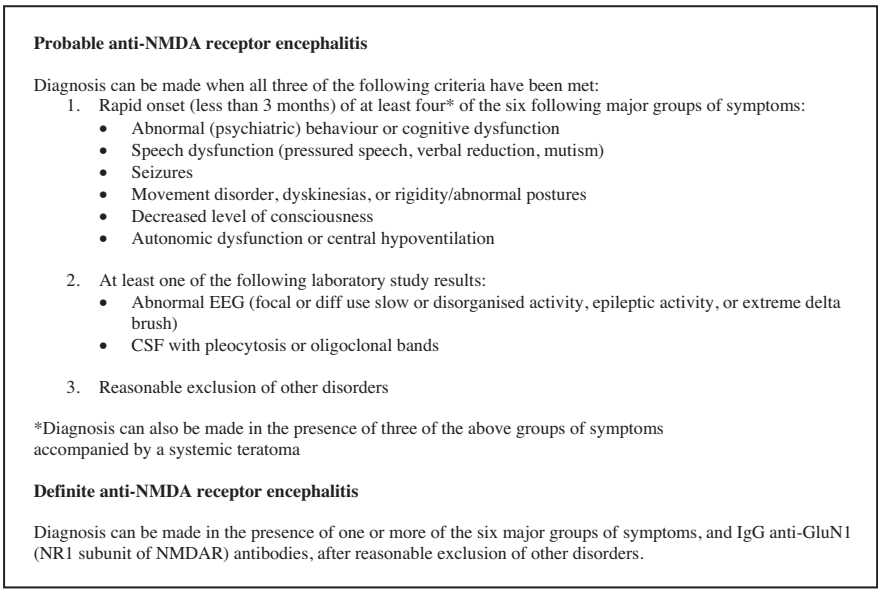
Subgroup	Examples	Likely pathogenesis	Therapeutic options
Infectious encephalitis	Herpes simplex virus encephalitis	Direct invasion of the CNS by bacteria, viruses, or other microorganisms	Antibacterials
	Enterovirus encephalitis	Secondary inflammation and even autoimmunity may occur after some infections	Antivirals
			Probable role for immune suppression or immune modulation in some cases
Infection-associated encephalopathy	Clinico-radiological syndromes such as	General lack of inflammatory cell infiltration[a]	Unclear, possible role of targeted immune modulation of innate immune system or cytokines[a]
	Acute necrotizing encephalopathy (ANE), mild encephalopathy with reversible splenium involvement (MERS), fever induced refractory epilepsy syndrome (FIRES), acute encephalopathy with biphasic seizures and diffusion restriction (AESD)	More likely genetic vulnerability associated 'cytokine storm' of the CNS, with cytotoxic injury	
Autoimmune encephalitis	Cell surface auto-antibodies (anti-NMDAR antibodies, see Table 2)	Predominantly neuronal disease	Immune suppression
		Expansion of auto-reactive lymphocyte and production of auto-reactive antibodies, and access to CNS with or without intrathecal auto-antibody production	Immune modulation
Autoimmune demyelination or astrocytopathy	Anti-MOG antibody associated demyelination	Predominately oligodenrocyte/ astrocyte and neuronal disease	Immune suppression
	Anti-AQP4 antibody associated astrocytopathy/demyelination	Expansion of auto-reactive lymphocyte and production of auto-reactive antibodies, and access to CNS with or without intrathecal auto-antibody production	Immune modulation
Autoimmune movement disorders	Clinical syndromes with characteristic clinical phenotypes but no diagnostic biomarkers	Likely acquired autoimmune CNS disorders, and some evidence of auto-antibody (non proven), B cell or T-cell-driven disease	Remove or treat trigger when present (tumour, infection)
	Opsoclonus myoclonus ataxia syndrome.		Immune suppression
	Sydenham chorea		Immune modulation
Infection-associated relapsing remitting CNS syndromes	Infection triggered or suspected immune disorders	Unclear, possible innate immune, autoimmune or other[a]	Prevent trigger when possible (antibiotics). Immune modulation probably more than immune suppression[a]
	Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS).		
	Paediatric acute neuropsychiatric syndrome (PANS).		

CNS, central nervous system; MOG, myelin oligodendrocyte glycoprotein.
[a]There are limited data in some areas.

Table 2. Auto-antibody syndromes in children

Auto-antibody syndrome	Assay type	Epitope, antigen	Trigger	Typical clinical syndrome	MRI neuroimaging	Pathogenesis	Relapse rate	Refs
Anti-NMDAR encephalitis	CBA	Amino terminus of NR1 subunit of NMDA receptor	Ovarian teratoma, CNS infection (HSV), peripheral infection, idiopathic	Encephalopathy Psychosis Agitation Dyskinesia Speech deficit Seizures Dysautonomia	Often normal	In-vitro and animal model evidence of auto-ab pathogenicity	~12%	[3–6]
Anti-MOG antibody associated demyelination	CBA	P42S mutation in CC loop of MOG (most common)	Peripheral infection, idiopathic	Encephalopathy Pyramidal deficit Optic neuritis Myelitis	Demyelination of CNS (not typically MS-like), longitudinal lesions of optic nerve or spinal cord	In-vitro and animal model evidence of auto-ab pathogenicity, probable role of B and T cell and complement deposition	~30%	[7–12]
Anti-GABA-A receptor encephalitis	CBA	Alpha 1 beta 3 subunit of GABA-A receptor	Personal history of autoimmunity in some	Anti-NMDAR encephalitis like, status epilepticus or epilepsia partialis continua	Multifocal cortical/ sub-cortical lesions	In-vitro evidence of auto-ab pathogenicity	Unclear	[13]
Antiglycine receptor encephalitis	CBA	Epitope common to alpha 1–3 subunits of glycine receptor	Rarely infection or tumour, personal history of autoimmunity in some	Progressive encephalomyelitis, rigidity and myoclonus (PERM), other encephalitis syndromes (limbic encephalitis, demyelination)	Often normal	In vitro evidence of auto-ab pathogenicity	~13%, chronic course in some	[14]
Basal ganglia encephalitis	CBA	Amino terminus of Dopamine 2 receptor	Peripheral infection, idiopathic	Dystonia-parkinsonism, emotional liability	Bilateral selective basal ganglia lesions	In vitro evidence of auto-ab pathogenicity	~50%	[15,16]
Anti-GAD encephalitis	RIA or immunoblot	Glutamic acid decarboxylase 65 or 67	Idiopathic, tumour rarely, personal history of autoimmunity	Limbic encephalitis, cerebellar ataxia	Often normal, or limbic encephalitis	Unclear, suspected T-cell pathogenesis	Unclear	[17,18]

Auto-ab, auto-antibody; CBA, cell-based assay; CNS, central nervous system; GAD, glutamic acid decarboxylase; MS, multiple sclerosis; NMDAR, N-Methyl D-Aspartate receptor; RIA, radioimmunoassay.
Assay type, epitope and auto-antigen, triggers of encephalitis, clinical syndrome, MRI neuroimaging, suspected pathogenesis and risk of relapse. The more common syndromes are listed first.



Probable anti-NMDA receptor encephalitis

Diagnosis can be made when all three of the following criteria have been met:

1. Rapid onset (less than 3 months) of at least four* of the six following major groups of symptoms:
   - Abnormal (psychiatric) behaviour or cognitive dysfunction
   - Speech dysfunction (pressured speech, verbal reduction, mutism)
   - Seizures
   - Movement disorder, dyskinesias, or rigidity/abnormal postures
   - Decreased level of consciousness
   - Autonomic dysfunction or central hypoventilation
2. At least one of the following laboratory study results:
   - Abnormal EEG (focal or diff use slow or disorganised activity, epileptic activity, or extreme delta brush)
   - CSF with pleocytosis or oligoclonal bands
3. Reasonable exclusion of other disorders

*Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma

Definite anti-NMDA receptor encephalitis

Diagnosis can be made in the presence of one or more of the six major groups of symptoms, and IgG anti-GluN1 (NR1 subunit of NMDAR) antibodies, after reasonable exclusion of other disorders.

FIGURE 1. Diagnostic criteria for a diagnosis of anti-NMDAR encephalitis (taken from Graus *et al.* [1]).

reason, NMDARE is unlikely in patients with psychosis unless accompanied by other symptoms such as seizures. Unlike in adults in whom women with ovarian teratomas form the majority of patients (paraneoplastic disease), in children under 10 years of age, the sex ratio is more equal, and ovarian teratomas are rare [3]. Some children have a prodromal infection, and some have evidence of direct viral encephalitis before onset (Herpes simplex virus encephalitis being the best example, discussed in separate review in this edition). Anti-NMDAR encephalitis is a potentially serious disease with mortality of 5%, although 81% have a favourable outcome (modified Rankin score of 0–2) at 2-year follow-up [3].

Myelin oligodendrocyte glycoprotein is an antigen on the cell surface of myelin. MOG has been an attractive auto-antigen for decades and has been used in animal models of demyelination. Only since the use of cell-based assays has the importance of MOG antibody become apparent [27]. MOG antibody is seen in approximately 50% of children with acute disseminated encephalomyelitis (ADEM) [28], and is commonly seen in non-MS optic neuritis and myelitis in children (neuromyelitis optica spectrum disorder) [29]. Although MOG antibody can be associated with a relapsing course, patients usually have a distinct non-multiple sclerosis (MS) phenotype, such as relapsing optic neuritis, Neuromyelitis spectrum disorder (NMOSD) or relapsing ADEM [7,30,31]. Intrathecal oligoclonal bands are uncommon, the MS HLA DRB1∗1501 is not over-expressed (unlike in MS), and patients may have evidence of systemic inflammation (raised ESR) during active phases of disease [24]. Although MOG antibody-associated disease is less destructive than AQP4-ab-associated NMOSD, morbidity is still possible, particularly with myelitis or severe acute episodes, and some patients with optic neuritis develop retinal nerve fibre atrophy [7,27].

Anti-GABA-A receptor encephalitis is a multifocal encephalitis that can phenotypically mimic anti-NMDAR encephalitis or present with status epilepticus [13]; encephalitis associated with glycine receptor auto-antibodies include the 'classical' syndrome of progressive encephalomyelitis with startle, rigidity and myoclonus (PERM) [14], and basal ganglia encephalitis associated with or without dopamine-2 receptor antibodies [15], are rarer immune responsive neurologic syndromes in children, detailed further in Table 2. Antibodies against glutamic acid decarboxylase (GAD) are found in stiff person syndrome, limbic encephalitis, and cerebellar ataxia are also reported in children, although it should be highlighted GAD is an intracellular rather than 'cell surface' antigen, and its pathogenic potential is therefore unclear [17].

Recently, a number of dual-positive 'overlapping' syndromes have been identified, such as anti-NMDAR encephalitis with demyelination episodes (dual positive for NMDAR and MOG or AQP4 antibodies) [32,33], and some autoimmune encephalitis syndromes are dual positive for GAD and GABA-A receptor or glycine receptor antibodies (inhibitory synaptic proteins) [14,17].

THE CHALLENGE OF SERONEGATIVE, SUSPECTED AUTOIMMUNE ENCEPHALITIS

A large proportion of patients with suspected autoimmune encephalitis are seronegative. In the first study to examine this, only 44% of patients with

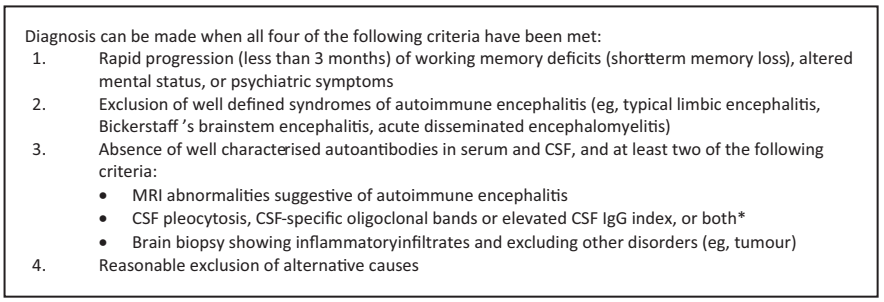


FIGURE 2. Proposed diagnosis for auto-antibody-negative but probable autoimmune encephalitis (taken from Graus *et al.* [1]).

suspected autoimmune encephalitis had a positive auto-antibody, and as some of these positive auto-antibodies were VGKC-complex antibodies (as discussed above), this proportion may be over-inflated [34]. A first consensus definition for 'seronegative but suspected autoimmune encephalitis' was generated by Graus *et al.* (Fig. 2); however, a revised definition may be required for children. There are many children with suspected autoimmune encephalitis, who have negative MRI and normal routine CSF testing, and who would fail to fulfil current criteria (Fig. 2, personal observations). These 'seronegative autoimmune encephalitis' syndromes are seen in previously normal children, but also in children with autistic spectrum disorder or Down's syndrome. It is conceivable that many of these children have immune mechanisms that are not auto-antibody-associated, such as cellular or innate immune processes. More detailed CSF analysis and molecular techniques to examine the immune system are required for these patients. The clinician must remain vigilant to an alternate, non-immune diagnosis in such children.

THE THERAPEUTIC PATHWAY DURING THE ACUTE ILLNESS

In a systematic review of the treatment of adults and children with autoimmune encephalitis, there were three main themes that were present, regardless of auto-antibody association [35]:

(1) Patients given immune therapy do better than patients given no therapy.
(2) Patients given treatment early do better than those given treatment late.
(3) If a patient does not respond to first line therapy, second line therapy improves outcomes.

It must, however, be emphasized that the evidence is currently based mostly on retrospective, uncontrolled cohort studies with associated confounders, variables and reporting bias [35].

The general approach to immune therapy is summarized in Fig. 3, noting that differences in therapeutic preferences and doses may vary across centres.

Firstly, triggers of disease should be treated or removed such as infections or tumour. In general, first-line therapy should almost always include corticosteroids, which generally penetrate the brain, have broad mechanisms of action on the immune system and modulate the blood–brain barrier. Intravenous immunoglobulin is often used in conjunction with corticosteroids, and Intravenous immunoglobulin (IVIG) has broad immune modulatory properties. Plasma exchange (PLEX) can also be performed (preferably before IVIG), and a recent systematic review of PLEX in anti-NMDAR encephalitis highlights the paucity of good evidence, but suggests that early PLEX, and concomitant corticosteroid

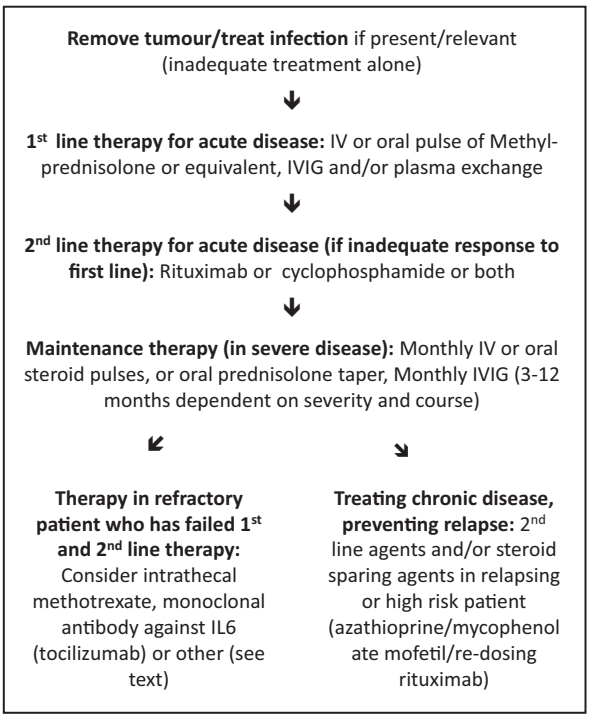


FIGURE 3. Possible therapeutic pathway for the patient with anti-NMDAR encephalitis and related autoimmune encephalitis. The approach is based on retrospective cohort descriptions, rather than randomized controlled trials.

usage, improves outcomes [36]. In general, there is little evidence to determine whether IVIG or PLEX is superior; therefore, it should be recommended that clinicians use whichever approach they are most familiar with; however, PLEX may present specific challenges in the agitated patient.

In more severe syndromes like anti-NMDAR encephalitis, maintenance therapy comprising of either protracted oral steroid taper, pulsed steroid or IVIG, ranging from 6 to 12 months, is often pragmatically employed following acute treatment.

A significant proportion of autoimmune encephalitis patients will respond to first-line therapy and show improvements in the first 1–2 weeks after initiation of therapy. In patients who do not respond, second-line therapy typically features rituximab for anti-NMDAR encephalitis and other auto-antibody-associated encephalitis syndromes, due to its B-cell depletion mechanism of action, although it is noted that rituximab does not target antibody-producing plasma cells directly, and B-cell depletion results in significantly reduced pro-inflammatory CD4 and CD8 T-cell responses, highlighting that rituximab is a broad immune suppressant [37]. Rituximab is generally well tolerated, although infusion reactions affect about 12% of children, and serious infectious side effects do occasionally occur [38]. Of 144 children given rituximab for inflammatory CNS indications, 4 patients had grade 4 or 5 infectious adverse events including two fatal outcomes [38]. We would recommend B-cell measurement at 2–4 weeks to demonstrate B-cell depletion, as occasional patients can fail to deplete B cells despite adequate dosages [39]. We would also recommend periodic monitoring of B cells and immunoglobulins to assess for B-cell repopulation (and determine if B-cell repopulation correlates with return of symptoms), and to monitor for hypogammaglobulinemia [38,39]. Cyclophosphamide is the alternative second-line therapy, and has broad cellular immune suppression effects. Cyclophosphamide is best given intravenously monthly for 3–6 months. Interestingly, 58 of 144 patients given rituximab for inflammatory CNS disease received additional cyclophosphamide, and these patients did not have higher rate of adverse events, which provides reassurance that when required, cyclophosphamide should be given in addition to rituximab [38]. Although clinicians have become more comfortable with the use of rituximab, cyclophosphamide remains a very important therapy, and should be given in severe disease, or in patients who fail to respond to rituximab. The major limitation with cyclophosphamide is the potential for long-term risks of infertility and secondary malignancy; however, as these correlate with lifetime cumulative dose, short courses (aiming to be less than 7.5 g/m^2) is justified in severely ill patients.

Although most of the therapeutic literature is from the treatment of anti-NMDAR encephalitis, other autoimmune encephalitis syndromes should probably follow the same approach, at this time. In the acute phase of MOG antibody-associated demyelination, most patients will respond to corticosteroids with or without IVIG or PLEX, and do not typically need second-line therapies.

If the first-line and second-line therapies fail (both rituximab and cyclophosphamide) (Fig. 3), the literature is very limited to generate recommendations. However, some therapies require consideration. Firstly, bortezomib – a protease inhibitor which inhibits pro-inflammatory signalling cascades and reduces plasma cells and antibody production – has been described to be effective in two severe treatment refractory adult patients with anti-NMDAR encephalitis [40]. Secondly, drugs targeting the pleiotropic pro-inflammatory cytokine interleukin (IL)-6 such as tocilizumab may have a role [41]. Although the cytokine IL-6 does not have an established role in autoimmune encephalitis pathogenesis, CSF IL-6 is elevated in the majority of children with encephalitis including anti-NMDAR encephalitis and MOG antibody-associated disease [42]. The other reported treatment for refractory autoimmune encephalitis is intrathecal steroids and methotrexate, which have been used in a few case reports of paediatric anti-NMDAR encephalitis who failed conventional therapy [43].

Finally, although treating the underlying disease with immune therapy is paramount, it is necessary to discuss the symptomatic management of anti-NMDAR encephalitis patients as the agitation, psychiatric features, movement disorders, sleep disruption and seizures result in major management challenges and risk to the patients. General principles of symptomatic management are simple and involve sedating agents, agents to induce and maintain sleep, and agents to treat agitation and emotional dysregulation. Benzodiazepines, clonidine, antiepileptic drugs and chloral hydrate or other sleep-inducing agents are often used with some benefit [44]. Neuroleptics appear to have a high incidence of adverse events (neuroleptic malignant syndrome or rigidity) in anti-NMDAR encephalitis, and should be used with caution [44]. Interestingly, agents that act on the NMDA receptor such as ketamine, appear to be tolerated.

RELAPSING COURSE AND OUTCOMES

Relapses are fortunately uncommon in autoimmune encephalitis (Table 2). At this time, a relapsing course

can be anticipated in approximately 12% of anti-NMDAR encephalitis cases within 2 years [3]. The relapse rate has reduced since the initial descriptions of the disease [23], possibly due to the increasing use of second-line therapies and chronic immune suppression, which may be altering the natural history of disease. Given that patients with autoimmune encephalitis generally have monophasic disease, most clinicians use induction therapy that typically provides 6–12 months of immune suppression/modulation (apart from MOG antibody disease when the duration of therapy is shorter), but do not plan to give ongoing immune suppression beyond this point.

In anti-NMDAR encephalitis, the relapses tend to be less severe and can be mono-symptomatic, such as isolated seizures or movement disorder, unlike the initial episode when the disease is almost always poly-symptomatic [3]. If a patient relapses, or if there is ongoing concern that residual immune activity may be occurring, then a chronic immune suppression strategy can be considered such as mycophenolate mofetil, azathioprine or re-dosing rituximab [39].

Although the majority of children with anti-MOG antibody-associated disease have monophasic disease, approximately 30% of children will relapse, typically with ADEM, optic neuritis or myelitis [24,27]. Although many patients have normal MRI brain scans or complete resolution of brain lesions, and are therefore clearly distinguishable from MS, other patients are more challenging. There are little data to base clear recommendations for the relapsing MOG antibody-positive patient, but low dose steroids, monthly IVIG, mycophenolate mofetil or rituximab are the options [7,24,28].

Relapses in other autoimmune encephalitis syndromes are all reported (Table 2), but usually occur in the minority, although the patient numbers are too small to draw confident conclusions.

CHALLENGES AND FUTURE DIRECTIONS

As more information becomes available, it is possible to discuss the differences between syndromes (Table 3 [45,46]). For example, in anti-NMDAR encephalitis, typically there is intrathecal production of NMDAR antibodies, a slow response to immune therapy and second-line treatments are commonly required. By contrast, in anti-MOG antibody-associated disease, there is rarely intrathecal production of antibodies, patients commonly respond quickly to immune therapy, and patients rarely require second-line immune therapy in the acute phase.

One of the fundamental challenges is whether all patients with anti-NMDAR encephalitis should receive rituximab 'upfront' at diagnosis. At this time, clinical observations and the published literature are conflicting on this matter. It is recognized that patients who do not respond to first-line therapy do better if they receive second-line therapy [3]. However, it is recognized that some patients respond quickly to first-line therapy only, and achieve good outcomes without second-line therapy [3]. And furthermore, it is noted that in centres which use second-line therapy (rituximab) in the majority of their patients, the outcomes are not better than other described cohorts [47]. Therefore, at this time, rather than giving all patients upfront rituximab, a therapeutic cascade of first-line

Table 3. Comparison of immunology, pathology and therapy of the two most common auto-antibody-associated encephalitis syndromes in children (anti-NMDAR encephalitis and anti-MOG antibody-associated demyelination)

Characteristic	Anti-NMDAR encephalitis	Anti-MOG-associated demyelination
CSF oligoclonal bands (OCB)	Intrathecal OCB or mirrored OCB typical	Mirrored OCB or negative OCB typical
CSF intrathecal production of auto-antibodies	Common intrathecal production of NMDA-R antibody	Uncommon intrathecal production of MOG antibody
Pathology	B-cell and plasma cell perivascular parenchymal infiltration, deposition of IgG, no complement	B-cell and T-cell perivascular parenchymal infiltration with demyelination, deposition of IgG and complement ('MS type II lesion')
CSF cytokine/chemokine	B-cell chemokine CXCL13 correlates with severity and outcome	Cytokine profile suggests involvement of B cell, Th17 and neutrophils
Speed of response to first line immune therapy (steroids, IVIG, PLEX)	Commonly slow (weeks-months)	Commonly fast (days-weeks)
Need for second-line therapy in acute phase (rituximab, cyclophosphamide)	Common	Uncommon

The two disorders have similarities, but notable differences [27, 45, 46], and personal observations.
MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; PLEX, plasma exchange.

Table 4. The challenges, current practice and future research priorities

Challenges	Current practise	Future clinical research priorities
The 'suspected AE' seronegative patient: auto-antibodies are only found in a proportion of patients	A similar therapeutic approach to box 3 can be followed when: The clinical syndrome is reminiscent of AE, such as anti-NMDAR or limbic encephalitis (despite negative antibody) There is a clear acquired encephalopathy syndrome and there is evidence of inflammation (MRI or CSF), and infection is adequately excluded	Further iteration of the definition of seronegative autoimmune encephalitis that is applicable to children is required, but will be challenging due to absence of clinically available biomarkers (see next row)
Patients with suspected seronegative AE may be immunological heterogeneous	Clinicians should remain aware that non-auto-antibody processes could be operating, that may respond to alternate therapies, for example cyclophosphamide may be better if T cell processes dominate	Biomarkers (radiological, CSF, blood) of the immune process beyond auto-antibodies may have a role including cytokine/chemokine profiles, cellular and molecular biomarkers
CSF biomarkers of inflammation are lacking in routine practise (other than disease specific auto-antibodies)	CSF pleocytosis, protein, oligoclonal bands have limited sensitivity. CSF immunophenotyping is sporadically used and normative data for children is limited, particularly for more complex cell types	CSF neopterin is a sensitive biomarker of inflammation but is not widely available in a time-sensitive manner. CSF cytokine panels may lack disease specificity, but could be useful markers of CNS inflammation CSF oligoclonal bands may have a role in therapeutic decision making and needs investigation Neuronal markers of injury (s100b or neurofilament) could help clinicians identify at risk patients with injurious processes to intensify therapy
When to escalate immune therapy in AE:	It is acknowledged that early therapy is generally better than late.	The issue of whether all patients with moderate-severe AE should receive 'upfront' first-line rituximab needs to be considered, acknowledging some milder patients will respond adequately to first line therapies only.
A significant proportion of patients with AE need second line therapy, but the timing of escalation is not always easy to determine	At this time second line therapies should be strongly considered in patients with anti-NMDAR encephalitis who: Have a severe course, such as needing intensive care Have not responded to first line therapies after 1–2 weeks and remain unwell	The role of second line therapies in seronegative AE is very challenging and can only be judged on a 'case-by-case' manner, and should be reserved for moderate-severe patients only.
The patient who is not improving:	At present, current monitoring includes:	A disease severity score for AE, particularly anti-NMDAR encephalitis, would help clinicians monitor, and aid future clinical trials.
In a patient who is not recovering well, is this due to residual injury or ongoing brain inflammation?	Understanding the natural history. Clinical monitoring remains the most important marker of disease. Auto-antibodies often decline during recovery but can remain positive despite good clinical recoveries (and *vice versa*), so should not be relied on for monitoring. If residual inflammation is possible, further therapeutic escalation can be considered after 'risk versus benefit' considerations.	CSF biomarkers (such as neopterin, CSF CXCL13 or other cytokine/chemokines) could provide insight in to patient recovery and disease monitoring.
Current outcome measures fail to adequately measure cognitive and behavioural outcomes	At present, modified Rankin scores are used, which fail to detect the primary concerns to patient and family (cognitive and behaviour) adequately.	Monitoring and outcome measures that are designed for AE including cognitive and behavioural outcomes are needed, which can facilitate patient management and future clinical trials.

Table 4 (*Continued*)

Challenges	Current practise	Future clinical research priorities
Neuroprotective strategies are not adequately developed in paediatric AE	The inflamed and altered brain is likely to be vulnerable to excitotoxic or metabolic stress, with potential neuronal injury. There is limited literature on neuroprotection in AE.	Lessons from neuroprotective strategies in traumatic brain injury and multiple sclerosis can be considered and applied to AE.
Treating secondary biological dysfunction such as synaptic or receptor hypofunction	Analogous to treating myasthenia gravis with pyrisdostigmine, animal studies are now suggesting additional role of ameliorating receptor hypofunction in anti-NMDAR encephalitis.	Other strategies to enhance receptor function such as studying the role of microglia that we know are crucial in neurodevelopmental processes.

AE, autoimmune encephalitis; CSF, cerebrospinal fluid; NMDAR, N-Methyl D-Aspartate receptor.

followed by second-line therapy should be probably adopted until the literature is more clear on this matter.

Other challenges and future priorities including disease monitoring, and neuroprotective and synaptic strategies are explored further in Table 4.

CONCLUSION

All surface auto-antibodies have changed practice in paediatric neurology, and empowered clinicians to use immune suppressive agents in children with inflammatory brain disease. Despite the great advances, there are no randomized controlled trials to guide treatment, and a large number of children with suspected immune brain disease lack a diagnostic biomarker and remain 'seronegative' and 'unexplained'.

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Conflicts of interest

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