

INVITED REVIEW

Navigating the diagnostic and therapeutic complexities of autoimmune encephalitis

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Abstract

Characterized by immune-mediated inflammation of the brain, autoimmune encephalitis (AE) encompasses a diverse array of disorders, each presenting with unique as well as overlapping clinical manifestations, and underlying autoantibodies targeting neuronal and glial surface antigens. The clinical spectrum can range from subtle cognitive and behavioural changes to severe seizures, movement disorders, and altered consciousness. However, what truly sets AE apart from other encephalitides is its potential reversibility when identified early and managed appropriately.

The identification of N-methyl-D-aspartate receptor (NMDAR) antibody encephalitis in 2007 heralded the discovery of a spectrum of immunotherapy-responsive AE. However, misdiagnosis remains prevalent despite diagnostic algorithms, resulting in unnecessary immunotherapies and delayed treatment of the correct diagnosis. AE diagnosis requires a judicious blend of diagnostic algorithms, antibody testing, and clinical acumen. Testing for antibodies against neuronal surface antigens, preferably in cerebrospinal fluid, is essential, but should be contextual to clinical relevance.

Treatment guidelines are largely based on retrospective studies due to a dearth of randomized and prospective data. However, early immunotherapy initiation has proven to be pivotal for optimal outcomes. The therapeutic landscape in AE continues to evolve with the introduction of novel targeted immunotherapies.

This review highlights the complexities, and proposes a systematic approach, to the diagnosis and treatment of AE.

KEYWORDS

Autoimmune, encephalitis, antibodies, NMDAR, diagnosis, treatment

INTRODUCTION

The first evidence that immunotherapy could improve some forms of encephalitis came from the identification of voltage-gated potassium channel (VGKC) antibodies in association with limbic encephalitis (LE) in 2004.¹ Although the antibody targets were later identified as VGKC-associated proteins rather than VGKC itself, this study was the harbinger for the discovery of immunotherapy-responsive autoimmune encephalitis (AE). The subsequent discovery of N-methyl-D-aspartate receptor (NMDAR) antibody encephalitis (NMDARE) in 2007 and its

detailed characterisation^{2,3} was the catalyst for the discovery of an expanding group of immunotherapy-responsive AE mediated by autoantibodies directed against neuronal and glial cell surface antigenic targets (Table 1). Some of these syndromes are associated with tumours. In contrast, paraneoplastic neurological syndromes in which antibodies are directed against intracellular antigenic targets poorly respond to immunotherapy since antibodies directed against intracellular antigenic targets are not themselves pathogenic.⁴ However, some syndromes with antibodies against intracellular targets, such as glial fibrillary acidic protein (GFAP)⁵ and glutamic acid



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decarboxylase (GAD), may respond to immunotherapy, perhaps due to coexistence of other yet unidentified pathogenic antibodies.⁶

AE has emerged as the third most common cause of encephalitis after infections and acute disseminated encephalomyelitis.^{7,8} Thus, AE is increasingly considered in the differential diagnoses of patients presenting with subacute memory loss, cognitive dysfunction, psychiatric symptoms or refractory seizures. Despite diagnostic algorithms for AE being proposed in 2016,⁹ misdiagnosis remains a frequent clinical problem leading to morbidity resulting from unnecessary immunotherapies and delayed treatment of the correct diagnosis.¹⁰

Treatment guidelines in AE syndromes are largely based on retrospective studies due to the paucity of randomised or prospective data.¹¹ Despite the overall success of immunotherapy, treatment decisions in AE are hindered by the potential of immunomodulatory medications to cause serious complications and the lack of evidence to guide the optimal duration, and timing of escalation, of treatment.

This review highlights the complexities, and proposes a systematic approach, to the diagnosis and treatment of AE.

Diagnosis of AE

The clinical utility of the diagnostic algorithms proposed in 2016 has been endorsed by their extensive use and several validating studies.¹²⁻¹⁴ The following four considerations are likely to reduce misdiagnosis.

First, the fulfilment of the three minimal requirements for possible autoimmune encephalitis (Panel 1) is crucial.

Most of the misdiagnoses occur when AE is considered in patients not fulfilling the three essential criteria (Panel 1).¹⁰ The commonest pitfall was to consider AE in people with

chronic symptoms (>3 months) without inflammatory changes in the brain Magnetic Resonance Imaging (MRI) scan or cerebrospinal fluid (CSF). The third requirement of the criteria is an imperative for rigorous consideration and careful exclusion of mimics of AE including infectious and post-infectious encephalitis/encephalopathy, Central Nervous System (CNS) vasculitis, CNS lymphoma, epileptic syndromes and psychiatric disorders. Adherence to the first two criteria for possible AE had high specificity of about 90% in ruling out primary psychiatric disorders.¹⁵

Second, the three requirements for possible AE should not be used as standalone diagnostic criteria. Instead, these criteria should be used as a checkpoint for entry into the algorithm for the differential diagnosis of AE. Clinical criteria to diagnose AE without the need for antibody testing are shown in Panel 2. A critical caveat to the use of these criteria is that they are not applicable to patients in the very early stages of the disease when they may have few symptoms or an isolated symptom (e.g., only seizures), as the differential diagnosis is too broad.

Third, testing for antibodies against neuronal surface antigens should include CSF. All neuronal surface antibodies occur more frequently in CSF than in serum although anti-LGI1 antibodies are better detected in serum when using currently available cell-based assays¹⁶. Myelin oligodendrocyte glycoprotein (MOG) antibodies occur more frequently in serum than CSF. Half of the diagnostic errors in patients misdiagnosed with AE occurred due to analysis of serum instead of CSF.¹⁰

Fourth, detection of autoantibodies must be considered in context of clinical relevance. For example, the frequency of thyroid antibodies in patients with autoimmune CNS disorders is not different from that seen in patients with alternative diagnoses or people who are healthy while low titres of GAD65 antibodies are detected in about 8% of healthy people.^{16,17}

Panel 1. Diagnostic criteria for possible AE (all three of the following criteria must be met)

1. Subacute onset (rapid progression of <3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms
2. At least one of the following:
 - New focal Central Nervous System (CNS) findings
 - Seizures not explained by a previously known seizure disorder
 - Cerebrospinal fluid (CSF) pleocytosis (white blood cell count of more than 5 cells per mm³)
 - Magnetic Resonance Imaging (MRI) features suggestive of encephalitis
3. Reasonable exclusion of alternative causes

Panel 2. Clinical criteria for AE

Probable NMDARE⁹

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:
 - 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 electroencephalogram (EEG) (focal or diffuse 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 autoimmune limbic encephalitis (LE)⁹

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

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system
2. Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes
3. At least one of the following:
 - CSF pleocytosis (white blood cell count of more than 5 cells per mm³)
 - EEG with epileptic or slow-wave activity involving the temporal lobes
4. Reasonable exclusion of alternative causes

Probable Leucine-rich glioma-inactivated 1 (LGI1)-LE¹⁵

1. Subacute onset (<3 months) of
 - Cognitive dysfunction AND
 - Faciobrachial dystonic seizures (FBDS) or frequent (>5 per day) stereotypical focal seizures
2. Reasonable exclusion of alternative causes

GAD65 antibodies assume clinical significance in neurological disorders only if detected at titres over 1000 IU/ml.¹⁸

Among the alternative disorders for exclusion, new onset psychosis has a high frequency of misdiagnosis as AE. Patients with psychosis caused by a psychiatric disease rarely develop focal CNS deficits, seizures, or MRI inflammatory changes.^{16,19} Although many patients with NMDARE do not have neurologic symptoms at disease onset, about 80% have CSF pleocytosis and >95% have EEG abnormalities.¹⁹ Thus, a diagnosis of AE should not be considered in patients presenting with isolated psychiatric symptoms unless they have NMDAR antibodies in CSF (not serum) or evidence of CSF or MRI inflammatory changes, or EEG abnormalities. It is noteworthy that only <5% of patients with NMDARE would have a monosymptomatic presentation.¹⁹ Thus, a first episode of psychosis or isolated refractory seizures should be considered in context of the diagnostic algorithm (Panel 1 and 2) if a diagnosis of AE is considered.

Up to half of the patients with clinically probable AE may not have detectable autoantibodies²⁰ and are classified as autoantibody negative AE. Diagnostic criteria for antibody negative AE are shown in Panel 3.

It must be noted that patients with encephalitis mediated by antibodies not included in standard diagnostic panels might be considered seronegative. MOG antibodies may not be routinely tested in patients presenting with focal encephalitis (FLAMES – FLAIR-hyperintense lesions in MOG antibody associated encephalitis with seizures) which may result in it

being classified as antibody-negative AE. Gamma-aminobutyric acid_A (GABA_A) receptor encephalitis (mainly in children) and anti-neurexin-3 α encephalitis at its onset may clinically mimic NMDARE (Table 1), but may be misclassified if specific antibodies are not tested.

Given the severity of its clinical presentation, new-onset refractory status epilepticus (NORSE) is likely to be over diagnosed as antibody-negative AE. NORSE is a poorly defined syndrome that represents multiple disorders. Adherence to the diagnostic algorithm is likely to avoid misdiagnosis and escalation of immunotherapy that is ineffective in non-immune NORSE.

Lack of an objectively measured clinical response after 3 to 4 months of immunotherapy may be considered as evidence against a diagnosis of AE in patients initially diagnosed as antibody-negative AE.¹⁶

Treatment of AE

Evidence from retrospective studies have demonstrated significant benefit of early initiation of first line immunotherapy in AE.¹¹ However, there is a lack of randomised or prospective data to guide optimal treatment regimens, timing of escalation to second- or third-line therapies and the duration for maintenance therapy in individual AE syndromes. The tiers of immunotherapy in AE is shown in Table 2. This review will focus on the two most common types of AE, namely NMDARE and Leucine-rich glioma-inactivated 1 (LGI1)-LE.

Panel 3. Autoantibody negative AE

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

1. Rapid progression (< 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms
2. Exclusion of well-defined syndromes of AE (eg, limbic encephalitis, Bickerstaff brainstem encephalitis, acute disseminated encephalomyelitis)
3. Absence of well characterised autoantibodies in serum and CSF, and the presence of at least two (one if paediatric) of the following criteria:
 - MRI abnormalities suggestive of autoimmune encephalitis
 - CSF pleocytosis, CSF-specific oligoclonal bands or elevated CSF IgG index, or both
 - Brain biopsy showing inflammatory infiltrates and excluding other disorders (e.g., tumour)
4. Reasonable exclusion of alternative causes

TABLE 1 Characteristics of neural surface-antibody AE syndromes

Target antigen	When to suspect (distinctive features)						Tumour association	Relapse rate
Common								
	Sex F:M	Age (range), years	Clinical profile	MRI	CSF	EEG		
NMDAR	3:1	95% <45 (2 months to 85)	Subacute onset; multistage progression; flu-like symptoms, psychiatric/behavioural disturbances, seizures/status epilepticus, movement disorders, altered consciousness, autonomic dysfunction, central hypoventilation	60% NAD	20% NAD 80% lymphocytic pleocytosis; 65% OCB	Epileptiform, encephalopathic; 5-10% extreme delta brush	20% ovarian teratoma; 2% extra-ovarian teratoma or other	10-20%; <5% risk of chronic epilepsy
LGI1	1:2	Median 64 (20-92)	Faciobrachial dystonic/stereotypical focal seizures, amnesia, cognitive impairment, hyponatraemia	50% mesial temporal T2H	75% NAD	50% NAD	<10% thymoma	30%
Uncommon								
CASPR2	1:9	Median 60 (1.5-80)	Neuromyotonia, autonomic dysfunction, LE, disordered sleep; myokymia on EMG	25% mesial temporal T2H	20% lymphocytic pleocytosis; 25% OCB	40% epileptiform	20% thymoma	30%
AMPAR	2:1	Median 55 (20-90)	LE, seizures, amnesia, cognitive impairment, disordered sleep	Frequent mesial temporal T2H	Lymphocytic pleocytosis	30% epileptiform	50-70% SCLC, breast, thymus, and ovarian cancers	Tumour relapses
GABA _A R	1:1	Median 40 (1-90)	Encephalitis, refractory seizures / status epilepticus, movement disorders	Multifocal cortical and subcortical fluffy T2H	60% lymphocytic pleocytosis	80% epileptiform	<20% tumours	10%; risk 15% of chronic epilepsy
Neurexin -3α	3:1	Median 45 (20-60)	Prodromal fever, gastrointestinal symptoms, orofacial dyskinesia, seizures, encephalopathy	20% mesial temporal T2H	Lymphocytic pleocytosis		None	40% mortality
DPPX	1:2	Median 55 (13-90)	Prodromal diarrhoea and weight loss with progressive cognitive impairment and seizures, hallucinations and agitation, movement disorders, hyperekplexia, autonomic dysfunction	NAD	30% lymphocytic pleocytosis	70% focal or diffuse slowing	10% B cell neoplasms	30%
GlyR	3:2	Median 45 (1-80)	Progressive encephalomyelitis, with rigidity, central myoclonus, and hyperekplexia, 60% CMUA on EMG	5% mesial temporal T2H	40% lymphocytic pleocytosis	60% slowing	10% mainly thymoma, lymphoma, breast,	15%
IgLON-5	1:1	Median 64 (13-85)	Chronic progressive, RBD and non-REM parasomnias, disordered sleep, parkinsonism	80% NAD	30% lymphocytic pleocytosis	90% NAD	None	60% mortality

AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2, contactin-associated protein-like 2; DPPX, dipeptidyl-peptidase-like protein-6; GABA, gamma-amino butyric acid; GlyR, glycine receptor; LE, limbic encephalitis; LGI1, leucine-rich glioma-inactivated 1; NAD, no abnormalities detected; NMDAR, N-methyl-D-aspartate; OCB, oligoclonal bands; SCLC, small cell lung cancer; T2H, T2 hyperintensities on MRI

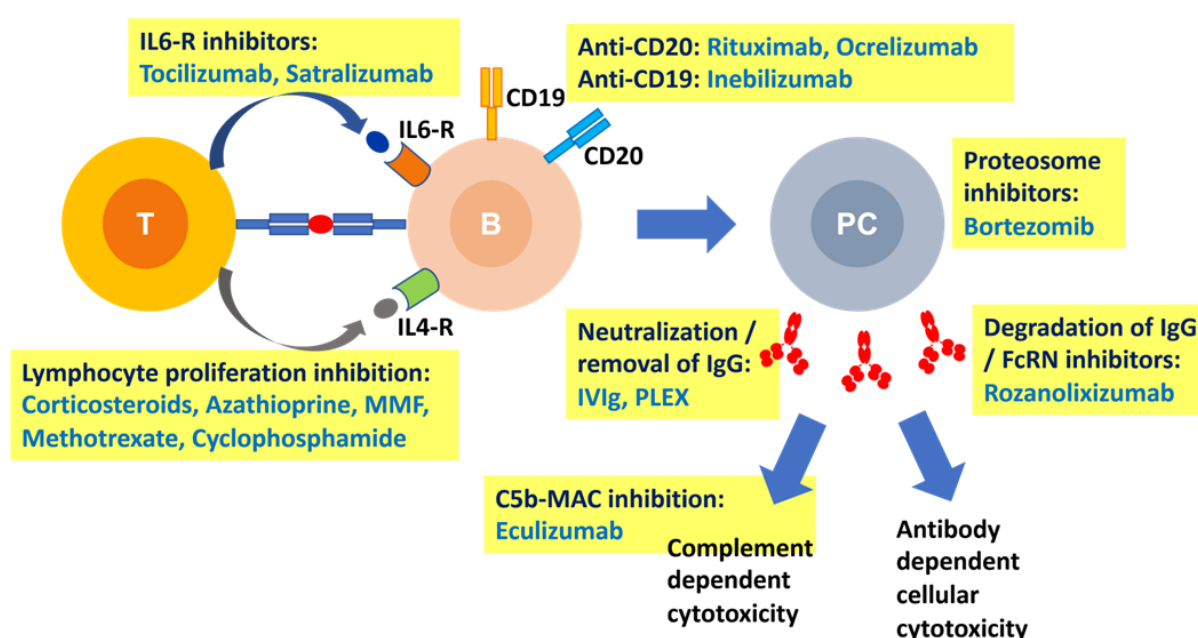
TABLE 2 Immunotherapeutic agents in AE

Immunotherapy tier	Agent
First line	Corticosteroids, intravenous immunoglobulins, plasma exchange
Second line	Rituximab, azathioprine, mycophenolate, methotrexate, cyclophosphamide
Third line	Tocilizumab, bortezomib

The number of targeted immunotherapeutic agents effective in AE are likely to expand when the results of the following ongoing trials become available: Inebilizumab in NMDARE (ExTINGUISH trial), humanised IL6 inhibitor in NMDARE and LGI1-LE (<https://clinicaltrials.gov/ct2/show/NCT05503264>), Bortezomib in refractory AE (<https://clinicaltrials.gov/ct2/show/NCT03993262>), and Rozanolixizumab in LGI1-LE (<https://clinicaltrials.gov/ct2/show/NCT04875975>).

An understanding of the mechanisms by which the autoantibodies are generated and perpetuated have important implications for rationalising the choice of immunotherapy in AE. Evaluating serum and CSF antibody titres in individuals across multiple AE syndromes demonstrates that autoantibodies are persistently present at higher levels in serum compared to CSF, thereby suggesting that the initial generation of autoantibodies is peripheral.²¹ Hence, therapeutic options

targeting peripheral B-cell compartments or soluble circulating IgG have significant potential and proven efficacy. However, the presence of antigen-specific B-cells in the CSF mediating intrathecal synthesis of autoantibodies highlight the need to simultaneously target the intrathecal compartment in the treatment of AE.²¹ The immunological targets of currently available immunotherapies are outlined in Figure 1.



B – B lymphocytes; FcRN – neonatal Fc receptor; IL – interleukin; IVIg – intravenous immunoglobulins; MAC – membrane attack complex; MMF – mycophenolate mofetil; PC – plasma cells; PLEX – plasma exchange; T – T lymphocytes.

FIGURE 1

NMDARE

The best outcomes in NMDARE have been reported in patients who received early immunotherapy^{22, 23} and early removal of an associated tumour, particularly ovarian teratomas that contain B cells with NMDAR reactivity.²³ A lack of immunotherapy within 30 days of disease onset was associated with an almost 3-fold increased odds of poor outcome.²²

In patients who failed first-line immunotherapies, second-line treatments have been shown to result in good outcomes.^{22, 23} Overall, there is a 10-15% risk of relapse at 2 years, which is significantly lowered in those who receive second-line immunotherapies.²⁴ Emerging evidence show that rituximab administration is associated with a greater likelihood of achieving a good outcome (mRS 2)²⁵ and 6-fold reduced odds of relapse after ≥ 24 months follow-up.²² Although there is insufficient evidence to guide the exact timing of escalating treatment, it has been observed that patients receiving earlier initiation of second-line immunotherapy (within 60 days of disease onset) was associated with 7-fold reduced odds of poor outcome compared with later initiation.²² Generally, it is reasonable to escalate to second-line immunotherapy, particularly rituximab, if there is no improvement within 14 days of commencing first-line immunotherapy. In NMDARE, it is usually not necessary to give maintenance doses of rituximab after an initial course. Cyclophosphamide is considered if there is no response within 4 weeks after the first dose of rituximab, or simultaneously with rituximab in patients with severe disease.

Third line immunotherapy is considered in patients with refractory AE not responding to rituximab and/or cyclophosphamide. Tocilizumab, which blocks the interleukin-6 (IL-6) receptor (Figure 1), has been used in combination with teratoma removal, corticosteroids, IVIg and rituximab in a large prospective cohort, demonstrating superior outcomes when compared to either the use of rituximab monotherapy, or the use of only first-line therapies.²⁶

A limitation of all cluster of differentiation (CD)-20-targeted approaches such as rituximab is that they do not eliminate the non-CD20 expressing, long-lived plasma cells, which has led to the consideration of monoclonal antibody targeting of antigens specific to these cells. Bortezomib, which targets the proteasome, shows a theoretical predilection for plasma cells, and has been reported to be efficacious in small series of severe refractory cases.²⁷

LGI1-LE

Immunotherapy has been shown to significantly cause cessation of faciobrachial dystonic seizures (FBDS), prevent cognitive impairment and improve long term outcomes.^{28, 29} Although first-line immunotherapies have been shown to be efficacious in the treatment of LGI1-LE,³⁰ the evidence for rituximab has been conflicting.^{25, 31}

Seizures in LGI1-antibody encephalitis are thought to represent acute symptomatic seizures rather than a persisting epileptogenic focus. Thus, the prolonged use of antiseizure medications is often not required in these patients.

Chronic immunotherapy in AE

The role for chronic immunotherapy in AE has not been adequately addressed in the literature. AE can follow a monophasic or relapsing course. Rapid discontinuation of immune suppression, particularly corticosteroids, has been noted to result in early recurrence. Thus, a tapering strategy is recommended once patients have achieved maximal clinical response to the initial immunomodulatory therapy.

Common tapering strategies include an oral prednisolone taper, monthly intravenous methylprednisolone, monthly intravenous immunoglobulin, and rituximab. The latter two agents are preferred when corticosteroids cause intolerable adverse effects. The duration of the taper typically extends over a 2-to-6-month period. Patients who received either rituximab or cyclophosphamide in their initial immunotherapy may not need a taper since these agents achieve a longer-sustained immunosuppression and have been shown to be associated with a lower risk of relapse²².

The optimal duration of maintenance therapy in patients with relapsed disease is unknown. Expert opinion supports a treatment period of three years.³² Azathioprine and mycophenolate mofetil have traditionally been used in this setting, overlapping with oral glucocorticoids for at least 2-to-6 months.

Conclusion

Mimics of AE are common. AE diagnosis should be guided by careful application of diagnostic algorithms and by judicious antibody testing. However, clinical reasoning should prevail in interpreting antibody results, and to do so, clinicians must become familiar with the syndromes of AE and related inflammatory disorders of the CNS. The best outcomes in AE are achieved with early initiation of immunotherapy. The therapeutic landscape of AE is expanding with the introduction of targeted immunotherapy.

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