

AUTOIMMUNE ENCEPHALITIS: DIAGNOSTIC CHALLENGES, CLINICAL DIFFERENTIATION FROM INFECTIOUS CAUSES, AND EVOLVING IMMUNOTHERAPEUTIC STRATEGIES

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Abstract

Autoimmune encephalitis (AE) is a diverse group of inflammatory brain disorders that involve the production of antibodies against either neuronal, synaptic or glial antigens, and/or T cells. It has advanced from a largely paraneoplastic notion to a wide range of diseases, such as antibody-mediated syndromes involving cell surfaces, antigen-mediated syndromes involving intracellular antigens, post-infectious encephalitis, immune checkpoint inhibitor-induced encephalitis, and clinically probable antibody-negative AE. The main clinical problem is to identify a proper clinical syndrome early, in addition to identifying a neural antibody, which also needs to be differentiated from the other inflammatory disorders, malignancy, and epilepsy-related states, toxic-metabolic encephalopathy and primary psychiatric illness. Thus, a safe diagnostic approach combines tempo, phenotype and magnetic resonance imaging (MRI), electroencephalography (EEG), studies of cerebrospinal fluid (CSF), paired serum-CSF antibody testing, microbiological studies, and tumor screening based on the phenotype. The course of therapy with acyclovir should be started when herpes simplex virus encephalitis is considered possible, but should not be unnecessarily delayed in a severe, clinically coherent AE syndrome if it has been reasonably excluded or controlled. High dose corticosteroid, intravenous immunoglobulin and/or plasma exchange are first line agents and rituximab/cyclophosphamide for non-response, severe disease or relapse. Other targeted therapies (tocilizumab, bortezomib, daratumumab, FcRn antagonists and others) are promising but have limited evidence in the form of observational evidence, small case series, or ongoing trials. The

recovery process is often delayed and good motor outcome is possible in the presence of ongoing cognitive, psychiatric, language and epilepsy-related disabilities. Future progress relies on biomarkers validated in multiple trials, and standardized outcome measures, as well as randomized and adaptive trials and equitable precision-medicine frameworks which integrate clinical information, immunophenotyping and multi-omics. (Abboud et al., 2021; Almweisheer et al., 2026; Chen et al., 2026; Thilak et al., 2026).

Introduction

Immuno-mediated dysfunction of the brain with inflammation, typically manifesting over days to weeks, with signs of altered mental status, memory loss, psychiatric or behavioral changes, seizures, language dysfunction, movement abnormalities, sleep disturbance or autonomic instability, is defined as autoimmune encephalitis as it is a syndrome level diagnosis. It includes disorders with antibodies to extracellular neuronal and/or synaptic targets, disorders associated with antibodies to intracellular onconeural antigens and CT-cell injury, and perhaps antibody-negative syndromes, evidenced clinically and paraclinically. The phenotype is diffuse, limbic, cortical, brainstem-predominant or mixed, meaning AE should be considered as a collection of different diseases with similar characteristics and not as a single disease. (Dalmau & Graus, 2018; Graus et al., 2016; Sechi & Flanagan, 2021).

The recognition of AE has revolutionized the field of neurology as several types are potentially treatable even though they may present with dramatic features, mimicking primary psychosis, viral encephalitis, refractory epilepsy, rapidly progressive dementia or toxic-metabolic coma. It then came to be known as anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis but later on other antibodies such as LGI1, CASPR2, GABAB receptor, AMPA receptor, GABAA receptor, DPPX, glycine receptor, IgLON5 and more were identified, which led to a wider clinicopathological spectrum. Biological localization of the antigen is clinically useful, as antibodies against cell surface or synaptic targets tend to lead to disruption of receptor/channel function, and may respond well to immune therapy whereas intracellular-antigen syndromes tend to reflect T-cell mediated destruction of the

affected neurons, a greater association with cancer and less complete treatment responses. (Dalmau et al., 2008; Dalmau & Graus, 2018; Prüss, 2021; Sechi & Flanagan, 2021).

AE is particularly significant in emergency and critical care as the condition can develop into status, intense agitation, dyskinesia, autonomic instability, central hypoventilation, coma and/or respiratory failure. Because of these complications, there is a limited time frame in which intervention to stabilize the patient can be made, the need for empirical anti-infective therapy when indicated, lumbar puncture and neurodiagnostic testing, and the need to determine whether or not it is appropriate to begin immunotherapy before the results of antibody testing. Diagnostic delay is correlated with longer hospital stay, increased treatment intensity and poorer functional or neurocognitive outcome, particularly in children, and in patients with anti-NMDAR encephalitis. (Byrne et al., 2015; Lin et al., 2026; Thilak et al., 2026; Titulaer et al., 2013).

This narrative review covers the immunopathogenesis and classification of AE; the clinical features; clinical and paraclinical differentiation of autoimmune from infectious encephalitis; clinical value of MRI, EEG, CSF, antibody testing and tumour screening; management in the acute and intensive care setting, current and emerging immunotherapies, prognosis and priorities for biomarker-driven precision therapy. Special focus is given to diagnostic reasoning, as neither a positive antibody level nor a negative pathogen test is, alone, enough to make a correct diagnosis. (Almweisheer et al., 2026; Dalmau & Graus, 2023; Van Steenhoven et al., 2023).

Methodology

Review Design

This study was designed as a complete narrative assessment of the existing information on autoimmune encephalitis (AE), with a focus on diagnostic problems, separation from viral encephalitis, and emerging immunotherapeutic options. The study utilized a structured literature search and evidence synthesis approach while retaining the flexibility of a narrative review to incorporate developing concepts and expert advice.

Literature Search

A comprehensive literature search was performed using PubMed/MEDLINE, Scopus, Web of Science, Google Scholar, and Embase. Articles published between January 2021 and June 2026 were prioritized to provide the most up-to-date evidence. Landmark publications published before 2021 were also included when they represented the original description of disease entities, internationally accepted diagnostic criteria, or established therapeutic recommendations. The search strategy combined Medical Subject Headings (MeSH) and free-text keywords, including: *autoimmune encephalitis*, *anti-NMDAR encephalitis*, *limbic encephalitis*, *infectious encephalitis*, *viral encephalitis*, *diagnostic biomarkers*, *cerebrospinal fluid*, *MRI*, *electroencephalography*, *autoantibodies*, *immunotherapy*, *rituximab*, *intravenous immunoglobulin*, *plasma exchange*, *tocilizumab*, and *precision medicine*. Boolean operators ("AND", "OR") were used to refine the search.

Study Selection

Peer-reviewed original research articles, systematic reviews, meta-analyses, narrative reviews, clinical guidelines, consensus statements, observational cohort studies, and clinically important case series were considered eligible for inclusion. Studies were selected based on their relevance to autoimmune encephalitis diagnosis, clinical presentation, differential diagnosis, immunopathogenesis, management strategies, prognosis, and emerging therapeutic approaches. Conference abstracts without full publications,

duplicate studies, non-English publications lacking reliable translation, and reports with insufficient clinical information were excluded.

Evidence Synthesis and Data Extraction

The selected studies provided relevant information on epidemiology, immunopathogenesis, antibody-associated syndromes, clinical manifestations, diagnostic investigations, differentiation from infectious encephalitis, treatment strategies, prognosis, and future therapeutic developments. Evidence from worldwide consensus recommendations and large multicenter observational studies was prioritized whenever possible. Because randomized controlled trials in autoimmune encephalitis are scarce, particularly for new immunotherapies, data of treatment efficacy were taken with caution. Experimental therapies were obviously distinguishable from standard therapeutic practice.

Quality Consideration

High-quality evidence was prioritized, including worldwide consensus guidelines, multicenter cohort studies, systematic reviews, and landmark publications. When evidence was inconsistent or predominantly based on retrospective studies or case series, this limitation was noted throughout the review.

Review Approach and Scope

The article presents a summary and synthesis of the literature supplied for 2021-2026 and some foundational studies mentioned in the provided literature. Recommendations that were reached by consensus, large observational studies, studies on the diagnosis of the disease, recent reviews on the disease, and new studies on biomarkers or treatment were prioritized. Due to the predominance of retrospective cohorts and uncontrolled series in therapeutic experience with AE, statements on the relative efficacy of various treatment options are presented with explicit caution and investigational therapies are separated from established clinical practice. (Gumienny, 2026; Thilak et al., 2026).

Results and Discussion**Epidemiology and Clinical Significance**

This rise in the apparent incidence of AE is the result of the discovery of neural antibodies, the increasing availability of cell-based assays and the increased awareness of clinicians. Population-based studies indicate that autoimmune encephalitis and infectious encephalitis have similar orders of magnitude in some contexts, though with differences in age, geographic, testing patterns, case definition and referrals. Anti-NMDAR encephalitis is seen more often in children and young adults, LGI1 encephalitis more often in older adults, and paraneoplastic intracellular-antigen syndromes are related to the epidemiology of the associated cancers. (Dubey et al., 2018; Lin et al., 2026; Sechi & Flanagan, 2021).

AE underestimation by only using modified Rankin Scale (mRS) or survival as outcome measure. Some patients may have residual memory, executive function, processing speed, language, social cognition, mood, academic/occupational performance and sleep deficits upon regaining ambulation and independence. Apparent good motor recovery may not be enough for children, requiring long-term educational support, and adults may have lasting

fatigue, psychiatric problems, reduced earning potential or problems with epilepsy. (Lin et al., 2026; McKeon et al., 2018; Thilak et al., 2026).

The effects of health systems are also significant, as patients can make repeat emergency department visits, be admitted to psychiatric beds, have lengthier EEG monitoring, stay in intensive care, receive mechanical ventilation, have more microbiological testing, be screened for cancer, undergo rehabilitation, and receive repeated courses of immunotherapy. It is therefore clinically and economically relevant to have a diagnostic pathway that can identify those at high risk of having the disease as early as possible without overdiagnosing. (Almweisheer et al., 2026; Thilak et al., 2026; Van Steenhoven et al., 2023).

Across large autoimmune encephalitis cohorts, anti-NMDAR encephalitis was the most commonly observed antibody-mediated subtype, particularly among younger females. ICU hospitalization rates varied from 34-75%, reflecting the prevalence of severe neurological sequelae. Nonetheless, early immunotherapy led in favourable functional recovery (modified Rankin Scale 0-2) in around 72-81% of patients, with relapse rates generally remaining below 15%, emphasising the importance of early detection and long-term follow-up (Figure 1).

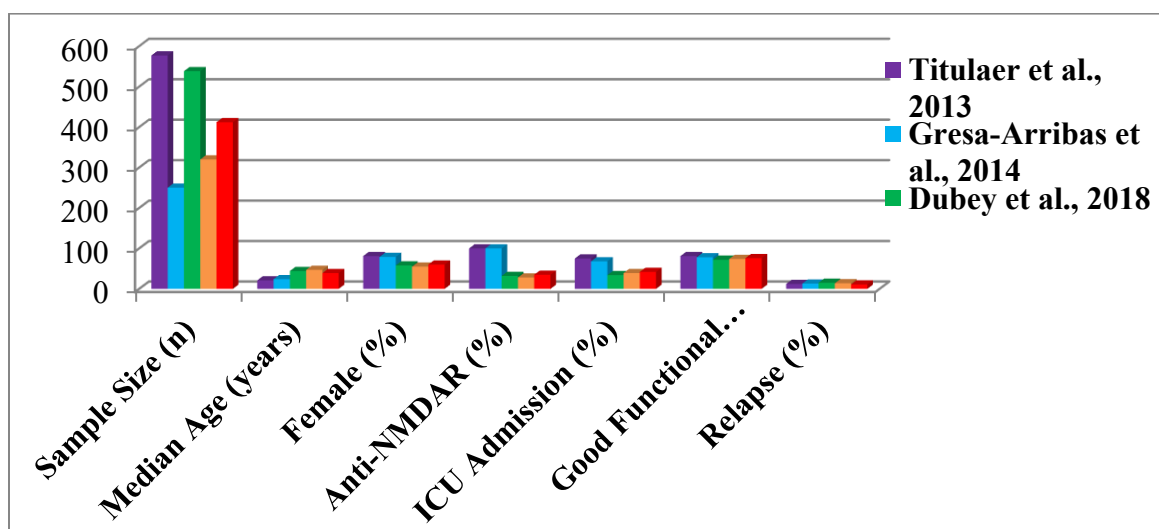


Figure 1: The key epidemiological findings in major autoimmune encephalitis at clinical studies
Immunopathogenesis

AE may occur when a tumor, infection, side effect of a drug or an unknown factor affects immunity and causes a loss of tolerance. This leads to a response that can include activation of autoreactive B cells, differentiation into plasmablasts and plasma cells, intrathecal antibody production, recruitment of T cells, release of inflammatory cytokines, activation of complement in certain syndromes, activation of microglia, and changes in the blood brain barrier permeability. The contribution of these pathways varies with the antigen, immunoglobulin subclass, stages of the disease and host factors. (Chen et al., 2026; Prüss, 2021; Ryding et al., 2023).

Antibodies to the extracellular domains can be directly pathogenic. Experimental studies on anti-NMDAR encephalitis show that the antibodies activate cross-linking and endocytosis of NMDARs, which decreases the number of synapses containing NMDARs, but does not necessarily kill the neurons. Mechanisms that are related include changes in receptor trafficking, blocking protein-protein interactions, dysfunction of ion channels, and changes in the organization of synapses. This functional pathophysiology may provide some answers to why neuropsychiatric disease can be reversible and why some clinical improvement can still occur for months after immune therapy (Dalmau et al., 2008; Dalmau & Graus, 2018).

LGI1 and CASPR2 antibodies are often of the IgG4 subclass which has poor complement activation and may block extracellular protein interactions. LGI1 autoimmunity is an autoimmune disorder that affects the LGI1-ADAM22/23 synaptic complex and is linked to limbic encephalitis, hyponatremia and

faciobrachial dystonic seizures. Autoimmunity to CASPR2 can involve central and peripheral nervous systems, resulting in symptoms of the limbic system, neuropathic pain, peripheral nerve hyperexcitability, dysautonomia or Morvan syndrome (Irani et al., 2010; Irani et al., 2011; Sechi & Flanagan, 2021).

Antibodies to intracellular antigens (Hu, Ma2, CRMP5/CV2, Ri, and amphiphysin) are typically the markers of an immune response that involves the involvement of cytotoxic T cells. The syndromes have often been associated with tumors and are commonly associated with irreversible loss of neurons, which may be the reason why they have a poor response to pure antibody removal therapy. GAD65 falls between the extremes: although the target is intracellular, and high titres and intrathecal production indicate neurological autoimmunity, there is also some clinical heterogeneity and a range of potential pathologies including significant infiltrates of T-cells, cerebellar ataxia, stiff-person spectrum disease, chronic epilepsy, or overlapping antibodies (Qiu et al., 2026).

The interaction between microbe and immune system is seen in post infectious autoimmunity. Patients with anti-NMDAR encephalitis are a subset who develop anti-NMDAR encephalitis following HSV encephalitis and typically experience new psychiatric symptoms, movement disorder, seizures or neurological deterioration following a period of recovery. The suggested mechanisms are antigen release from damaged neurons, exposure of normally sequestered antigens, and maturation of autoreactive B-cell responses that are locally present in the CNS (Armangue et al., 2018).

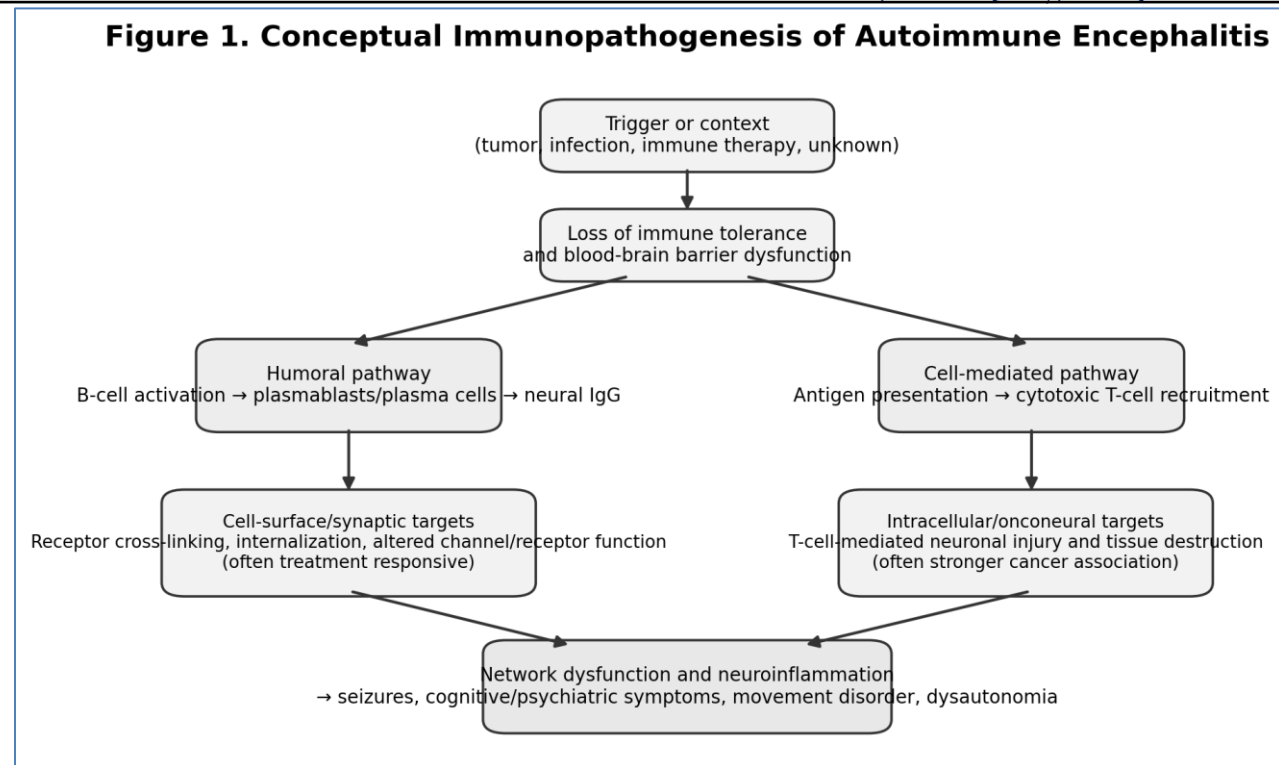


Figure 1: Conceptual immunopathogenesis of autoimmune encephalitis. The schematic distinguishes predominantly antibody-mediated cell-surface/synaptic disease from intracellular-antigen syndromes in which cytotoxic T-cell injury is often central. Adapted conceptually from Dalmau and Graus (2018), Prüss (2021), Ryding et al. (2023), and Thilak et al. (2026).

Classification and Antibody-Phenotype Associations

It is useful to make a distinction between cell-surface or synaptic antibodies and intracellular antibodies, but it is important to realize that this distinction is not completely predictive of pathogenicity, the risk of cancer or treatment sensitivity. Generally, the case for antibody-directed therapy is stronger for the cell surface syndromes; the case for intracellular-antigen syndromes is even stronger and calls for more intense suppression of cellular immunity. The significance of seronegative AE is maintained due to the fact that there are not all antigens included in the commercially available panels, and some may be primarily cell mediated. (Almweisheer et al., 2026; Sechi & Flanagan, 2021).

Patients with anti-NMDAR encephalitis may present with behavioral changes, insomnia, anxiety, psychosis, language disturbances or seizures followed by dyskinesia, catatonia-like

syndrome, impaired level of consciousness, autonomic instability and severe cases, central hypoventilation. The risk of ovarian teratoma is greatest in adolescent and adult females, less in prepubertal girls and different in various populations and of varying incidence depending on age and sex. MRI may be normal, while EEG is typically abnormal, and may exhibit very intense delta brush (Dalmau et al., 2011; Lin et al., 2026; Schmitt et al., 2012).

LGI1 encephalitis features rapid progression of short-term memory loss, confusion, sleep disturbances, focal seizures, faciobrachial dystonic seizures, and recurrent hyponatremia. Prompt immunotherapy is important since faciobrachial dystonic seizures can be a precursor to full limbic encephalitis and are often not adequately controlled with antiseizure medication. CASPR2 disease is wider and encompasses encephalitis, neuromyotonia, neuropathic pain, autonomic symptoms and Morvan syndrome – thymoma is a

significant association in some CASPR2 phenotypes (Irani et al., 2011; Sechi & Flanagan, 2021; Singla et al., 2026).

GABAB receptor encephalitis can often be accompanied by severe seizures or status epilepticus and is highly associated with small cell lung cancer. Clinical signs of AMPA receptor encephalitis consist of limbic dysfunction, and may be associated with breast, lung or thymic tumors. Exaggerated startle, myoclonus,

agitation, weight loss and prominent diarrhea may be symptoms of DPPX disease. IgLON5 disease typically presents a chronic course characterised by parasomnias, sleep-disordered breathing, bulbar dysfunction, gait instability, movement abnormalities and inflammatory findings which may be present or absent, and respond to treatment in varying ways (Sechi & Flanagan, 2021; Thilak et al., 2026) (Table 1).

Table 1: Major antibody-associated autoimmune encephalitis syndromes

Antibody/target	Location	Typical phenotype	Important tumor association	Treatment implication
NMDAR (GluN1)	Cell surface/synaptic	Behavioral or psychiatric change, seizures, language dysfunction, dyskinesia, autonomic instability	Ovarian teratoma; risk varies by age and sex	Often responsive; CSF testing essential
LGI1	Secreted synaptic protein	Limbic encephalitis, faciobrachial dystonic seizures, hyponatremia	Usually non-paraneoplastic	Prompt immunotherapy can prevent cognitive decline
CASPR2	Cell surface	Limbic encephalitis, neuropathic pain, neuromyotonia, Morvan syndrome	Thymoma in selected cases	Central and peripheral manifestations may coexist
GABAB receptor	Cell surface/synaptic	Severe seizures or status epilepticus, limbic encephalitis	Small-cell lung cancer	Aggressive tumor search and immunotherapy
AMPA receptor	Cell surface/synaptic	Limbic encephalitis, memory and psychiatric symptoms	Breast, lung, thymic tumors	Relapse and tumor surveillance important
GABAA receptor	Cell surface/synaptic	Encephalopathy, refractory seizures, multifocal cortical lesions	Variable	May require rapid escalation
DPPX	Cell surface	Diarrhea, weight loss, agitation, tremor, myoclonus, startle	Uncommon	Systemic prodrome can be a clue
IgLON5	Cell surface with tauopathy overlap	Parasomnia, sleep apnea/stridor, bulbar and gait dysfunction	No consistent tumor association	Often chronic with variable immune response
GAD65	Intracellular enzyme	Chronic temporal epilepsy, limbic encephalitis, stiff-person spectrum, ataxia	Usually not strongly paraneoplastic	Often less complete response; confirm high titer/intrathecal synthesis

Antibody/target	Location	Typical phenotype	Important tumor association	Treatment implication
Hu, Ma2, CRMP5, Ri, amphiphysin	Intracellular/oncogenic neural	Limbic, brainstem, sensory, cerebellar, or multifocal syndromes	Strong, antibody-specific cancer associations	Tumor treatment and T-cell-directed strategy are central

Note. Phenotypes and tumor associations are probabilistic rather than absolute. Sources: Sechi and Flanagan (2021), Singla et al. (2026), and Thilak et al. (2026).

Clinical Presentation and Temporal Evolution

The course of AE is typically subacute (occurring over weeks or less than 3 months) although for some syndromes, the course is hours, months or chronic. It may have a vague prodrome consisting of headache, low grade fever, malaise, sleep disturbance or gastrointestinal symptoms, but this doesn't make the diagnosis insignificant. The most important clinical cue is the onset of a new cognitive, psychiatric, convulsive, movement, language, sleep or autonomic symptom or combination of symptoms not otherwise explained (Graus et al., 2016; Thilak et al., 2026).

Psychiatric symptoms include anxiety, agitation, paranoia, hallucinations, mania like state, disinhibition, emotional lability, catatonia and severe insomnia. In patients with isolated psychiatric illness, expansion of the antibody screen is not indicated, but if there are suggestive clinical features (e.g. new seizures, fluctuating conscious level, abnormal movements, autonomic instability, focal deficits, significant cognitive change, inflammatory CSF, or abnormal EEG), the child should be assessed by a neurologist. What can occur is overdiagnosis, which occurs if there's some statistical information in the serum that may be pretty common and is misinterpreted by a common psychiatric disease and without neurological proof. What can happen is overdiagnosis which is when you're getting some statistical information in the serum that's very common and you're misinterpreting that with a common psychiatric disorder and no neurological evidence (Almweisheer et al., 2026; Dalmau & Graus, 2023; Van Steenhoven et al., 2023).

Seizures occur in all AE subtypes and can be focal, bilateral tonic-clonic, nonconvulsive or status

epilepticus. Immune-mediated, infectious, genetic, toxic, metabolic and cryptogenic are all possible causes of new-onset refractory status epilepticus (NORESS). The fact that faciobrachial dystonic seizures are a high value clue to LGI1 autoimmunity while anti-NMDAR encephalitis can involve mixed seizure types and dyskinesia and encephalopathy should alert you to the possibility of autoimmunity. If structural injury or intracellular-antigen-associated mechanisms have resulted in irreversible network damage the likelihood of persistent epilepsy following the active inflammatory phase is greater (Irani et al., 2011; Singla et al., 2026; Steriade et al., 2020).

Orofacial dyskinesias, choreoathetosis, dystonia, stereotypies, myoclonus, tremor, rigidity and abnormal posturing are all types of movement disorders. Continuous video-EEG and careful bedside correlation is essential in anti-NMDAR encephalitis as movements can occur along with electrographic seizures, effect from medications or catatonic features. Sedatives and dopamine blocking agents may mask the examination and could worsen hypotension, arrhythmia and/or neuroleptic malignant syndrome (NMS) in unstable patients (Dalmau et al., 2011; Thilak et al., 2026).

Autonomic and respiratory manifestations include labile blood pressure, tachycardia or bradycardia, arrhythmias, hyperthermia or hypothermia, hypersalivation, gastrointestinal dysmotility, urinary dysfunction and central hypoventilation. If dysautonomia is marked, it is a significant clinical sign to warrant intensive care monitoring as sudden changes in hemodynamics or rhythms can occur. Clinical course is often episodic and recovery is a non-linear process with motor or

autonomic function recovering before language, executive function, mood, or social behavior

(Thilak et al., 2026).

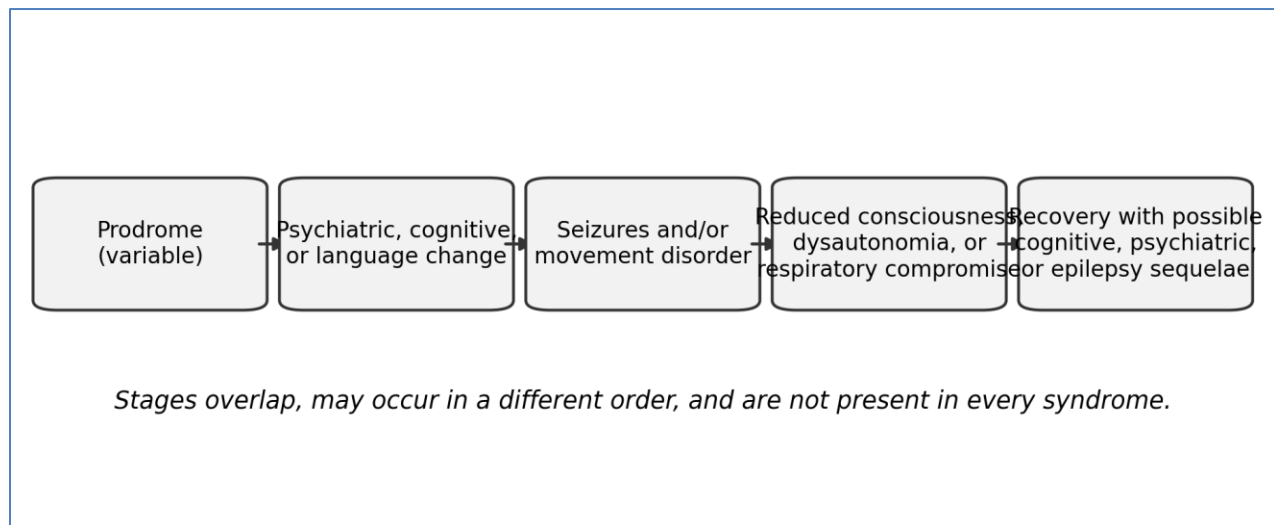


Figure 2: Typical but non-universal clinical evolution. Stages frequently overlap, and *LGII*, *GAD65*, *IgLON5*, pediatric, and paraneoplastic syndromes may follow different trajectories. Based on Dalmau et al. (2011), Lin et al. (2026), and Thilak et al. (2026).

Diagnostic Challenges and Common Mimics

The first diagnostic challenge is that criteria that have been developed are intentionally more sensitive at the point of possible AE. A variety of systemic inflammatory, metabolic, vascular, epileptic, neurodegenerative, neoplastic, or infectious conditions can cause subacute mental status change, seizures, CSF pleocytosis, or abnormalities of the MRI. The terms probable antibody-negative AE should only be used when, after extensive consideration of the various possibilities, a clinical and paraclinical framework suitable for antibody-negative AE is fulfilled. (Graus et al., 2016; Dalmau & Graus, 2023).

Interpretation of antibodies is the second difficulty. Different to different pretest probabilities, specimen types, immunoglobulin class, titers, assay methods, and phenotype. Certain antibodies are best detected in CSF, others are more sensitive in serum and isolated positive serum results may be non-specific. Analysis with a commercial line blot or fixed cell-based assay can be misinterpreted, especially for rare antibodies; any results that are unexpected should be verified with a reference laboratory by

performing a tissue-based IHC assay in conjunction with antigen-based cell-based assays. (Almweisheer et al., 2026; Sechi & Flanagan, 2021).

The third challenge is the diagnostic anchoring one. A psychiatric, infectious, epileptic or toxic-metabolic diagnosis may be first made and subsequently data may be squeezed into such a classification. On the other hand, if an autoimmune diagnosis is suspected, a positive pathogen test might be neglected or be ignored or a drug side effect, septic encephalopathy, primary epilepsy, lymphoma, mitochondrial disease or neurodegeneration might be overlooked. It is particularly important to repeat the assessment of the course when there is a deviation from the expected course. (Thilak et al., 2026; Van Steenhoven et al., 2023).

Other common mimics include HSV and other encephalitides of other viral causes, bacterial or fungal meningoencephalitis, tuberculous meningitis, brain abscess, CNS lymphoma, leptomeningeal malignancy, neurosarcoidosis, primary CNS vasculitis, acute disseminated encephalomyelitis, MOG antibody-associated

disease, Hashimoto encephalopathy-like presentations, Wilson disease, porphyria, drug intoxication or withdrawal, serotonin syndrome, neuroleptic malignant syndrome, metabolic encephalopathy, Creutzfeldt-Jakob disease, and functional or primary psychiatric disorders. Brain biopsy is usually not necessary, but might be considered when imaging or CSF is still not typical and a neoplasm, infection or vasculitis have not been excluded. (Sechi & Flanagan, 2021; Thilak et al., 2026; Van Steenhoven et al., 2023).

Differentiating Autoimmune from Infectious Encephalitis

There is considerable overlap between autoimmune and infectious encephalitis, and none of the features at the bedside is highly specific to either of the two conditions. Both may present with fever, headache, and seizures, with altered consciousness, focal deficits, CSF pleocytosis and MRI abnormalities. A hyperacute febrile presentation, predominate meningism, systemic inflammatory signs, characterised CSF pleocytosis, low CSF glucose, high lactate, pathogen exposure or a compatible positive microbiological assay favours ID; predominate psychiatric change, faciobrachial dystonic seizures, characteristic movement disorder, dysautonomia or a coherent antibody/phenotype association favours AE. These are not laws but differences that can be expected to occur randomly (Thilak et al., 2026; Xu et al., 2025).

HSV encephalitis is particularly important as the risk of death and disability are heightened with delayed acyclovir therapy. It is recommended to begin empiric IV acyclovir immediately if clinical suspicion is high for HSV and not delay until results of PCR are available. Repeat testing may be necessary in the event of a suspicion or if an early (before 10 days or just after technically limited sampling) negative HSV PCR. Immunotherapy should thus be considered along with evaluation of infectious diseases and not simply in the dichotomy of acyclovir vs steroids (Solomon et al., 2012; Thilak et al., 2026).

MRI patterns may be useful but cannot be diagnostic. HSV typically involves the medial temporal and orbitofrontal regions, and can lead to diffusion restriction, hemorrhage or necrosis, while autoimmune limbic encephalitis typically causes hyperintensity of the medial temporal structures on T2/FLAIR without distinctive destruction. Anti-NMDAR encephalitis often presents with a normal or non-specific MRI, though, and can be radiographically non-specific in the early stages of viral disease. In both autoimmune diseases and infectious diseases, bilateral or extra-temporal lesions are possible (Lin et al., 2026; Sechi & Flanagan, 2021; Thilak et al., 2026).

Mild lymphocytic CSF pleocytosis, normal or slightly elevated CSF protein, oligoclonal bands and elevated CSF IgG index are typical findings in CSF of AE, however CSF can be normal in AE, particularly LGI1 or CASPR2. A similar lymphocytic profile may be seen in viral encephalitis; however, more inflammation, erythrocytes in HSV, intrathecal antibody to the virus or positive nucleic-acid testing can help to support the diagnosis of infection. Prior antivirals or antibiotics, immune status and local prevalence of pathogen should all be taken into account when interpreting CSF results (Blinder & Lewerenz, 2019; Lin et al., 2026; Xu et al., 2025).

A combination of clinical parameters, routine laboratory parameters, phenotyping of the immune system or soluble co-stimulatory molecules may help to enhance early discrimination in emerging predictive models. A recent single-center model using 2025 samples that includes symptoms, CSF glucose, serum chemistry, and PD-1/ICOS-related variables performed well, but the small sample size, the biochemistry assays used were not routine for clinical practice, so further validation is required. These models should be used in conjunction with, not in lieu of, pathogen testing and clinical decision making by experts (Xu et al., 2025).

Table 2: Clinical differentiation of autoimmune and infectious encephalitis

Feature	More suggestive of autoimmune encephalitis	More suggestive of infectious encephalitis	Key limitation
Tempo	Subacute evolution over days to weeks; fluctuating polysymptomatic course	Hyperacute or acute febrile encephalopathy	Both can evolve over days and exceptions are common
Fever/systemic inflammation	Absent, low grade, or limited to prodrome	Prominent fever, meningism, systemic inflammatory response	Fever can occur in AE; immunocompromised infection may be afebrile
Psychiatric and movement features	Prominent psychosis, catatonia, dyskinesia, sleep disturbance, dysautonomia	Usually secondary to delirium or focal injury	Not specific without neurological red flags
Seizures	Common; FBDS strongly suggests LGI1; mixed seizures in NMDAR disease	Common; focal seizures often accompany temporal viral disease	Seizure type alone rarely distinguishes etiology
CSF	Mild lymphocytosis, OCBs/IgG index; can be normal	Often inflammatory; pathogen PCR/culture or intrathecal pathogen antibody may be positive	Early PCR can be false negative; AE can be inflammatory
MRI	Mesial temporal or multifocal inflammatory changes; often normal in NMDAR disease	Temporal/orbitofrontal diffusion restriction, hemorrhage, or necrosis in HSV; other pathogen-specific patterns	Substantial radiological overlap
EEG	Diffuse/focal slowing; extreme delta brush in a minority of NMDAR cases	Diffuse/focal slowing, seizures, periodic patterns	Most EEG findings are nonspecific
Therapeutic response	Improvement with immunotherapy supports but does not prove AE	Improvement with anti-infective therapy supports infection	Response may be delayed or confounded; steroids can transiently affect other diseases

Note. The table describes relative patterns, not diagnostic rules. Empirical acyclovir is required when HSV encephalitis is plausible. Sources: Solomon et al. (2012), Xu et al. (2025), and Thilak et al. (2026).

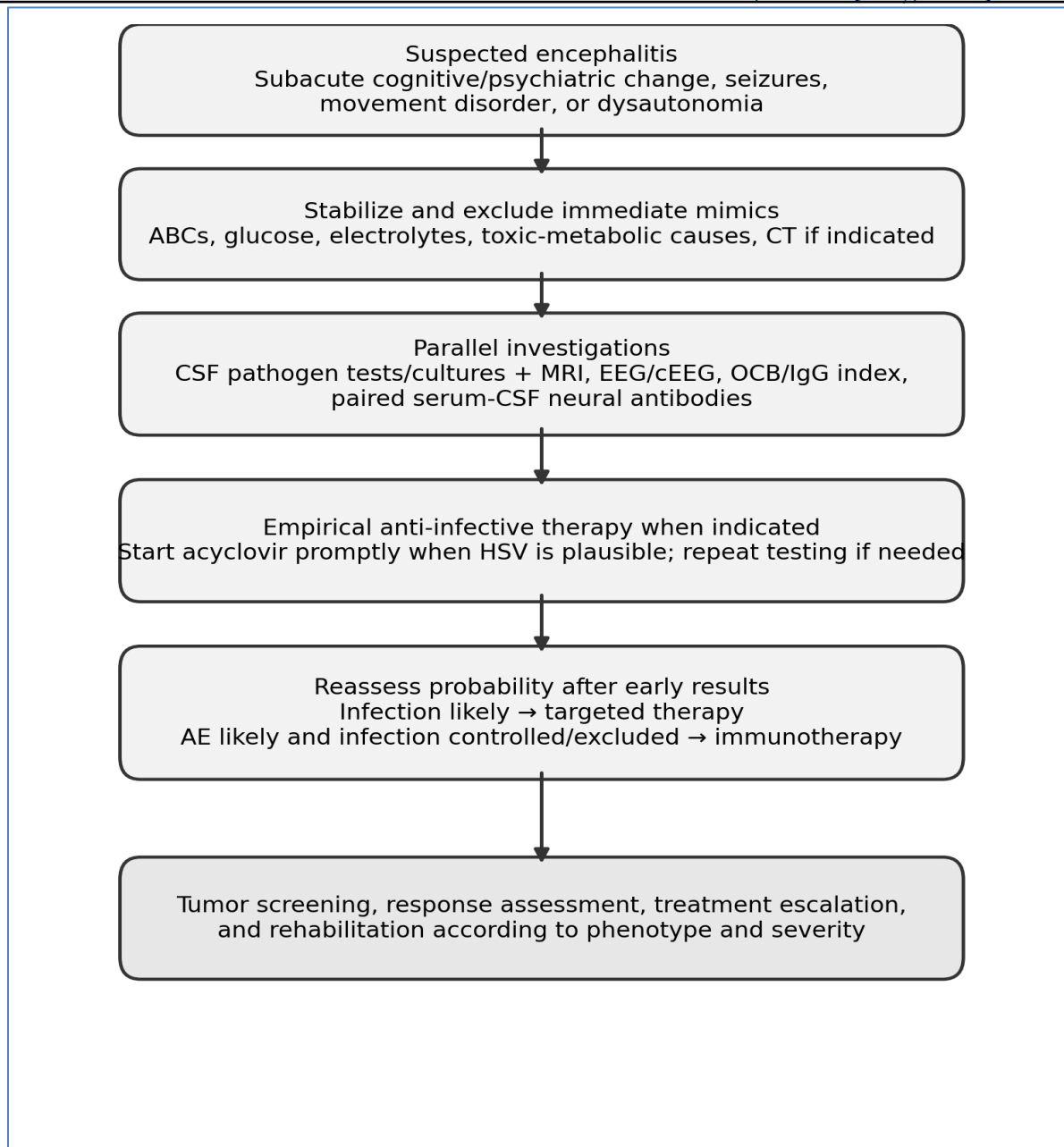


Figure 3: Integrated diagnostic pathway for suspected autoimmune encephalitis. Infectious and autoimmune investigations proceed in parallel; a clinically appropriate empirical anti-infective strategy should not preclude timely immunotherapy once infection is reasonably excluded or controlled. Based on Abboud et al. (2021), Almweisheer et al. (2026), and Thilak et al. (2026).

Diagnostic Work-up

Careful characterization of onset, progression, exposures, immune status, recent infection, vaccination, cancer history, medication changes, substance use, pregnancy and systemic autoimmune features are all part of the diagnostic

work-up. Cognition, language, behavior, cranial nerve examination, movement phenomenology and focal deficits, meningeal signs, autonomic instability, peripheral nerve or neuromuscular involvement should be documented. A single evaluation is not often as useful as repeated

evaluations due to the evolution of the phenotypes (Abboud et al., 2021; Thilak et al., 2026).

Baseline investigations to include glucose, FBC, electrolytes, renal and hepatic function tests, calcium, magnesium, inflammatory markers, thyroid testing if appropriate, toxicology and cultures/scan to assess systemic disease as appropriate. The presence of hyponatremia is a helpful, but not specific, clue in LGI1 encephalitis. Treatment should be started quickly for metabolic derangements which can cause encephalopathy and reduce the seizure threshold (Irani et al., 2011).

When possible, opening pressure should be included with lumbar puncture; a cell count and differential count; protein and glucose (with paired serum glucose); bacterial culture; HSV-1/2 and VZV PCR; other tests based on age, geography, season, exposure and immune status; oligoclonal bands and IgG index; and adequate CSF for future testing. Metagenomic sequencing is useful in some cases where a diagnosis is not reached, but currently is not available on a routine basis due to time, cost, contamination, and interpretation (Abboud et al., 2021; Thilak et al., 2026; Wilson et al., 2019).

In paired serum and CSF samples, the CSF sample should be collected as early as possible, in the absence of plasma exchange IVIG, which could otherwise delay the collection of CSF. Monitor CSF is important for NMDAR antibodies, and may be more specific for a number of syndromes; serum can be more sensitive for LGI1, CASPR2 and some systemic and paraneoplastic antibodies. There is a need for a comprehensive but phenotype guided panel rather than blanket testing and if unexpected, discordant serum-CSF or low specificity results occur, laboratory consultation and confirmatory testing is warranted (Almweisheer et al., 2026; Gresa-Arribas et al., 2014).

The MRI should be performed with high-quality T1, T2, FLAIR, diffusion weighted, susceptibility sensitive and post contrast sequences and should include medial temporal structures, cortex, basal ganglia, diencephalon, brainstem, cerebellum, and meninges. AE can be ruled out with a normal MRI. Follow-up imaging can identify changes to the abnormalities or atrophy; fluorodeoxyglucose PET can also demonstrate metabolic abnormalities in cases in which there is no detection of abnormalities with MRI imaging; but pattern of metabolic changes is not sufficiently specific to use as a standalone test (Lin et al., 2026; Moreno-Ajona et al., 2020; Thilak et al., 2026).

EEG is very sensitive for cerebral dysfunction and in general non-specific. Examples of findings are focal or generalized slowing, epileptiform discharges, electrographic seizures, periodic patterns and nonconvulsive status epilepticus. The anti-NMDAR encephalitis is driven by extreme delta brush in the right setting, but is not seen in the majority of patients. Continuous EEG is useful in comatose, sedated and movement disordered patients, since movements occurring at the bedside cannot reliably be differentiated from seizures versus dyskinesias (Moise et al., 2021; Schmitt et al., 2012).

Imaging should not be the sole indicator of screening for tumors, which should be individualized based on antibody and phenotype. Pelvic ultrasound or MRI is of particular value in adolescent and adult females with anti-NMDAR encephalitis; CT of chest, abdomen and pelvis, mammography or breast MRI, testicular ultrasound and whole-body FDG-PET may be considered in certain syndromes. If there is a high risk paraneoplastic antibody, the child may be required to have repeated surveillance as symptoms in the nervous system may precede the detection of the tumour (Abboud et al., 2021; Sechi & Flanagan, 2021; Thilak et al., 2026).

Table 3: Diagnostic modalities: strengths, limitations, and clinical use

Modality	Main contribution	Important limitations	Best-practice use
Clinical criteria	Early recognition before antibody results	Possible AE criteria are sensitive and include mimics	Use as a structured starting point and reassess alternatives

Modality	Main contribution	Important limitations	Best-practice use
CSF routine studies	Inflammation and exclusion of infection	Can be normal in AE; viral and autoimmune profiles overlap	Include pathogen testing, OCBs/IgG index, and stored aliquots
Paired serum-CSF antibodies	Defines many syndromes and guides cancer risk	Assay-dependent false positives/negatives; specimen sensitivity differs	Test both compartments and confirm unexpected results
MRI	Identifies limbic, cortical, demyelinating, neoplastic, or vascular patterns	Normal in many cases; NMDAR abnormalities may be nonspecific	Use protocolled MRI and repeat when clinically indicated
EEG/cEEG	Detects encephalopathy, seizures, nonconvulsive status	Most patterns are nonspecific	Use continuous recording in severe, sedated, or fluctuating cases
FDG-PET	May reveal metabolic abnormalities when MRI is negative	Limited specificity, access, radiation, and ICU feasibility	Use selectively after conventional evaluation
Tumor screening	Identifies treatable antigen source	Initial imaging can be negative; strategy varies by antibody	Use antibody-, age-, sex-, and phenotype-directed surveillance
Brain biopsy	Can exclude lymphoma, infection, vasculitis, or unusual pathology	Invasive; often nonspecific in AE	Reserve for unresolved atypical cases

Note. No test should be interpreted independently of phenotype and pretest probability. Sources: Almweisheer et al. (2026), Sechi and Flanagan (2021), and Thilak et al. (2026).

Emergency and Intensive-Care Management

First treatment is based on resuscitation guidelines: Airway protection, oxygenation and ventilation, hemodynamic support, rapid glucose normalization, hyperthermia treatment, convulsive status epilepticus control. Empiric use of Acyclovir and other antimicrobials should be used when appropriate, preferably following blood cultures and lumbar puncture but not at the expense of delay. The involvement of doctors in related specialties: neurology, infectious diseases, intensive care, psychiatry, oncology, gynecology, and laboratory medicine, at an early stage in decision making, lessens "fractured" decision making (Abboud et al., 2021; Thilak et al., 2026). Treatment of status epilepticus should follow standard guidelines with benzodiazepines, second line antiseizure medication and anesthetic therapy

if indicated as a refractory status. Immunotherapy is not immediate anti-seizure therapy, but is directed at the underlying inflammatory driver. Continuous EEG is useful in escalation and de-escalation, especially when this is not possible through neurological examination due to neuromuscular blockade or deep sedation. In highly resistant cases, special diet (Ketogenic diet) and other special methods may be tried at specialized centers. (Singla et al., 2026).

Continuous rhythm and blood-pressure monitoring and careful fluid and vasoactive management, temperature control and avoiding drugs that may exacerbate conduction abnormalities or hypotension are necessary in dysautonomia. Long ventilation and tracheostomy may be required due to central hypoventilation, dysfunction in the bulbar regions, problems of

aspiration, high amounts of sedatives and/or agitation. Venous thromboembolism, pressure injury, infection, ileus, malnutrition and deconditioning are all a part of neurological recovery (Thilak et al., 2026)

A low stimulation environment, involvement of family members, sleep normalization, reorientation and the use of the minimum effective doses of pharmacological agents should be implemented to manage behavioral disturbance. Antipsychotics may be needed, but should be used with caution in patients who are dysautonomic, have a movement disorder, have a prolonged QT interval or have features that resemble catatonia. A few cases of anti-NMDAR have been reported with electroconvulsive therapy (ECT), which requires multidisciplinary skills and personalized evaluation of the risks (Thilak et al., 2026)

Immunotherapeutic Strategies

Treatment should be started when there is enough clinical probability of AE and when there are reasonable alternatives to AE that are dangerous. When the criteria are met clinically, CSF findings are supportive, and MRI or EEG is supportive, and a recognizable syndrome is present, the decision is most solid. The threshold should take into account the severity of the disease, as well as the diagnostic coherence, in order to avoid exposing patients to infections, metabolic complications and diagnostic delay in a weakly supported presentation (Abboud et al., 2021; Dalmau & Graus, 2023).

The initial treatment with high dose intravenous steroids, IVIG, plasma exchange or a combination. Ineffectiveness of corticosteroids on the expression of inflammatory genes and the trafficking of immune cells; several immunomodulatory effects of IVIG; the removal of circulating antibodies and inflammatory mediators occurs rapidly with plasma exchange. Sequential therapy or combination therapy is sometimes employed in severe anti-NMDAR encephalitis and/or critical illness, but there are limited randomized comparisons of first-line therapy (Abboud et al., 2021; Gumienny, 2026; Thilak et al., 2026).

Phenotype and comorbidity should be taken into consideration in therapeutic choice. Steroids can aggravate uncontrolled infection, hyperglycemia, psychosis or gastrointestinal bleeding. IVIG may be beneficial if infection is not properly controlled, but has potential side effects of thrombosis, renal dysfunction, hemolysis and aseptic meningitis. Plasma exchange (PE) necessitates vascular access, hemodynamic stability, and the removal of immunoglobulin administered prior to PE and certain drugs, and can also be complicated by impaired coagulation and/or electrolyte management. (Abboud et al., 2021).

A multi-dimensional approach should be used to assess the response. Apart from the serum antibody level, there is a greater significance to improvement in seizure burden, level of consciousness, language, movement disorder, autonomic stability, requirement for ventilation and functional participation. In extreme cases of illness (ICU level) escalation may be considered within days when the person is deteriorating or is obviously not responding to the initial treatment; in more mild and stable illness, a longer period of observation may be warranted (Gresa-Arribas et al., 2014).

For many cell surface antibody syndromes and antibody-negative AE, rituximab is a second line treatment of choice since it targets CD20-positive B-cells and its long-term safety concerns are more familiar. There are some syndromes in which there appears to be a reduction in relapse rates and improved outcomes in observational cohorts, but there is a confounding by indication issue. When possible, screening for hepatitis B, tuberculosis risk, immunoglobulin deficiency, and vaccination status should be performed before the treatment; and infection prophylaxis should be personalized (Lee et al., 2016a; Thilak et al., 2026).

Cyclophosphamide is used in severe refractory disease and in paraneoplastic and intracellular-antigen syndromes where cellular immunity is known to play a major role, and has been shown to have anti-B cell and anti-T cell activity. Limited use due to myelosuppression, infectious risk, hemorrhagic cystitis, gonadotoxicity, teratogenicity

and secondary malignancy risk. It is vital to provide fertility counseling, fluids, urothrophic medications, management of blood counts and to be aware of cumulative doses (Sechi & Flanagan, 2021).

Tocilizumab is an interleukin-6 receptor antagonist that has been demonstrated to be beneficial in institutionalized "rituximab-refractory" AE. Bortezomib is an anti-plasma cell agent, which has been applied to anti-NMDAR and other antibody-mediated syndromes that have proven refractory. In addition to CD38-targeted drugs such as daratumumab, which has a therapeutic effect on CD38-positive plasma cells and has been reported in severe refractory cases, other biologics (such as inebilizumab, satralizumab, FcRn antagonists, complement-directed therapy) are being studied. These strategies should be focused in specialist centres or clinical trials due to the uncertainty of the evidence, optimal sequence, infection risk, and toxicity over the long-term (Gumienny, 2026; Lee et al., 2016b; Scheibe et al., 2017).

Not all patients will need to be maintained on immunotherapy. It may be used for relapsing disease, high risk features, specific antibody syndromes, no removable tumor, or frequent relapses on taper. These can be given for periods of time (as intermittent rituximab, mycophenolate mofetil, azathioprine, or other steroid-sparing agents) but should be tailored to each individual, as long-term use of immunosuppression raises the risk of infections, malignancies, reproductive problems, and metabolic effects (Lin et al., 2026). Treatment of the tumour is a form of immunology and oncological treatment. Removal of an ovarian teratoma in anti-NMDAR encephalitis may help with neurological improvement if this is the cause of the encephalitis and treatment of a small-cell lung cancer, thymoma, breast cancer, or other associated malignancy may also do this. The balance of tumor control, immune suppression, marrow toxicity, infection and neurological urgency are important considerations in coordinating cancer therapy and immunotherapy (Dalmau et al., 2011).

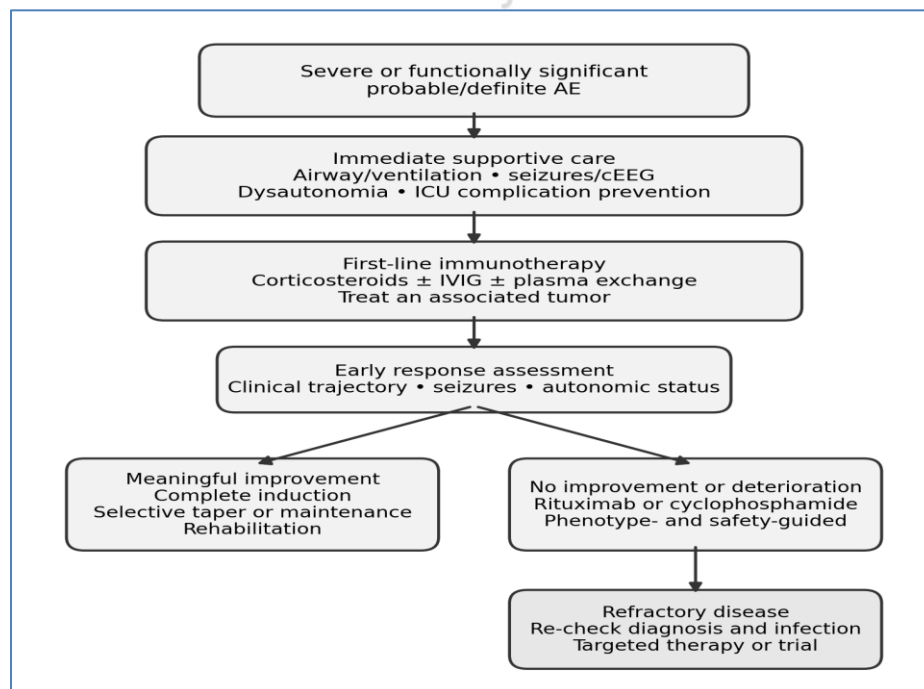


Figure 4: Acute-care management and immunotherapy escalation. Timing should be individualized; critically ill patients who deteriorate after first-line therapy may require earlier escalation than stable patients with mild disease. Based on Abboud et al. (2021) and Thilak et al. (2026).

Table 4: Current and emerging immunotherapies for autoimmune encephalitis

Therapy	Mechanism/role	Typical adult example	Major cautions	Evidence position
IV methylprednisolone	Broad anti-inflammatory induction	1 g daily for 3-5 days, then individualized taper	Infection, hyperglycemia, psychiatric effects, GI and bone complications	Established first-line practice; limited comparative trials
IVIG	Fc-mediated and broad immune modulation	2 g/kg total over 2-5 days	Thrombosis, renal injury, hemolysis, aseptic meningitis	Established first-line practice
Plasma exchange	Removes circulating antibodies and mediators	Approximately 5-7 exchanges over 7-14 days	Vascular access, hypotension, coagulopathy, electrolyte shifts	Established first-line practice, often combined in severe disease
Rituximab	CD20-positive B-cell depletion	1 g IV twice 2 weeks apart or 375 mg/m ² weekly for 4 weeks	Infusion reactions, hepatitis B reactivation, hypogammaglobulinemia, infection	Common second-line option; observational support
Cyclophosphamide	Broad B- and T-cell cytotoxicity	600-1,000 mg/m ² monthly for 3-6 months	Myelosuppression, cystitis, infertility, malignancy, infection	Second-line/refractory; favored in some paraneoplastic syndromes
Tocilizumab	IL-6 receptor blockade	Example 8 mg/kg IV every 4 weeks in reported protocols	Infection, neutropenia, liver injury, rare GI perforation	Refractory disease; cohort evidence
Bortezomib	Proteasome inhibition and plasma-cell depletion	Example 1.3 mg/m ² on days 1, 4, 8, and 11 in cycles	Neuropathy, cytopenia, zoster, GI and cardiac toxicity	Case series and trials in refractory disease
Daratumumab	CD38-positive plasma-cell targeting	Protocol varies by center/report	Infusion reactions, cytopenia, infection, interference with blood-bank testing	Experimental/off-label refractory use
Inebilizumab/FcRn or other targeted agents	Broader B-cell depletion or accelerated IgG clearance	Trial-specific	Infection and class-specific risks	Investigational; clinical trial setting preferred

Note. Doses are illustrative adult regimens reported in reviews and are not prescribing instructions; pediatric dosing and individual protocols differ. Sources: Lin et al. (2026), Gumienny (2026), and Thilak et al. (2026).

Tumor Screening and Paraneoplastic Disease

There is a significant variation in the risk of cancer with different antibodies, age, sex and phenotypes.

The intensive search for an underlying tumor should be conducted for high-risk antibodies that are found inside the cell, and less intensive search

is recommended for cell surface antibodies. GABAB receptor encephalitis has been strongly associated with small-cell lung cancer, AMPA receptor encephalitis can occur with breast or lung malignancy, CASPR2 can occur with thymoma and anti-NMDAR encephalitis could be associated with ovarian teratoma. If the neurological syndrome or antibody is highly suggestive of a paraneoplastic cause, then the initial screening is not entirely without risk (Sechi & Flanagan, 2021).

Surveillance strategy should be tailored to each individual and should not be limited to a whole-body scan. Conventional screening, focused imaging, pelvic or testicular ultrasound, CT scan, MRI, mammography and FDG PET can be used together based on the risk of the individual. In high-risk syndromes, repeated screening over time is appropriate and should be spaced out and/or continued based upon the antibody, smoking history, symptoms and the competing radiation or cost concerns (Abboud et al., 2021; Sechi & Flanagan, 2021).

Special Populations and Emerging Contexts

Instead of the adult language of psychosis or amnesia, children's symptoms are often in the form of behavioral change, the regression of language, seizures, sleep disturbance, dyskinesia or developmental loss. Although anti-NMDAR encephalitis is the most commonly recognized form of a pediatric AE, MOG antibody-associated disease can be associated with encephalopathy, cortical seizures, or an ADEM-like demyelination and seronegative patients are a diagnostic challenge. Cognitive assessment in children is age specific, psychiatric symptoms are interpreted with caution, therapy is weight adjusted, and fertility planning and vaccination surveillance is long term. (Cellucci et al., 2020; Lin et al., 2026).

There is a need to differentiate acute symptomatic seizures in encephalitis from chronic autoimmune-associated epilepsy following the resolution of inflammation in autoimmune epilepsy. Immunotherapy may yield significant improvement in seizures in cell surface antibody syndromes, but may result in only partial

improvement in chronic GAD65-associated temporal lobe epilepsy due to T cell mediated injury and established structural network change. Treatment with antiseizure drugs is still required during the acute period and, if the clinical and paraclinical evidence is favorable, immunotherapy should be used. (Qiu et al., 2026; Singla et al., 2026; Steriade et al., 2020).

Neurological immune-related adverse events (nerae) may occur with immune checkpoint inhibitors and can affect the central nervous system, peripheral nervous system and encephalitis. Presentations can be unusual and/or rapidly progressive, corticosteroid-unresponsive, and/or with myositis or myocarditis or myasthenia-like disease. The need for exclusion of metastasis, infection, metabolic causes, and paraneoplastic syndromes; prompt stopping or replacing the checkpoint inhibitor if appropriate; and early immunomodulation with close oncological coordination are important to management. (Kawazoe et al., 2026; Sechi & Flanagan, 2021).

There are special challenges for the elderly, immunocompromised, the pregnant and patients in low-resource settings. A new encephalitic syndrome can easily be confused for baseline cognitive impairment, use of immunotherapy is influenced by infection status, prevalence of tumors increases with age, and MRI, EEG, reference antibody laboratories, plasma exchange and biologics may be unavailable. For the sake of practical algorithms, safety of diagnosis and treatment on the basis of clinical probability should be maintained, provided that advanced testing is not possible. (Gumienny, 2026).

Prognosis, Relapse, and Rehabilitation

The outcome is determined by the type of antibodies, the age, severity, tumor status, treatment delay, requirement for intensive care, length of status epilepticus, autonomic and respiratory complications, and first-line treatment response. The fact that there are large anti-NMDAR cohorts means that many patients are able to become functional, with recovery taking 18 months or more, and early recovery does not

mean that full cognitive recovery will occur. An intracellular-antigen syndrome and refractory status are more likely to have a poor prognosis. (Thilak et al., 2026; Titulaer et al., 2013).

The risks of relapse differ based on the syndrome and are influenced by inadequate or delayed immunotherapy, incomplete tumor therapy and perhaps by maintenance therapy. The relapse can manifest as the same initial symptoms or in a more subtle way, as sleep, mood, memory, seizure or behavioral changes. While CSF antibody titres may help correlate with disease activity in anti-NMDAR encephalitis, along with the clinical phenotype, clinical monitoring is more useful than routine monitoring of antibody titres alone. (Gresa-Arribas et al., 2014; Titulaer et al., 2013).

Rehabilitation needs to start in the acute stage and should be continued through care transitions.

Physical, occupational, speech-language, swallowing, neuropsychological, psychiatric, sleep, educational and/or vocational interventions may be required. Families require counselling around the fact that variable behaviour, tiredness, decreased initiation, emotional lability and executive dysfunction could be a reflection of the brain's recovery, and not on purposeful noncompliance. (Lin et al., 2026).

Research on outcomes should go beyond the modified Rankin scale. There is a need for instruments to assess memory, executive function, psychiatric symptoms, seizure burden, return to school/work, caregiver burden, and health-related quality of life, both in clinical care and for trials. There should be developmental trajectories instead of one end-point assessment for pediatric follow-up. (Gumienny, 2026; Lin et al., 2026).

Table 5: Prognostic factors and follow-up implications

Factor	Association	Clinical implication
Early recognition and immunotherapy	Generally associated with better functional and cognitive outcome	Use syndrome-based treatment thresholds rather than waiting for all results
Cell-surface/synaptic antibody	Often greater reversibility than intracellular-antigen disease	Expect prolonged recovery but maintain rehabilitation intensity
Intracellular/onconeural antibody	Greater tumor association and irreversible neuronal injury	Prioritize tumor therapy and realistic counseling
ICU admission, ventilation, dysautonomia, refractory status	Associated with prolonged hospitalization and poorer outcome	Aggressive complication prevention and early rehabilitation
Tumor removal/control	Improves immune control in relevant syndromes	Coordinate neurological and oncological treatment
Delayed treatment or first-line failure	Associated with worse outcome and escalation needs	Use early response assessment and specialist review
Pediatric age	Motor recovery may be good but cognitive/academic deficits persist	Provide longitudinal neuropsychology and school support
Relapse	May cause cumulative morbidity and can be subtle	Educate families and individualize maintenance therapy

Note. Associations vary by syndrome and evidence is primarily observational. Sources: Lin et al. (2026), Thilak et al. (2026), and Titulaer et al. (2013).

Future Directions

The most apparent research gap is for quality therapeutic evidence. Conventional placebo-controlled trials are challenging due to rare

diseases, phenotypic heterogeneity and the need to treat these patients promptly; however, here are other options to consider that will allow for the comparison of induction regimen, escalation

timing, maintenance therapy, and targeted biologics: adaptive platforms, basket designs, registry-based randomization, and harmonized international networks. Mortality and ambulation are not the only outcomes to be reported in trials; recovery of cognition and psychiatric problems should be included. (Gumienny, 2026)

The shift in biomarker development is from detection of an antibody to disease activity and treatment stratification. Possible candidate markers include CSF CXCL13, interleukin-6, BAFF, soluble CD27, NF-L, GFAP, intrathecal immunoglobulin measures, subsets of immune cells and electroclinical signatures. Most are still preliminary and lack thresholds, assay platforms and are confounded by blood-brain barrier dysfunction and lack external validation. (Chen et al., 2026; Lin et al., 2026)

Multi-omics will be able to combine genomics, epigenomics, transcriptomics, proteomics, metabolomics, B-cell receptor and T-cell receptor sequencing, single-cell analysis, imaging, EEG, and longitudinal clinical parameters. The goal is not just to form molecular aggregates, but to generate reproducible and interpretable models to pinpoint antibody dominated, cytokine dominated, T-cell dominated, or neurodegeneration dominated states and connect these to rational therapeutics.

There are several obstacles such as small samples, batch effects, overfitting and disproportionate access. (Chen et al., 2026)

AI could be used for EEG pattern matching, MRI quantification, multimodal risk assessment and laboratory decision support, but algorithms need to be validated and calibrated outside of the lab and uncertainty needs to be addressed. A successful model from a single specialist center might not be applicable in a different population that experiences different pathogens, referral patterns, or assay availability or prevalence of disease. Clinicians need to be able to provide reasons for the use of a model and how and when output from a model should be disregarded. (Chen et al., 2026; Xu et al., 2025)

Potential targets for future immunotherapy are more targeted plasma-cell depletion, antigen-specific tolerance, engineered regulatory cells, CAR-T or CAR-Treg, bispecific antibodies and targeted cytokine or complement modulation. These strategies are conceptually appealing, but were not represented as proven AE treatment until demonstrated in prospective studies in terms of safety, durability, neurological outcomes and infection risk (Alsayb, 2025; Chen et al., 2026; Gumienny, 2026).

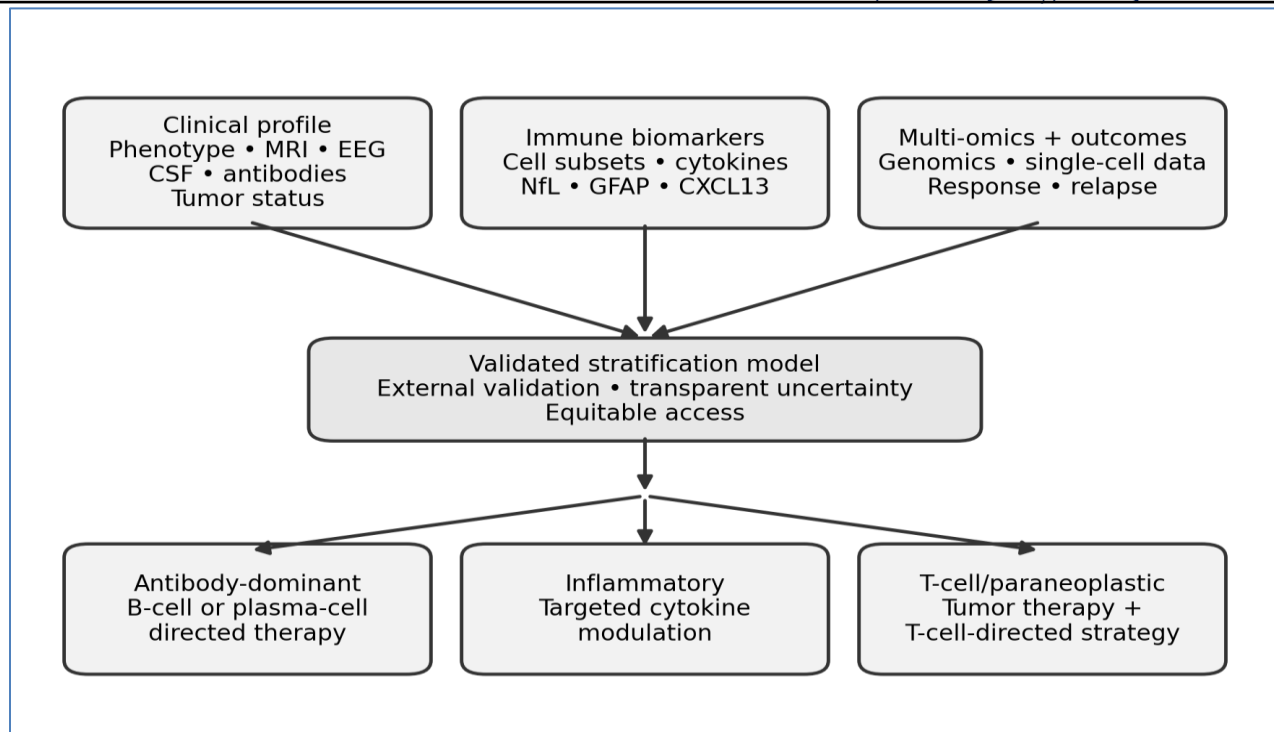


Figure 5: Research framework for precision neuroimmunology. Most proposed biomarker-guided treatment branches remain investigational and require prospective multicenter validation. Based on Chen et al. (2026) and Gumienny (2026).

Conclusions

Autoimmune encephalitis is a treatable neurological emergency where disciplined integration of clinical phenotype, disease tempo, MRI, EEG, CSF, paired serum-CSF antibody testing, microbiology and tumor assessment is key to diagnostics. When there is any reasonable doubt about the cause of encephalitis, prompt treatment of infectious encephalitis should be considered, but a compatible severe AE syndrome should not be left undiagnosed or untreated for an extended period of time after controlling or excluding an infection. Paralell investigation, continued reassessment and early multidisciplinary care is the safest option. (Abboud et al., 2021; Almweisheer et al., 2026; Thilak et al., 2026). The use of high-dose corticosteroids, IVIG, and plasma exchange is still consider the primary treatment and if needed can be supplemented with rituximab or cyclophosphamide in more severe disease and/or when response is suboptimal. Newly approved biologics and precision-medicine approaches are promising new ways to extend

therapeutic options, but with less evidence than is suggested by clinical enthusiasm. Functional independence does not always mean complete recovery of the brain and cognition and behavior, language, epilepsy, education, employment and family burden must all be addressed during long-term care (Chen et al., 2026; Gumienny, 2026; Lin et al., 2026).

Declarations

Consent for publication

All subjects gave their “informed consent” for the publication of details within the text (“informed consent”) to be published in the above Journal and Article. Written “informed consent” was obtained from all authors for the publication of this manuscript.

Availability of data and materials

The data generated are provided within the manuscript and will be available from the author upon reasonable request.

Competing Interest

All authors declare that there are no competing interests.

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