Received: 24 January 2024 | Accepted: 13 April 2024

DOI: 10.1002/epd2.20231

Epileptic Disorders

SEMINAR IN EPILEPTOLOGY

Autoimmune-associated seizure disorders

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Abstract

With the discovery of an expanding number of neural autoantibodies, autoimmune etiologies of seizures have been increasingly recognized. Clinical phenotypes have been identified in association with specific underlying antibodies, allowing an earlier diagnosis. These phenotypes include faciobrachial dystonic seizures with LGI1 encephalitis, neuropsychiatric presentations associated with movement disorders and seizures in NMDA-receptor encephalitis, and chronic temporal lobe epilepsy in GAD65 neurologic autoimmunity. Prompt recognition of these disorders is important, as some of them are highly responsive to immunotherapy. The response to immunotherapy is highest in patients with encephalitis secondary to antibodies targeting cell surface synaptic antigens. However, the response is less effective in conditions involving antibodies binding intracellular antigens or in Rasmussen syndrome, which are predominantly mediated by cytotoxic T-cell processes that are associated with irreversible cellular destruction. Autoimmune encephalitides also may have a paraneoplastic etiology, further emphasizing the importance of recognizing these disorders. Finally, autoimmune processes and responses to novel immunotherapies have been reported in new-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES), warranting their inclusion in any current review of autoimmune-associated seizure disorders.

KEYWORDS

autoimmune encephalitis, autoimmune seizure disorders, epilepsy, seizure

1 | INTRODUCTION

Autoimmune etiologies of seizures and epilepsy have been increasingly recognized in recent years. Several neural autoantibodies targeting both cell surface and intracellular antigens have been discovered, which aid diagnosis of these conditions. Many of these antibodies are found in patients presenting with autoimmune encephalitis, who have seizures as a prominent feature.[1] The diagnosis of autoimmune-associated seizure disorders is dependent on clinical presentation and ancillary testing, including neuroimaging, cerebrospinal fluid (CSF), and autoantibody testing. The recognition of these conditions is crucial, as seizures associated with autoimmune encephalitis and

antibodies to neural surface antigens respond to immunotherapy and usually have a poor response to antiseizure medications (ASMs). Outcomes with respect to seizures are generally favorable in cell surface antibody-mediated disorders such as autoimmune encephalitis associated with anti-leucine-rich glioma-inactivated 1 (LGI1) and anti-N-methyl-D-aspartate receptor (NMDAR) antibodies, and less favorable for disorders associated with antibodies targeting intracellular antigens such as chronic temporal lobe epilepsy associated with glutamic acid decarboxylase 65 (GAD65) antibodies. Other disorders have strong evidence for immune etiology but lack an antibody biomarker, such as Rasmussen syndrome, and new-onset refractory status epilepticus (NORSE) (including the variant predominantly occurring in pediatrics referred to as febrile infection-related epilepsy syndrome (FIRES)). The response to current first- and second-line immunotherapies in these disorders is unfortunately limited; however, advances in knowledge of their underlying immunopathogenesis may lead to more effective treatments in the future.

In this comprehensive review, the terminology, epidemiology, pathophysiology, clinical presentation, imaging findings, treatment, and outcomes of the more common autoimmune-associated seizure disorders are described, with a focus on diagnosis and treatment.

Competencies and learning objectives from the ILAE curriculum[2]

1.0 Diagnosis

1.1 Demonstrate working knowledge of etiologies of focal and generalized epilepsies in children and adults

1.1.6 Describe the common immune causes of epilepsy (e.g., Rasmussen encephalitis, LGI1 antibodies, NMDAR antibodies, etc.)

1.4 Interpret EEG and describe common EEG patterns in children and adults

1.4.9 Recognize and describe interictal abnormalities

1.4.10 Recognize and describe ictal patterns

1.5 Accurately order and interpret neuroimaging as it pertains to epilepsy

1.5.5 Interpret and apply the results of specialized neuroimaging accurately in the clinical context

1.7 Accurately diagnose and classify epilepsies and epilepsy syndromes using the most recent ILAE classification

1.7.1. Accurately distinguish acute symptomatic seizures from epilepsy

3.0 Pharmacological Treatment

3.2 Recommend appropriate therapy based on epilepsy presentation

3.3 Demonstrate up-to-date knowledge about special aspects of pharmacological treatment

3.3.6 Define treatment strategies for immune-mediated causes of epilepsy and seizures

7.0 Biology of Epilepsy

7.1 Demonstrate working knowledge of ictogenesis

7.2 Demonstrate working knowledge of epileptogenesis

Key points

- Antibodies to LGI1, NMDAR, and GAD65 are the most common antibodies found in patients with autoimmune encephalitis and autoimmune-associated seizure disorders.
- LGI1 encephalitis is associated with faciobrachial dystonic seizures in approximately half of patients and an extremely high seizure frequency, often multiple per day.
- NMDAR encephalitis is associated with psychiatric presentations, dyskinesias, as well as seizures.
- GAD65 is associated with chronic temporal lobe epilepsy that may be musicogenic; however, limbic encephalitis presentations may also occur.
- Immunotherapy is the main treatment in acute symptomatic seizures secondary to autoimmune encephalitis, but outcome is highly dependent on etiology, timing of initiation of therapy, treatment dosage and duration, and whether encephalitis-associated structural brain injury is present.
- Corticosteroids are generally first-line treatment in autoimmune-associated seizure disorders.
- Disorders associated with cell surface antibodies have better outcomes than Rasmussen syndrome and disorders with antibodies directed at intracellular epitopes, where the immunopathogenesis is largely T-cell mediated and the antibodies are more likely an epiphenomenon.
- There is mounting evidence that cryptogenic NORSE and FIRES may be related to excessive activation of the innate immune system and proinflammatory cascade.
- Cognitive impairment and chronic epilepsy are common sequelae for survivors of NORSE and FIRES.

2 | TERMINOLOGY AND EPIDEMIOLOGY

While the term "autoimmune epilepsy" was used in the past to describe seizures associated with an underlying autoimmune etiology, this term was criticized due to the fact that the seizures and need for ASMs in these disorders may resolve with immunotherapy, thus lacking an enduring predisposition to seizures implied by the term "epilepsy".[3] To address this issue and to distinguish seizures due to a reversible provoking factor (i.e., immunotherapy-responsive

neuroinflammation) from those due to continued seizure predisposition, the International League Against Epilepsy (ILAE) Autoimmunity and Inflammation Taskforce proposed the terms "acute symptomatic seizures secondary to autoimmune encephalitis" and "autoimmune-associated epilepsy" (Table 1).[4] The modified term autoimmune *encephalitis*-associated epilepsy has been recently introduced to highlight the link between encephalitis and epilepsy in many of these cases.[5] Making the distinction between acute symptomatic seizures and epilepsy reflects potential differences in seizure prognosis in these cases, which frequently depends on the underlying etiology. Seizures in the setting of autoimmune encephalitis which resolve following immunotherapy warrant the term "acute symptomatic seizures secondary to autoimmune encephalitis," while patients with autoimmune encephalitis resulting in structural brain injury and continued seizures are best conceptualized as having "autoimmune associated epilepsy".[4] Seizures in many patients with cell surface antibodies such as those targeting NMDAR and LGI1 resolve following immunotherapy, warranting the term acute symptomatic seizures as opposed to epilepsy. While relapses may occasionally occur in these disorders, a relapse of immunotherapy-responsive neuroinflammation leading to recurrent seizures would still be considered as recurrence of acute symptomatic seizures.[4] While there is no set timeframe to define a relapse, some studies have classified relapses as recurrence or clear worsening of symptoms after 3 months of resolution or plateau of prior symptoms.[6] Disorders associated with antibodies-targeting intracellular antigens on the other hand, such as seizures in patients with high GAD65 antibody titers or with high-risk paraneoplastic antibodies, or in those with Rasmussen syndrome, often develop an enduring seizure predisposition justifying the term autoimmune-associated epilepsy. Application of these terms, while somewhat predictable based on etiology, still requires passage of time to determine whether the predisposition for seizures resolves or persists. For example, a minority of patients with antibodies to cell surface antigens continue to have seizures despite an adequate trial of immunotherapy and resolution of active autoimmune encephalitis, thus justifying the designation of autoimmune-associated epilepsy despite the initiating etiology.[7]

Recently, the prevalence and incidence of autoimmune encephalitis have been determined to be comparable to infectious encephalitis.[8] The prevalence of the presence of underlying neural autoantibodies among persons with seizures ranges significantly among studies from 0 to 24% and is most likely in patients with new-onset focal seizures of unknown cause.[9] One study found that 10.5% of patients with new-onset focal seizures had serum autoantibodies to cell surface antigens.[10] Another study reported that only 3.4% of adults with focal seizures of unknown cause had an autoimmune etiology, where GAD65 antibodies were the most frequently detected.[11] The studies assessing the rate of antibody positivity among patients with seizures have predominately or exclusively included adults, and therefore, cannot be considered applicable to children.

3 | PATHOPHYSIOLOGY

The pathogenesis and ictogenesis of these disorders are diverse and comprise cytotoxic mechanisms with neural damage as well as direct effects of associated autoantibodies on neural surface proteins facilitating hyperexcitability. Figure 3 in the review in The New England Journal of Medicine by Dalmau and Graus provides a helpful diagram illustrating the pathophysiologic mechanisms of specific antibodies as currently understood.[12] The pathogenesis of central nervous system disorders with neural autoantibodies against intracellular antigens appears to be T-cell mediated, leading to initial inflammation and tissue edema followed by cytotoxic neural destruction, apoptosis, and subsequent brain atrophy. Examples of T-cell-mediated disorders include Rasmussen syndrome, chronic epilepsy associated with antibodies against GAD65, and encephalitis associated with high-risk paraneoplastic antibodies.[4,13,14] In general, the GAD65 and high-risk paraneoplastic antibodies are not directly pathogenic but are thought to occur as an epiphenomenon, serving primarily as disease biomarkers. Examples of the latter include tumor-associated paraneoplastic neurological syndromes.[3,15] The seizures in these diseases are unlikely to respond completely to ASMs or immunotherapy.

Conversely, antibodies against extracellular surface antigens are often directly pathogenic, leading to neurophysiologic dysfunction and ultimately seizures. The seizures in these disorders often respond definitively to immunotherapy when the direct effects of antibodies on their synaptic and cell surface epitopes subside.[3] This response may be quick, sometimes within a few days (e.g., in LGI1 encephalitis) but may take weeks for resolution in other disorders (e.g., NMDAR encephalitis). Recent clinical and preclinical studies have provided insights into pathophysiology of seizures in these disorders.

3.1 | Mechanism of hyperexcitability in NMDAR encephalitis

Antibodies to the NMDAR in patients with autoimmune encephalitis are of the IgG subtype. The antibodies target the amino-terminal domain of the obligate GluN1 subunit.[16] Binding of pathogenic antibodies typically leads to crosslinking of NMDAR and subsequent internalization

TABLE 1 Differentiation between acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy.

	Acute symptomatic seizures secondary to autoimmune encephalitis	Autoimmune-associated epilepsy
Underlying antibodies or conditions	Often occurs with antibodies against cell surface antigens, such as NMDAR and LGI1	Often occurs with antibodies against intracellular antigens, such as high titers of GAD65 and high-risk paraneoplastic antibodies, as well as Rasmussen syndrome Persistent seizure predisposition after treatment of cell surface antibody-mediated encephalitis may also uncommonly occur
Pathogenesis	Typically antibody-mediated pathogenesis that is immunotherapy responsive	Typically T-cell mediated inflammation that is immunotherapy-resistant and/or has led to structural brain injury
Outcome	Seizure predisposition resolves with immunotherapy Recurrence of seizures after seizure freedom is more likely a clue for relapse than a sign of transition to epilepsy	Seizure predisposition persists despite immunotherapy and seizures are often drug resistant

and reduction in their expression on the neural surface.[17] In vitro and in vivo evidence in primary neural cell cultures and passive-transfer animal models show reduction in NMDAR-mediated excitatory postsynaptic currents, reduction in postsynaptic Ca^{2+} influx, and severely affected synaptic plasticity in the hippocampus.[16,18] Also, passive transfer of patient-derived antibodies led to reductions in seizure threshold in epilepsy mouse models where levels of immunoglobulin G bound to the hippocampus were higher in the test mice, suggesting this may have a role in seizure susceptibility.[19] Recent studies demonstrated that NMDAR antibodies alter complex neural network signaling and critically affect excitatory and inhibitory balance. This results in increased gamma oscillations, which may result in disturbed rhythmogenesis and seizures.[20]

3.2 | Antibodies to LGI1: Synaptic and extrasynaptic effects on neural excitability

LGI1 is a neural-secreted intrasynaptic protein and consists of two primary subdomains, a leucine-rich repeat (LRR) at the N-terminus and an epitempin domain at the C-terminus. LGI1 mediates a transsynaptic complex at excitatory synapses through adaptor proteins ADAM22 and 23, presynaptic Kv1.1 channels, and postsynaptic AMPA receptors.[15] Patient-derived antibodies enhance synaptic excitation primarily through reduction in presynaptic Kv1.1 expression, which results in action-potential broadening and increased neurotransmitter release.[21,22] In addition, LGI1 has an important role at the axon initial segment (AIS), via anchoring and clustering Kv1 channels. Recent reports provide evidence that patient-derived antibodies, in particular those directed at the LRR subdomain, induce changes in AIS molecular composition and Kv1 distribution, resulting in neural hyperexcitability and increased action potential firing rates.[22–24]

4 | CLINICAL PRESENTATION AND SEIZURE CHARACTERISTICS

NMDAR encephalitis typically affects young women with a median age in the 20s, but a wide range of ages have been reported ranging from young children to the elderly (Table 2).[16,25,26] The mean annual incidence of NMDAR encephalitis has been determined to be 1:1 000 000.[25] Many patients first experience a headache, low-grade fever, and nonspecific viral-like symptoms in the weeks preceding symptoms of encephalitis.[16] Acute or subacute psychiatric and cognitive symptoms are typically prominent in the early presentation and include delusions, hallucinations, bizarre behavior, and memory loss.[16] Dyskinesias, most commonly orofacial dyskinesias with grimacing, forceful jaw movements, and chewing movements may be present. Autonomic dysfunction, including dysthermia, blood pressure instability, and hyperhidrosis in addition to decreased level of consciousness are also frequent but typically occur later.[27] Seizures are usually acute symptomatic seizures which are prevalent in the acute phase, occurring in approximately 70–80% of patients, and may be more common among younger patients and more likely to be the presenting symptom in men.[28–30] In one study, frontal onset seizures were the most common, but temporal seizures occurred as well.[29] More than one seizure type may occur, and status epilepticus is not infrequent. While there is no pathognomonic seizure semiology described

TABLE 2 Clinical presentation of the three most common antibody-associated seizure disorders: NMDAR, LGI1, and GAD65.

Antibody	Demographic affected	Symptoms	Seizure semiology	Cancer association	MRI	EEG	Cerebrospinal fluid
NMDAR	Female predominance, median age in the 20s (but wide age range reported)	Psychiatric and cognitive symptoms, dyskinesias, dysautonomia, seizures	Focal aware and impaired awareness, focal to bilateral tonic–clonic seizures	Ovarian teratoma	Normal in 70%, or T2 hyperintensities	Generalized rhythmic delta activity; extreme delta brush (characteristic, but not always present)	Mononuclear pleocytosis and protein elevation in the majority; antibody may only be present in CSF
LGI1	Male predominance, with median age in 60s	Memory impairment and seizures	Faciobrachial dystonic seizures, frequent focal seizures with sensory or motor symptoms, piloerection, paroxysmal dizziness spells, and frequent subclinical seizures	Infrequently thymoma	Normal, or T2 hyperintensities in the mesial temporal lobes, insula, and basal ganglia Hippocampal swelling or atrophy	Temporal onset seizures, including subclinical. May not have EEG correlate	May have mild pleocytosis and mild protein elevation, but normal in 50% of cases
GAD65	Female predominance	Type 1 diabetes, autoimmune thyroid disease, pernicious anemia, stiff-person spectrum disorders, cerebellar ataxia, chronic temporal lobe seizures, and limbic encephalitis	Temporal onset, déjà vu common, and musicogenic seizures	Rarely thymoma and carcinoma (mainly in limbic encephalitis, not in chronic temporal lobe seizures)	Normal or T2 hyperintensities in mesial temporal lobes	Temporal onset seizures	Typically normal. Rarely, mild pleocytosis or protein elevation. CSF-specific oligoclonal bands.

associated with NMDAR encephalitis, motor onset seizures and bilateral tonic–clonic seizures are frequently encountered.[31] Underlying tumors are present in around 35% and are most frequent in female patients aged 12–45 where ovarian teratoma is the most common tumor type.[26] Tumors are rare in children with NMDAR encephalitis.[26] Patients may develop an autoimmune encephalitis after treatment for herpes simplex virus that is responsive to immunotherapy, and many of these patients demonstrate NMDAR antibodies, particularly in the pediatric age group.[32,33] Seizures may be present in these patients, but are less common than cases of NMDAR encephalitis not associated with herpes simplex virus, occurring in only 29% in one series.[33]

LGI1 encephalitis typically presents in older patients with a median age of 64 years and shows a male predominance.[34,35] Subacute cognitive dysfunction with deficits in memory and abnormal behavior occurs in most patients.[36] Seizures are present in 90% and may be frequent, often occurring at a rate of several per day.[6,37] Faciobrachial dystonic seizures (FBDS), present in almost half of the patients, have been recognized as a highly characteristic seizure type associated with LGI1 encephalitis, manifested by brief but frequent episodes of contraction of one arm usually with the ipsilateral face.[38] FBDS may also involve the lower extremity, sometimes leading to falls. Other features of seizures suggestive of LGI1 encephalitis include subclinical seizures, extremely high seizure frequency, short individual seizure duration, multifocal seizures with sensory or motor symptoms, and pilomotor seizures.[6,37,39–41] In addition, seizures induced by hyperventilation have been described, which is important to keep in mind as hyperventilation is often deferred in older patients.[42] LGI1 encephalitis is very rare in children, and when present, the phenotype may differ from that seen in adults, with lack of FBDS.[43]

High-titer GAD65 antibodies (defined as >20 nmol/L or >2000 U/mL in serum using radioimmunoassay, and >10 000 IU/mL in serum or >100 IU/mL in CSF using enzyme-linked immunosorbent assay[44,45]) are associated with diverse neurological presentations, including stiff-person spectrum disorders (SPSD), cerebellar ataxia, temporal lobe epilepsy, limbic encephalitis, and overlap of these presentations.[46] Type 1 diabetes, autoimmune thyroid disease, and pernicious anemia are also associated with GAD65 antibodies.[14] Women are affected much more often than men.[46] Seizures are classically present in two contexts in association with GAD65 antibodies: acutely as a part of limbic encephalitis presentation, and as chronic drug-resistant temporal lobe epilepsy.[46,47] Interestingly, however, drug-resistant epilepsy was significantly more frequent among those with GAD65 antibodies and seizures in isolation who were evaluated for epilepsy management, compared to those with seizures as part of an overlap syndrome who may have been evaluated for management of SPSD or cerebellar ataxia.[46] Musicogenic seizures have also been reported with high-titer GAD65 antibodies, suggesting involvement of Heschl's gyrus in the perisylvian region.[48]

Multiple other antibody-mediated encephalitides have been associated with seizures, although these are less common than the above. This includes $GABA_BR$ encephalitis, which may present with status epilepticus, and CASPR2 encephalitis, which has been associated with focal, nonmotor seizures and episodic ataxia as well as with peripheral neuromyotonia.[49,50] $GABA_AR$ encephalitis is frequently associated with seizures and may present in children.[51] Seizures are common in autoimmune encephalitis associated with high-risk paraneoplastic antibodies, most commonly ANNA-1/Hu, Ma2, and CRMP5/CV2.[52] Identification of these antibodies should prompt appropriate evaluation for the occult malignancies associated with the antibody in question.

A proportion of cases of autoimmune encephalitis may not have an underlying antibody, warranting the diagnosis of antibody-negative autoimmune encephalitis. Given the lack of a defining biomarker, this disorder has proven to be difficult to define and diagnose. Alternative diagnoses need to be appropriately excluded and antibody investigations in CSF as well as serum need to be comprehensive before making the diagnosis.[53] Prior studies have shown that a number of patients who were diagnosed with antibody-negative autoimmune encephalitis were found to harbor pathogenic antibodies when more comprehensive antibody testing was completed.[54] Therefore, further work is necessary to understand and characterize this diagnosis.

5 | EVALUATION

5.1 | Laboratory findings and CSF evaluation

The central role of laboratory evaluation for seizures of autoimmune etiology revolves around screening for neural autoantibodies, both in serum and CSF. In the cases of LGI1 and CASPR2 antibodies, serum is more sensitive than CSF, so a spinal fluid examination is not always necessary.[55–57] High-titer GAD65 antibodies in serum may also not warrant CSF evaluation if the clinical syndrome is classical for chronic temporal lobe seizures associated with GAD65 autoimmunity.[46] In cases where a characteristic phenotype matching a certain identified antibody is lacking, a CSF evaluation should be undertaken and include general testing for intrathecal inflammation (cell count, glucose, protein, and oligoclonal banding)

TABLE 3 Differential diagnosis of autoimmune encephalitis.

Etiology	Examples
Infection/Inflammatory	Herpes simplex virus 1 and 2
	Epstein–Barr virus
	West Nile virus
	HIV
	Listeria
	Mycoplasma
	Fungi
	Sarcoidosis
	Systemic lupus erythematosus
Vascular	Vasculitis
	Posterior reversible encephalopathy syndrome
	Embolic or venous infarction
Metabolic	Hyperglycemia or hypoglycemia
	Vitamin deficiencies
Neurodegenerative	Creutzfeldt–Jakob disease
	Alzheimer's disease
	Frontotemporal dementia
	Dementia with Lewy bodies
Malignancy	Glioma
	Primary central nervous system lymphoma
	Metastatic disease—parenchymal and meningeal
Structural	Focal cortical dysplasia
Psychiatric disease	Schizophrenia
	Functional neurologic disorder
	Depression
	Anxiety

to gather further corroborative evidence of CNS autoimmunity. CSF cytokine profiles are emerging as an additional line of investigation. Other causes in the differential diagnosis (Table 3) should be evaluated and excluded,[58] including infectious etiologies (e.g., viral PCR). In addition, neoplastic, vascular, metabolic, and neurodegenerative disorders may present with subacute cognitive decline and seizures, thus mimicking autoimmune encephalitis. Routine laboratory panels commonly performed in the course of evaluating medical patients may provide clues to the diagnosis. For example, hyponatremia frequently accompanies LGI1 encephalitis.[55,59] Serologic evaluation for comorbid systemic autoimmune disorders such as Hashimoto thyroiditis or rheumatologic conditions may also need to be considered if clinical features of these disorders are present.

5.2 | EEG

Prolonged EEG monitoring should be considered in the acute period as subclinical seizure activity may be present. It is important to note that interictal EEG may be normal, and absence of epileptiform abnormalities in these patients can lead to diagnostic delay and misdiagnosis of anxiety and functional disorders. Patients with LGI1 encephalitis may show frequent subclinical temporal lobe seizures, so the presence of this in a patient with new-onset seizures should suggest this diagnosis (Figure 1A).[60] During FBDS, there may be no EEG abnormalities.[34] However, diffuse electrodecrement has been described during FBDS,[61] and use of ultralow high-pass filter settings can demonstrate a contralateral frontocentral slow-wave complex in association with this seizure type (Figure 1B).[62,63] In one study evaluating the yield of EEG in LGI1-associated FBDS, 24% of patients had ictal epileptiform abnormalities.[34] After diagnosis, patients may underreport their seizures, as was demonstrated in a series of LGI1 and CASPR2 encephalitis evaluated with 48-hour ambulatory EEG, so prolonged EEG may need to be considered in order to supplement seizure diary information.[64] The EEG is typically abnormal in NMDAR encephalitis and may serve as an early clue to the diagnosis while awaiting antibody results.[65] Generalized rhythmic delta,[66] with or without superimposed beta bursts (referred to as "extreme delta brushes (EDB)"), has been reported with NMDAR encephalitis (Figure 1C,D),[67] and anecdotally in FIRES.[68] EEG may also be helpful prognostically—in NMDAR encephalitis, the absence of a posterior dominant rhythm and the presence of EDB correlate with poor outcome.[65,67] Similarly, in autoimmune encephalitis with cell surface antibodies, interictal epileptiform discharges correlate with increased risk of ongoing seizures in the follow-up period.[69]

5.3 | Cancer screening

Age-appropriate malignancy screening (Table 4) should be considered in any patient with autoimmune encephalitis. Targeted searches for specific tumor types should be undertaken in certain clinical scenarios—for example, transvaginal ultrasound or pelvis MRI in NMDAR encephalitis to evaluate for ovarian teratoma and testicular ultrasound in Ma2 antibody positivity. Periodic malignancy screening is generally performed for 2 years after the initial diagnosis in patients with a negative initial tumor evaluation who harbor intermediate- or high-risk paraneoplastic antibodies.[70,71] In chronic

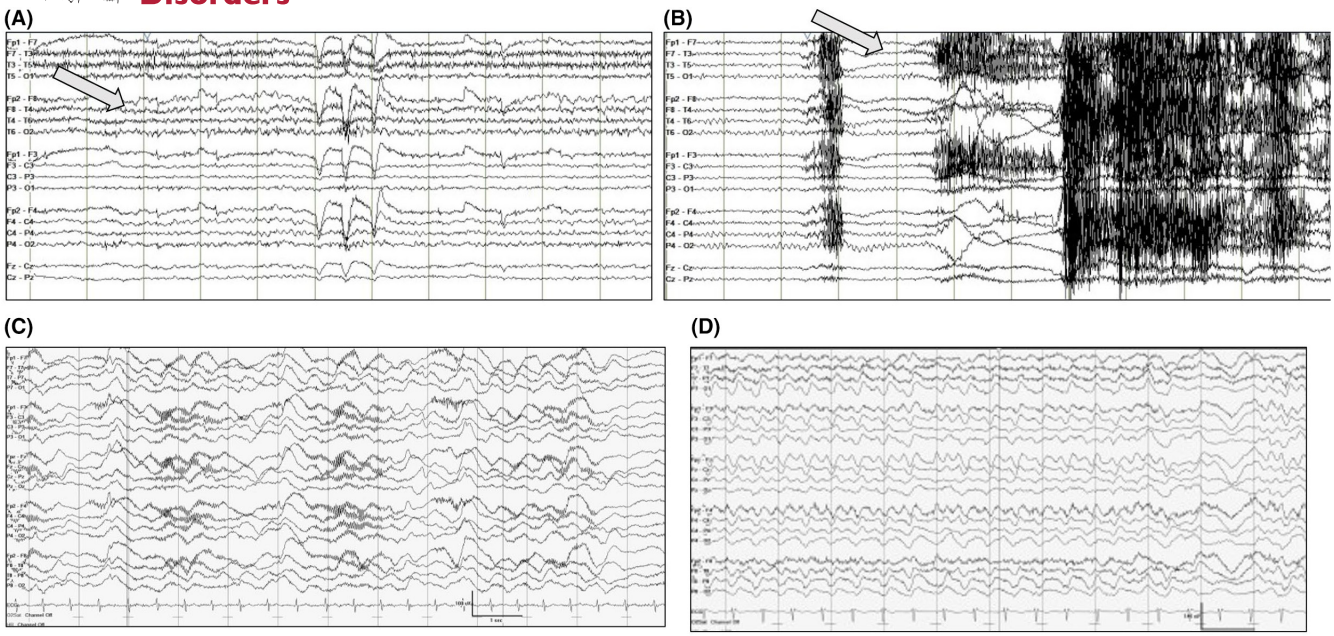

FIGURE 1 EEG findings in autoimmune-associated seizure disorders. (A, B) EEG findings in LGI1 encephalitis. (A) EEG in 56-year-old man presented with involuntary spasms of the face, arm, or leg occurring multiple times an hour. He was admitted for video EEG which showed frequent subclinical seizures arising from the right and left temporal regions (subtle right temporal seizure shown in panel A (arrow). (B) EEG shows diffuse electrodecrement preceding FBDS events during which time myogenic artifact obscures the EEG. (C, D) EEG findings in NMDAR encephalitis. (C) 24-year-old woman was admitted with altered mental status, psychiatric symptoms, and seizures. EEG showed frequent bursts of generalized semi-rhythmic delta with superimposed beta bursts consistent with extreme delta brush. (D) In another patient with NDMAR encephalitis, the EEG shows generalized rhythmic mixed delta activity at 2 Hz posteriorly and 4 Hz anteriorly.

GAD65-associated temporal lobe epilepsy, malignancy screening is not universally performed.

5.4 | Imaging

Certain structural brain magnetic resonance imaging (MRI) abnormalities suggest the possibility of an autoimmune cause (Figure 2). Mesial temporal lobe T2-FLAIR hyperintensities and amygdalohippocampal edema may be present in the acute phase. However, mesial temporal lobe T2 hyperintensities may also be observed in other conditions, such as peri-ictal state, infectious encephalitis, and glioma, so thorough consideration of alternative diagnoses in the presence of this finding is essential.[72–74] It should also be noted that while these changes are characteristic of autoimmune encephalitis, their absence does not exclude the diagnosis, as negative brain MRI has been reported in 25–50% of cases in general and in 70% of NMDAR specifically.[55,56]

In addition to mesial temporal lobe T2 hyperintensities, numerous other MRI abnormalities have been identified in patients with seizures due to autoimmune etiology.[75] These findings vary depending on the specific condition in question. Examples include unilateral cortical T2 hyperintensity in certain MOG antibody-associated disease subtypes,[76,77] unihemispheric atrophy in Rasmussen syndrome,[78] multifocal cortical–subcortical T2 hyperintensities (seen most characteristically in $GABA_AR$, ADEM variant of MOG antibody-associated disease, as well as with ANNA1/Hu and others[51,79–81]), basal ganglia T1/T2-hyperintensity (seen with LGI1 encephalitis and FBDS),[82] and radial perivascular enhancement (autoimmune GFAP astrocytopathy).[83] Importantly, none of these imaging findings are pathognomonic and have an associated differential diagnosis that needs to be vetted before settling on an autoimmune etiology. These include malignant, infectious, rheumatologic, vascular, toxic–metabolic, degenerative, and genetic diseases.

As noted above, negative MRI imaging is not rare, which can lead to diagnostic delay and in some cases, misdiagnosis. Conditions in which this is the case include those due to the most common antibodies including NMDAR, LGI1, and GAD65.[26,46,55] Brain FDG-positron emission tomography (PET) may show abnormalities in patients with normal MRI imaging. These include mesial temporal lobe hypermetabolism,[84] basal ganglia hypermetabolism (in patients with FBDS due to LGI1 encephalitis),[85] and occipital hypometabolism (in patients with NMDAR encephalitis).[86]

TABLE 4 Associated malignancies and recommended screening by antibody.

Antibody	Associated malignancy	Approximate risk of malignancy	Recommended screening
NMDAR	Ovarian teratoma	35% (age/sex dependent)	MRI abdomen and pelvis, pelvic ultrasound in females aged 12–45; CT chest, abdomen, and pelvis or FDG-PET in patients >45 years. Consider MRI chest in children <5 years
LGI1	Thymoma and various others	<10%	CT chest
GAD65	Various	<5%	Routine age- and sex-appropriate screening
CASPR2	Thymoma	~25% (higher in patients with Morvan syndrome)	CT chest
$GABA_BR$	Small cell lung cancer	>50% (uncommon in children)	CT chest, abdomen, and pelvis or FDG-PET
Ma2	Testicular, non-small cell lung cancer	>70%	Testicular ultrasound in men <45 years, and CT chest or FDG-PET in older adults
Hu/ANNA1	Small cell lung cancer, non-small cell lung cancer, and neuroendocrine tumors	85%	CT chest, abdomen, and pelvis or FDG-PET
AMPAR	Thymoma, small cell lung cancer, and breast adenocarcinoma	>50%	CT chest, abdomen, and pelvis or FDG-PET
CV2/CRMP5	Small cell lung cancer and thymoma	>80%	CT chest, abdomen, and pelvis or FDG-PET
$GABA_AR$	Thymoma, other carcinomas, and myeloma	30%	CT chest, abdomen, and pelvis or FDG-PET, and monoclonal protein study

6 | DIAGNOSIS

In 2016, criteria were published to provide syndrome-based diagnostic algorithms for the clinical diagnosis of possible, probable, and definite autoimmune encephalitis (Table 5).[1] Criteria for the diagnosis of autoimmune encephalitis have also been published for pediatric patients.[87] Of note, while seizures are included in these criteria, they are not emphasized and seizures and EEG abnormalities are not required to render a diagnosis. In reviewing these criteria, it is important to note that patients with autoimmune encephalitis do not always fulfill all of these criteria.

To aid recognition, several clinical scoring scales have been developed to determine likelihood of neural antibody positivity in order to identify those with highest yield for neural antibody testing and to predict response to immunotherapy (Table 6).[11,75,88,89] The individual scoring systems vary in their composition and perform better when used on the population in which they were developed. For example, the APE2 score shares numerous items with the syndrome-based criteria for autoimmune encephalitis and may be better suited for patients with seizures in the context of a subacute encephalitic presentation. On the other hand, the ACES score was developed in patients without initially recognized features suggesting an autoimmune etiology and may be a better choice in those presenting in the clinic with seizures who lack overt features of encephalitis.

APE2 score of ≥4 had 99% sensitivity and 93% specificity for neural antibodies. RITE2 score ≥7 had 96% sensitivity and 86% specificity for favorable initial immunotherapy response. McGinty score ≥0 had sensitivity of 66.7% and specificity of 84.9% for predicting neural cell surface antibodies. ACES score of ≥2 had 100% sensitivity and 84.9% specificity for neural antibodies. Subsequent evaluations have shown differences in sensitivity and specificity. APE2: Antibody prevalence in epilepsy 2 score. ACES: Antibodies contributing to focal epilepsy signs and symptoms score. RITE2: Responsive to immunotherapy in epilepsy and encephalopathy. *Addenbrooke's cognitive examination attention domain score.

7 | TREATMENT: IMMUNOTHERAPY

Because ASMs have limited benefit in new-onset autoimmune-associated seizures, trials of immunotherapy should be undertaken once the diagnosis is reasonably confirmed, provided an immunotherapy-responsive disorder is identified. Acute symptomatic seizures secondary to autoimmune encephalitis with pathogenic

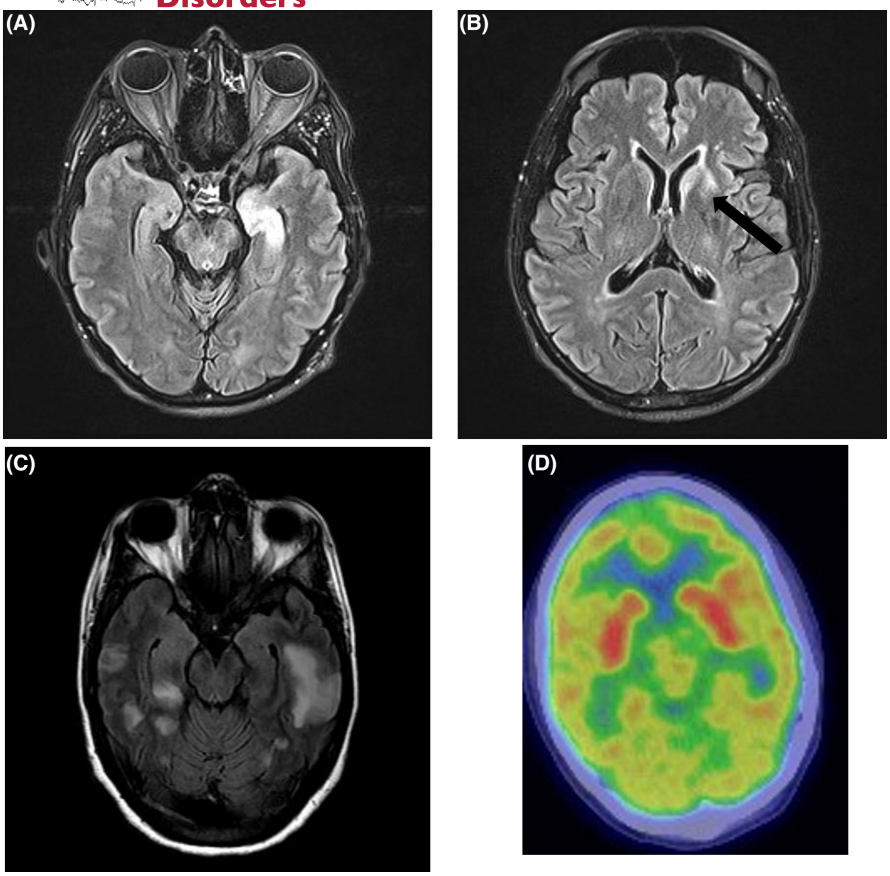

FIGURE 2 Imaging findings in autoimmune-associated seizure disorders. (A, B) Imaging in a patient with LGI1 encephalitis shows T2 hyperintensity in the left>right mesial temporal lobe (A) and the left putamen and caudate (B, black arrow). (C) Imaging in a patient with $GABA_AR$ encephalitis showing multifocal T2 FLAIR hyperintensities. (D) Patchy diffuse cortical hypometabolism on FDG-PET in a patient with NMDAR encephalitis with relatively preserved basal ganglia FDG uptake.

cell surface antibodies have the greatest response to immunotherapy.[7,26,90] A shorter interval between symptom onset to initiation of treatment has been associated with a higher likelihood of immunotherapy response.[26,38,69,91] In patients with diseases associated with cytotoxic T-cell-mediated pathogenesis (as in limbic encephalitis associated with GAD65 and high-risk paraneoplastic antibodies), response to immunotherapy is limited, and complete resolution of seizures does not typically occur.[48,80] Because of the rarity of autoimmune-associated seizure disorders, most treatment strategies are based on class IV evidence (retrospective clinical data or expert opinion), and the treatments described below are the approaches utilized and recommended by the authors of this manuscript.

7.1 | Typical treatment approach

First-line treatment consists of high-dose corticosteroids and/or intravenous immunoglobulin (IVIg) (0.4 g/kg ideal body weight daily for 5 days or 1 g/kg ideal body weight daily for 2 days).[92] Plasma exchange (5–7 treatments over 10–14 days) is also utilized in severe cases. Corticosteroids are typically administered as methylprednisolone 30 mg/kg (maximum 1 g) daily for 5 days followed by either high-dose oral prednisone (e.g., 60 mg or 1 mg/kg/day followed by a gradual taper) or weekly methylprednisolone infusions for a period of weeks varying from 5 to 12 weeks, followed by gradual lengthening of the dose interval (e.g., every other week, then every 3rd week, and then monthly).

Depending on response, these initial treatments may be followed by a second-line, longer-acting immunosuppressant, such as rituximab or cyclophosphamide. Rituximab is more commonly used as it only requires two infusions (750 mg/m^2 (max 1 g) each, usually given 2 weeks apart), has a more tolerable side-effect profile, fewer risks, and lacks the potential for infertility compared to cyclophosphamide. Therapies previously considered second line are increasingly initiated before assessing the response to first-line therapies for certain antibody-mediated encephalitides. For example, rituximab is increasingly used early in the treatment course of NMDAR encephalitis to induce longer-acting immune suppression targeting precursors of IgG-producing plasma cells (B lymphocytes) and reduce the duration of corticosteroid use, as studies have suggested treatment may be associated with improved outcomes.[26] In syndromes associated with intracellular antigen-directed antibodies, which are cytotoxic T cell-mediated, cyclophosphamide is sometimes used,

TABLE 5 Diagnostic criteria for possible and definite autoimmune encephalitis[a].

Diagnosis of possible autoimmune encephalitis can be made when all three of the following criteria are present	Diagnosis of definite autoimmune limbic encephalitis can be made when all four of the following criteria have been met
1. Subacute onset of working memory deficits, altered mental status, and/or psychiatric symptoms	1. Subacute onset of working memory deficits, seizures, and/or psychiatric symptoms suggesting involvement of the limbic system
2. At least one of the following:	2. Bilateral brain abnormalities on T2-weighted FLAIR MRI restricted to the mesial temporal lobes
• New focal central nervous system finding	3. At least one of the following:
• New onset seizures	• CSF pleocytosis
• CSF pleocytosis	• Temporal epileptic or slow-wave activity on EEG
• MRI of the brain suggestive of encephalitis	4. Reasonable exclusion of alternative causes
3. Reasonable exclusion of alternative causes	

[a]Adopted from Graus et al.[1]

although the effects are often limited. The decision of whether and when to start cyclophosphamide depends on a number of factors. Patients with high-risk paraneoplastic antibodies associated with malignancy may require chemotherapy agents with cytotoxic effects that prohibit the concurrent use of cyclophosphamide, or if surgery for their malignancy is required, cyclophosphamide may not be started until after satisfactory wound healing is accomplished. For cases not associated with malignancy, severe or progressive neurological deficits may prompt the initiation of cyclophosphamide. Also, in GAD65 antibody-associated epilepsy, the presence of ongoing inflammation in chronic cases is often in doubt, and given the low likelihood of response in general, second-line therapy with cyclophosphamide may be best considered in patients with a relatively short illness duration, as active inflammation in chronic cases is unlikely thus not warranting treatment risk.

Most autoimmune-associated seizure disorders are monophasic, although relapses may occur. The appropriate duration of initial therapy is not evidence based at present, but given it may take time for CNS inflammation to completely subside, treatment over weeks and months is suggested by most authorities, as opposed to shorter treatment durations. Our practice is to slowly taper and discontinue first-line immune treatment completely over several weeks to months in a gradual manner. Relapses occur in approximately 20–30% of patients with LGI1 encephalitis and 10–20% of those with NMDAR-encephalitis relapse, necessitating an additional round of acute treatment followed by long-term immunotherapy.[26,56] Options for long-term immune suppression currently include rituximab, mycophenolate mofetil, azathioprine, or methotrexate. Prognosis appears to be better in those treated earlier, in those without hippocampal abnormalities on MRI. Prognosis is also generally better in cell surface antibody-mediated encephalitides such as LGI1 and NMDAR encephalitis, in comparison with GAD65 and T-cell-mediated paraneoplastic disorders.[93]

7.2 | Clinical trials

Clinical trials now underway seek to formally address the role of early depletion of plasmablasts, B cells, and B cell precursors (using anti-CD19-directed inebilizumab in NMDAR encephalitis), targeting of B-cell-stimulating interleukin-6 (using IL-6 receptor directed satralizumab in LGI1-encephalitis and NMDAR-encephalitis) or through inhibition of the IgG-recycling neonatal Fc receptor (rozanolixizumab in LGI1 encephalitis). All studies aim to assess long-term immunosuppression early in the treatment course after a short course of first-line treatment has been administered to both treatment and placebo arms. While IVIg has been demonstrated to have efficacy in a randomized controlled trial in LGI1 encephalitis, data from retrospective series suggest greater efficacy with corticosteroids in this disorder.[90,94] Targeting plasma cells by proteasome inhibition via bortezomib is currently being evaluated in patients with severe autoimmune encephalitis and antibodies to neural surface antigens after failure of second-line therapy with rituximab.[95]

8 | TREATMENT: ANTISEIZURE MEDICATIONS AND NEUROSTIMULATION

While many autoimmune-associated seizure disorders are resistant to ASMs, ASMs still play a role albeit more limited. There are no prospective trials examining efficacy of ASMs in autoimmune-associated seizure disorders, and data from retrospective studies are confounded by nonstandardization of therapy regimens, concurrent use of immunotherapy, and lack of control groups. While levetiracetam is often used initially due to its ease of use and common practice patterns, it is usually ineffective, and a significant proportion of patients may experience behavioral side effects.[7] Overall, carbamazepine and other sodium channel-blocking medications have potential efficacy at least with respect to seizures, particularly in LGI1 encephalitis. However, this is limited, with seizure control reported in 15% without immunotherapy.[7,96] In addition, there is an increased risk of rash and hyponatremia in association with carbamazepine and oxcarbazepine therapy in this setting which needs to be monitored.[6,7] There are limited data on the use of neurostimulation for patients with autoimmune-associated seizure disorders. There are case reports and small case series that report efficacy for the use of deep brain stimulation or responsive neurostimulation, most commonly in patients with chronic epilepsy related to GAD65 antibodies.[97–99]

9 | OUTCOME AND PROGNOSIS

9.1 | Seizure outcomes (extra- vs. intracellular targets)

Outcome and prognosis largely depend on the underlying immunological process leading to the seizures. Patients with antibodies targeting cell surface antigens, like NMDAR or LGI1, exhibit direct functional effects (pathogenic), and at least in the case of NMDAR, are associated with relatively less neural damage.[3] The subacute/acute phase and associated seizures are mostly provoked by active encephalitis. However, once inflammation has been adequately treated with immunotherapy, the seizure activity may quickly diminish.[7,38] Most patients with autoimmune encephalitis and pathogenic antibodies (like NMDAR, $GABA_BR$, or CASPR2) will become seizure free following immunotherapy.[3,7,100] In one study of patients with NMDAR encephalitis, 80% were seizure free by 6 months and 100% were seizure free within 2 years.[28] There is debate as to the risk of autoimmune-associated epilepsy following LGI1 encephalitis as seizure-free rates have varied between 75% and 97%.[6,7,38,64,69,96] Some things need to be kept in mind when interpreting these data. First, studies

TABLE 6 Scoring scales to identify patients with an autoimmune cause of seizures and to predict response to immunotherapy.

Symptoms/signs	Points
APE2 score[89]	
New onset, rapidly progressive mental status changes over 1–6 weeks, or new-onset seizures	+1
Neuropsychiatric changes	+1
Autonomic dysfunction	+1
Viral prodrome	+2
Faciobrachial dystonic seizures	+3
Facial dyskinesias	+2
Seizure refractory to at least 2 antiseizure medications	+2
CSF findings of inflammation	+2
Brain MRI suggesting encephalitis	+2
Systemic cancer	+2
Score of ≥4 predictive of neural antibody positivity	
RITE2 Score[89]	
Criteria for APE2 score above with the additional criteria:	up to 18
Immunotherapy started within 6 months of symptom onset	+2
Neural plasma membrane autoantibody detected (NMDAR, GABAAR, GABABR, AMPAR, DPPX, mGluR1, mGluR2, mGluR5, LGI1, IgLON5, CASPR2, or MOG)	+2
Score of ≥7 suggestive of favorable initial immunotherapy response	
McGinty et al.[10]	
Brain MRI suggesting encephalitis	+2
Age ≥ 54	+1
Ictal piloerection	+2.5
Self-reported mood disturbance	+1
ACE attention score ≥ 16	−1.5
Epilepsy risk factors	−1.5
Score of >0 predictive of neural antibody positivity	
ACES Score[11]	
Autonomic dysfunction	+1
Brain MRI suggesting encephalitis	+1
Behavioral changes	+1
Cognitive symptoms	+1
Speech problems	+1
Autoimmune diseases	+1
Score of ≥2 predictive of neural antibody positivity	

[Correction added on 11 June 2024, after first online publication: The citation numbers in the table were corrected.]

involving patients evaluated at tertiary epilepsy clinics have reported higher seizure recurrence rates, raising the possibility of bias favoring refractory cases. Second, subtle or subclinical seizures might be overlooked leading to underreporting, inadvertently overestimating the rates of seizure freedom.

Questions as to the duration for which ASMs should be continued often arise in the course of care. It is generally accepted to consider a taper of ASMs 6–12 months after resolution of the acute episode in seizure-free patients. The recurrence of seizures after initially successful ASM discontinuation should lead to evaluation for relapse, which may necessitate escalation or resumption of immunotherapy if present.

High-titer GAD65 antibodies form the largest group of patients with nonpathogenic antibody-associated seizures. Often, there is no subacute onset and the etiology may be difficult to distinguish clinically from other types of temporal lobe epilepsy.[44,46,101] The response to immunotherapy is inconsistent, and seizure freedom is rare. Patients are often pharmacoresistant to ASMs, and nonpharmacological interventions (epilepsy surgery) are usually ineffective.[102,103] A recent small series ($n = 8$) showed promising results of combined use of cenobamate and clobazam (92% seizure reduction),[104] although these findings require replication in larger series. Long-term data related to other antibodies, like Hu/ANNA1,[52] or "probable antibody-negative autoimmune encephalitis"[1] are largely lacking, with research of the latter suffering from lack of a diagnostic gold standard or biomarker to secure specificity of the diagnosis. The risk of developing epilepsy is higher in these disorders.[3,52]

9.2 | Cognitive and functional outcomes

Cognitive and behavioral sequelae are frequent, although extensive studies are lacking. As most patients with antibodies to cell surface antigens become seizure-free, cognitive deficits in many cases become more relevant than seizures in impacting long-term quality of life.[56,105,106] Common deficits involve attention, executive functioning, (episodic) memory, visuospatial function, and fatigue.[56,90,105–108] Rehabilitation efforts are warranted when these disabilities are present. Marked improvement can occur in the first 6 months and continue over the ensuing 2–4 years.[26,56,108] Patients with GAD65 antibodies also suffer from cognitive deficits related to temporal lobe dysfunction, ASM therapy, and seizures. Over time, objective neuropsychological evaluations do not show consistent deterioration, although the subjective perception from patients is often less positive.[47]

10 | RASMUSSEN SYNDROME

Rasmussen syndrome is a rare neurologic condition characterized by unilateral cerebral cortical inflammation, leading to drug-resistant epilepsy and progressive neurologic decline lateralized to the affected side. The pathogenesis has been determined to be mediated by cytotoxic T-cell inflammatory processes, although other immune mechanisms are also present.[13] Rasmussen syndrome most commonly affects children, and less frequently begins in late adolescence or early adulthood. MRI characteristically shows hemiatrophy that progresses over time, as well as cortical signal change and ipsilateral caudate atrophy. CSF studies are normal in approximately 50% but may show mild pleocytosis, elevated protein, or CSF-specific oligoclonal bands. Criteria have been published to aid in diagnosis, although biomarkers are otherwise currently lacking and a specific autoantibody has not been identified.[13] Responses to immunotherapy are unfortunately inconsistent and surgical hemispheric disconnection is frequently necessary to achieve seizure control. However, timing of surgery is challenging, with the decision to proceed taking into account the likelihood of the occurrence of neurological deficits related to the procedure.[13]

11 | NORSE AND FIRES

11.1 | Epidemiology and pathogenesis

NORSE is defined as a condition with new onset of refractory status epilepticus without a clear acute or active structural, toxic, or metabolic cause in a patient without active epilepsy. FIRES is considered a subtype of NORSE in which a fever is present within 2 weeks of seizure onset.[109] NORSE appears to be more common in adults and FIRES in children,[110,111] the latter of which had an estimated incidence in a German cohort of 1/1 000 000 children.[112] An etiology is eventually identified in up to half of NORSE cases, including infectious, autoimmune, and metabolic/genetic causes, with the residual remaining cryptogenic.[111,113] Most hypotheses regarding pathogenesis of NORSE invoke the occurrence of a systemic inflammatory trigger, in a patient with as-of-yet unidentified genetic predisposition(s) to excessive activation of the innate immune system. These factors result in a proinflammatory cascade involving synthesis of a number of mediators of inflammation, including interleukin (IL)-1 and IL-6.[114]

11.2 | Presentation and evaluation

Patients often present with a prodromal viral illness.[111,115] Seizures are typically focal in onset and gradually

culminate in refractory status epilepticus (RSE) within days.[68,115] Patients with NORSE/FIRES secondary to autoimmune encephalitis tend to have other neuropsychiatric symptoms in addition to seizures compared to cryptogenic cases.[113]

On EEG, delta–beta complexes, focal high-frequency activity at electrographic seizure onset, and a signature ictal pattern with shifting laterality have been described.[68] Initial brain MRI shows abnormalities in half of patients, typically consisting of T2 hyperintensities in varying locations, such as the temporal cortex, hippocampi, basal ganglia, insula, pulvinar, and claustrum. Diffuse atrophy often develops over time.[110,111] CSF profiles may show mild pleocytosis and elevated protein, with or without CSF-specific oligoclonal bands and neopterin; however, it is not rare for no abnormalities to be present on standard testing.[110,111] CSF cytokine abnormalities have been identified that may correlate with response to specific therapies.[116] These findings warrant future research.[117] CSF neopterin, a neuroinflammatory and excitotoxic metabolite, is often elevated and is considered a possible early biomarker suggesting an inflammatory etiology in RSE.[118]

In addition to continuous EEG, MRI, and CSF, expert consensus recommends an extensive work-up including serum and CSF autoimmune encephalitis antibody panels, systemic rheumatologic antibodies, region-specific infectious etiology testing, metabolic screen, paraneoplastic evaluation for occult tumor with ultrasound and cross-sectional imaging, and genetic testing in order to determine etiology.[119] Although the yield of genetic testing is generally low, identification of certain genetic etiologies could identify potential targets for therapy and may contribute to future understanding of this syndrome.[120]

11.3 | Treatment

Treatments are limited to those published in case reports, series, and expert consensus. Given the rarity and gravity of the condition, controlled trials are unfortunately lacking.[119,121,122] ASMs and continuous infusions of anesthetic levels of sedation are typically required to maintain seizure control. Intravenous methylprednisolone and/or IVIg are often utilized. Plasma exchange can be considered, but its role in the absence of a defined antibody is unclear. Ketogenic diet, which has been shown to have anti-inflammatory properties specifically targeting the IL-1 cascade,[123] is a therapeutic option that should be considered within 1 week of onset if seizures are ongoing. Ketogenic diet is chiefly utilized in FIRES at present and warrants greater evaluation in adult NORSE in which there currently is a paucity of data.

At present, there is consensus to consider rituximab in cases in which there is a high index of suspicion of an autoimmune etiology and infectious and neoplastic causes have been excluded. IL-1 receptor and IL-6 receptor antagonist therapy with anakinra and tocilizumab, respectively, has been used in cryptogenic NORSE/FIRES.[119] The use of intrathecal dexamethasone has been reported and can be considered if other immunomodulation fails.[124] Neuromodulation and resective epilepsy surgery have also been utilized in select cases.[119,125] If deemed effective, targeted immunotherapy and/or ketogenic diet are typically continued for at least 3 months. No specific ASM has been found to be uniquely effective in the treatment of epilepsy resulting from NORSE after resolution of the acute phase of illness.[119]

11.4 | Outcome

The outcome in NORSE and FIRES is generally poor, with mortality rates of 10–25%. Most survivors have cognitive impairment and chronic epilepsy, which is medically intractable in at least half.[115] Early immunomodulation may improve short-term outcome in some cases, although initial studies do not suggest a benefit on long-term cognitive outcome.[126] Neopterin levels may aid early diagnosis, and cytokine profiles have the potential to serve as biomarkers of disease severity.[116] Assessing long-term effectiveness and safety of targeted immunomodulation therapies based on specific biomarkers of inflammation identified in patients may allow the development of precision therapies in the future.

12 | CONCLUSION

Autoimmune-associated seizure disorders are crucial to recognize, given the seizures in some cases may respond definitively to immunotherapy and that they are unlikely to improve with ASM treatment alone. The discovery of autoantibodies has helped in the diagnosis of multiple autoimmune-associated seizure disorders, and characteristic phenotypes have been clarified that correlate with specific underlying antibodies, aiding early diagnosis. Immunotherapy remains a cornerstone of treatment, but outcomes are dependent on timeliness of initiation, treatment dosing and duration of therapy, and underlying cause. Immunotherapy responses in autoimmune-associated seizure disorders due to antibodies targeting intracellular antigens (e.g., anti-GAD65 and high-risk paraneoplastic antibodies) and in Rasmussen syndrome remain disappointing, and other treatments are needed. Cryptogenic NORSE and FIRES are hypothesized to

have inflammatory pathogenesis, but further research is required to determine the specific immunologic mechanisms of these syndromes in order to identify more consistently effective treatment strategies.

12.1 | Case 1

A 73-year-old right-handed man began to experience unsteadiness and episodes of dizziness. Two months later, he began to have episodes of a brief jerk of the left arm and face, and then separate episodes involving the right face and arm. These episodes occurred up to once every 2–10 min. Over the same period, he developed cognitive symptoms. His EEG was normal, including during recorded typical events. He was trialed on three ASMs over a short period of time, including levetiracetam, valproic acid, and clonazepam, which were ineffective. MRI of the brain showed no significant abnormalities. LGI1 antibody was identified in serum. He was treated with IV methylprednisolone and transitioned to oral prednisone with a prolonged taper. Due to progressive weakness and fatigue, he was admitted to the hospital and found to have a myopathy, likely related to steroid therapy, prompting transition to IVIg. He recovered well with immunotherapy, experiencing complete resolution of FBDS. Four years after his initial presentation, he developed recurrence of FBDS (up to 50 a day) and worsening cognition. He was diagnosed with relapse, which was supported by the presence of LGI1 antibody positivity. MRI showed no acute changes. He was again treated with immunotherapy.

12.2 | Case 2

A 36-year-old left-handed woman presented with recurrent, stereotyped events lasting approximately 30 seconds, consisting of sudden onset of anxiety associated with a rising abdominal sensation, nausea, and an intense feeling of déjà vu. She had a mild sense of confusion after some of the episodes. They were occurring every 3–4 days but could cluster, with up to 3–4 events in 1 day. MRI of the brain was normal. Habitual events were recorded on EEG and determined to be seizures of left temporal onset. Seizures continued despite adequate doses of levetiracetam and lamotrigine. She was found to have a markedly elevated GAD65 antibody titer in serum of 332 nmol/L (normal <.02 nmol/L). She also had evidence of Hashimoto's thyroiditis with elevated TPO antibody and thyroglobulin antibody concentration. She was treated with IV methylprednisolone, and while there was a moderate reduction in seizure frequency, she continued to have two seizures per week. After discontinuation of steroids, the seizures increased again prompting reinitiation of methylprednisolone and the addition of mycophenolate mofetil. Despite this, seizures continued at a frequency of 30–60 per month. Subsequent prolonged EEGs recorded seizures of independent left temporal and right temporal onset. Over time, she also noticed that seizures could be triggered by listening to specific country music songs, leading to the diagnosis of musicogenic seizures.

In consultation with autoimmune neurology subspecialist colleagues, based on their extensive experience, further immunotherapy was not recommended as it was determined that this was unlikely to be beneficial. Multiple other ASMs were trialed including carbamazepine, valproic acid, topiramate, and cenobamate, without significant benefit. Eventually, a vagus nerve stimulator (VNS) was placed which led to an initial seizure frequency reduction which unfortunately was not sustained. She continues to have frequent focal seizures at last follow-up.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Smith KM, Budhram A, Geis C, McKeon A, Steriade C, Stredny CM, et al. Autoimmune-associated seizure disorders. Epileptic Disord. 2024;00:1–20. https://doi.org/10.1002/epd2.20231

Test yourself

1. Seizures related to encephalitis that resolve with immunotherapy should be referred to as which of the following?
   A. Autoimmune epilepsy
   B. Acute symptomatic seizures secondary to autoimmune encephalitis
   C. Autoimmune associated epilepsy
   D. Chronic epilepsy
2. Antibodies in LGI1 encephalitis do which of the following?
   A. Target intracellular antigens
   B. Enhance synaptic excitation through reduction of presynaptic Kv1.1 expression
   C. Alter the function of GABA
   D. Bind to the aminoterminal domain of the obligate GluN1 subunit
3. Faciobrachial dystonic seizures are associated with which of the following antibodies?
   A. NMDAR
   B. ANNA1/Hu
   C. LGI1
   D. GAD65
4. GAD65 antibodies are associated with which of the following?
   A. Musicogenic seizures
   B. Reading epilepsy
   C. Absence seizures
   D. Photoparoxysmal response to photic stimulation
5. Extreme delta brush is suggestive of what underlying antibody?
   A. LGI1
   B. NMDAR
   C. ANNA1/Hu
   D. GAD65
6. Which of the following is a first-line treatment option for autoimmune-associated seizure disorders?
   A. Methylprednisolone
   B. Azathioprine
   C. Cyclophosphamide
   D. Mycophenolate
7. Which of the following antiseizure medications has been shown to result in seizure control in 15% of patients with LGI1 encephalitis?
   A. Levetiracetam
   B. Perampanel
   C. Zonisamide
   D. Carbamazepine
8. Long-term seizure outcomes are most favorable in which of the following?
   A. NORSE or FIRES
   B. GAD65-associated epilepsy
   C. NMDAR encephalitis
   D. Autoimmune encephalitis associated with high-risk paraneoplastic antibodies
9. Cryptogenic NORSE or FIRES is associated with which of the following?
   A. Antibodies to intracellular antigens
   B. Pre-existing epilepsy
   C. Good long-term seizure outcomes
   D. Activation of the innate immune system and proinflammatory cascade
10. What is the most common cause of NORSE?
    A. Infection
    B. Cryptogenic
    C. LGI1 encephalitis
    D. NMDAR encephalitis

Answers may be found in the supporting information.