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Disorders related to anti-neuronal antibodies: Autoimmune epilepsy

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Abbreviations

ILAE, International League Against Epilepsy; GAD, glutamic acid decarboxylase; NMDAR, N-methyl-d-aspartate receptor; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid; GABA, gamma-aminobutyric acid; LGI1, leucine-rich glioma inactivated 1; Caspr2, contactin-associated protein-like 2; MOG, myelin-oligodendrocyte glycoprotein; GFAP, glial fibrillary acidic protein; NMOSD, neuromyelitis optica spectrum disorder; SLE, systemic lupus erythematosus; ICOS, Inducible T-cell co-stimulator; Tfh, follicular helper T cell.

Abstract

Autoimmune epilepsy is characterized as a subtype of autoimmune encephalitis, where epileptic seizures serve as the primary or predominant manifestation of the disease. Among patients who are refractory to antiepileptic drug therapy, a part of them experiences improved seizure control with immunotherapy. Some of these individuals have been found to possess autoantibodies that target neuronal surface, intracellular, or extracellular antigens. In 2017, the International League Against Epilepsy (ILAE) proposed a new classification of epilepsy syndromes that, for the first time, recognized "immune" as one of the etiologies of epilepsy. Since early and prompt diagnosis and treatment of autoimmune epilepsy may improve prognosis, it is crucial to actively consider the utilization of reported diagnostic features and treatment with immunotherapy in the management of patients with refractory epilepsy. We herein provide a review of the literature concerning the clinical features, laboratory findings, pathophysiology, and treatment options associated with this disease.

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Introduction

Epilepsy is defined as a chronic brain disorder characterized by a predisposition to epileptic seizures.[1] It is estimated that 0.5% to 1% of the world's population is affected by epilepsy, which has a wide variety of causes, some of which have unknown etiology and no effective treatment. It has long been known empirically that immunotherapy is effective in some patients with epilepsy refractory to antiepileptic drugs.[2] Patients with autoimmune diseases also have an increased risk of epilepsy compared to those without autoimmune diseases.[3] Recent advances in antibody detection techniques have led to the detection of autoantibodies in a subset of epilepsy patients, further supporting an immune-mediated mechanism and revealing the existence of so-called "autoimmune epilepsy". In particular, epilepsy associated with antibodies to neuronal surface antigens is thought to respond well to immunotherapy.[4] This may provide new and beneficial treatment options for patients with refractory epilepsy.

Anti-neural antibodies and autoimmune encephalitis

Classically, antibodies targeting intracellular neuronal antigens, such as the Hu antibody, [5] the Ma antibody[6, 7] and the glutamic acid decarboxylase (GAD) antibody,[8] are known to be associated with paraneoplastic neurological syndrome and other encephalitides and encephalopathies. More recently, with the development of antibody detection methods that preserve the three-dimensional structure, antibodies targeting antigens on the surface of neuronal cells and in the synaptic cleft, such as N-methyl-d-aspartate receptor (NMDAR) antibodies, [9] alpha-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid (AMPA) receptor antibodies, [10] gamma-aminobutyric acid (GABA-B[11] and GABA-A[12]) receptor antibodies, leucine-rich glioma inactivated 1 (LGI1) antibodies,[13] and contactin-associated protein-like 2 (Caspr2) antibodies,[14] have been identified. In addition to these cell surface antigens, antibodies against myelin oligodendrocyte glycoprotein (MOG) [15] and glial fibrillary acidic protein (GFAP) of astrocytes [16, 17] that can cause autoimmune-mediated meningoencephalitis, are among the antibodies associated with autoimmune encephalitis in a broad sense.

Autoantibodies particularly those directed against cell surface antigens, induce disease by a variety of pathophysiologic mechanisms. Autoimmune epilepsy causes disease by a mechanism that blocks neuronal transmission through receptor blockade or alteration of synaptic structures.[18] Of note, early diagnosis of autoimmune encephalitis targeting cell surface antigens, is important because early therapeutic intervention is effective in improving prognosis. Graus et al. proposed the following diagnostic criteria for autoimmune limbic encephalitis: 1) subacute clinical symptoms of the limbic system, 2) MRI images, 3) cerebrospinal fluid or electroencephalographic findings as evidence of inflammation, and 4) exclusion of infectious

encephalitis such as acute herpes encephalitis.[19] It is superior in that the diagnosis can be made promptly without waiting for the results of anti-neuroantibody testing, based on the findings of the neurologic examination and the results of conventional tests that can be widely performed by physicians.

Terminology of autoimmune epilepsy

In 2017, the ILAE proposed a new classification of epilepsy syndromes that included immunity as one of the etiologies of epilepsy. Autoimmune encephalitis characterized by seizures is now called autoimmune epilepsy, referring mainly to NMDAR antibody-positive and LGI1 antibody-positive encephalitis. In a certain number of cases of autoimmune encephalitis with autoantibodies against cell surface antigens, seizures resolve completely with treatment and antiepileptic drugs can be discontinued. On the other hand, it is also known that there are some refractory cases of autoimmune encephalitis with cell surface antibodies, which seizures persist despite adequate immunotherapy and resolution of inflammatory findings. Autoantibodies against intracellular antigens are often associated with persistent seizures with poor response to antiepileptic drugs and immunotherapy. Many cases associated with cell surface antibodies that have allowed discontinuation of antiepileptic drugs do not fit the definition of epilepsy as "chronic, recurrent seizures", and some have pointed out that it is inappropriate to conflate the above conditions and refer to them as autoimmune epilepsy.[20] With this in mind, the ILAE Autoimmunity and Inflammation Task Force in 2020 defined "acute symptomatic seizures secondary to autoimmune encephalitis" as seizures that occur during the active phase of autoimmune encephalitis, and "autoimmune-associated epilepsy" as seizures that persist despite adequate attempts at immunotherapy or in the absence of clear evidence of active inflammation.[21] However, there are also smoldering cases due to high inflammatory activity or inadequate immunotherapy that do not fit the description of "acute" symptomatic disease. There are also cases of recurrent seizures, such as LGI1 antibody-positive encephalitis, and it is sometimes difficult to make a clear distinction between these two types of epilepsy. Therefore, we have adopted autoimmune epilepsy as the integrated terminology in this review. The definitions of autoimmune epilepsy need to be validated in the future.

Clinical features of autoimmune epilepsy

Epileptic seizures are known to be one of the major symptoms of autoimmune encephalitis. Of note, the diagnosis of refractory epilepsy is often made in patients with immune-mediated epileptic seizures. Autoimmune epilepsy is defined as autoimmune encephalitis in which epileptic seizures are the sole or primary symptom. A summary of the clinical features of the disease, such as APE and ACES scores, have been reported as diagnostic

criteria for autoimmune epilepsy as a predictor of anti-neuronal autoantibodies and several diagnostic algorithms have been proposed.[22-24] The clinical features of autoimmune epilepsy are often accompanied with those of autoimmune encephalitis, with a variable course often presenting with acute or subacute onset, memory impairment, psychiatric symptoms (irritability, personality changes, etc.), somnolence and apathy. Prolonged inflammation may cause chronic epileptic seizures, cognitive dysfunction, and psychiatric symptoms. Other symptoms may include dystonia, cerebellar symptoms, and myotonia.[19] On the other hand, the diagnosis of epileptic seizures alone, without these symptoms, is often difficult. Epileptic seizures are characterized by 1) acute or subacute onset (maximum seizure frequency within 3 months), 2) diversity of seizure types or faciobrachial dystonic seizure (FBDS), 3) resistance to antiepileptic drugs, and 4) autonomic symptoms (tachycardia, hyperventilation, goose bumps, fever, etc.) during or after seizures.[25] FBDS is a very brief (less than a few seconds), frequent (up to 50-100 times per day), and habitual dystonic attack of the ipsilateral face and upper extremities. These attacks may be associated with jerking of the affected limb.

Laboratory findings in autoimmune epilepsy

In general, as with autoimmune encephalitis, the diagnosis of autoimmune epilepsy is made by CSF, MRI, FDG-PET, electroencephalography (EEG), etc., in addition to antibody testing. CSF may show mild abnormalities, such as only slightly elevated protein but often shows normal findings unless the case is severe. Brain MRI may show abnormal signals in the bilateral temporal lobes or parenchyma, while autoimmune encephalitis cannot be ruled out even if MRI is normal. Even with normal MRI, FDG-PET scan may show focal hypermetabolic activity reflecting inflammation. A recent meta-analysis reported that the sensitivity of FDG-PET is 87% compared with 56% for MRI.[26] There are reports that cerebral blood flow SPECT also shows hyperperfusion in inflammatory areas, and is expected to be an alternative nuclear medicine test to FDG-PET,[27] but studies with larger numbers of patients are desirable.
EEG is useful in the diagnosis and prognosis of autoimmune epilepsy. Epileptic discharges recorded independently in the bilateral temporal regions are considered to be a relatively highly specific finding. Autoimmune encephalitis may be associated with tumors, and different tumors are associated with different types of anti-neuronal antibodies. Although the complication rate varies, a systemic search using imaging studies (e.g., whole-body CT and FDG-PET) and a search for tumor markers is necessary. Recently, Sakamoto et al. proposed that autoimmune epilepsy can be diagnosed when at least two of the laboratory findings are abnormal after evaluation of the patient's history and clinical symptoms; the flowchart of the diagnostic algorithm is shown in Figure 1.[28]

Pathophysiology of autoimmune epilepsy

Although the pathomechanisms of autoimmune epilepsy is not fully understood, we can learn it from that of autoimmune encephalitis.[29] In autoimmune encephalitis, which is often associated with tumors, in which tumor cells express neuronal surface molecules or synaptic proteins that are recognized by antibodies. Thus, ectopic expression of neuronal proteins by tumors is thought to disrupt immune tolerance to these proteins, which contribute to the development of immune responses.[30] On the other hand, more than half of autoimmune encephalitis occurs without concomitant tumor. We describe characteristics of autoimmune encephalitis with higher epileptic seizure frequency for each anti-neuronal antibody (Figure 2).

GAD antibody

Patients with GAD antibodies are known to present with type 1 diabetes mellitus, Stiff-person syndrome, cerebellar ataxia, seizures, limbic encephalitis, and paraneoplastic syndrome.[31] Approximately 70% of patients with GAD antibody encephalitis have seizures, often temporal lobe seizures.[32, 33] In tumor-associated syndrome and possibly GAD antibody encephalitis, infiltrating cytotoxic T cells are thought to promote epileptogenesis by causing neurophagocytosis, granzyme B-induced neurotoxicity, neuronal cell injury, and gliosis.[34] GAD is the enzyme that synthesizes the inhibitory transmitter GABA from the excitatory transmitter glutamate. Studies in Stiff-person syndrome suggest that because GABAergic neurons express high levels of GAD, GAD-targeted neuronal injury decreases GABA synthesis, resulting in reduced GABAergic transmission and, consequently, a hyperexcitatory state in neurons.[35, 36] However, the mechanism of epileptogenesis in GAD-antibody encephalitis is not clear.

NMDAR antibody

Seizures occur 75% of patients with NMDAR antibody encephalitis.[20, 32] EEG patterns such as extreme delta brush have been reported to occur primarily in severe cases, to increase with disease progression, and to disappear prior to improvement of clinical symptoms in response to immunotherapy.[37, 38] Extreme delta brush was thought to be characteristic of NMDAR encephalitis, but it has recently been reported to rarely occur in encephalopathies of nonautoimmune etiology.[39] Autoantibodies against NMDAR recognize the GluN1 subunit and induce synaptic conformational changes that cause reversible impairment of NMDAR and impair glutamate receptor signaling, leading to the learning, memory and other behavioral deficits, and epileptic seizures observed in NMDAR encephalitis.[40] The pathology of NMDAR encephalitis shows a milder inflammatory infiltrate, limited or absent neurophagocytosis, more

frequent B cell or plasma cell infiltrates, and antibody deposition without complement system activation.[9, 41, 42]

GABA-B receptor antibody

Patients with GABA-B antibodies have early and prominent seizures due to limbic encephalitis in about 90% of cases due to limbic encephalitis. They may also present with status epilepticus.[32, 43] GABA-B antibodies recognize the β1 subunit.[11] This autoantibody does not alter cell surface or synaptic receptor levels, but can directly block receptor function.[44] In addition, cytotoxic CD8+ T cells have been detected in the brain parenchyma in close proximity to neurons.[45]

GABA-A receptor antibody

88% of GABA-A receptor antibodies predispose to seizures and chronic-phase epilepsy.[32] GABA-A antibodies act on the extracellular β3 subunit present in the postsynaptic membrane, resulting in a selective reduction of the GABA-A receptor cluster that relocates extrasynaptic sites. This phenomenon reduces fast inhibitory neurotransmission and allows synaptic hyper-glutamate cytotoxicity resulting in epileptic seizures.[46, 47] This autoantibody is associated with viral infections in children and malignancies in adults.[48]

Antibodies related to voltage-gated potassium channels (VGKC)

Antibodies related to voltage-gated potassium channels (VGKCs) include LGI1 and Caspr antibodies.[49] 15-20% of LGI1 receptor antibodies predispose to chronic-phase epilepsy.[50] In LGI1 antibody-positive encephalitis, subclinical EEG seizure patterns are reported to be frequent (more than 10 times per day), and high seizure frequency is associated with limited long-term recovery, and has been proposed as a candidate marker of inflammatory activity and prognosis.[51-53] LGI1 antibodies prevent LGI1 binding to ADAM23 and ADAM22 and decrease total and synaptic levels of Kv1.1, resulting in increased glutamatergic transmission, higher presynaptic release probability, and ultimately induce neuronal hyperexcitation, and memory impairment or epilepsy.[54] Caspr2 is widely expressed in central and peripheral nerves and is also highly expressed on the surface of pain-related dorsal root ganglion cells.[55] The Caspr2 antibody, an IgG4 subclass, inhibits the interaction between Caspr2 and Contactin2 but does not cause internal migration of Caspr2, which causes peripheral nerve hyperexcitability, neuromyotonia, neuropathic pain, insomnia, and dysautonomia.[56, 57]

MOG antibody

Seizures were observed in the initial or relapsing episodes of 15-24% of patients who tested positive for MOG antibodies, particularly in those who presented with

meningoencephalitis.[58, 59] MOG is a membrane protein expressed on the surface of oligodendrocytes and myelin in the central nervous system.[60] Brain biopsy from a patient with MOG antibody-associated demyelination showed inflammatory demyelination with partial axonal preservation and scarring of reactive astrocytes, inflammatory infiltration of T lymphocytes, activated macrophages or microglia, and complement deposition in the demyelinated areas.[61] IgG derived from MOG antibody-positive pediatric patients has been suggested to be cytotoxic and to induce natural killer (NK)-mediated cell death on surface MOG-expressing cells in vitro, with a correlation between antibody titer and the degree of antibody-dependent cell-mediated cytotoxicity.[62] Although the frequency of seizures is higher in patients with MOG antibodies compared to other demyelinating diseases of the central nervous system, it remains to be elucidated how MOG antibodies induce seizures. Of note, it has been reported that MOG antibodies can coexist with other antibodies, especially NMDAR antibodies. In these patients, seizures are common, have a high recurrence rate, and represent a variety of seizure types in addition to generalized tonic-clonic seizures. [63-67]

In terms of antibody production mechanisms, antineuronal antibodies and other autoantibodies have been reported to be produced by plasmablasts and long-lived plasma cells. [68] Recent advances in this field have revealed that elevated levels of plasmablasts are observed in some autoantibody-associated autoimmune diseases such as systemic lupus erythematosus (SLE), neuromyelitis optica spectrum disorder (NMOSD), and IgG4-related disorders.[69] particularly, in NMOSD, an autoantibody against astrocytes involved in the disease pathogenesis, plasmablasts are elevated in PBMCs and produce pathogenic autoantibodies. [70] Recently, circulating plasmablasts and follicular helper T cells have been reported to be increased in autoantibody-positive autoimmune epilepsy, including patients with NMDAR-, LGI1-, and MOG-antibodies.[71] Increasing evidence showing the dynamics of plasmablasts in relation to disease activity in autoantibody-associated autoimmune diseases, including autoimmune epilepsy, highlights the potential of this B cell subset as a representative immune phenotype termed “autoimmune plasmablastosis”.[71] In addition, these patients have an abnormal immune background of B cell differentiation. Inducible T cell co-stimulator (ICOS) and its ligand are required for active regulation of B cell responses by interacting with ICOS on T follicular helper (Tfh) cells and ICOS ligands on B cells and are involved in IgG production. ICOS-expressing circulating Tfh cells were increased in autoantibody-positive autoimmune epilepsy, suggesting that the dynamics of enhanced B cell differentiation are involved in autoimmune epilepsy similar to other autoantibody associated diseases such as myasthenia gravis and idiopathic thrombocytopenic purpura.[71-73]

Treatment

Treatment of autoimmune epilepsy is often preceded by antiepileptic drugs, but it may also include immunotherapy as in autoimmune encephalitis, surgery and chemotherapy in patients with malignant tumors. Immunotherapy in the acute phase of the disease includes steroid pulse therapy (intravenous methylprednisolone: IVMP) and intravenous immunoglobulin therapy (IVIg).[74] Plasma exchange therapy has also been reported to be useful.[19, 74] Second-line agents such as rituximab or cyclophosphamide are also recommended in cases of unsuccessful response. In a randomized, double-blind, placebo-controlled trial of IVIg in 17 patients with LGI1- and Caspr2-positive autoimmune epilepsy, 75% of patients treated with IVIg achieved a 50% or greater reduction in seizures at 5 weeks, compared with only 22% of patients treated with placebo.[75]

Regarding maintenance therapy, there are only a few reports showing that long-term low-dose steroid maintenance therapy reduces the seizure recurrence rate in patients with LGI1 antibody-positive encephalitis.[50] There is little consensus or evidence regarding the pros and cons of treatment and its content (dose and duration). In autoimmune epilepsy, patients are often refractory to antiepileptic drugs, and this refractoriness should raise the suspicion of autoimmune encephalitis.[23] Although immunotherapy is obviously important in autoimmune epilepsy, recent reports have shown that antiepileptic drugs are effective in some patients with chronic seizures even after immunotherapy has been completed, and that Na channel inhibitors such as carbamazepine and lacosamide tend to be more effective than levetiracetam, although the seizure resolution rate is only about 10%.[76, 77] In autoimmune encephalitis and epilepsy, antiepileptic drug-associated cutaneous reaction have been reported at high rates of 30% to 50%,[76-78] and caution must be exercised in drug selection. In the future, it is necessary to accumulate cases through prospective large cohort studies and to verify the efficacy of different antiepileptic drugs.

Conclusion

This review describes representative autoantibodies, disease definitions, pathophysiology, and clinical features of autoimmune epilepsy. In autoimmune encephalitis, seizures may be the main or only symptom, and the diagnosis tends to be delayed. We hope to be able to suspect this disease at an early stage, and to use diagnostic algorithms to promptly administer immunotherapy and improve prognosis.

Disclosure of Ethical Statements

1. Approval of the research protocol: N/A
2. Informed Consent: N/A
3. Registry and the Registration No. of the study/trial: N/A

4. Animal Studies: N/A

Conflict of Interest: None declared.

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Figure legends

FIGURE 1

Algorithm for diagnosing autoimmune epilepsy without evaluating antineuronal antibodies. The most optimal cutoff point was between groups C and D, with a sensitivity of 0.79 and specificity of 0.76. The second most optimal cutoff point was between groups D and E, with a sensitivity of 0.93 and specificity of 0.65. [28] AE, amygdala enlargement; AED, antiepileptic drugs; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalography; FBDS, faciobrachial dystonic seizure; FH, family history; MRI, magnetic resonance imaging; mT, medial temporal; OCB, oligoclonal bands; PET, positron emission tomography; PH, past history.

FIGURE 2

A)

In cases where autoantibodies target intracellular antigens, the activation of cytotoxic $CD8^+$ T cells is induced by helper T cells, resulting in neuronal cell death through the secretion of granzyme B and various other mechanisms.

B)

In cases where autoantibodies target cell surface antigens, the activation of B cells by follicular T cells leads to the differentiate of plasmablasts, which produce antibodies. These autoantibodies induce alteration in the synaptic structure, ultimately causing a reversible impairment of the receptor or blocking neurotransmission by binding to the receptors. However, the precise mechanism by which MOG antibody-associated diseases contribute to epileptic seizure remains poorly understood.

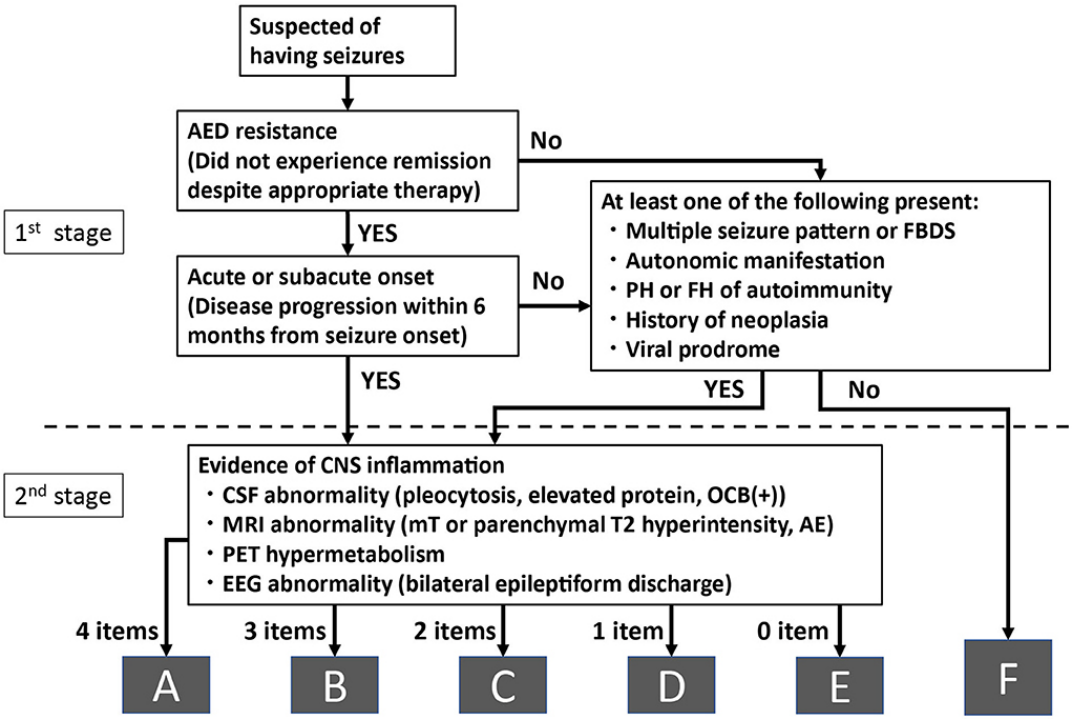

Fig. 1

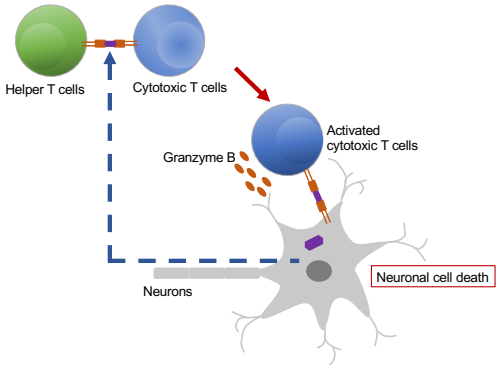

Fig. 2A

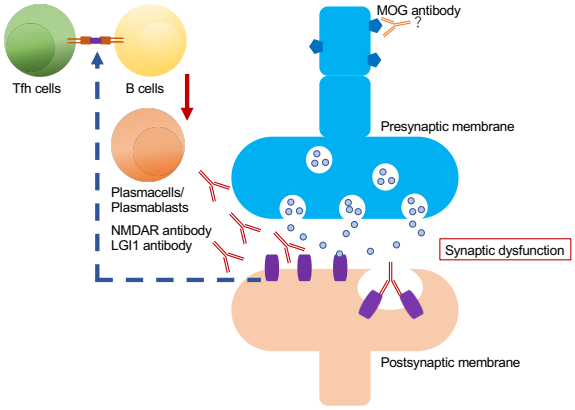

Fig.2B