https://doi.org/10.14802/jmd.21077 / J Mov Disord 2022;15(2):95-105
pISSN 2005-940X / eISSN 2093-4939

REVIEW ARTICLE

Diagnosis and Clinical Features in Autoimmune-Mediated Movement Disorders

Pei-Chen Hsieh,[1] Yih-Ru Wu[1,2]

[1]Department of Neurology, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan, Taiwan
[2]Department of Neurology, Chang Gung University, College of Medicine, Taoyuan, Taiwan

ABSTRACT

Movement disorders are common manifestations in autoimmune-mediated encephalitis. This group of diseases is suspected to be triggered by infection or neoplasm. Certain phenotypes correlate with specific autoantibody-related neurological disorders, such as orofacial-lingual dyskinesia with N-methyl-D-aspartate receptor encephalitis and faciobrachial dystonic seizures with leucine-rich glioma-inactivated protein 1 encephalitis. Early diagnosis and treatment, especially for autoantibodies targeting neuronal surface antigens, can improve prognosis. In contrast, the presence of autoantibodies against intracellular neuronal agents warrants screening for underlying malignancy. However, early clinical diagnosis is challenging because these diseases can be misdiagnosed. In this article, we review the distinctive clinical phenotypes, magnetic resonance imaging findings, and current treatment options for autoimmune-mediated encephalitis.

Keywords Autoimmune-mediated encephalitis; Movement disorders; Treatment.

INTRODUCTION

Autoimmune-mediated encephalitis has heterogeneous presentations, and an increasing number of autoantibodies have been discovered. Movement disorders are one of the most common features in these kinds of diseases. Certain movement disorders can correlate with specific autoantibodies. Most are also comorbid with limbic encephalitis, epilepsy, or peripheral neuropathy. Diagnosing these disorders as early as possible is crucial because some antibodies are associated with occult neoplasia, which is potentially treatable. Delayed diagnosis may have life-threatening consequences or cause permanent morbidity.[1,2] However, autoantibodies can cause many overlapping presentations, and variable presentations can occur with each autoantibody. Therefore, clinical diagnosis is challenging.

In this review, we summarize the distinctive phenotypes, clinical course, tumor association, imaging investigation, and laboratory examination for autoimmune-mediated encephalitis. This serves as a practical guide for differential diagnosis as well as the possible treatment options for the spectrum of diseases.

CLASSIFICATION OF AUTOANTIBODIES AND PATHOPHYSIOLOGICAL MECHANISMS

Autoantibodies are distinguished by their different immunological mechanisms and fall into three groups: neuronal surface antibodies, antibodies targeting intracellular synaptic proteins, and antibodies targeting cytoplasmic and nuclear antigens. These autoantibodies can trigger T-cell or B-cell immune reactions (Table 1).[3,4]

The first group of antibodies is neuronal surface antibodies, which are correlated less strongly with malignancy than are intracellular antibodies. Autoantibodies have been found to be produced from B cells induced by antigens from tumor cells or

Received: June 3, 2021 **Revised:** April 16, 2022 **Accepted:** April 18, 2022
Corresponding author: Yih-Ru Wu, MD
Department of Neurology, Chang Gung Memorial Hospital, Linkou Medical Center, Chang Gung University, College of Medicine, 259 Wen-Hwa 1st Road, Kwei-Shen, Taoyuan 333, Taiwan / **Tel:** +886-3-3281200 EXT 8349 / **Fax:** +886-3-3287226 / **E-mail:** yihruwu@cgmh.org.tw

Table 1. Autoantibody-associated central nervous system symptoms

Location	Neuronal surface antibody	Antibodies targeting intracellular synaptic protein	Antibodies targeting cytoplasmic and nuclear antigen
Possible mechanism	Internalization or crosslinking of the receptors, complement pathway activation, or direct blockage of receptors	Controversial; reduction of neuron's presynaptic vesicle pool by internalizing antibodies	Paraneoplastic syndromes; antibodies on the tumor trigger an immune response and ectopic expression of these neuronal proteins
Major symptoms	Limbic encephalitis, epilepsy, Morvan's syndrome	SPS, PERM	Limbic encephalitis, cerebellar ataxia with cerebellum degeneration
Example antibodies	NMDA, LGI1, CASPR2, DPPX	GAD, amphiphysin	Hu, CV2, Yo*, Ma, Ri*
Tumor prevalence	Variable, lower frequency	Moderate	High
Neuropathology	B-cell or plasma cell infiltration	Active T-cell response	Autoreactive CD8 cytotoxic T-cell response against the nervous system, characterized by lymphocytic infiltration
Immunotherapy response	Favorable results under immunotherapy	Variable	Less responsive to immunotherapy
Outcome	Generally good, possible spontaneous remission	Moderate	Poor

*purkinje cell cytoplasmic antibody type 1. NMDA, N-methyl-D-aspartate; LGI1, leucine-rich glioma inactivated protein 1; CASPR2, contactin-associated protein 2; DPPX, dipeptidyl peptidase–like protein 6; SPS, stiff-person syndrome; PERM, progressive encephalomyelitis with rigidity and myoclonus; GAD, glutamic acid decarboxylase; CV2, collapsin response mediator protein 5; Hu, Hu proteins; Yo,Yo protein; Ri, Ri proteins.

viruses.[5,6] The autoantibodies target surface receptors and internalize target receptors or influence protein−protein interactions, causing secondary receptor dysfunction.[4,7,8] The antibodies and receptor effects are considered to be reversible. The possible pathophysiology of N-methyl-D-aspartate (NMDA) receptor encephalitis may be caused by autoantibodies targeting neuron surface antigens. The alteration of the receptor that may induce internalized NMDA receptors causes NMDA receptor hypofunction. The interneuron in pyramidal cells may change the nucleus accumbens (NAc) activity. Increasing the production of dopamine causes limbic encephalitis and dyskinesia (Figure 1).[5,9-11] Most patients present with seizures, cognitive dysfunction, and variable movement disorders, such as orolingual dyskinesia, ataxia, and parkinsonism.[4,12-15] Furthermore, these movement disorders are thought to have a favorable prognosis with early immunological treatment as well as adequate tumor removal.[12,15,16]

The second group of antibodies targets intracellular synaptic proteins and is primarily associated with stiff-person syndrome (SPS) and ataxia.[17,18] Typically, the target protein antigens are located in the intracellular space of the synapse and prompt the vesicle pool to release an inhibition signal.[17,19] Uncertainty remains regarding the pathophysiology, but both T-cell and B-cell involvement is suspected.[20] Some reports have shown intrathecal synthesis and neuron internalization of anti-glutamic acid decarboxylase antibody (anti-GAD Ab);[21,22] another study revealed that GAD65-reactive CD4 T-cells may produce interferon-gamma (INF-γ).[23] GAD65 is one of two enzymes that catalyze the formation of the major neuroinhibitor gamma-aminobutyric acid (GABA). Anti-GAD Ab disturbs synaptic vesicles and then decreases the secretion of GABA. The reduction in GABA levels may induce an increase in glutamate due to a lower inhibition signal. Glutamate may further activate microglia and reduce the reuptake of glutamate by impairing excitatory amino acid transporters (EAATs). The increase in glutamate concentration may induce stimulation of neuronal nitric oxide synthase and calpain I, leading to mitochondrial dysfunction and cell apoptosis (Figure 2).[24,25] The possible pathophysiological mechanism related to ataxia is an imbalance between GABA and glutamate, which causes excitotoxicity to neuronal cells.[25,26] The association with malignancy differs among each antibody, and the prognosis for disorders associated with this group of antibodies is more favorable than that for anticytoplasmic and nuclear antigen antibody disorders; however, these antibodies are more refractory than neuronal surface antibodies.[12]

The final group of antibodies, which target cytoplasmic and nuclear antigens, are also known as onconeural antibodies and are associated with several paraneoplastic neurological syndromes.[27-30] These syndromes most often present as limbic encephalitis, which may be accompanied by subacute cerebellar ataxia, chorea, and parkinsonism (Table 2).[12,29,31] The pathophysiological mechanism for this group of diseases is that onconeural antigen-specific CD4 T-cells may recruit tumor antigen-specific cytotoxic CD8 T cells and activate plasma cells to produce onconeural antibodies (Figure 3).[32,33] These onconeural antigen-specific T cells cross the blood brain barrier and reach the central nervous system. Then, the intracellular antigen upregulates major histocompatibility complex class 1, which causes a cytotoxic CD8 T-cell misdirected response against the nervous system, which induces variable manifestation.[3,4,29] These autoantibodies may not be the major cause of neuronal damage, but they are a potential biomarker for this group of diseases.[3] Pathology findings have indicated lymphocyte infiltration with extensive neuron degeneration, which

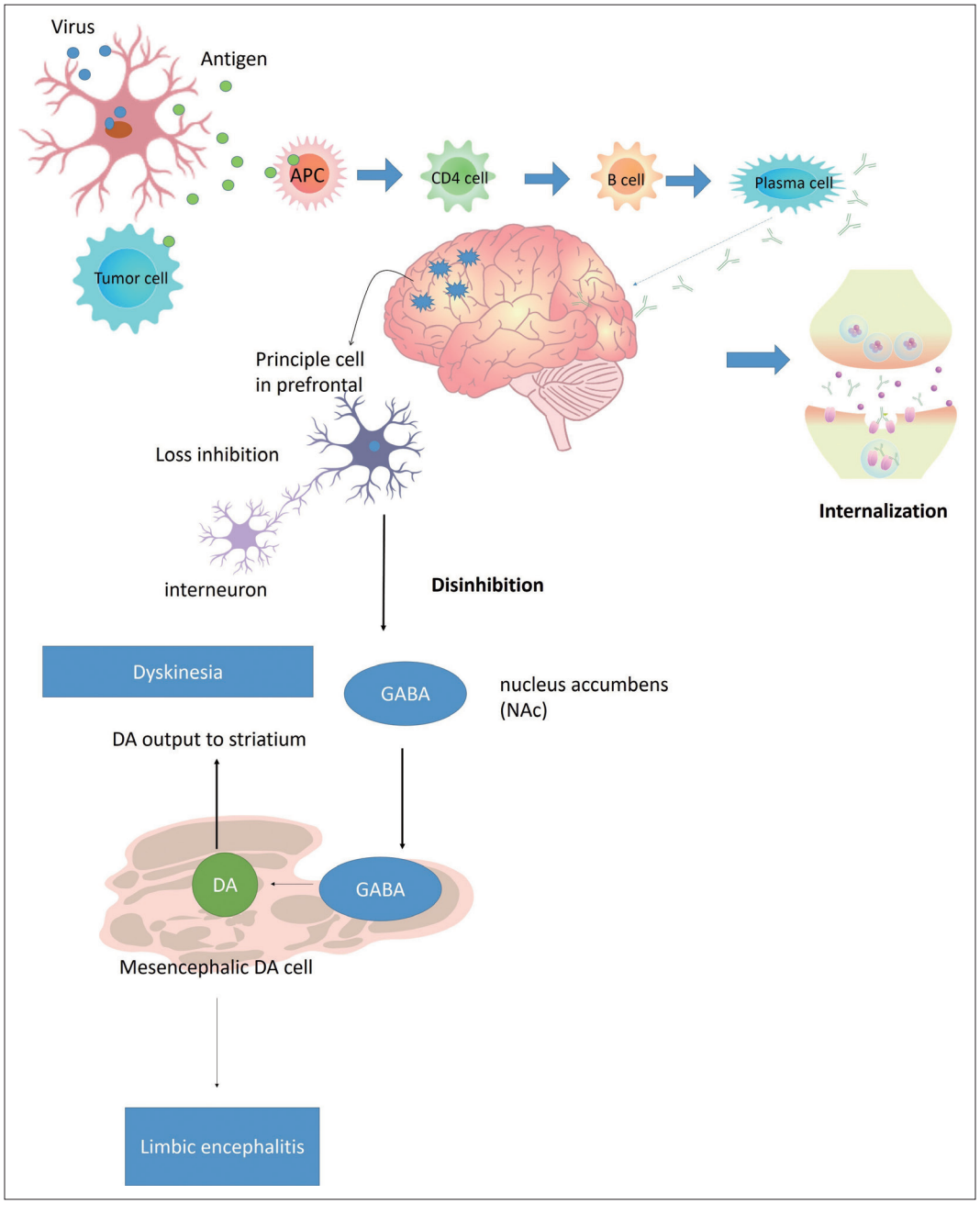

Figure 1. Possible pathophysiology of NMDA receptor encephalitis. The possible pathophysiology of NMDA receptor encephalitis may be caused by autoantibodies targeting neuron surface antigens. The alteration of the receptor may induce internalization of NMDA receptors, which is related to NMDA receptor hypofunction. The interneuron in pyramidal cells may change NAc activity. In terms, increasing the production of DA in the striatum and dorsal lateral prefrontal cortex may be related to limbic encephalitis and dyskinesia. APC, antigen-presenting cells; GABA, gamma-aminobutyric acid; NAc, nucleus accumbens; DA, dopamine; NMDA, N-methyl-D-aspartate.

is considered to be primarily involved with pathogenic cytotoxic T cells.[3,8,34] Most neurological symptoms of encephalitis related to this group of autoantibodies are highly associated with malignancy as well as a poor response to immunotherapy.[29,34]

CLINICAL APPROACH AND DIAGNOSIS

The diagnosis of autoimmune-mediated autoantibodies is challenging in clinical practice. A careful history assessment may be helpful. The clinical courses of these disorders usually involve subacute onsets of cognitive change or psychiatric presentation.[15,35] If patients present with variable movement manifestations, espe-

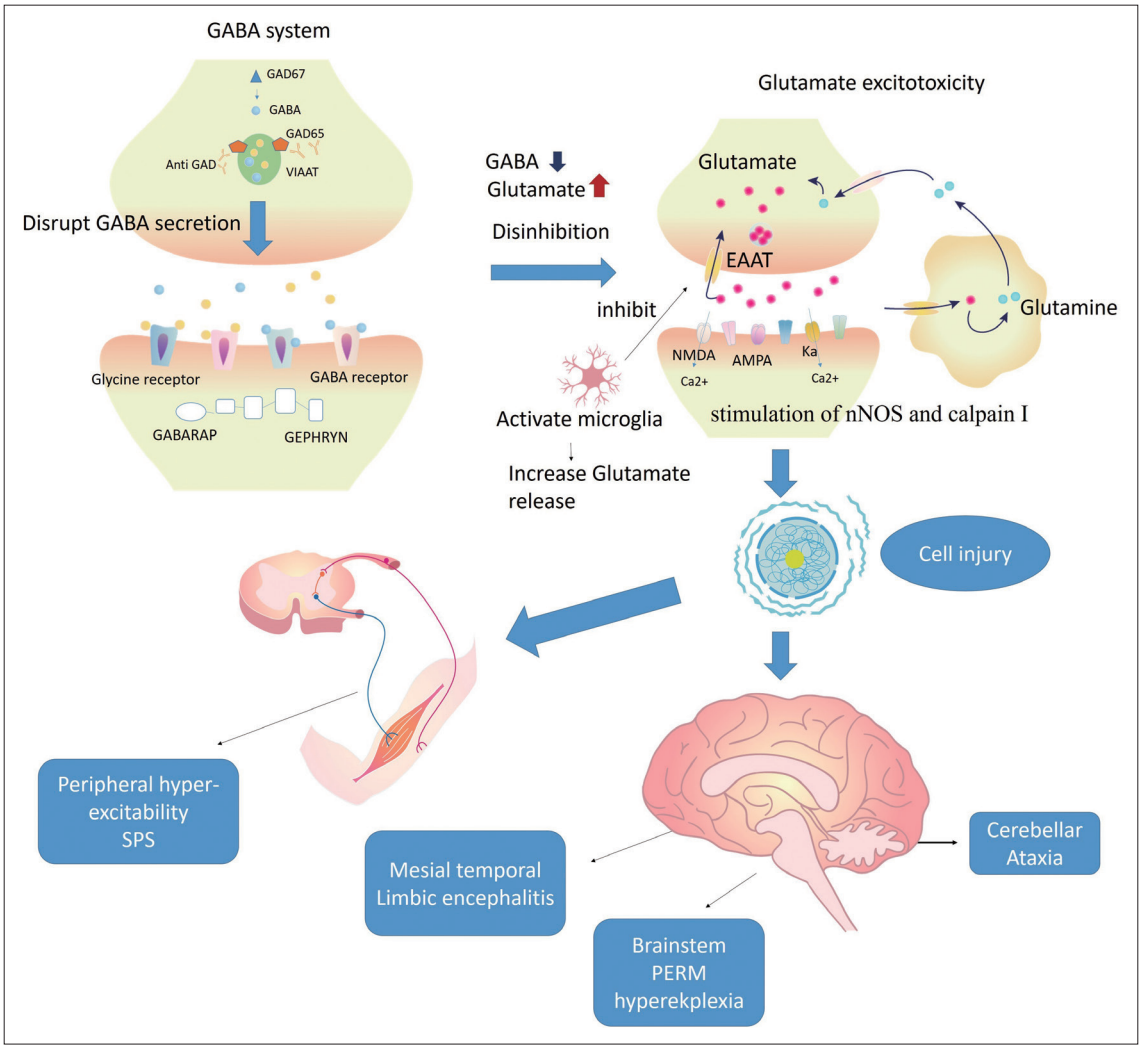

Figure 2. Possible pathophysiology of anti-GAD antibody-related disorders. The possible pathophysiological mechanism is an imbalance between GABA and glutamate, which causes excitotoxicity to neuronal cells. Anti-GAD Ab internalized and disturbed the synaptic vesicles, GAD65, and secreted GABA. The reduction of GABA levels may induce an increase in glutamate due to a lower inhibition signal. Glutamate may further activate microglia, leading to increased glutamate release and reduced reuptake of glutamate by impaired EAATs. The increase in glutamate concentration may induce stimulation of nNOS and calpain I, leading to mitochondrial dysfunction and cell apoptosis. A decrease in GABA may cause hyperexcitability in the peripheral or central nervous system. GABA, gamma-aminobutyric acid; GAD, glutamic acid decarboxylase; VIAAT, vesicular inhibitory amino acid transporter; GABARAP, gamma-aminobutyric acid receptor-associated protein; anti-GAD ab, anti-glutamic acid decarboxylase antibody; EAAT, excitatory amino acid transporter, NMDA, N-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; nNOS, neuronal nitric oxide synthase; SPS, stiff-person syndrome, PERM, progressive encephalomyelitis with rigidity and myoclonus.

cially combined movement disorders, neuronal surface antibodies are more likely. Moreover, if patients present with SPS, intracellular synaptic protein antibodies are the first to be considered. In contrast, if a patient's major symptom is subacute onset ataxia and suspected opsoclonus-myoclonus syndrome, clinicians may consider antibodies targeting intracellular nuclear antigens (Supplementary Table 1 in the online-Data Supplement).

Cerebral spinal fluid (CSF) may exhibit pleocytosis, which could be misdiagnosed as virus-related encephalitis. Electroencephalograms (EEGs) often reveal diffuse slow wave activity, epileptiform discharge, or even status epilepticus.[4,6,36] Brain magnetic resonance imaging (MRI) findings are typically normal, but they may show hyperintense unilateral or bilateral T2/fluid-attenuated inversion recovery (FLAIR) signals in the mesial temporal lobes and restricted diffusion relative to normal.[4,13] In addition, fluorine-18 deoxyglucose-positron emission tomography (^{18}F-FDG-PET) scans may play a crucial role in diagnosis. ^{18}F FDG-PET may be more sensitive than brain MRI, and the presence of some antibodies may be associated with specific metabolic patterns.[37-39]

Table 2. Movement disorders associated with autoantibodies

Syndrome	Neuronal surface antibodies	Antibodies targeting intracellular, synaptic proteins	Antibodies targeting cytoplasmic and nuclear antigens
Chorea/dyskinesia	CASPR2, LGI1, NMDAR, Neurexin-3α, GABAAR, Dopamine-2-R, IgLON5		CV2/CRMP5, Hu
Dystonia	Dopamine-2-R, NMDAR, LGI1, GABAAR, IgLON5		CV2/CRMP5, Ri, Ma2
Myoclonus	CASPR2, LGI1, DPPX, Neurexin-3α	GlyR	
Opsoclonus-myoclonus syndrome	VGCC, NMDAR, GABAAR, GABABR, DPPX, GlyR	GAD	CV2/CRMP5, Hu, Ri, Ma2, Zic4, Yo
Parkinsonism	Dopamine-2-R, IgLON5, DPPX, LGI1		Ri, Ma2, CV2/CRMP5
Ataxia	CASPR2, DPPX, NMDAR, IgLON5, VGCC, mGluR1	GAD	Yo, Hu, Ri, PCA2, Zic4, Sox1, GFAP
Tremor	CASPR2, LGI1, NMDAR, DPPX		GFAP, Yo
Stiff person syndrome	DPPX, GABAAR, GlyR	GAD, Amphiphysin, Gephyrin, GABARAP	Ri
Progressive encephalomyelitis with rigidity and myoclonus	DPPX, GlyR	GAD	
Paroxysmal dyskinesia	LGI1, NMDAR, AQP4		

CASPR2, contactin-associated protein 2; LGI1, leucine-rich glioma inactivated protein 1; NMDAR, N-methyl-D-aspartate receptor; GABAAR/GABABR, g-aminobutyric acid type A and type B receptors; IgLON5, IgLON family member 5; DPPX, dipeptidyl peptidase–like protein 6; VGCC, voltage-gated calcium channel; GlyR, glycine receptor; AQP4, antiaquaporin-4 antibody; GAD, glutamic acid decarboxylase; GABARAP, gamma-aminobutyric acid receptor-associated protein; CRMP5/CV2, collapsin response mediator protein 5; Hu, Hu proteins; Ri, Ri proteins; Yo,Yo protein; mGluR5, metabotropic glutamate receptor 5; Sox1, sry-like high mobility group box protein 1; GFAP, glial fibrillary acidic protein; PCA2, Purkinje cell cytoplasmic antibody type 2; Zin4, zinc-finger proteins 4.

TREATMENT PRINCIPLES

Symptomatic therapy for involuntary movement should be provided for most patients. Of patients who have severe disease, 87% present movement disorders.[3] Metabolic problems such as infection, electrolyte imbalance or pain may exacerbate hyperkinetic movement disorders. Acute respiratory failure or rhabdomyolysis may be induced by uncontrolled dystonia or dyskinesia. Deep sedative medication should be used for refractory movement disorders or status epilepticus.[3,34]

Immunotherapy must be initiated as soon as possible. The first-line therapy is intravenous (IV) methylprednisolone at a dosage of 1 g for 3−5 days, which has efficacy due to wide function for immunosuppression as well as T-cell depletion, followed by oral prednisolone; IV immunoglobulin (IVIg) at a dosage of 0.4 g/kg for 5 days; and/or plasmapheresis.[4,8,30] If patients are highly suspected of autoimmune-mediated encephalitis by classical onconeuronal antibodies, methylprednisolone or other T-cell-directed therapies are preferred options over IVIg or plasmapheresis.[3,35,36] However, patients with classical onconeuronal antibody-related encephalitis may show only modest effects on immunosuppression and tend to respond best to cancer therapy.[3,35] Combined therapy is suggested if patients have a severe initial presentation, such as new onset refractory status epilepticus, or fail to respond to the initial agent.[3,13]

If the patient is refractory to first-line treatment, second-line therapy should be considered after 2−3 weeks.[40,41] Clinicians should consider rituximab anti-CD20 therapy for 4 weeks with or without IV cyclophosphamide for 3−6 months.[30,37-39] A common regimen of rituximab is 375 mg/m^2 weekly for 4 weeks. In addition, the common regimen for cyclophosphamide is 750 mg/m^2 for 3−6 months.[3] If the patient still responds poorly, alternative treatment should be considered, such as interleukin (IL)-6 inhibition (tocilizumab), low-dose IL-2, or bortezomib.[30,38-40,42] Recently, a Janus kinase inhibitor, tofacitinib, may be a new option if patients are refractory to second-line therapy.[41,42] In addition, careful examination for underlying malignancy is essential. Tumor removal is crucial in patients with any type of autoimmune-mediated encephalitis. Patients may exhibit some improvement after tumor ablation. Long-term maintenance therapy, such as low-dose prednisolone and steroid-sparing medication, should be considered for patients whose diseases relapse or who respond poorly to medication (Figure 4).[38,39]

MOVEMENT DISORDERS ASSOCIATED WITH ANTI-NEURONAL SURFACE PROTEIN ANTIBODIES

Clinical presentation and diagnosis of anti-N-methyl-D-aspartate receptor encephalitis

Anti-NMDA receptor encephalitis is a well-known type of au-

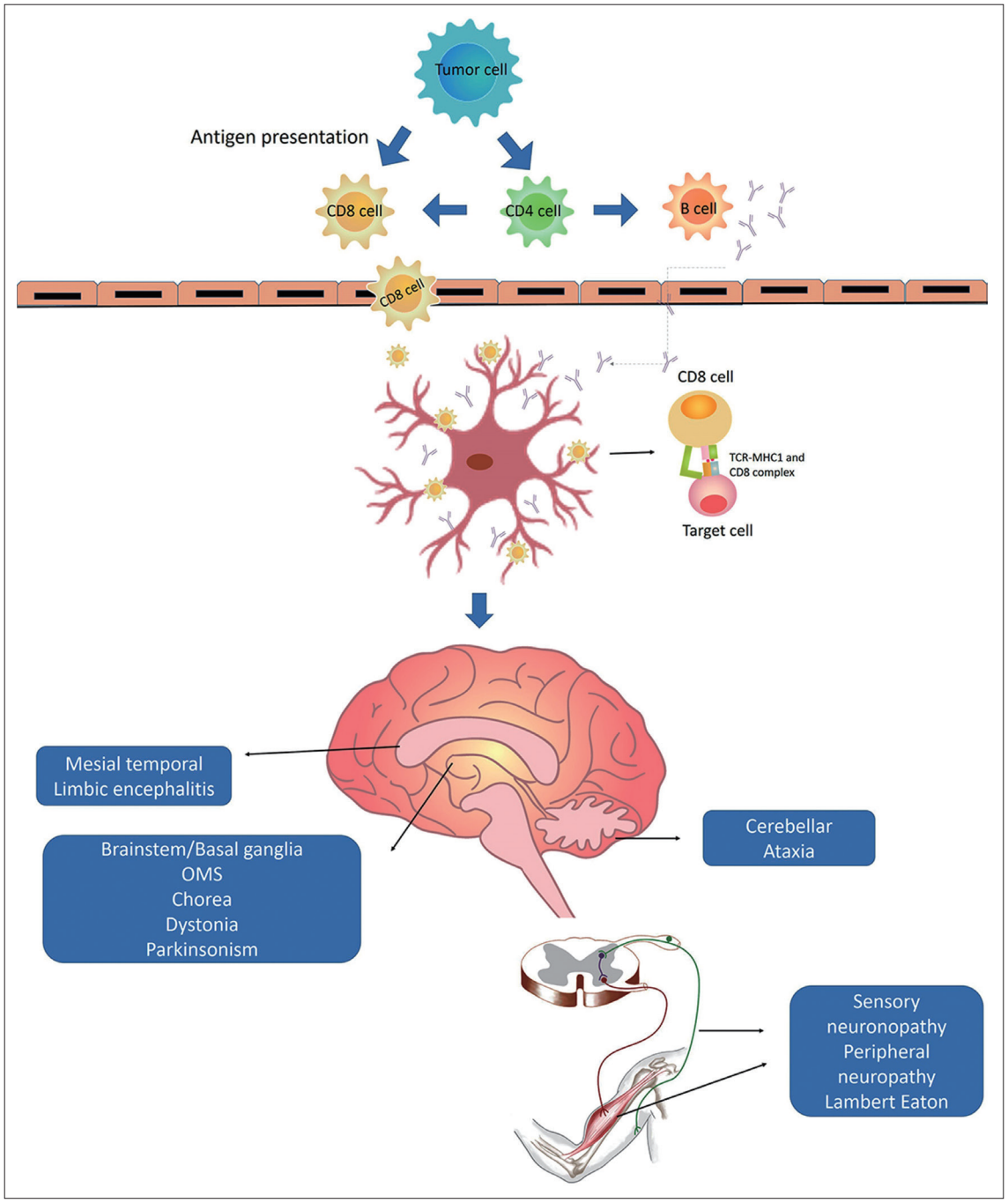

Figure 3. Possible mechanism in onconeural antibody-related disorders. Onconeural antigens are expressed in tumor cells. Onconeural antigen-specific CD4 T cells may recruit tumor antigen-specific cytotoxic CD8 T cells and activate plasma cells to produce onconeural antibodies. These onconeural antigen-specific T cells cross the blood brain barrier and reach the central nervous system. Then, the intracellular antigen upregulates MHC class 1, which causes a cytotoxic CD8 T-cell misdirected response against the nervous system and induces variable disorders. MHC, major histocompatibility complex; TCR, T cell receptor; OMS, opsoclonus-myoclonus syndrome.

toimmune-mediated encephalitis. It typically affects young women between the ages of 16 and 42 years, and 25%–50% of cases present with ovarian teratoma.[1,36] Nontumor cases are usually observed in male patients or very young girls.[36,43] The disease course generally seems to follow the same pattern.[1,36] In the prodromal stage, 70% of patients experience headaches, fever, and upper respiratory infection symptoms. Following this stage, agitation, psychiatric symptoms, catatonia, hallucinations, new-onset seizures, and speech and memory impairment can be observed. After weeks to months, orolingual-facial dyskinesia is the most

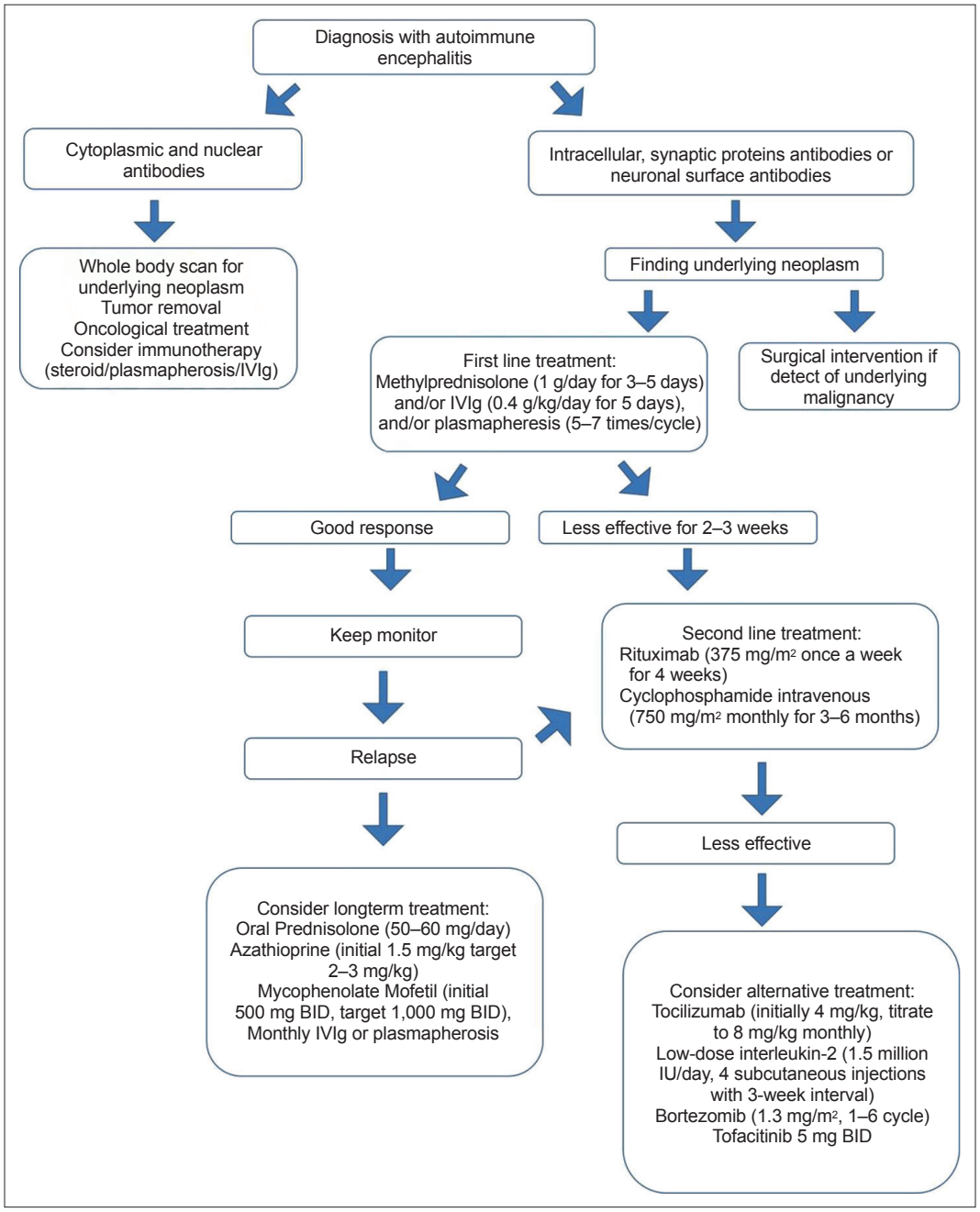

Figure 4. Treatment principle for autoimmune-mediated encephalitis. IVIg, intravenous immunoglobulin.

characteristic feature in anti-NMDA receptor encephalitis, accompanied by dystonia, chorea, myoclonus, stereotypic movement, ataxia, and parkinsonism over the trunk and all extremities (Supplementary Table 2 in the online-only Data Supplement).[1,36,43,44] Clinicians should be aware of these combined movement disorders, which may cause self-injury. Overall, the most common movement disorders are dystonia, stereotypies, and chorea.[4,43,45] Tetrabenazine, clonazepam, or botulinum injection might provide some symptomatic control. Some patients may present with hyperkinetic crises, which warrant the use of intensive sedative medication. In addition, decreased levels of consciousness, dysautonomia, and central hypoventilation may increase the patient's risk of mortality.[44]

CSF analyses have revealed a rate of lymphocyte pleocytosis of 68%−98%, normal to mildly elevated protein levels, and oligoclonal bands (OCB) in 50%−60% of patients.[36,46-48] Anti-NMDA receptor antibodies can be found in CSF with a higher sensitivity than in serum, and a higher titer may yield a poorer outcome.[49]

Abnormal EEG findings were observed in 80% of patients.[50] The most characteristic presentation in anti-NMDA receptor encephalitis is extreme delta brush, which is associated with poor recovery.[51,52] Brain MRI revealed unremarkable findings in half of patients, and half of patients may exhibit T2/FLAIR signal hyperintensity in the hippocampus, temporal cortex, frontal cortex, and brainstem.[53] FDG-PET has revealed that medial occipital lobe hypometabolism may be an early biomarker and may correlate with improving neurologic status.[37,38,53]

Clinical presentation and diagnosis of leucine-rich glioma inactivated protein 1 antibody–related syndromes

Leucine-rich glioma inactivated protein 1 (LGI1) antibodies are voltage-gated potassium channel (VGKC)-associated proteins. They usually affect middle-aged male patients.[54] Less than 20% of cases are associated with tumors, which are usually thymoma.[13,55] The common initial symptoms are amnesia and seizures. The most distinctive feature is faciobrachial dystonic seizures (FBDS), which in some patients may be combined with focal seizures or general tonic–clonic seizures. FBDS typically occur in clusters 2–3 weeks before cognitive impairment, followed by personality change and psychosis. Sleep disorders occur in 50% of patients.[2,12,31,55,56] Very rarely, patients present with Morvan's syndrome. Other movement disorders, including chorea, parkinsonism, and myoclonus, are unusual.[12,55]

CSF analysis may reveal normal results in 60%–75% of patients, and LGI1 antibodies are mostly detected in CSF.[46] Hyponatremia occurs in 70% of patients.[54,57] EEG may reveal epileptiform discharges or focal slow wave activity. However, most patients who present with FBDS do not exhibit epileptiform discharges.[56] Brain MRI reveals T2 hyperintensity in the mesial temporal lobe in more than half of patients.[56,58] MRI reveals basal ganglia involvement only in patients with FBDS.[59] PET scans may reveal frontal lobe hypometabolism.[13] Early immunotherapy can yield favorable outcomes and may also prevent limbic encephalitis.[57]

Clinical presentation and diagnosis of contactin-associated protein-like 2 antibody–related syndromes

Contactin-associated protein-like 2 (CASPR2) antibodies are also VGKC-associated antibodies. CASPR2 antibody–related syndromes typically affect middle-aged and older male adults. Fewer than 30% of patients have associated tumors; these are usually thymoma,[60] but other neoplasms have also been reported.[61-63] The core symptoms of CASPR2 antibody–related autoimmunity are Morvan's syndrome, neuropathic pain, peripheral nerve hyperexcitability, and limbic encephalitis. Cognitive decline is observed in 80% of patients.[54] Muscle cramps, stiffness, and neuromyotonia occur because of peripheral nerve hyperexcitability.[56] This is one of the core features of Morvan's syndrome, which suggests the need for detailed screening of the underlying thymoma.[64] Various movement disorders are observed, especially cerebellar ataxia.[65] Chorea and orthostatic myoclonus have also been reported.[12,45,66]

CSF analysis may show mildly elevated protein levels or pleocytosis in 30% of patients as well as T2/FLAIR bilateral mesial temporal hyperintensity.[13,60] Electromyography (EMG) can detect neuromyotonia, fasciculation, and myokymic discharge. CASPR2 antibodies have been detected in both serum and CSF; these findings mostly revealed neuromyotonia in the serum group and epilepsy in the CSF group.[55,60] The disease is usually responsive to treatment, and patients have a fair prognosis.

MOVEMENT DISORDERS ASSOCIATED WITH ANTI-INTRACELLULAR SYNAPTIC PROTEIN ANTIBODIES

Clinical presentation and diagnosis of anti-glutamic acid decarboxylase antibody–related syndromes

Anti-GAD Ab typically affects middle-aged female patients.[67] These antibodies are often comorbid with type 1 diabetes mellitus and thyroiditis. In rare cases, they are associated with small cell lung cancer or thymoma.[68] The clinical course can involve chronic or subacute onset stiff-person spectrum disorder, cerebellar ataxia, palatal myoclonus, episodic vertigo, limbic encephalitis, and drug-resistant epilepsy.[18,68,69] Some patients present with progressive encephalomyelitis with rigidity and myoclonus.[70] CSF analysis may reveal anti-GAD Ab and OCB in 25%–67% of patients.[46,71] EMG demonstrates continuous agonist and antagonist motor activity, typically in axial muscles, and clinical observation reveals painful spasms in limb and axial muscles.[19,72] EEG may show epileptiform discharge, and brain MRI can be normal or reveal T2 FLAIR bilateral mesial temporal hyperintensity.[8,17] The antibody titers do not correlate with disease severity and treatment response.[73] First-line immunotherapy can produce a partial response.[74-76] Second-line therapy with rituximab and/or cyclophosphamide has been proposed. Patients with SPS and epilepsy may benefit from high-dose benzodiazepines combined with baclofen and anticonvulsants for symptomatic therapy. The disease outcome is variable and usually requires long-term immunosuppressive therapy.[12,17,74,77]

MOVEMENT DISORDERS ASSOCIATED WITH ANTIBODIES AGAINST INTRACELLULAR ANTIGENS

Clinical presentation and diagnosis of anti-Hu antibody–related syndromes

Anti-Hu syndrome is one of the most prevalent paraneoplastic neurological disorders. It is associated with small cell lung cancer in 85% of patients and mostly affects middle-aged and older adult male patients.[78] Presentation tends to vary; the most common presentation is sensory neuronopathy, seen in more than half of patients, followed by cerebellar ataxia (10%–22% of patients), limbic encephalitis (9%–15% of patients), and brainstem encephalitis (8% of patients). Some patients with sensory neuropathy may have autonomic symptoms.[78,79] Movement disorders usually present as cerebellar ataxia.[12,31] Some patients exhibit chorea, opsoclonus-myoclonus, and pseudoathetosis related to sensory neuropathy.[48] CSF analysis findings are typically normal or show mildly elevated protein levels and pleocytosis. In addition, anti-Hu autoantibodies can be detected in CSF and serum, but the titers are not correlated with the outcome.[80,81] EEG may reveal focal or generalized epileptiform discharge as well as focal slow or normal wave activity.[82] MRI shows hyperintensity in deep gray nuclei, temporal lobe, or white matter T2/FLAIR signals.[83] FDG-PET can reveal extensive bilateral mesiotemporal hypermetabolism and help to detect underlying neoplasms.[84,85] Overall, the prognosis is poor, but some patients may improve with tumor ablation or adequate chemotherapy with or without immunotherapy.[34,79]

CONCLUSION

Recognizing the warning signs of autoimmune–mediated encephalitis is crucial because some types may be treatable, especially when treatment is started early. Otherwise, long-term morbidity or mortality may occur because o1f severe complications. The underlying mechanisms of pathogenesis causing nervous system dysfunction remain unclear. Furthermore, many patients do not substantially improve with current immunotherapy. More precise medication must be developed for specific autoantibodies and groups of autoimmune-mediated encephalitis.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.21077.

Conflicts of Interest

The authors have no financial conflicts of interest.

Funding Statement

This work was supported by Chang Gung Memorial Hospital, Taipei, Taiwan (BMRP 778).

Author Contributions

Conceptualization: Yih-Ru Wu, Pei-Chen Hsieh. Supervision: Yih-Ru Wu. Validation: Yih-Ru Wu. Visualization: Yih-Ru Wu. Writing—original draft: Pei-Chen Hsieh. Writing—review & editing: Pei-Chen Hsieh, Yih-Ru Wu.

ORCID iDs

Pei-Chen Hsieh https://orcid.org/0000-0001-5258-5950
Yih-Ru Wu https://orcid.org/0000-0003-1191-2542

REFERENCES

1. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013;12:157-165.
2. Irani SR, Stagg CJ, Schott JM, Rosenthal CR, Schneider SA, Pettingill P, et al. Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. Brain 2013;136(Pt 10):3151-3162.
3. Dalmau J, Geis C, Graus F. Autoantibodies to synaptic receptors and neuronal cell surface proteins in autoimmune diseases of the central nervous system. Physiol Rev 2017;97:839-887.
4. Damato V, Balint B, Kienzler AK, Irani SR. The clinical features, underlying immunology, and treatment of autoantibody-mediated movement disorders. Mov Disord 2018;33:1376-1389.
5. Mckeon A, Vincent A. Autoimmune movement disorders. Handb Clin Neurol 2016;133:301-315.
6. Dalmau J, Graus F. Antibody-mediated encephalitis. N Engl J Med 2018;378:840-851.
7. Moscato EH, Jain A, Peng X, Hughes EG, Dalmau J, Balice-Gordon RJ. Mechanisms underlying autoimmune synaptic encephalitis leading to disorders of memory, behavior and cognition: insights from molecular, cellular and synaptic studies. Eur J Neurosci 2010;32:298-309.
8. Lancaster E, Dalmau J. Neuronal autoantigens--pathogenesis, associated disorders and antibody testing. Nat Rev Neurol 2012;8:380-390.
9. Jodo E, Suzuki Y, Katayama T, Hoshino KY, Takeuchi S, Niwa S, et al. Activation of medial prefrontal cortex by phencyclidine is mediated via a hippocampo-prefrontal pathway. Cereb Cortex 2005;15:663-669.
10. Hunter D, Jamet Z, Groc L. Autoimmunity and NMDA receptor in brain disorders: where do we stand? Neurobiol Dis 2021;147:105161.
11. Gruber O, Chadha Santuccione A, Aach H. Magnetic resonance imaging in studying schizophrenia, negative symptoms, and the glutamate system. Front Psychiatry 2014;5:32.
12. Balint B, Vincent A, Meinck HM, Irani SR, Bhatia KP. Movement disorders with neuronal antibodies: syndromic approach, genetic parallels and pathophysiology. Brain 2017;141:13-36.
13. Hermetter C, Fazekas F, Hochmeister S. Systematic review: syndromes, early diagnosis, and treatment in autoimmune encephalitis. Front Neurol 2018;9:706.
14. Lancaster E. The diagnosis and treatment of autoimmune encephalitis. J Clin Neurol 2016;12:1-13.
15. Dubey D, Toledano M, McKeon A. Clinical presentation of autoimmune and viral encephalitides. Curr Opin Crit Care 2018;24:80-90.
16. Evoli A, Spinelli P, Frisullo G, Alboini PE, Servidei S, Marra C. Spontaneous recovery from anti-NMDAR encephalitis. J Neurol 2012;259:1964-1966.
17. Baizabal-Carvallo JF. The neurological syndromes associated with glutamic acid decarboxylase antibodies. J Autoimmun 2019;101:35-47.
18. McKeon A, Tracy JA. GAD65 neurological autoimmunity. Muscle Nerve 2017;56:15-27.

19. Rakocevic G, Floeter MK. Autoimmune stiff person syndrome and related myelopathies: understanding of electrophysiological and immunological processes. Muscle Nerve 2012;45:623-634.
20. Witherick J, Highley JR, Hadjivassiliou M. Pathological findings in a case of stiff person syndrome with anti-GAD antibodies. Mov Disord 2011;26:2138-2139.
21. Gresa-Arribas N, Ariño H, Martínez-Hernández E, Petit-Pedrol M, Sabater L, Saiz A, et al. Antibodies to inhibitory synaptic proteins in neurological syndromes associated with glutamic acid decarboxylase autoimmunity. PLoS One 2015;10:e0121364.
22. Hampe CS, Petrosini L, De Bartolo P, Caporali P, Cutuli D, Laricchiuta D, et al. Monoclonal antibodies to 65kDa glutamate decarboxylase induce epitope specific effects on motor and cognitive functions in rats. Orphanet J Rare Dis 2013;8:82.
23. Suzuki R, Shimada A, Maruyama T, Funae O, Morimoto J, Kodama K, et al. T-cell function in anti-GAD65+diabetes with residual beta-cell function. J Autoimmun 2003;20:83-90.
24. Ali F, Rowley M, Jayakrishnan B, Teuber S, Gershwin ME, Mackay IR. Stiff-person syndrome (SPS) and anti-GAD-related CNS degenerations: protean additions to the autoimmune central neuropathies. J Autoimmun 2011;37:79-87.
25. Mitoma H, Manto M, Hadjivassiliou M. Immune-mediated cerebellar ataxias: clinical diagnosis and treatment based on immunological and physiological mechanisms. J Mov Disord 2021;14:10-28.
26. Ishida K, Mitoma H, Wada Y, Oka T, Shibahara J, Saito Y, et al. Selective loss of Purkinje cells in a patient with anti-glutamic acid decarboxylase antibody-associated cerebellar ataxia. J Neurol Neurosurg Psychiatry 2007;78:190-192.
27. Storstein A, Monstad SE, Haugen M, Mazengia K, Veltman D, Lohndal E, et al. Onconeural antibodies: improved detection and clinical correlations. J Neuroimmunol 2011;232:166-170.
28. Horta ES, Lennon VA, Lachance DH, Jenkins SM, Smith CY, McKeon A, et al. Neural autoantibody clusters aid diagnosis of cancer. Clin Cancer Res 2014;20:3862-3869.
29. Dalmau J, Rosenfeld MR. Paraneoplastic syndromes of the CNS. Lancet Neurol 2008;7:327-340.
30. Graus F, Delattre JY, Antoine JC, Dalmau J, Giometto B, Grisold W, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry 2004;75:1135-1140.
31. Panzer J, Dalmau J. Movement disorders in paraneoplastic and autoimmune disease. Curr Opin Neurol 2011;24:346-353.
32. Yshii L, Bost C, Liblau R. Immunological bases of paraneoplastic cerebellar degeneration and therapeutic implications. Front Immunol 2020;11:991.
33. Devine MF, Kothapalli N, Elkhooly M, Dubey D. Paraneoplastic neurological syndromes: clinical presentations and management. Ther Adv Neurol Disord 2021;14:1756286420985323.
34. Pignolet BS, Gebauer CM, Liblau RS. Immunopathogenesis of paraneoplastic neurological syndromes associated with anti-Hu antibodies: a beneficial antitumor immune response going awry. Oncoimmunology 2013;2:e27384.
35. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016;15:391-404.
36. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011;10:63-74.
37. Solnes LB, Jones KM, Rowe SP, Pattanayak P, Nalluri A, Venkatesan A, et al. Diagnostic value of 18F-FDG PET/CT versus MRI in the setting of antibody-specific autoimmune encephalitis. J Nucl Med 2017;58:1307-1313.
38. Probasco JC, Solnes L, Nalluri A, Cohen J, Jones KM, Zan E, et al. Decreased occipital lobe metabolism by FDG-PET/CT: an anti-NMDA receptor encephalitis biomarker. Neurol Neuroimmunol Neuroinflamm 2018;5:e413.
39. Morbelli S, Djekidel M, Hesse S, Pagani M, Barthel H; Neuroimaging Committee of the European Association of Nuclear Medicine (EANM); Brain Imaging Council of the Society of Nuclear Medicine and Molecular Imaging (SNMMI). Role of (18)F-FDG-PET imaging in the diagnosis of autoimmune encephalitis. Lancet Neurol 2016;15:1009-1010.
40. Ramanathan S, Al-Diwani A, Waters P, Irani SR. The autoantibody-mediated encephalitides: from clinical observations to molecular pathogenesis. J Neurol 2021;268:1689-1707.
41. Abboud H, Probasco JC, Irani S, Ances B, Benavides DR, Bradshaw M, et al. Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. J Neurol Neurosurg Psychiatry 2021;92:757-768.
42. Cordani R, Micalizzi C, Giacomini T, Gastaldi M, Franciotta D, Fioredda F, et al. Bortezomib-responsive refractory anti-N-methyl-d-aspartate receptor encephalitis. Pediatr Neurol 2020;103:61-64.
43. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091-1098.
44. Dalmau J, Armangué T, Planagumà J, Radosevic M, Mannara F, Leypoldt F, et al. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models. Lancet Neurol 2019;18:1045-1057.
45. Varley JA, Webb AJS, Balint B, Fung VSC, Sethi KD, Tijssen MAJ, et al. The movement disorder associated with NMDAR antibody-encephalitis is complex and characteristic: an expert video-rating study. J Neurol Neurosurg Psychiatry 2019;90:724-726.
46. Blinder T, Lewerenz J. Cerebrospinal fluid findings in patients with autoimmune encephalitis—a systematic analysis. Front Neurol 2019;10:804.
47. Wang R, Guan HZ, Ren HT, Wang W, Hong Z, Zhou D. CSF findings in patients with anti-N-methyl-D-aspartate receptor-encephalitis. Seizure 2015;29:137-142.
48. Baizabal-Carvallo JF, Jankovic J. Autoimmune and paraneoplastic movement disorders: an update. J Neurol Sci 2018;385:175-184.
49. Gresa-Arribas N, Titulaer MJ, Torrents A, Aguilar E, McCracken L, Leypoldt F, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. Lancet Neurol 2014;13:167-177.
50. Gillinder L, Warren N, Hartel G, Dionisio S, O'Gorman C. EEG findings in NMDA encephalitis - a systematic review. Seizure 2019;65:20-24.
51. Veciana M, Becerra JL, Fossas P, Muriana D, Sansa G, Santamarina E, et al. EEG extreme delta brush: an ictal pattern in patients with anti-NMDA receptor encephalitis. Epilepsy Behav 2015;49:280-285.
52. Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology 2012;79:1094-1100.
53. Bacchi S, Franke K, Wewegama D, Needham E, Patel S, Menon D. Magnetic resonance imaging and positron emission tomography in anti-NMDA receptor encephalitis: a systematic review. J Clin Neurosci 2018;52:54-59.
54. Irani SR, Alexander S, Waters P, Kleopa KA, Pettingill P, Zuliani L, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain 2010;133:2734-2748.
55. van Sonderen A, Schreurs MW, Wirtz PW, Sillevis Smitt PA, Titulaer MJ. From VGKC to LGI1 and Caspr2 encephalitis: the evolution of a disease entity over time. Autoimmun Rev 2016;15:970-974.
56. van Sonderen A, Petit-Pedrol M, Dalmau J, Titulaer MJ. The value of LGI1, Caspr2 and voltage-gated potassium channel antibodies in encephalitis. Nat Rev Neurol 2017;13:290-301.
57. van Sonderen A, Thijs RD, Coenders EC, Jiskoot LC, Sanchez E, de Bruijn MA, et al. Anti-LGI1 encephalitis: clinical syndrome and long-term follow-up. Neurology 2016;87:1449-1456.
58. Wang M, Cao X, Liu Q, Ma W, Guo X, Liu X. Clinical features of limbic encephalitis with LGI1 antibody. Neuropsychiatr Dis Treat 2017;13:1589-1596.

59. Flanagan EP, Kotsenas AL, Britton JW, McKeon A, Watson RE, Klein CJ, et al. Basal ganglia T1 hyperintensity in LGI1-autoantibody faciobrachial dystonic seizures. Neurol Neuroimmunol Neuroinflamm 2015;2:e161.
60. van Sonderen A, Ariño H, Petit-Pedrol M, Leypoldt F, Körtvélyessy P, Wandinger KP, et al. The clinical spectrum of Caspr2 antibody-associated disease. Neurology 2016;87:521-528.
61. Boyko M, Au KLK, Casault C, de Robles P, Pfeffer G. Systematic review of the clinical spectrum of CASPR2 antibody syndrome. J Neurol 2020; 267:1137-1146.
62. Ghimire P, Khanal UP, Gajurel BP, Karn R, Rajbhandari R, Paudel S, et al. Anti-LGI1, anti-GABABR, and Anti-CASPR2 encephalitides in Asia: a systematic review. Brain Behav 2020;10:e01793.
63. Balint B, Regula JU, Jarius S, Wildemann B. Caspr2 antibodies in limbic encephalitis with cerebellar ataxia, dyskinesias and myoclonus. J Neurol Sci 2013;327:73-74.
64. Joubert B, Saint-Martin M, Noraz N, Picard G, Rogemond V, Ducray F, et al. Characterization of a subtype of autoimmune encephalitis with anti–contactin-associated protein-like 2 antibodies in the cerebrospinal fluid, prominent limbic symptoms, and seizures. JAMA Neurol 2016;73:1115-1124.
65. Becker EB, Zuliani L, Pettingill R, Lang B, Waters P, Dulneva A, et al. Contactin-associated protein-2 antibodies in non-paraneoplastic cerebellar ataxia. J Neurol Neurosurg Psychiatry 2012;83:437-440.
66. Gövert F, Witt K, Erro R, Hellriegel H, Paschen S, Martinez-Hernandez E, et al. Orthostatic myoclonus associated with Caspr2 antibodies. Neurology 2016;86:1353-1355.
67. Guasp M, Solà-Valls N, Martínez-Hernández E, Gil MP, González C, Brieva L, et al. Cerebellar ataxia and autoantibodies restricted to glutamic acid decarboxylase 67 (GAD67). J Neuroimmunol 2016;300:15-17.
68. Ariño H, Höftberger R, Gresa-Arribas N, Martínez-Hernández E, Armangue T, Kruer MC, et al. Paraneoplastic neurological syndromes and glutamic acid decarboxylase antibodies. JAMA Neurol 2015;72:874-881.
69. Saiz A, Blanco Y, Sabater L, González F, Bataller L, Casamitjana R, et al. Spectrum of neurological syndromes associated with glutamic acid decarboxylase antibodies: diagnostic clues for this association. Brain 2008; 131(Pt 10):2553-2563.
70. Degeneffe A, Dagonnier M, D'hondt A, Elosegi JA. A case report of rigidity and recurrent lower limb myoclonus: progressive encephalomyelitis rigidity and myoclonus syndrome, a chameleon. BMC Neurol 2018;18:173.
71. Jarius S, Stich O, Speck J, Rasiah Ch, Wildemann B, Meinck HM, et al. Qualitative and quantitative evidence of anti-glutamic acid decarboxylase-specific intrathecal antibody synthesis in patients with stiff person syndrome. J Neuroimmunol 2010;229:219-224.
72. Armon C, McEvoy KM, Westmoreland BF, McManis PG. Clinical neurophysiologic studies in stiff-man syndrome: use of simultaneous video-electroencephalographic-surface electromyographic recording. Mayo Clin Proc 1990;65:960-967.
73. Rakocevic G, Raju R, Dalakas MC. Anti-glutamic acid decarboxylase antibodies in the serum and cerebrospinal fluid of patients with stiff-person syndrome: correlation with clinical severity. Arch Neurol 2004;61:902-904.
74. Malter MP, Frisch C, Zeitler H, Surges R, Urbach H, Helmstaedter C, et al. Treatment of immune-mediated temporal lobe epilepsy with GAD antibodies. Seizure 2015;30:57-63.
75. Nanri K, Okita M, Takeguchi M, Taguchi T, Ishiko T, Saito H, et al. Intravenous immunoglobulin therapy for autoantibody-positive cerebellar ataxia. Intern Med 2009;48:783-790.
76. Dalakas MC, Fujii M, Li M, Lutfi B, Kyhos J, McElroy B. High-dose intravenous immune globulin for stiff-person syndrome. N Engl J Med 2001; 345:1870-1876.
77. Georgieva Z, Parton M. Cerebellar ataxia and epilepsy with anti-GAD antibodies: treatment with IVIG and plasmapheresis. BMJ Case Rep 2014;2014:bcr2013202314.
78. Graus F, Keime-Guibert F, Reñe R, Benyahia B, Ribalta T, Ascaso C, et al. Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. Brain 2001;124(Pt 6):1138-1148.
79. Sillevis Smitt P, Grefkens J, de Leeuw B, van den Bent M, van Putten W, Hooijkaas H, et al. Survival and outcome in 73 anti-Hu positive patients with paraneoplastic encephalomyelitis/sensory neuronopathy. J Neurol 2002;249:745-753.
80. Schwenkenbecher P, Chacko LP, Wurster U, Pars K, Pul R, Sühs KW, et al. Intrathecal synthesis of anti-Hu antibodies distinguishes patients with paraneoplastic peripheral neuropathy and encephalitis. BMC Neurol 2016;16:136.
81. Corsini E, Gaviani P, Chiapparini L, Lazzaroni M, Ciusani E, Bisogno R, et al. Intrathecal synthesis of onconeural antibodies in patients with paraneoplastic syndromes. J Neuroimmunol 2016;290:119-122.
82. Rudzinski LA, Pittock SJ, McKeon A, Lennon VA, Britton JW. Extratemporal EEG and MRI findings in ANNA-1 (anti-Hu) encephalitis. Epilepsy Res 2011;95:255-262.
83. Kelley BP, Patel SC, Marin HL, Corrigan JJ, Mitsias PD, Griffith B. Autoimmune encephalitis: pathophysiology and imaging review of an overlooked diagnosis. AJNR Am J Neuroradiol 2017;38:1070-1078.
84. Younes-Mhenni S, Janier MF, Cinotti L, Antoine JC, Tronc F, Cottin V, et al. FDG-PET improves tumour detection in patients with paraneoplastic neurological syndromes. Brain 2004;127(Pt 10):2331-2338.
85. Baumgartner A, Rauer S, Mader I, Meyer PT. Cerebral FDG-PET and MRI findings in autoimmune limbic encephalitis: correlation with autoantibody types. J Neurol 2013;260:2744-2753.

Supplementary Table 1. Autoantibodies and movement disorders

	Neuronal surface antibodies													Antibodies targeting intracellular, synaptic proteins			Antibodies targeting cytoplasmic and nuclear antigens								
	NMDA	Neurexin-3α	LGI1	CASPR2	GABAAR	GABABR	VGCC	AQP4	IgLON5	DPPX	Dopamine-2-R	mGluR5	Anti-GlyR	GAD65	Amphiphysin	Gephyrin	Hu	CV2/CRMP5	Ri	Tr	Ma2	Yo	PCA2	Sox1	GFAP
Oro-lingual-facial dyskinesias	★	V																							
Dystonia	★				V				V		V								★						
Chorea	V		V		V	V			V		V						V	★							V
Myoclonus	V		V	V									V												
Parkinsonism	V		V						★		★								★		★				
Tremor	V									V	V														V
Athetosis	V																★								
FBDS			★																						
Ataxia	V			★		V	★		★	V		V		★			★	V	V	★		★	★	★	V
OMS					V	V	V			V							V	V	★		V				
SPS					V					V			★	★	★	★			V						
Paraoxysmal dyskinesia								V																	
PERM										★			★	V											
Trismus													★												

V: Probable movement disorders in autoantibody-mediated encephalitis. ★: Common movement disorders in autoantibody-mediated encephalitis. FBDS, faciobrachial dystonic seizures; OMS, opsoclonus–myoclonus syndrome; SPS, stiff-person syndrome; PERM, progressive encephalomyelitis with rigidity and myoclonus; NMDA, N-methyl-D-aspartate; LGI1, leucine-rich glioma inactivated protein 1; CASPR2, contactin-associated protein 2; GABAAR/GABABR, g-aminobutyric acid type A and type B receptors; VGCC, voltage-gated calcium channel; AQP4, antiaquaporin-4 antibody; IgLON5, IgLON family member 5; DPPX, dipeptidyl peptidase–like protein 6; mGluR5, metabotropic glutamate receptor 5; GlyR, glycine receptor; GAD, glutamic acid decarboxylase; Hu, Hu proteins; CV2/CRMP5, collapsin response mediator protein 5; Ri, Ri proteins; Tr, delta/Notch-like epidermal growth factor–related receptor; Yo, Yo protein; PCA2, Purkinje cell cytoplasmic antibody type 2; Sox1, sry-like high mobility group box protein 1; GFAP, glial fibrillary acidic protein.

Supplementary Table 2. Antibody-associated movement disorders and tumor associations

Antigen	Movement disorder features	Other clinical features	MRI: T2/FLAIR Sequences	Tumor association and frequency	Gender frequency
Neuronal surface antibodies					
NMDA receptor	Orolingual-facial dyskinesias, catatonia, limb dystonia, chorea, myoclonus, ataxia, parkinsonism	Psychiatric symptoms, amnesia, seizures, dysautonomia, hypoventilation	Normal or mesial temporal lobe, cerebral/cerebellar cortex, basal ganglia, brainstem hyperintensity	Ovarian teratoma (40%), lung, breast, pancreatic cancer	F >>> M
Neurexin-3α	Orolingual-facial dyskinesias	Seizures, amnesia, psychomotor agitation	Normal	No	N/A
LGI1	Faciobrachial dystonic seizure, myoclonus, chorea, parkinsonism	Limbic encephalitis, hyponatremia, sleep disorders	Mesial temporal lobe hyperintensity (80%), basal ganglia hyperintensity	< 20%; thymoma, rectal carcinoma, small cell lung cancer	M > F
CASPR2	Ataxia, myoclonus	Limbic encephalitis, seizure, Morvan's syndrome, neuromyotonia, neuropathic pain, insomnia, muscle cramps and fasciculation	Normal, bilateral mesial temporal hyperintensity (30%–53%), hippocampal atrophy, mesial temporal sclerosis	< 30%; thymoma, prostate cancer, lung adenocarcinoma	M >>> F
GABAAR	Dystonia, OMS, chorea, SPS	Encephalopathy and seizures, cognitive impairment, hallucination	Multifocal cortical and subcortical involvement	Approximately 40%: thymoma, small cell lung cancer, non-Hodgkin lymphoma	M = F
GABABR	Ataxia, OMS, chorea	Limbic encephalitis with prominent status epilepticus	Some cases show unilateral or bilateral mesial temporal lobe hyperintensity	Approximately 60%: small cell lung cancer > breast cancer	M = F
VGCC	OMS, ataxia	Lambert-Eaton myasthenic syndrome, encephalopathy	Normal or cerebellar atrophy	20%–90%: small cell lung cancer	M > F
AQP4	Paraoxysmal dyskinesia, tonic painful spasm	Hiccup, optic neuritis, sensory symptom, myelopathy	Long segment transverse myelitis, optic nerve enhancement with optic chiasma involvement, midbrain and hypothalamus involvement, area postrema	Very rare; lung or breast cancer	F >> M
IgLON5	Cerebellum ataxia, chorea, parkinsonism, dystonia	NREM and REM sleep disorders, vertical gaze palsy, cognitive decline, stridor and bulbar symptoms, dysautonomia	Normal	None	M = F
DPPX	PERM, ataxia, tremor, OMS, SPS	Encephalopathy, dysautonomia, diarrhea, body weight loss, seizure	Normal	< 10% B-cell lymphoma	M > F
Dopamine-2-R	Dystonia, chorea, parkinsonism; Sydenham's chorea	Psychiatric symptoms (obsessive compulsive behavior), seizure	Basal ganglia and brainstem hyperintensity	Not known	F = M
mGluR5	Cerebellar ataxia	Ophelia syndrome (limbic encephalitis with predominate memory deficits)	Usually normal	Hodgkin lymphoma	M > F
Anti-GlyR	SPS, myoclonus, hyperekplexia, ataxia, PERM, trismus	limbic encephalitis or epileptic encephalopathy, bulbar symptom, Oculomotor disturbance	White matter lesion, temporal lobe inflammation	11% thymoma and lymphoma, breast cancer	M = F
Antibodies targeting intracellular, synaptic proteins					
GAD65	SPS, cerebellar ataxia, hyperekplexia, PERM	Limbic encephalitis, focal epilepsy	Normal or bilateral mesial temporal hyperintensity then mesial temporal sclerosis	< 25%, small cell lung cancer, thymoma, lymphoma	F >> M
Amphiphysin	SPS	Sensory ganglionopathy, encephalomyelitis, myelopathy	Normal or nonspecific change	Breast cancer, small cell lung cancer	N/A
Gephyrin	SPS, hyperekplexia	Autism and schizophrenia, temporal lobe epilepsy	N/A	N/A	N/A
Antibodies targeting cytoplasmic and nuclear antigens					
Hu/ANNA-1	Ataxia, chorea, OMS, pseudoathetosis	Sensory neuronopathy, lower motor neuron disease, limbic encephalitis, encephalomyelitis, brainstem encephalitis, gastrointestinal pseudoobstruction	Bilateral posterior thalamic hyperintensities, bilateral/unilateral mesial temporal lobe hyperintensities or as CV2	Mostly small cell lung cancer, neuroblastoma, ovarian carcinoma	M > F
CV2/CRMP5	Chorea, ataxia, dystonia	Sensory neuronopathy, sensorimotor neuropathy, limbic encephalitis, encephalomyelitis, retinopathies	Often FLAIR mesial temporal, basal ganglia, white matter hyperintensities	Small cell lung cancer, thymoma	M > F
Ri/ANNA-2	Jaw dystonia, cerebellar ataxia, OMS, parkinsonism, SPS	Brainstem encephalitis, cognitive decline	Bilateral pontine tegmentum hyperintensity	Breast cancer, small cell lung cancer, gynecologic cancer	F > M
Tr/DNER	Cerebellar ataxia	Encephalitis, neuropathy	No report	Hodgkin lymphoma, lung cancer	M >> F
Ma2/Ta	OMS, parkinsonism, supranuclear gaze palsy, cataplexy	Limbic encephalitis, diencephalic–hypothalamic involvement, brainstem encephalitis, muscle atrophy, myelopathy (rare), radiculoplexopathy (rare)	Unilateral or bilateral mesial temporal lobe hyperintensity, thalamus and spinal cord hyperintensity	Testicular cancer	M >>> F
Yo/PCA1	Cerebellar ataxia	Peripheral neuropathy	Cerebellar atrophy	Gynecological cancer, breast cancer	F >>> M
PCA2	Cerebellar ataxia	Limbic encephalitis, Lambert–Eaton syndrome, myelitis, peripheral neuropathy, brainstem encephalitis	Normal or mesial temporal lobe and limbic system hyperintensity	Small cell lung cancer	N/A
Sox1	Cerebellar ataxia	Lambert–Eaton syndrome, sensory/sensorimotor neuropathy, brainstem encephalitis, status epilepticus (rare)	Normal	Small cell lung cancer, squamous-cell lung cancer	M >> F
GFAP	Cerebellar ataxia, tremor, chorea	Meningoencephalomyelitis, epilepsy, psychiatric symptoms, optic neuropathy dysautonomia, myelitis	T1+C show linear perivascular radial enhancement in the white matter perpendicular to the ventricle, longitudinal extensive lesions in the spinal cord	30% prostate and gastroesophageal adenocarcinomas, myeloma, melanoma	F > M

NMDA, N-methyl-D-aspartate; LGI1, leucine-rich glioma inactivated protein 1; CASPR2, contactin-associated protein 2; GABAAR/GABABR, g-aminobutyric acid type A and type B receptors; VGCC, voltage-gated calcium channel; AQP4, antiaquaporin-4 antibody; IgLON5, IgLON family member 5; DPPX, dipeptidyl peptidase–like protein 6; mGluR5, metabotropic glutamate receptor 5; GlyR, glycine receptor; GAD, glutamic acid decarboxylase; Hu/ANNA-1, Hu proteins (HuD, HuC)/ anti-neuronal nuclear autoantibody type 1; CRMP5/CV2, collapsin response mediator protein 5; Ri/ANNA-2: anti-neuronal nuclear autoantibodies of type 2; Tr/DNER, delta/Notch-like epidermal growth factor–related receptor; Yo/PCA1, Purkinje cell cytoplasmic antibody type 1; PCA2, Purkinje cell cytoplasmic antibody type 2; Sox1, sry-like high mobility group box protein 1; GFAP, glial fibrillary acidic protein; OMS, opsoclonus-myoclonus syndrome; SPS, stiff-person syndrome; PERM, progressive encephalomyelitis with rigidity and myoclonus; NREM, non-rapid eye movement; REM, rapid eye movement; N/A, no report; F, female; M, male.