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Autoimmune Movement Disorders: a Clinical and Laboratory Approach

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Abstract Autoimmune movement disorders are caused by an aberrant immune response to neural self-antigens. These disorders may be paraneoplastic, parainfectious, or (most commonly) idiopathic. The neurological presentations are diverse, and sometimes multifocal. Movement disorders can occur as part of the spectrum with phenotypes including chorea, myoclonus, ataxia, CNS hyperexcitability (including stiff-person syndrome), dystonia, and parkinsonism. Symptoms are subacute in onset and may have a fluctuating course. The best characterized disorders are unified by neural autoantibodies identified in serum or cerebrospinal fluid. The antibody specificity may predict the association with cancer and the response to immunotherapy. In this article, we review autoimmune-mediated movement disorders, associated cancers, diagnosis, and treatment.

Keywords Autoimmunity · Movement disorders · Paraneoplastic · Neuronal autoantibodies · Immunotherapy

This article is part of the Topical Collection on *Movement Disorders*

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Introduction

Autoimmune movement disorders are rare disorders characterized by abnormal immune responses against neural (neuronal or glial) self-antigens. In most cases, neural IgG autoantibodies can be detected in serum or cerebrospinal fluid (CSF) of affected patients [1, 2]. These disorders may be of paraneoplastic, idiopathic, or parainfectious origin [3, 4]. Adults as well as children can be affected. Age of onset and sex may serve as diagnostic clues as some diseases occur predominantly in children or in women [5–8]. Some patients, but not all, respond well to immunotherapy [9, 10•]. Some neural autoantibodies may be predictive of disease course and outcome. Epidemiologic data is limited. Autoimmunity enters the differential diagnosis for all movement disorder phenotypes, though some (such as myoclonus and chorea) are more commonly encountered in the senior author's clinical practice than others (such as parkinsonism). In Olmsted County Minnesota, autoimmune chorea is the second most common type after Huntington disease [11].

Neural Autoantibodies

The neural antibodies serving as biomarkers of autoimmune movement disorders can be classified into two broad categories based on cellular antigen location (intracellular and plasma membrane), (Table 1, Fig. 1). Antibodies reactive with intracellular antigens are derived from a response against processed polypeptides, presented to T helper cells in the context of upregulated MHC class I, and not considered to be pathogenic [12]. Many of these antibodies are encountered in patients with classical paraneoplastic disorders, for instance, Purkinje cytoplasmic antibody type 1

Table 1 Neuronal antibodies associated with autoimmune movement disorders

Antibodies	Movement disorders	Other neurological syndrome	Cancer association
Neuronal nuclear, nucleolar, and cytoplasmic antibodies (intracellular)			
CRMP5/CV2	Chorea, ataxia	LE, encephalomyelitis, radiculopathies, neuropathies	SCLC, thymoma
Amphiphysin	SPS	Encephalomyelitis	SCLC, breast
GAD65	Cerebellar ataxia, SPS, extrapyramidal disorders	LE, myelopathy	Rare; thymoma, lung, breast, colon
PCA-1/Yo	Cerebellar ataxia	PCD	Ovary, breast
Ma2	Parkinsonism, ataxia	LE, brainstem encephalitis	Testes, breast, colon
Tr/DNER	Cerebellar ataxia	Encephalopathy	Hodgkin disease
ANNA-1/Hu	Ataxia	Brainstem encephalitis, neuropathy	SCLC
ANNA-2/Ri	Jaw dystonia, OMS	BE	SCLC, breast
Neuronal cell surface antibodies (extracellular)			
LGI1	Chorea, ataxia, myoclonus, parkinsonism	BE	(Rare) thymoma, SCLC, breast, prostate
CASPR2	Chorea	LE, Morvan syndrome	Thymoma
NMDA-R	Orofacial dyskinesia, OMS	Encephalitis	Ovarian teratoma
$GABA_BR$	Ataxia, OMS	LE	SCLC
VGCC	Ataxia, myoclonus	Lambert-Eaton syndrome	SCLC, breast
GlyR α1	SPS and variants	Seizures, demyelinating disorders	Thymoma, lymphoma
DPPX	PERM	Encephalopathy, dysautonomia, cognitive dysfunction	B cell lymphoma, leukemia
mGluR1	Ataxia	Seizures, cognitive dysfunction	Hodgkin lymphoma
IgLON5	Chorea, ataxia, parasomnias	Non-REM sleep disorder	None reported
Neurexin-3α	Dyskinesias	Seizure	None reported

LE limbic encephalitis, *BE* brainstem encephalitis, *PERM* progressive encephalomyelitis with rigidity and myoclonus, *SCLC* small cell lung carcinoma, *PCD* paraneoplastic cerebellar degeneration, *CRMP-5* collapsin-response mediated protein 5, *ANNA* anti-neuronal nuclear antibody, *GAD65* glutamic acid decarboxylase, 65 kDa isoform, *VGCC* voltage-gated calcium channel, *PCA* Purkinje cell cytoplasmic antibody, *GABA-R* gamma aminobutyric acid receptor, *GlyRα1* alpha 1 subunit of glycine receptor, *NMDAR* N-methyl-D-aspartic acid receptor, *HNK-1* human natural killer 1, *DPPX* dipeptidyl-peptidase-like protein-6, *LGI-1* leucine-rich glioma inactivated 1, *CASPR2* contactin-associated protein 2, *mGluR1* metabotropic glutamate receptor type 1

(PCA-1, also known as anti-Yo). Predictive values for cancer are often high, and responses to immunotherapy poor, though stabilization is possible after appropriate oncological therapy and immunotherapy. In contrast, antibodies reactive with extracellular domains of receptors (e.g., N-methyl-D-aspartate receptor), ion channels and water channels on neural plasma membranes have the potential to interact with neural antigens in their native conformational state. These interactions have the potential to downregulate expression of the antigen in question (antigenic modulation), activate complement, and impair channel function [13, 14].

Neuropathological evaluations of autopsied brain from patients with antibodies to intracellular antigens (for instance Yo) are typically abundant with CD8+ T cells-predominant infiltrates, with immunohistochemical granzyme and perforin stains (markers of cytotoxicity) positive in brain parenchyma. Conversely, for NMDA-R autoimmunity, CD8+ T cells infiltrates are scant in brain parenchyma, but plasmablasts and plasma cells (antibody generating) are abundant [2].

Clinical Disorders

Hyperkinetic

Chorea

Sydenham's chorea is a classical autoimmune neurological disorder of childhood []. It occurs as one of the main manifestations of rheumatic fever, a complication of group A B-hemolytic streptococcus (GABHS) infection. Patients may present with one or more clinical features including abnormal movements (chorea), carditis and arthritis []. Molecular mimicry between the pathogen and neural antigen is suggested as part of the pathophysiological mechanism of the disease [15, 16]. However, there is no proven autoantigen, though various antibodies have been described in the literature [17–19]. Kirvan et al. have shown that antibodies from Sydenham chorea patients are reactive with cell wall carbohydrate of GABHS, and may cross react with the central nervous system (CNS) gangliosides [15]. The autoimmune nature of Sydenham chorea is also supported by the response of the

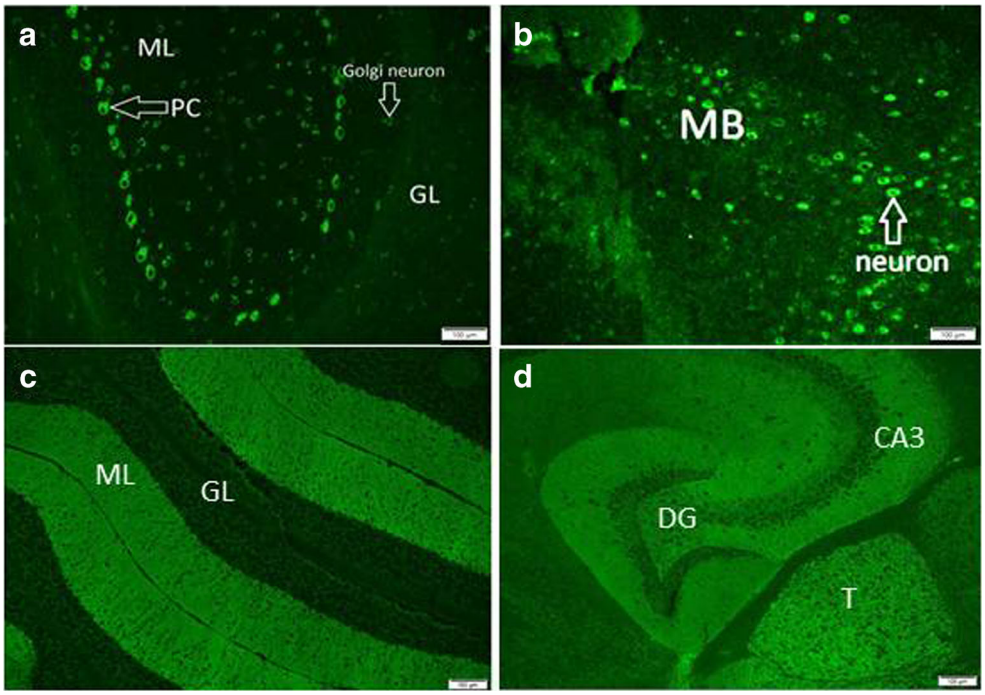

Fig. 1 PCA-1 (**a**, **b**) and mGluR1-IgG (**c**, **d**). Tissue-based indirect immunofluorescence assay of cerebellum (**a**) and cerebrum (**b**) demonstrates PCA-1 immunoglobulin G in patient serum. PCA-1 reactivity is seen in cytoplasm of Purkinje cells (*PC*), molecular layer (*ML*), Golgi (*G*) neurons (**a**), and midbrain (*MB*) neurons (**b**). The CNS pattern of mGluR1 immunoreactivity is most prominent in the ML of the cerebellum (**c**), and also thalamus (*T*), and hippocampus (CA3 region, dentate gyrus (*DG*) (**d**)). Panels **c** and **d** (ref. 91) reproduced with permission from Wolters Kluwer Health, Inc.

patients to immunotherapy [20, 21]. Among patients who had Sydenahm's chorea as children, chorea can recur in adulthood, often in the context of pregnancy or hormonal therapy [22].

In children, rare cases of paraneoplastic chorea, opsoclonus, and ataxia have been reported. One patient had gamma amino butyric acid receptor B ($GABA_BR$) antibodies with small cell lung cancer [23].

In adults, autoimmune chorea may be paraneoplastic or idiopathic [11]. A well-known paraneoplastic form is encountered in patients with collapsin-response mediated protein 5 (CRMP-5) IgG autoimmunity, associated with small cell lung cancer (SCLC, 70%) and thymoma (30%) [24, 25]. Rare CRMP5 IgG-positive patients with chorea have had non-Hodgkin lymphoma, tonsillar squamous cell carcinoma among others. Anti-neuronal nuclear antibody, type 1 (ANNA-1, or anti-Hu) is the second most common antibody associated with paraneoplastic chorea [11]. Diverse other cancers have been rarely encountered in patients with autoimmune chorea. These include chronic myeloid leukemia and adenocarcinoma (breast and prostate) [11]. Glutamic acid decarboxylase 65 (GAD65), contactin-associated protein 2 (CASPR2), and leucine-rich glioma inactivated 1 (LGI1) antibodies are found mostly in association with non-paraneoplastic autoimmune chorea responsive to treatment [11, 26]. IgLON5 antibody is a recently described antibody encountered in patients with a constellation of CNS findings including chorea, parasomnias, brainstem disorders, and dysautonomia [27•]. This initial report suggests a lack of immunotherapy response, sudden death and neurodegenerative-type tau pathology in these patients [27•].

Myoclonus

In children, myoclonus classically presents as opsoclonus-myoclonus syndrome (OMS) and is associated with neuroblastoma in 50% of cases [28]. Aside from ANNA-1 (anti-Hu) [29], no specific neuronal autoantibodies have been detected in the pediatric population, though some patients produce autoantibodies that seem to recognize cerebellar and brainstem neurons in vitro [30, 31].

In adults, OMS may be of paraneoplastic, idiopathic, or parainfectious origin [32]. The associated tumors are small cell lung carcinoma, breast adenocarcinoma, ovarian teratoma, and other types, such as testicular seminoma [33, 34]. In the majority of cases, OMS precedes the detection of the neoplasm. Onconeuronal antibodies associated with OMS are ANNA-2 (anti-Ri), Ma1 and Ma2 antibodies, and CRMP-5 IgG [34, 35]. Neural antibodies targeting plasma membrane proteins reported include alpha 1 subunit of glycine receptor (GlyRα1) antibody and NMDA-R antibody, respectively associated with small cell lung cancer (SCLC) and ovarian teratoma [34]. A novel antibody against the human natural killer 1 (HNK-1) epitope was recently identified in OMS patients with lung cancer (SCLC and non-SCLC) [34]. Patients with systemic infections (HIV, hepatitis C virus, mycoplasma pneumoniae, adenovirus infections and others) may develop OMS as a parainfectious autoimmune disorder [36–39]. Idiopathic cases are typically neural antibody negative, but some rare cases are associated with $GABA_AR$, $GABA_BR$ and GAD65 antibodies [34, 40, 41]. Idiopathic and parainfectious OMS often responds well to immunotherapy [33].

Dyskinesia in NMDA-R Encephalitis

NMDA-R encephalitis is more common in children and young adults, and predominantly affects female patients (ratio of 8:1) []. Patients develop behavioral changes, psychiatric symptoms associated with orofacial dyskinesia, and dystonic posture of the limbs. The significant increase of extracellular glutamate and alterations in GABAergic signalling that result may contribute to the array of manifestations of anti-NMDAR encephalitis: cognitive, behavioral changes, and abnormal movements [].

Children occasionally have an accompanying neoplasm, usually teratoma. Adults more commonly have a paraneoplastic cause, with ovarian teratoma being the most common accompaniment [42–44]. Older adults (>40 years) who develop NMDA-R encephalitis may have one of a diverse number of cancers common in that age group (lung, breast, testicular, pancreatic, thymic) [44, 45]. Over 80% of NMDAR-IgG positive patients respond well to immunotherapy [44].

NMDA-R antibodies, target the N-terminal domain of the NR1 subunit of the NMDA receptor, and are likely pathogenic. Incubation of hippocampal neurons or injection of NMDAR-IgG into hippocampus of rat provokes the internalization of the receptor and diminished function [46–48]. Co-injection of the antibodies with ephrinB2 prevents the effects of the antibodies [49••]. Ephrinb2 is a receptor tyrosine kinase that regulates NMDA receptor synaptic content and trafficking [50].

Neurexin-3α antibody is a newly identified antibody associated with severe encephalitis [51]. Five patients have been reported, to date, presenting with confusion, decreased level of consciousness, seizures, orofacial dyskinesias, and myoclonic jerks. No neoplasms were detected. Three patients partially improved with immunotherapy and two died [51].

Tics and Stereotypies

Around two decades ago, the first cases of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) were reported [52]. The patients presented with obsessive compulsive disorder (OCD) and tics triggered by GABHS infections [52]. However, the role of GABHS infection, and the existence of PANDAS as a distinct nosological entity is very controversial. A link to a streptococcal infection could not be found in some patients with OCD and tics. New terms such as pediatrics acute-onset neuropsychiatric syndromes (PANS) were coined to define a larger spectrum with clinical syndromes from various etiologies [53]. Antibodies against neuronal antigens (neuronal isoforms of glycolytic enzymes aldolase C, neuron-specific enolase etc.) were reported in PANDAS patients, though disease specificity for the disease is controversial [54]. Other potential autoantigens reported (though not reproduced) include dopamine receptor 1, dopamine receptor 2 and anti lysoganglioside antibodies [17, 55].

Other Hyperkinetic Disorders

Dystonia

Dystonia may occur as a manifestation of an autoimmune or paraneoplastic neurological disease. Jaw dystonia is characteristic of patients with brainstem encephalitis in the context of ANNA-2 [56]. These are mainly female patients with breast cancer. Axial and neck dystonia, and laryngospasm were present in some patients. Some patients show improvement after immunotherapy, chemotherapy, or botulinum toxin injections [56]. Limb dystonia may be encountered in pediatric NMDAR encephalitis [57].

Pseudoathetosis

Patients with sensory neuropathy may present with pseudoathetosis caused by loss of proprioception. Sensory neuropathies may have paraneoplastic origin. The patient, then, presents with asymmetric, severe and rapidly progressive joint position loss [58]. Paraneoplastic sensory neuropathy is most commonly associated with small cell lung cancer and ANNA-1 [59]. This phenomenon has also been reported with other types of cancer (lymphoma, thymoma) and other autoantibodies (CRMP5-IgG) [58].

Catatonia

Catatonia is a psychomotor syndrome with various potential causes, most commonly as a manifestation of severe depression or mania. However, catatonia has also been reported among patients with NMDA-R encephalitis [46], and is highly associated with that disorder among psychiatric patients with neural antibodies detected [60].

Stiff-Person Syndrome (SPS) and Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM)

SPS is a rare neurological disease characterized by muscle rigidity and painful muscular spasms involving the limbs and the trunk. It was first reported in 1956 at Mayo Clinic [61]. Some patients may presents with a limited form of the disease, involving only one or two limbs, or trunk (partial SPS). At the severe end of the CNS hyperexcitability spectrum is a generalized form, accompanied by encephalomyelitis and dysautonomia (progressive encephalomyelitis with rigidity and myoclonus) [62].

GAD65 antibody is the most common antibody detected among patients with SPS or variants [63]. GAD65 is an intracellular synaptic protein responsible for the synthesis of

GABA, an important inhibitory neurotransmitter. GAD65 antibody-associated SPS is usually idiopathic, though some paraneoplastic cases with accompanying neoplasms of the thyroid, kidney, colon, and thymus have been reported. [63–66] Other organ-specific autoimmune disorders commonly coexist in patients with GAD65-neurological autoimmunity, primarily type 1 diabetes and thyroid disease [63]. GAD65-antibody positive SPS patients often improve following immunotherapy, cancer treatment, or treatment with GABA-ergic drugs (benzodiazepines or baclofen) [63]. Other GAD65 autoimmune neurological disorders include brainstem, cerebellar, and extrapyramidal syndromes [67]. When GAD65 autoimmunity is detected in a classic paraneoplastic neurological context, such as limbic encephalitis, neoplasia (of lung, thymus, and breast) is often detected [68, 69]. These patients are typically older and more frequently male than classical SPS patients and have worse treatment responses [69].

GlyRα1 antibody is the second most common antibody associated with CNS hyperexcitability. GlyRα1 antibodies may be detected among any of the disorders of the SPS spectrum, though has particular significance for PERM [70]. GlyRα1 autoimmunity is often idiopathic but may occur in patients with lymphoma or thymoma [70, 71]. GlyRα1 antibody may co-exist with GAD65 antibody [71]. There is a correlation between the variants and the type of antibody: GAD65 antibody-positive patients are more likely to have "classic" SPS while GlyRα1-IgG positivity has a higher association with the other variants [72]. Although many SPS patients in general seem to respond well to treatment (immunotherapy or γ-aminobutyric acid agent) [63], GlyRα1 positivity is predictive of an immunotherapy response [71, 72].

Amphiphysin antibody is associated with an SPS-like disorder. Patients typically have extremity stiffness, often associated with myeloneuropathic symptoms and signs [63]. This disorder is usually encountered in women with breast cancer [73, 74], some of whom have a good response to immunotherapy and cancer treatment [75]. Other amphiphysin-IgG associated phenotypes include encephalopathy, neuropathy, and myelopathy. The search for cancer should also include small cell carcinoma. Amphiphysin is a synaptic protein that belongs to the BAR (Bin-Amphiphysin-Rvsp) superfamily of proteins [76]. This plays an important role in clathrin-mediated synaptic vesicle endocytosis. Because amphiphysin is an intracellular antigen, not accessible by antibody in vivo, pathogenesis is likely mediated by cytotoxic T cells [74].

Dipeptidyl-peptidase-like protein-6 (DPPX) antibody is also associated with CNS hyperexcitability, often a PERM phenotype, but not classical SPS [77, 78]. Neurological disorders are diverse and include encephalopathy, myelopathy, dysautonomia, and sleep disorders. Responses to treatment are variable, though sustained, aggressive immunotherapy may bring about significant improvements [77]. DPPX is a subunit of Kv4.2 potassium channels within the CNS and cardiac conduction systems. Neuronal hyperexcitability seems likely the cause of DPPX-induced symptomatology [79]. Consistent with this hypothesis, DPPX antibody has been shown to lead to antigen internalization in neuronal cell culture and increase the excitability and action potential in enteric neurons, consistent with antibody pathogenicity [80•].

SPS is very rarely reported among children. In a retrospective study conducted at Mayo Clinic over a 29-year period, 5% of SPS patients were children [8]. They presented with all variants of SPS; 87.5% were GAD65 antibody-positive and 37.5% had coexisting GlyRα1 antibody. The patients improved with immunotherapy or diazepam.

Hypokinetic Disorders

Parkinsonism

Parkinsonism or an atypical parkinsonian syndrome may be a component of an autoimmune disorder, usually reflecting brainstem localization (rhomboencephalitis). Patients usually present with a spectrum of eye movement disorders, bradykinesia, rigidity, gait disorders, postural instability, dysarthria, dysphagia, and sleep disorders (REM sleep behavior disorder and narcolepsy). MRI may be normal or may show lesions in the midbrain, hippocampus, amygdala, globus pallidum, pons, or medial temporal lobe [81, 82]. This syndrome is classically associated with Ma2 antibody or Ma1 and Ma2 antibodies coexisting [83]. Ma2 antibody positivity in isolation is usually associated with testicular neoplasms in young male patients [84]. The oncological accompaniments of seropositivity for both Ma1 and Ma2 antibodies are more diverse and include tonsillar squamous cell carcinoma, B cell lymphoma, pancreatic, renal, and pulmonary carcinoma [81, 85]. Though the cancers are often treatable, the neurological prognosis for these disorders tends to be poor, with limited or no responses to immune therapies [83, 86, 87]. Female patients with ANNA-2 antibodies and breast cancer may present also with parkinsonism [56].

Parkinsonism has also been reported among patients with LGI1 neurological autoimmunity, and responses to immunotherapy have been favorable in some [88–90]. As discussed earlier, GAD65 neurological autoimmunity may present with eye movement disorders, bradykinesia, and postural instability. This presentation appears to occur more commonly among African-Americans and improvements with immunotherapy sometimes occur [67].

Ataxia

Unlike patients with degenerative or hereditary forms of ataxia, patients with autoimmune cerebellar ataxia generally have disease of subacute onset and rapid progression, leading to severe disability [91]. The context for this can be paraneoplastic or idiopathic. In the paraneoplastic group, Purkinje cell cytoplasmic antibody type 1 (PCA-1, or anti-Yo) cerebellar ataxia is the most common and well-studied form (Fig. 1). Patients are almost exclusively female, and present in 90% of cases with gynecologic or breast adenocarcinomas. The treatment of the associated cancer is often successful. In contrast, the neurological syndrome displays no substantial improvement after immunotherapy or treatment of the tumor [5, 91]. Voltage-gated calcium channel (VGCC) antibodies may co-exist with PCA-1 antibodies [5].

Metabotropic glutamate receptor type 1 (mGluR1) antibody is also associated with cerebellar ataxia. In contrast to PCA-1, mGluR1 neurological autoimmunity affects men and women. Patients may have dysgeusia prior to the development of subacute ataxia. Classically, this disorder was encountered in patients with Hodgkin lymphoma, though a recent report of a relatively large number of patients revealed a predominance of non-paraneoplastic cases [92•, 93].

Antibodies reactive with various antigens in the glutamate/calcium pathway of Purkinje cells are also associated with autoimmune cerebellar ataxia. These antibodies, individually rare, are often referred to as "Medusa-head" antibodies, due to the appearance of patient antibody staining of cerebellar molecular layer. Antigens include Homer-3, Sj/ITPR1, CARP VIII, PKCγ, GluRδ2, Ca/ARHGAP26, and Nb/AP3B2/beta-NAP [94–96]. They are associated with various cancers such as melanoma, ovarian adenocarcinoma, and lung carcinomas (small cell and non-small cell).

The antibody type (directed against either intracellular or cell surface antigens) and cancer (presence or absence) determines the response to treatment and outcome [10•]. Patients with non-paraneoplastic disorders respond better to immunotherapies. Patients with antibodies against plasma membrane antigens have better treatment responses and outcomes than those with nuclear or cytoplasmic antibodies. The exception to the rule is patients with GAD65 autoimmunity and cerebellar ataxia. These patients have similar treatment responses and outcomes to those harboring antibodies targeting neural plasma membrane proteins [10•].

Diagnosis of Autoimmune Movement Disorders

Clues from the Clinical Presentation

Autoimmune movement disorders generally have a subacute onset and rapid progression [11]. Disorders (unlike classical neurodegenerative disorders) may be multifocal (Table 2). For example, patients with paraneoplastic chorea frequently develop peripheral neuropathy simultaneously [11, 24]. Other examples of coexisting neurological disorders include encephalopathy, myelopathy, and neuropathy. Personal and family histories tend to be negative for movement disorders, but common autoimmune diseases (such as diabetes mellitus, thyroid disease, or systemic lupus erythematosus) frequently coexist [63].

Most often, symptoms and signs progress rapidly over a period of weeks or months. However, an insidious onset and slow progression of the disease does not exclude an autoimmune diagnosis. For example, patients with DPPX-associated PERM may progress slowly [78]. One should also be aware of some other unusual prodromal symptoms associated with certain antibodies. For instance, patients with DPPX encephalitis may present with diarrhea before the onset of neurological symptoms [78, 97]. One should also consider demographic information (age, sex, and race). Imaging and electrophysiological findings may also help to suggest a specific disorder.

Immunological Testing

The evaluation should include both serum and CSF analyses. Serological screening can include testing for non-neural antibodies (reactive with thyroid and connective tissue antigens). Though not nervous system specific, seropositivity for one or more of these antibodies may serves as diagnostic clues, particularly among patients who are neural antibody negative. In addition to antibody testing of CSF, it is important to look for markers of CSF inflammation: elevated protein concentration and white cell count, CSF-exclusive oligoclonal bands, elevated IgG index and synthesis rate [98].

Autoantibody Testing

The existence of a neural-specific antibody assists in making definitive neurological and oncological diagnoses. CSF and serum are used for antibody testing. Some antibodies (such as NMDA-R antibody) are best detected in CSF [99, 100] while others (such as aquaporin-4 IgG) are best detected in serum [101, 102]. Various techniques are used for antibody detection: enzyme-linked immunosorbent assay (ELISA), tissue-based immunohistochemistry (IHC, including indirect immunofluorescence, Figure), immunoblotting, cell-based assays (including observer-interpreted and flow cytometric assays), and radioimmunoassays [98]. The technique used for antibody detection depends on a number of factors, including the physical properties of the antibody and antigenic target, and performance of the assay in a clinical testing environment. For instance, intracellular antibodies can easily be detected by ELISA, tissue-based IHC and immunoblotting [4]. Neuronal cell surface antibodies may recognize their specific antigens in

Table 2 Autoantibody-mediated movement disorders

Syndrome	Antibodies	Common cancer association
Chorea	CRMP-5, ANNA1/Hu, GAD65, VGCC, ANNA2/Ri, $GABA_BR$, IgLON5	SCLC, thymoma, breast adenocarcinoma, non-Hodgkin lymphoma, CML
Myoclonus	ANNA2/Ri, Ma2, Zic4, CRMP5, GlyRα1, NMDAR, HNK-1, GAD65, GABA-B-R, DPPX,	Neuroblastoma, SCLC, breast adenocarcinoma, ovarian teratoma, testicular seminoma
Dyskinesia	NMDAR, neurexin-3α,	Ovarian teratoma
Parkinsonism	Ma1/Ma2, LGI1, GAD65	Testicular seminoma, non-small cell lung cancer, tonsillar squamous cell carcinoma, B cell lymphoma
Stiff-person spectrum disorders	GAD65, DPPX, amphiphysin, GlyRα1, $GABA_AR$, gephyrin.	Breast adenocarcinoma, thymoma, SCLC, HL, colon adenocarcinoma
Ataxia	ANNA-1, Ma1/Ma2, PCA-1/Yo, GAD65, VGCC, CASPR2, mGluR1, DPPX, IgLON5, GABA-B-R,	Small cell carcinoma, testicular neoplasms, Mullerian (gynecologic) tumors, breast adenocarcinoma, thymoma, lymphoma

SCLC small cell lung cancer, *CML* chronic myelogenous leukemia, *HL* Hodgkin lymphoma, *CRMP-5* collapsin-response mediated protein 5, *ANNA* anti-neuronal nuclear antibody, *GAD65* glutamic acid decarboxylase, *VGCC* voltage-gated calcium channel, *PCA* Purkinje cell cytoplasmic antibody, *GABA-R* gamma aminobutyric acid receptor, *GlyRα1* alpha 1 subunit of glycine receptor, *NMDAR* N-methyl-D-aspartic acid receptor, *HNK-1* human natural killer 1, *DPPX* dipeptidyl-peptidase-like protein-6, *LGI-1* leucine-rich glioma inactivated 1, *CASPR2* contactin-associated protein 2, *mGluR1* metabotropic glutamate receptor type 1

their native conformation. Thus, cell-based IHC assay can be used.

Cancer Detection

Autoimmune movement disorders may have a paraneoplastic cause. The evaluation for cancer may be based on a detected antibody (e.g., one would search for small cell carcinoma and thymoma in a CRMP-5 IgG positive patient) or on age- and sex appropriate considerations [24, 28]. Common cancers in a paraneoplastic neurological context include SCLC, breast adenocarcinoma, gynecologic adenocarcinoma, testicular seminoma, ovarian teratoma and thymoma [5, 42]. Testing modalities include computerized tomography (CT) scan of chest, abdomen, pelvis, mammography, testicular ultrasound and pelvic ultrasound. Whole-body positron emission tomography (PET) co-registered with CT may permit higher sensitivity for detection of certain cancers than CT alone [103••]. In some patients, if a primary or metastatic cancer is not detected by radiological methods, direct visualization with laparotomy or laparoscopy may help to identify the site of the cancer [5].

Treatment

Immunotherapy

Acute Therapy

Immunotherapy is usually given to patients with a confirmed or highly suspected autoimmune disease. The first-line therapy usually includes high dose intravenous corticosteroids, intravenous immunoglobulin (IVIg), or plasmapheresis [104]. The typical treatment protocols consist of 1000 mg daily of intravenous (IV) methylprednisone or 0.4 g/kg daily of IVIg for five consecutive days (inpatient or as an outpatient). For patients with limited to no responses to steroids, plasma exchange every other day for 10–14 days may be of benefit. In case of no improvement after 2 weeks of first-line treatment or if the condition worsens, a second-line treatment is started. The second-line therapy usually consists of rituximab (often 375 mg/m^2 weekly for 4 weeks) or cyclophosphamide (0.6 to 1 g/m^2 IV monthly for 6 months), Table 3 [104]. The type of autoantibodies may predict the response to immunotherapy. Patients with antibodies against neuronal cell surface antigen respond often to treatment. In contrast, in patients with intracellular antibodies, the response to immunotherapy is variable. Early treatment is associated with a better neurological outcome [10•, 98].

Chronic Therapy

A maintenance immunosuppressive therapy is considered in patients with response to the acute therapy but at risk for relapse [98]. Azathioprine or mycophenolate mofetil are often used (Table 3). Methotrexate, hydroxychloroquine, and oral cyclophosphamide are alternative options. The maintenance usually overlaps with the gradual tapering of steroids or IVIg for 6 to 8 months. Some patients are steroid-dependent and will need continuous low dose of oral prednisone (10–20 mg/day or every other day). Patients should be monitored for potential side effects. There is no established duration for the chronic immunotherapy. After 3–5 years without relapses, withdrawal of therapy may be considered [104].

Table 3 Common immunotherapies

Treatment	Regimen	Side effects
Acute therapy		
Methylprednisolone	1000 mg IV daily for 3 days followed by 1 dose weekly for 5–11 weeks	Peptic ulcer, glucose intolerance, agitation, anxiety, cataracts, glaucoma, electrolytes imbalance, fluid retention/edema, weight gain, avascular hip necrosis, insomnia
Prednisone	60 mg by mouth daily for 2–3 months then taper by 10 mg/month until at 10 mg/day, then 1 mg/month thereafter	Peptic ulcer, glucose intolerance, agitation, anxiety, cataracts, glaucoma, electrolytes imbalance, fluid retention/edema, weight gain, avascular hip necrosis, insomnia
IVIg	0.4 g/kg IV daily for 5 days, then 1 dose weekly for 5–11 weeks	Headache, infusion reactions, acute tubular necrosis, renal failure, autoimmune hemolytic anemia, pulmonary edema, aseptic meningitis, deep venous thrombosis
Plasma exchange	Every other day for 10–14 days	Hypotension, dyspnea, electrolytes abnormalities, coagulation abnormalities
Rituximab	375 mg/m^2 IV weekly for 4 weeks or 1000 mg 2 doses, each dose given 2 weeks apart	Allergic reaction, viral or TB reactivation, cytopenia, hypertension, weight gain, headache, insomnia
Cyclophosphamide	0.6–1 g/m^2 IV every month for 6 months	Nausea, vomiting, anorexia, diarrhea, alopecia, sterility, acute hemorrhagic cystitis, leukopenia, thrombocytopenia, anemia.
Chronic therapy		
Azathioprine	Initially 1.5 mg/kg/day PO. Progressive increase according to MCV to 2–3 mg/kg/day	Hypersensitivity reactions, fever, malaise, myalgias, nausea, vomiting, diarrhea, leukopenia, anemia, thrombocytopenia (must check thiopurine methyltransferase to ensure patient is metabolizer of thiopurines before starting treatment)
Mycophenolate mofetil	Initially 500 mg PO twice daily. Progressive increase to 1000 mg twice daily	Gastrointestinal disturbances, hypertension, edema, susceptibility to infections, CNS lymphoma, leukopenia, thrombocytopenia, anemia

MCV mean corpuscular volume

Cancer Therapy

Cancer treatment is of great importance for patients with paraneoplastic syndromes. Cancer treatment (surgery, chemotherapy, radiation therapy) may aid in the improvement of the neurological syndrome. In NMDA-R encephalitis, removal of ovarian teratoma (combined with immunotherapy) is associated with substantial improvement and a decrease rate of relapse [44] .

Symptomatic Therapy

Symptomatic therapies are sometimes helpful. They may be used as first-line treatment prior to immunotherapies, in combination with immunotherapies, or in patients who have not improved after immunotherapy trials. For instance, in SPS, GABAergic agonists (benzodiazepines, baclofen) often constitute the first line treatment [63]. Doses of diazepam required to treat SPS patients may be very high (even as high as 100 mg per day in divided doses). Patients with chorea or myoclonus may also benefit from benzodiazepines [11, 33]. Patients with chorea may respond to the dopamine-depleting drug tetrabenazine. For dystonia trihexiphenidyl and focal botulinum toxin injections may be considered [98]. However, all these agents tend to have significant side effects, and tolerability in adults may be poor.

Conclusions

The rapid growth in discovery of disease-specific IgG biomarkers of neurological autoimmunity has resulted in an increased recognition and awareness of autoimmune movement disorders. Recognition is important because of the possibility of an occult early-stage neoplasm as the trigger for autoimmunity, and also because some of these disorders are potentially treatable. Future improved understanding of the pathophysiological mechanisms of these disorders should lead to development of targeted drug immune therapies.

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Compliance with Ethical Standards

Conflict of Interest J. Archie Honorat declares no conflict of interest. Andrew McKeon receives research support from MedImmune, Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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