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Movement disorders in paraneoplastic and autoimmune disease

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Abstract

Purpose of review—The most relevant advances in immune-mediated movement disorders are described, with emphasis on the clinical–immunological associations, novel antigens, and treatment.

Recent findings—Many movement disorders previously considered idiopathic or degenerative are now recognized as immune-mediated. Some disorders are paraneoplastic, such as anti-CRMP5-associated chorea, anti-Ma2 hypokinesia and rigidity, anti-Yo cerebellar ataxia and tremor, and anti-Hu ataxia and pseudoathetosis. Other disorders such as Sydenham's chorea, or chorea related to systemic lupus erythematosus and antiphospholipid syndrome occur in association with multiple antibodies, are not paraneoplastic, and are triggered by molecular mimicry or unknown mechanisms. Recent studies have revealed a new category of disorders that can be paraneoplastic or not, and associate with antibodies against cell-surface or synaptic proteins. They include anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, which may cause dyskinesias, chorea, ballismus or dystonia (NMDAR antibodies), the spectrum of Stiff-person syndrome/muscle rigidity (glutamic acid decarboxylase, amphiphysin, GABA_A-receptor-associated protein, or glycine receptor antibodies), neuromyotonia (Caspr2 antibodies), and opsoclonus–myoclonus–ataxia (unknown antigens).

Summary—Neurologists should be aware that many movement disorders are immune-mediated. Recognition of these disorders is important because it may lead to the diagnosis of an occult cancer, and a substantial number of patients, mainly those with antibodies to cell-surface or synaptic proteins, respond to immunotherapy.

Keywords

antibodies; ataxia; autoimmune; chorea; dyskinesia; dystonia; encephalitis; immunotherapy; movement disorders; paraneoplastic

Introduction

Immune-mediated movement disorders may result from paraneoplastic [1] or autoimmune mechanisms that can be triggered by bacterial molecular mimicry or unknown causes. Although it is well known that classical paraneoplastic syndromes, as well as systemic lupus erythematosus (SLE), and antiphospholipid syndrome (APS) can result in abnormal movements, there is a new and expanding group of syndromes that are related to antibodies against cell surface or synaptic proteins and may cause prominent movement disorders. These disorders may occur with or without tumor association, can affect children and young adults, and are severe but responsive to treatment. This review focuses on all these disorders,

with emphasis on the clinical–immunological associations, novel antigens, and treatment strategies.

General concepts

Paraneoplastic neurological disorders (PNDs) usually develop before an underlying tumor is recognized, often leading to tumor diagnosis (Table 1) [2]. Symptoms progress faster than in noninflammatory degenerative disorders and this, along with the presence of cerebrospinal fluid (CSF) inflammatory changes, is an important diagnostic clue. During the early phase of most immune-mediated movement disorders, lymphocytic pleocytosis is present in the CSF. There is also a variable increase in CSF protein concentration, IgG index, and frequent oligoclonal bands [3]. A more specific finding is the presence of antineuronal antibodies. These antibodies establish that the syndrome is immune-mediated and, depending on the antibody, indicates the likelihood and type of associated neoplasm (Table 1) [4].

Paraneoplastic chorea and CRMP5 antibodies

The chorea associated with antibodies to CRMP5 is almost always paraneoplastic [5,6]. The choreic movements usually develop as part of a more extensive involvement of the nervous system that may include limbic encephalitis, cerebellar ataxia, peripheral neuropathy, uveitis, optic neuritis, or retinitis [6,7].

Brain MRI shows abnormal fluid-attenuated inversion recovery (FLAIR) hyperintensities involving limbic regions, striatum, basal ganglia, brainstem, or white matter [8]. The tumors more frequently involved are small cell lung cancer (SCLC) and thymoma. The management of this disorder focuses on treatment of the tumor and immunotherapy targeting T-cell-mediated mechanisms. The median survival is longer in patients with SCLC and anti-CRMP5-related paraneoplastic encephalitis compared to those with anti-Hu-related encephalitis [9].

Sydenham's chorea

Sydenham's chorea results from an autoimmune response following group A beta-hemolytic streptococcal (GABHS) infections. Sydenham's chorea is the most common acquired pediatric chorea, although its frequency has declined substantially in developed countries [10]. Chorea may develop over hours or days, can be unilateral [11], and may occur several months after GABHS infection. Accompanying symptoms include anxiety, obsessions, compulsions, decrease of attention, and paranoia [12]. Patients may have paucity of speech, poor articulation, masked faces, tics, and dystonia. Motor impersistence results in findings such as a 'milkmaid's grip' and 'darting tongue' [13].

Brain MRI is usually normal, although it may show mild basal ganglia enlargement and FLAIR/T2 hyperintensity [14]. Patients should be examined for other signs of rheumatic fever, including murmurs, arthritis, and EKG or echocardiogram abnormalities. Antistreptolysin O (ASO) and DNase B antibodies are elevated, but there is no correlation between antibody titers and disease severity or course [15].

Antibodies against basal ganglia are identified in most children with Sydenham's chorea [16], but they can also be found in patients with Huntington's disease, Parkinson's disease, and normal individuals [17,18]. Other antibodies target neuronal tubulin and cross-react with surface proteins of GABHS [19]. Moreover, the GABHS surface antigens M-protein and *N*-acetyl- β -D-glucosamine can trigger antibodies that react with human brain [20–22].

Prophylaxis with penicillin prevents exacerbations of chorea due to subsequent GABHS infections and decreases the risk of rheumatic heart disease [23]. Symptoms often resolve in 3–4 months, but can persist for years [24]. Nearly half of the patients have a relapse, which may occur during pregnancy (chorea gravidarum) [25]. Patients with severe or prolonged symptoms may benefit from immunotherapy, including corticosteroids, intravenous immunoglobulin (IVIg), or plasmapheresis [26]. Symptomatic therapies such as benzodiazepines, valproic acid, or neuroleptics are often useful [27,28].

Chorea associated with antiphospholipid syndrome and systemic lupus erythematosus

APS is defined by arterial or venous thrombosis associated with persistently positive antiphospholipid antibodies (lupus anticoagulant, cardiolipin antibodies, and β_2 glycoprotein antibodies) [29]. APS and SLE can cause a wide spectrum of neurological symptoms, including chorea. Overall, chorea occurs in 2% of patients with SLE and may be the presenting symptom [30]. Chorea is more common in women and may be precipitated by pregnancy [31]. The pathophysiology of APS or SLE-induced chorea is unknown. An ischemic etiology is unlikely due to the absence of MRI changes in the basal ganglia and the waxing and waning nature of the chorea [32]. Antiphospholipid antibodies bind to phospholipid-rich areas of the basal ganglia and may lead to neuronal injury; these antibodies can depolarize neurons directly [33]. Many brain-specific antibodies are found in patients with neuropsychiatric SLE, including antibodies to gangliosides, neurofilaments, the NR2 subunit of the *N*-methyl-D-aspartate receptor (NMDAR), microtubule-associated protein 2, triosephosphate isomerase, ribosomal P protein, and glial fibrillary acidic protein [34]. It is unclear whether these antibodies are pathogenic.

Although SLE and APS associate with thrombosis, there are no data supporting the use of anticoagulation in patients with chorea. The same immunotherapy and symptomatic treatment used in Sydenham's chorea can be beneficial in these patients.

Dyskinesias and movement disorders in anti-*N*-methyl-D-aspartate receptor encephalitis

Initially characterized in young women with ovarian teratomas, this disorder occurs in all demographic groups and is considered one of the most common immune-mediated encephalitides [35*]. Patients typically present with changes of mood, behavior, and personality resembling acute psychosis. They then often develop seizures, decreased level of consciousness, dyskinesias, fever, autonomic instability, and hypoventilation. Some patients may present with, or develop, nonconvulsive status epilepticus [36*]. Intensive care support and mechanical ventilation is often required [37].

Dyskinesias involving the face, trunk, abdomen, and extremities occur in 80% of patients; orobuccolingual dyskinesias are particularly prominent [38–40]. Patients may also have chorea, ballismus, or opisthotonic postures [37,41,42]. Excessive movements may alternate with periods of catatonia, catalepsy, dystonia, and rigidity. The co-occurrence of semi-rhythmic and dyskinetic movements with motor seizures can lead to underrecognition of the seizures or an unnecessary escalation of antiepileptics for nonepileptic movements [43].

Patients' antibodies target the NR1 subunit of the NMDAR, causing receptor internalization and a decrease of synaptic NMDAR-mediated currents [38,44**]. Almost half of the patients are children. Over 50% of adult women have an ovarian teratoma. In teenage girls, approximately one third have a teratoma. Girls under age 14 and adult men and boys infrequently have a tumor [38,45,46*].

In 50% of the patients, the brain MRI is normal. The most frequent MRI findings include mild or transient T2/FLAIR signal hyperintensity in the hippocampi, cerebellum, cerebral cortex, subcortical regions, basal ganglia, or brainstem [47]. Electroencephalograms show slow and disorganized activity. During the catatonic stage, continuous rhythmic delta-theta activity predominates, sometimes with electrographic seizures [46*,48]. The differential diagnoses include viral encephalitis, neuroleptic malignant syndrome, encephalitis lethargica, late onset autism, and childhood disintegrative disorder [49,50].

Seventy five per cent of patients have full or substantial neurological recoveries. Treatment consists of tumor removal and immunotherapy, usually corticosteroids, IVIg, or plasmapheresis. Patients refractory to these treatments may respond to cyclophosphamide or rituximab [35*,51,52]. Relapses occur in a quarter of patients, especially those without a tumor or who receive suboptimal immunotherapy. Symptoms may relapse months or years after the initial recovery [38,40,46*].

Anti-Ma2 encephalitis and hypokinesia

This disorder targets the limbic region, diencephalon, and upper brainstem [53]. Patients may present with short-term memory deficits, seizures, hypersomnia, narcolepsy–cataplexy, hyperthermia, hyperphagia, hypothalamic–pituitary axis dysfunction, Parkinsonism, or vertical gaze paresis. Parkinsonian features include bradykinesia, masked faces, hypophonia, and rigidity; tremor is less frequent. Forceful jaw opening and closure and oculogyric crisis may occur [54]. Brainstem involvement progresses rostro-caudally, leading to cranial neuropathies, horizontal ophthalmoparesis, and ataxia [55,56]. At presentation, Whipple's disease or progressive supranuclear palsy is often suspected [57]. The MRI frequently shows FLAIR/T2 hyperintensities in the medial temporal lobes, hypothalamus, thalamus, and upper brainstem, sometimes with contrast enhancement [55].

Male patients less than 50 years almost always have germ-cell tumors of the testis [58]. In women and in men more than 50 years, the associated tumors include non-SCLC, breast cancer, colon cancer, and lymphoma. About 35% of patients improve after treatment of the tumor and immunotherapy [55,59]. The Parkinsonian features may respond to carbidopa/levodopa, and the facial dystonia usually improves with muscle relaxants and botulinum toxin injections [60].

Stiff-person syndrome

Stiff-person syndrome (SPS) disorder can occur with or without an underlying tumor and the associated antibodies vary accordingly. Symptoms include muscle stiffness, rigidity, and painful spasms triggered by sensory or emotional stimuli. Electrophysiological studies demonstrate continuous motor unit activity simultaneously involving agonist and antagonist muscles that improves with benzodiazepines [61].

In 85% of the patients, the cause of SPS is idiopathic, and these patients usually have antibodies against glutamic acid decarboxylase 65 (GAD65). GAD65 antibodies can occur also in patients with cerebellar ataxia and refractory epilepsy, which may overlap with SPS. In rare instances, thymoma or other tumors have been found in patients with SPS and GAD65 antibodies [62]. Although these antibodies associate with type I diabetes, their detection in the CSF is specific for neurologic disease [63,64**].

The paraneoplastic form of SPS occurs in association with amphiphysin antibodies, and the tumors more frequently involved are SCLC and breast cancer [65–67]. Compared with the nonparaneoplastic cases, these patients are more likely to be older and to have asymmetric

and distal distribution of symptoms, cervical involvement, spinal myoclonus, and pruritus [68,69].

Patients' GAD65 antibodies can functionally impair GABAergic interneurons of the spinal gray matter [70], whereas the amphiphysin antibodies mediate reduced GABAergic inhibition [71^{**}]. Other antibodies are directed against GABA_A-receptor-associated protein (GABARAP); 70% of patients with SPS and GAD65 antibodies also have GABARAP antibodies, raising the question of which antibodies are pathogenic [72].

Some patients with progressive encephalomyelitis, rigidity, and myoclonus (PERM), a disorder in the SPS spectrum, or sometimes hyperekplexia, have antibodies against the $\alpha 1$ subunit of the glycine receptor [73^{**},74].

The management of paraneoplastic SPS involves treatment of the cancer and corticosteroids. For the nonparaneoplastic disorder, a benefit of IVIg has been demonstrated [75], but this remains unproven for the paraneoplastic syndrome. Drugs that enhance GABA-ergic transmission (diazepam, baclofen, sodium valproate, tiagabine, vigabatrin) usually improve symptoms [76].

Paraneoplastic cerebellar degeneration and tremor

This disorder typically presents with dizziness and vertigo followed by rapid development of ataxia, dysarthria, downbeat nystagmus, and tremor [77]. In pediatric patients, paraneoplastic cerebellar degeneration may mimic postinfectious cerebellitis [78]. Almost all known paraneoplastic antibodies can associate with cerebellar ataxia. However, three antibodies are preferentially associated with cerebellar symptoms: anti-Yo (Purkinje cell antibody-1) in patients with breast or ovarian cancer [79]; anti-Tr in patients with Hodgkin's lymphoma [80], and antibodies to voltage-gated calcium channels (VGCCs) in patients with SCLC [81]. Idiopathic VGCC antibodies may be also found in some cases of sporadic cerebellar ataxia previously regarded as degenerative [82,83].

Antibodies against the metabotropic glutamate receptor type 1 (mGluR1) have been identified in a few patients with idiopathic or paraneoplastic cerebellar ataxia associated with Hodgkin's lymphoma [84,85].

Except for some patients with Tr and mGluR1 antibodies who may improve with immunotherapy, most patients with paraneoplastic cerebellar degeneration do not respond to therapies [79,86,87].

Opsoclonus–myoclonus–ataxia syndrome

Opsoclonus consists of involuntary, arrhythmic, chaotic, multidirectional saccades without intersaccadic intervals. Opsoclonus–myoclonus–ataxia syndrome (OMAS) can be postinfectious or paraneoplastic [88,89]. Half of the children with OMAS have neuroblastoma. In adults, the associated tumors include SCLC and breast or ovarian cancer. The majority of patients do not have paraneoplastic antibodies, although a small subset of patients with breast or ovarian cancer develop anti-Ri antibodies [90]. Some pediatric patients have antibodies against the surface of cerebellar granular neurons and neuroblastoma cell lines [91,92]. CSF flow cytometry shows B-cell expansion that varies with disease treatment and course [93,94^{**}].

Treatment of pediatric OMAS involves resection of the neuroblastoma, if present, and immunotherapy, including corticosteroids, adrenocorticotrophic hormone, IVIg, plasmapheresis, rituximab, or cyclophosphamide [95^{*},96^{*}]. The eye movement disorder

often improves or resolves, but patients are frequently left with motor, speech, behavioral, and sleep disorders. Relapses are frequent, usually during intercurrent illnesses or attempts to reduce immunotherapy [97]. In adults, corticosteroids or IVIg can accelerate improvement in cases of idiopathic disease, but those with paraneoplastic OMAS only benefit from immunotherapy when the tumor is controlled [98,99].

Acquired neuromyotonia, peripheral nerve hyperexcitability, or Isaacs' syndrome

Patients with this disorder develop muscle cramps and stiffness, twitching (fasciculations or myokymia), delayed muscle relaxation (pseudomyotonia), and carpal or pedal spasms. The electromyogram (EMG) shows fibrillations, fasciculations, and doublet or multiplet single unit discharges that have a high intraburst frequency [100]. Some patients develop paresthesias, hyperhidrosis, confusion, mood changes, sleep disruption, and hallucinations (Morvan's syndrome) [101]. A small subset of patients are found to have a thymoma, SCLC, or rarely other tumors [102]. Patients with paraneoplastic peripheral nerve hyperexcitability (PNH) are usually older and have more weakness and myokymia, but less cramping, dysautonomia, and central nervous system involvement [103].

Antibodies to contactin-associated protein-2 (CASPR2) have been identified as an autoantigen of several disorders previously attributed to the voltage-gated potassium channel (VGKC), including PNH, Morvan's syndrome, and encephalitis [104^{**},105^{*},106^{*}]. However, many patients are antibody-negative [103]. The treatment of PNH includes oncologic therapy when appropriate, plasmapheresis, and symptomatic therapy with phenytoin or carbamazepine [107].

Sensory neuronopathy and pseudoathetoid movements

This disorder is caused by degeneration of the neurons of the dorsal root ganglia, likely by a T-cell-mediated immune response [108]. All modalities of sensation may be affected along with neuropathic pain and areflexia. The sensory deficit results in ataxia and dystonic or pseudoathetoid postures of the extremities. SCLC is the most frequently associated tumor; these patients usually have anti-Hu antibodies. The disorder is poorly responsive to treatment and at best, patients stabilize or have mild improvement after oncologic and immunologic therapies [109].

General management

If a paraneoplastic syndrome is suspected, the first concern should be the diagnosis and treatment of the tumor [77]. FDG-PET and computed tomography of the chest, abdomen, and pelvis are needed for most patients. Depending on the patient's age, sex, type of syndrome, and antineuronal antibody, other oncologic screening may be appropriate. Patients with classic onconeural antibodies without a detectable tumor should have repeat cancer screening within 3–6 months, and then every 6 months for 4 years [110^{**}].

Immunotherapy should be considered in most patients with PND and progressive neurological disease as well as in patients with idiopathic or postinfectious syndromes. When the antigens are intracellular (Hu, CRMP5, Yo, Ri), the associated disorder is often refractory to antibody or B-cell depleting immunotherapies, such as corticosteroids, plasmapheresis, and IVIg, although rituximab can be effective [111,112]. Immunotherapies directed at the cytotoxic T-cell response, such as cyclophosphamide, should be considered [113]. In contrast, disorders associated with antibodies against cell surface antigens (e.g. NMDAR, CASPR2) respond better to treatment [114]. Treatments directed at removing

antibodies from serum (e.g. plasmapheresis, IVIg) may initially be beneficial but often fail at later stages of the disease or when there is high intrathecal synthesis of antibodies. These disorders should be approached with aggressive immunotherapies such as rituximab or cyclophosphamide if the first-line treatment is not effective [115].

Conclusion

Many movement disorders are immune-mediated by mechanisms related to paraneoplasia, molecular mimicry or by other, as yet unknown, immunological triggers. In all these disorders, symptoms often progress more quickly than in noninflammatory neurodegenerative syndromes. This rapid clinical onset along with inflammatory changes in the CSF, and the presence of serum or CSF antineuronal antibodies are suggestive of an immune-mediated mechanism and, depending on the type of antibody, indicate the likelihood and type of associated neoplasm. There is a new and expanding group of syndromes that are associated with antibodies against cell surface or synaptic proteins. These disorders occur with or without tumor association and frequently affect children and young adults. Recognition of all these disorders is important because it may lead to the diagnosis of an occult cancer. In addition, a substantial number of patients, mainly those with antibodies against cell surface or synaptic proteins, respond to immunotherapy, although they may have relapses.

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References and recommended reading

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- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000-000).

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Key points

- Immune-mediated movement disorders may be paraneoplastic, postinfectious, or idiopathic.
- Antibodies against cell surface or synaptic proteins are increasingly recognized as a cause of severe neurologic disorders that may occur with or without tumor association, and are responsive to treatment.
- If an immune-mediated movement disorder is suspected, testing for appropriate antineuronal antibodies should be performed to confirm the diagnosis and to determine the likelihood and type of associated neoplasm.
- It is important to accurately diagnose immune-mediated movement disorders as they may respond to immunotherapy and can lead to the diagnosis of an occult cancer.

Table 1

Immune-mediated movement disorders

Syndrome	Abnormal movement	Antineuronal antibody	Predominant tumor
Encephalomyelitis	Chorea	CRMP5	SCLC, thymoma
Sydenham's chorea	Chorea, dystonia, tics	Unknown	None, associated with GABHS infection
Chorea associated with APS, SLE	Chorea	Unknown	None
Anti-NMDAR encephalitis	Orofacial dyskinesias, chorea, dystonia, stereotyped movements	NR1 subunit of the NMDAR	Teratoma of the ovary
Brainstem encephalitis	Hypokinesia, rigidity	Ma2	Germ-cell tumor of the testis, non-SCLC
Stiff-person syndrome, muscle rigidity	Axial rigidity and muscle spasms	Amphiphysin, GAD65, GABARAP, GlyR	If amphiphysin antibodies: breast cancer, SCLC
Cerebellar degeneration	Tremor, ataxia	Yo, Tr, VKCC, mGluR1, Ri, Hu	Breast, ovary and other gynecological tumors, SCLC, lymphoma
Opsoclonus–myoclonus–ataxia	Myoclonus, ataxia	Most cases without antibody; anti-Ri	Neuroblastoma, breast, SCLC
Neuromyotonia	Myokymias, difficulty in muscle relaxation	Caspr2	SCLC, thymoma
Sensory neuronopathy	Ataxia, pseudoathetoid movements	Hu	SCLC

APS, antiphospholipid syndrome; CASPR2, contactin-associated protein-2; CRMP5, collapsin response-mediated protein 5; GABARAP, GABA_A-receptor-associated protein; GABHS, group A beta-hemolytic streptococcus; GAD65, glutamic acid decarboxylase 65; mGluR1, metabotropic glutamate receptor type 1; NMDAR, *N*-methyl-D-aspartate receptor; SCLC, small cell lung cancer; SLE, systemic lupus erythematosus; VGCC, voltage-gated calcium channels.