Chapter 22
Anti-NMDA Receptor Encephalitis and Other Autoimmune and Paraneoplastic Movement Disorders

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This chapter contains video segments that can be found on the accompanying DVD.

Abstract A substantial number of movement disorders are mediated by immunological mechanisms. In some instances the immune response is triggered by the presence of a tumor that ectopically expresses a neuronal protein, leading to a brain autoimmune response or paraneoplastic syndrome. Other immune-mediated movement disorders may be post-infectious, likely triggered by molecular mimicry or other, as yet unknown, mechanisms. There is a new and expanding group of syndromes that are associated with antibodies against cell surface or synaptic proteins and may cause early and prominent movement disorders. Anti-NMDA receptor encephalitis is the most frequent of these disorders that may occur with or without tumor association, affect children and adults, and can be severe but responsive to treatment. Recognition of this and other immune responses to synaptic proteins is important because, different from classical paraneoplastic syndromes, they often respond to immunotherapy. Because the presentation and clinical course of immune-mediated syndromes often develop very quickly, and because failure to recognize and treat these disorders may lead to morbidity or even mortality, we believe that this qualifies these syndromes as movement disorder emergencies. This chapter focuses on anti-NMDAR encephalitis and other autoimmune or paraneoplastic movement disorders, with emphasis on their clinical presentations, differential diagnoses, immunological associations and antigens, and treatment strategies.

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Patient Vignette

A 22-year-old woman, previously in excellent health, developed a subacute deterioration over several weeks characterized by progressive obtundation, decreased responsiveness, autonomic instability and eventual respiratory insufficiency leading to ventilator support. Diffuse myoclonus and orobuccal-lingual dyskinesias were noted. Due to the recent recognition of the NMDA-receptor antibody association with ovarian teratoma, a search for a teratoma was initiated and confirmed, with high titers of paraneoplastic antibodies. Her hospital course was marked by months of intensive care treatment, with a persistent state of wakeful inattention, multiple medical complications, and slow improvement despite treatment with IVIG, plasmapheresis and steroids. She was eventually treated with cyclophosphamide, with good long-term recovery.

Introduction

Paraneoplastic and autoimmune mechanisms may result in movement disorders [1]. Paraneoplastic disorders (PND) occur in patients with cancer and can affect any part of the nervous system, including the basal ganglia and brainstem, causing abnormal movements. Many PND are immune-mediated; the patient's immune response against the cancer is misdirected against neurons, causing the syndrome. Other immune-mediated movement disorders may be post-infectious, likely triggered by molecular mimicry or other, as yet unknown, mechanisms. The etiology of many immune-mediated movement disorders however remains idiopathic, with no clear oncologic or infectious trigger [2]. There is a new and expanding group of syndromes that are associated with antibodies against cell surface or synaptic proteins and may cause early and prominent movement disorders [3]. Anti-NMDA receptor encephalitis is the most frequent of these disorders that may occur with or without tumor association, and although severe may respond to treatment. Because the presentation and clinical course of immune-mediated syndromes often develops quickly, and failure to diagnose can be lethal, we classify these disorders as movement disorder emergencies. This chapter focuses on anti-NMDAR encephalitis and other autoimmune or paraneoplastic movement disorders, with emphasis on their clinical presentations, differential diagnoses, immunological associations and antigens, and treatment strategies.

General Concepts

With a few exceptions, such as opsoclonus–myoclonus–ataxia syndrome in children with neuroblastoma, the majority of classic paraneoplastic syndromes resulting in movement disorders were until recently considered to affect adults or elder individuals.

This concept has changed in the last 4 years with the discovery of several syndromes associated with antibodies against cell surface or synaptic proteins, such as NMDAR, which often affects children and young individuals. Moreover, while symptoms related to classical paraneoplastic antibodies to intracellular antigens (e.g., anti-Hu or CRMP5) rarely improve if the tumor is not treated, and even so the improvement is usually mild or limited, those related to antibodies to cell surface or synaptic proteins may show dramatic responses to immunotherapy even before the tumor is identified or treated [3]. This, however, should not discourage physicians from searching for an underlying neoplasm, because if identified, removal of the tumor along with instituting immunotherapy usually expedites recovery and reduces relapses.

For most of these autoimmune encephalitic disorders (paraneoplastic or not), there is usually early evidence of cerebrospinal fluid (CSF) inflammatory changes, including lymphocytic pleocytosis and a variable increase in CSF protein concentration, IgG index, and oligoclonal bands [4]. This CSF inflammation fades over time and these parameters normalize. Therefore, CSF abnormalities and identification of antineuronal antibodies in serum or CSF are important clues for diagnosis and treatment. Some antibodies, usually targeting intracellular antigens (Hu, CRMP5, Ma2, amphiphysin) almost always associates with cancer, and the associated disorders are likely mediated by cytotoxic T-cell responses [5]. Other antibodies directed against cell surface antigens (NMDAR, LGI1) are excellent diagnostic markers of characteristic syndromes that can occur with or without tumor association, and probably result from a direct pathogenic effect of the antibodies. Of these, the most common and best studied is anti-NMDAR encephalitis [6].

Anti-NMDAR Encephalitis and other Disorders Resulting in an Excess of Movements

Anti-NMDAR Encephalitis

This disorder usually affects young women and children of both sexes [7]. This is a multistage illness that progresses from psychosis, memory deficits, seizures, and language disintegration to a state of unresponsiveness with catatonic features and autonomic and breathing instability [8]. Abnormal movements are prominent at this stage [9]. Dyskinesias are the most frequent and are observed in 80 % of patients. While they may involve any part of the body, orobuccolingual dyskinesias are particularly prominent. They manifest as pouting, grimacing, tongue protrusion and rolling, palatal elevation, nares flaring, smiling-like motions, frowning, bruxism, oculogyric crisis, and forceful jaw opening and closing severe enough to cause tongue, teeth and lip injuries [7, 8, 10]. Less commonly, chorea, ballismus, or opisthotonic postures may occur [11–13]. These hyperkinetic movements may alternate with catatonia, catalepsy, dystonia, and rigidity [14]. Due to the initial neuropsychiatric disturbances patients may be given antipsychotic medications, and the orobuccolingual dyskinesias may be misinterpreted as tardive dyskinesias, while hyperthermia,

rigidity, and elevated creatinine kinase or rhabdomyolysis that can occur even in the absence of antipsychotic medication may falsely be ascribed to neuroleptic malignant syndrome [15]. Motor or complex seizures can occur at any time during the disease. The overlap of abnormal movements and epileptic seizures may confound recognition of the seizures, or lead to unnecessary escalation of antiepileptics for movements that are misinterpreted as seizures [7, 16].

The association of anti-NMDAR encephalitis with an underlying tumor is related to the gender and age of the patient. In adult women, over 50 % have an ovarian teratoma, while only one-third of teenage girls have a proven teratoma. Girls and boys under age 14 and adult men only rarely have a tumor [6, 17].

The diagnosis can be made by recognition of the characteristic and progressive clinical syndrome. Half of the patients will have MRI findings that may include mild or transient T2/FLAIR signal hyperintensity in the hippocampi, cerebellum, cerebral cortex, subcortical regions, basal ganglia, or brainstem [8, 10]. The finding of CSF pleocytosis and mild fever at presentation can lead to an initial diagnosis of viral encephalitis, however viral studies will be negative and the progression of the clinical syndrome usually points to synaptic autoimmunity as the cause [18]. Other diagnoses that may be considered include encephalitis lethargica, late-onset autism, and childhood disintegrative disorders [19]. Primary inherited dystonias, such as DYT1 dystonia or dopa-responsive dystonia, can be excluded by the typically acute onset of symptoms in anti-NMDA receptor encephalitis, the presence of MRI changes, CSF inflammatory changes, and other associated symptoms such as encephalopathy and seizures [20]. In children with possible anti-NMDA receptor encephalitis and chorea, Sydenham's chorea (SC) may be considered. However, while patients with SC may have neuropsychiatric symptoms such as obsessive–compulsive disorder (OCD), anxiety, and paranoia [21], frank psychosis or encephalopathy is rare. Further, the MRI in SC is most often normal or shows only subtle basal ganglia changes [22]. As anti-NMDAR encephalitis progresses, the onset of autonomic instability and seizures also helps distinguish it.

Treatment is successful in 75 % of cases and is centered on removal of any associated tumor and immunotherapy, usually corticosteroids, IVIG, or plasmapheresis. Refractory patients may respond to cyclophosphamide or rituximab [6, 23, 24]. A quarter of patients may experience relapses, particularly those without a tumor or those who receive suboptimal immunotherapy. Relapse may occur months or years after the initial recovery [8, 10, 17]. A clinical presentation with isolated symptoms or with partial aspects of the full-blown syndrome is common. Treatment with immunotherapy of the first episode reduces the risk of relapses [25].

Paraneoplastic Chorea and CRMP5 Antibodies

Choreic movements can occur in association with antibodies to collapsin response mediator protein5 (CRMP5, also termed CV2). When these antibodies are found, the disorder is almost always paraneoplastic and the chorea is part of a diffuse

encephalomyelitis that may include limbic encephalitis, cerebellar ataxia, peripheral neuropathy, uveitis, optic neuritis, or retinitis [26–28]. The most commonly associated tumors are small cell lung cancer and thymoma [29]. In these patients brain MRI often shows abnormal FLAIR hyperintensities involving limbic regions, striatum, basal ganglia, brainstem, or white matter, which may resemble a leukoencephalopathy [30].

The associated neurological symptoms and MRI findings help to exclude many of the genetic causes of chorea such as Huntington's disease, neuroacanthocytosis, and Wilson's disease. Inflammatory causes of chorea such as systemic lupus erythematosus (SLE) or antiphospholipid antibody syndrome (APS) should be considered and might prove more difficult to exclude, since these disorders may present with chorea and other neuropsychiatric symptoms prior to any other systemic manifestations [2]. Discovery of the underlying tumor or appropriate serologic testing to screen for SLE/APS should clarify the diagnosis.

CRMP5 is an intracellular antigen that regulates neurite outgrowth, neuronal polarity, and dendritic branching in the developing brain [31, 32]; its role in the adult brain is not yet defined. CRMP5 expression is seen within almost all high-grade neuroendocrine lung tumors, including SCLC, but not in other lung tumors [33]. Exposure to this tumor antigen likely results in an immune response against CRMP5 expressed in brain.

The management of paraneoplastic chorea focuses on treatment of the tumor and, since the auto-antigen is intracellular, immunotherapy targeting T-cell-mediated mechanisms. Antibodies against CRMP5 may modify progression of the underlying oncologic disease; median survival is longer in patients with SCLC and anti-CRMP5 related encephalitis as compared to those patients with SCLC and anti-Hu related encephalitis, independent of the severity of the neurologic disease [34].

Pseudoathetoid Movements in Paraneoplastic Sensory Neuronopathy

Paraneoplastic sensory neuronopathy (PSN) may develop in isolation but is most often a fragment of paraneoplastic encephalomyelitis. Patients typically develop asymmetric pain and paresthesias that progresses to involve other extremities, and sometimes the trunk or cranial nerves. Eventually the severe involvement of all modalities of sensation results in dystonic or pseudoathetotic postures as well as a debilitating sensory ataxia [35].

Patients who develop PSN alone or as a component of paraneoplastic encephalomyelitis often have anti-Hu antibodies, and the associated cancer is almost always a SCLC, although other cancers (e.g., non-SCLC or breast carcinomas) may be found especially in those patients with PSN without anti-Hu antibodies [36]. The pathological substrate is an immune-mediated degeneration of the neurons of the dorsal root ganglia, likely caused by cytotoxic T-cells. The sensory neuronopathy may mimic disorders such as Guillain–Barré syndrome, particularly if there is also involvement of lower motor neurons and peripheral nerves [37].

PSN is poorly responsive to treatment and at best, patients will stabilize or have mild improvement after oncologic and immunologic therapies [38]. In some patients rituximab has been effective [39].

Opsoclonus–Myoclonus–Ataxia Syndrome

Opsoclonus is characterized by involuntary, arrhythmic, chaotic, multidirectional saccades without intersaccadic intervals. When paraneoplastic, opsoclonus is variably associated with encephalitis, myoclonus, and ataxia of the trunk and limbs (opsoclonus–myoclonus–ataxia syndrome, OMAS) and most commonly occurs in children between 6 months and 6 years of age [40, 41]. Half of these children will be found to have an associated neuroblastoma. In adults, the tumors more frequently associated include SCLC and breast or ovarian cancer. Other than a small subset of patients with breast or ovarian cancer who develop Ri antibodies [42], OMAS has not been consistently associated with any specific antineuronal antibody.

The differential diagnosis includes post-infectious cerebellitis, toxic ingestions, and posterior fossa tumors [43]. OMAS can be distinguished from cerebellitis by the presence of opsoclonus and the lack of symptomatic improvement within the expected timeframe. Early recognition of OMAS in children is important, because delay in the initiation of immunomodulatory treatment has been shown to increase long-term neurological deficits [44]. In adults, other degenerative or inflammatory causes of ataxia should be considered, but the presence of opsoclonus is relatively specific for this disease.

Treatment of OMAS in children involves resection of the neuroblastoma, if present, and immunotherapy, including corticosteroids, ACTH, IVIG, plasmapheresis, rituximab, or cyclophosphamide [44, 45]. Several case series suggest that high dose pulsed dexamethasone therapy may be beneficial [46, 47]. Although the opsoclonus and ataxia often improve or resolve, children are frequently left with motor, speech, behavioral, and sleep disorders. Relapses are frequent, usually during intercurrent illnesses or attempts to reduce immunotherapy; few children have a monophasic disease course [48]. In adults with idiopathic OMAS, corticosteroids or IVIG can accelerate improvement, but those with paraneoplastic disease only benefit from immunotherapy if the tumor is controlled [41, 49].

Myoclonic-Like Movements in Patients with LGI1 Antibodies

There is recent evidence that the target autoantigen related to limbic encephalitis and antibodies attributed to VGKC is in fact LGI1. Patients with these antibodies develop limbic encephalitis that at least in 40 % of cases is preceded or accompanied by myoclonic-like movements [50]. These movements are brief, short-lasting, repetitive and can involve face, arm, or leg [51]. In some patients they appear to

predominate in face and arm [52]. They can occur many times per day (in some patients 80–100 times) and have been described as "twitches," "myoclonus," or "stereotyped brief monomorphic movements" [53, 54]. Studies using continuous video EEG recordings have demonstrated that these movements are preceded by approximately 500 ms of electrodecremental events, typical of epileptic tonic seizures [51]. Using functional brain imaging, basal ganglia dysfunction was demonstrated in five of eight patients [52]. Recognition of the epileptic origin of these "myoclonic-like" movements is important because they usually precede the development of a full blown limbic encephalitis associated with LGI1 antibodies, and respond to immunotherapy [51, 52].

Tremor and Ataxia in Paraneoplastic Cerebellar Degeneration

Paraneoplastic cerebellar degeneration (PCD) is characterized by the acute to subacute development of severe pancerebellar dysfunction. In adults the rapidity of onset distinguishes PCD from inherited or neurodegenerative causes of cerebellar ataxia [55]. The disorder usually develops over days or weeks, but in some instances it has developed overnight, clinically suggesting a stroke. PCD has mostly been reported in association with gynecologic tumors, breast cancer, lung cancer (particularly SCLC), and Hodgkin's lymphoma. While almost all known paraneoplastic antibodies have been found in association with PCD, the most commonly associated are anti-Yo (also called PCA-1) in patients with breast or ovarian cancer [56]; anti-Tr in patients with Hodgkin's lymphoma [57], and antibodies to voltage-gated calcium channels (VGCC) in patients with SCLC [58]. Patients with Hodgkin's lymphoma can also develop cerebellar degeneration in association with antibodies against mGluR1 [59].

As with all paraneoplastic neurologic disorders, the best approach to treatment of PCD is identification and treatment of the underlying cancer and possibly immunotherapy. Except for some patients with Hodgkin's lymphoma and Tr or mGluR1 antibodies who may respond to treatment, most patients with PCD are refractory to treatment, suggesting that there is early and irreversible neuronal cell death [59, 60]. This is supported by autopsy studies demonstrating extensive loss of Purkinje neurons with relative preservation of other cerebellar neurons.

Disorders Resulting in a Paucity of Movement or Stiffness

Anti-Ma2 Encephalitis and Hypokinesis

Anti-Ma2 encephalitis is paraneoplastic and commonly occurs in young men with testicular tumors [61]. A few cases have been described in older men and women with lung or breast cancer [62]. In addition to short-term memory loss from limbic

encephalitis these patients also have involvement of the hypothalamus and brainstem leading to disorders of sleep and wakefulness such as hypersomnia or narcolepsy-cataplexy, hyperthermia, hyperphagia, and hypothalamic–pituitary dysfunction [63].

Parkinsonian features are prominent, including bradykinesia, masked facies, hypophonia, and rigidity; less frequently tremor is present. Dyskinesias may also occur, including forceful jaw opening and closure, and oculogyric crisis [64]. Rostrocaudal brainstem involvement often leads to progressive ophthalmoparesis, cranial neuropathies, and ataxia. Early eye movement deficits include vertical gaze paresis predominantly involving saccades, with relative preservation of pursuit and oculocephalic movements [65]. The facial and eye movement abnormalities can be confused for progressive supranuclear palsy or Whipple's disease [66]. Neuroimaging can be helpful, as half of patients with anti-Ma2 encephalitis will have FLAIR/T2 hyperintensities in the medial temporal lobes, hypothalamus, thalamus, or upper brainstem, at times with contrast enhancement [63, 64].

The parkinsonian features may respond to carbidopa/levodopa, and the facial dystonia usually improves with muscle relaxants or botulinum toxin injections [67]. However, all efforts should be made to identify and treat the underlying tumor, as this is critical to improving outcome. Case series have shown that 35 % of patients will improve after tumor treatment and immunotherapy, while immunotherapy in the absence of tumor treatment is ineffective [63, 68].

Stiff-Person Syndrome

Progressive muscle stiffness, aching, muscle spasms, and rigidity characterize this syndrome. Symptoms develop over months and are most prominent in the paraspinal muscles and lower limbs. The majority of cases (about 85 %) are idiopathic and not cancer associated [69]. 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 and rarely, are found in patients with paraneoplastic SPS, most often in association with thymoma [70]. Additionally, patients with SPS and anti-GAD65 antibodies may also have antibodies against $GABA_A$-receptor-associated protein (GABARAP), suggesting that both antibodies may play a role in the disorder [71].

When SPS is paraneoplastic the tumors more frequently found are SCLC and breast cancer. These patients will often have antibodies to amphiphysin. Compared to the idiopathic form of SPS, patients with paraneoplastic SPS are older and more likely to have asymmetric and distal symptoms [72, 73]. There has been one case report of a patient with SPS and mediastinal cancer who was found to have antibodies against gephyrin, a cytosolic protein associated with $GABA_A$ and glycine receptors [74].

Progressive encephalomyelitis, rigidity, and myoclonus (PERM) is likely related to SPS and is characterized by diffuse rigidity, painful spasms, and myoclonus. Antibodies against the $\alpha 1$ subunit of the glycine receptor have been reported in

some of these patients, as well as in patients with hyperekplexia, and atypical stiff-person or stiff-limb syndrome without GAD65 antibodies [75, 76].

For the non-paraneoplastic disorder, IVIG has been shown to be beneficial [77], but this remains unproven for the paraneoplastic syndrome. Paraneoplastic SPS should be managed by treatment of the underlying cancer and corticosteroids. Additional immunotherapy, such as IVIG or cyclophosphamide, can be considered in refractory cases, given that similar immunotherapies are used for other autoimmune encephalomyelitis [78]. Symptomatic improvement is provided by drugs that enhance GABAergic transmission such as diazepam, baclofen, sodium valproate, tiagabine, and vigabatrin [79].

Peripheral Nerve Hyperexcitability

Peripheral nerve hyperexcitability (PNH, also called acquired neuromyotonia or Isaacs' syndrome) results from spontaneous and continuous muscle fiber activity due to peripheral nerve dysfunction [80]. Patients develop muscle cramps, stiffness, muscle twitching, and pseudomyotonia. Other related symptoms include hyperhidrosis, fatigue, and exercise intolerance. Symptoms are most prominent in the calves, legs and trunk, but can also affect other body parts including the face and neck. At least a third of those affected also experience paresthesias. Approximately 25 % of patients with PNH have CNS symptoms (Morvan's syndrome) including confusion, mood changes, sleep disruption, and hallucinations [81].

In most cases, PNH has a non-paraneoplastic etiology. In addition to idiopathic cases, there are inherited causes of neuromyotonia such as that associated with voltage-gated potassium-channel (KCNA1) gene mutations. Multiple toxins, including gold, oxaliplatin, penicillamine, herbicides, insecticides, and toluene, may also cause neuromyotonia [82]. Patients with non-paraneoplastic PNH may have other autoimmune disorders, including myasthenia gravis, diabetes mellitus, chronic inflammatory demyelinating neuropathy, rheumatoid disease, systemic lupus erythematosus, and vitiligo [82, 83].

When paraneoplastic, the most commonly associated cancers are thymoma and SCLC [84]. In one series, patients with paraneoplastic PNH tended to be older and have more weakness and myokymia but less cramping and dysautonomia than those with non-paraneoplastic PNH [85].

Past research had suggested that antibodies to voltage-gated potassium channels (VGKC) might be causal in a significant subset of patients with PNH. However, in several disorders incorrectly attributed to VGKC antibodies, including PNH and Morvan's syndrome, antibodies to contactin-associated protein-like 2 (CASPR2) have now been identified as a target autoantigen [50, 86, 87]. The remaining cases are considered antibody negative at this time although further studies may identify specific antibody associations. Patients with CASPR2 antibodies may have additional antibodies, such as AChR or MuSK, giving rise to a complex manifestation

of symptoms that may suggest a motor neuron syndrome. Recognition of this disorder is important because patients respond to immunotherapy [88].

Other than oncologic therapy when appropriate, treatment recommendations for PNH are based on small cases series that have reported responses to plasmapheresis, IVIG, and prednisolone with or without azathioprine or methotrexate [89, 90]. Some patients have had symptomatic improvement with carbamazepine or phenytoin [91].

General Management Considerations

When a paraneoplastic movement disorder is suspected, the first concern should be the diagnosis and treatment of the underlying tumor as this offers the best chance for stabilization or improvement of the neurologic disorder [92]. For some disorders associated with antibodies to intracellular antigens (Hu, CRMP5, Ma2, amphiphysin) the search for a tumor should be aggressive (Table 22.1), and tumor screenings should be repeated regularly, every 6 months for at least 2 years. Moreover, the immunotherapy strategy for these disorders should consider that they are mediated by T-cells (amphiphysin may be an exception). Therefore, IVIG and plasma exchange usually fail in the treatment of the associated syndromes, and more aggressive immunotherapies, including rituximab (to reduce antigen presentation by B-cells) or cyclophosphamide should be promptly considered. Except for Ma2-associated encephalitis, which associates with improvement in ~30 % of the patients [63], the other disorders have limited response to treatments. Although GAD65 is an intracellular antigen, the related symptoms of the stiff-person syndrome (but less frequently cerebellar ataxia) may respond to IVIG [77]. Antibodies to amphiphysin may have a direct effect on the target antigen [93], but in many patients the response to plasma exchange or IVIG is unsatisfactory. The titers of most antibodies against intracellular antigens (except GAD65 and amphiphysin, which are located close to the cell surface) do not correlate well with the outcome of the disease.

In contrast, the disorders associated with antibodies against cell surface or synaptic extracellular epitopes (such as anti-NMDAR encephalitis or LGI1 encephalitis) are more responsive to immunotherapy. Patients who do not improve with first-line immunotherapies, such as corticosteroids, IVIG or plasma exchange, often improve with rituximab or cyclophosphamide. For anti-NMDAR encephalitis, there is evidence of a rapid and robust intrathecal synthesis of antibodies and intracerebral infiltrates of plasma cells, which probably explain the failure of plasma exchange, IVIG, and corticosteroids in some of these patients, particularly those with delayed diagnosis and treatment. Nevertheless, these patients often improve with cyclophosphamide and rituximab. Overall, 75–80 % of patients with syndromes related to cell surface antigens (NMDAR, LGI1, Caspr2) substantially improve or fully recover with immunotherapy, and treatment of the tumor when appropriate [3, 6]. As expected for antibodies with a potential pathogenic effect, the change of titers of these antibodies correlates well with the course of the disease; in some disorders, such as anti-NMDAR encephalitis, the CSF titers have better clinical correlation than serum titers.

Table 22.1 Paraneoplastic and autoimmune movement disorders

Neurologic syndrome	Movement disorder	Antineuronal antibody	Predominant tumor
Anti-NMDAR encephalitis	Orofacial dyskinesias, chorea, dystonia, stereotyped movements, ballismus, catatonia	NMDAR	Teratoma of the ovary
Encephalomyelitis	Chorea	CRMP5	SCLC, thymoma
Sensory neuronopathy	Pseudoathetoid movements due to sensory ataxia	Hu	SCLC
Opsoclonus–myoclonus–ataxia	Myoclonus, ataxia	Most cases without antibody; anti-Ri	Neuroblastoma, breast, SCLC
Anti-LGI1 limbic encephalitis	Myoclonic-like movements (tonic seizures)	LGI1 antibodies	Infrequently thymoma, SCLC
Cerebellar degeneration	Tremor, ataxia	Yo, Tr, VKCC, mGluR1, Ri, Hu	Breast, ovary and other gynecological tumors, SCLC, lymphoma
Brainstem encephalitis	Hypokinesis, rigidity, ophthalmoparesis	Ma2	Germ-cell tumor of the testis, non-SCLC
Stiff-person syndrome, muscle rigidity	Axial rigidity and muscle spasms	GAD 65, amphiphysin, GABARAP, GlyR	If amphiphysin antibodies: breast cancer, SCLC
Neuromyotonia	Myokymias, difficulty in muscle relaxation	Caspr2; many cases without antibodies	SCLC, thymoma

NMDAR N-methyl-D-aspartate receptor, *CRMP5* collapsin response mediated protein 5, *SCLC* small cell lung cancer, *LGI1* leucine-rich glioma inactivated 1, *mGluR1* metabotropic glutamate receptor type 1, *GAD65* glutamic acid decarboxylase 65, *GABARAP* GABA receptor-associated protein, *GlyR* glycine receptor, *Caspr2* contactin-associated protein-related 2

Muscle stiffness and rigidity may respond to pharmacologic treatment with GABAergic drugs, while muscle cramps and pseudomyotonia may respond to anti-convulsants that block sodium channels [79]. Although there is limited experience, some patients with anti-Ma2 or NMDA receptor encephalitis who had involuntary, forceful movements with the jaw that precluded feeding and carried the risk of tongue and mouth injuries benefited from local application of botulinum toxin [94].

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