Movement Disorders in Systemic Diseases

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KEYWORDS

• Movement disorders • Systemic disease • Basal ganglia • Autoimmune disorders
• Metabolic disorders • Endocrine disorders • Paraneoplastic disorders
• Intoxications

KEY POINTS

- Movement disorders may be the harbinger of an underlying systemic disease.
- Careful neurologic examination, considering associated systemic features in combination with neuroimaging and laboratory tests, will help narrow down the differential diagnosis and may lead to the final diagnosis.
- Management will often involve a multidisciplinary team including neurologists and the primary care physician, but also allied health professionals, such as physical, occupational, and speech and language therapists.
- Unlike neurodegenerative movement disorders, those occurring in the setting of systemic diseases are frequently amenable to causal treatment of the underlying condition, thus making early correct diagnostic classification a key priority.

Videos of Parkinsonism in cerebral toxoplasmosis and typical orofacial dyskinesias accompany this article http://www.neurologic.theclinics.com/

INTRODUCTION

The term *movement disorders* includes a variety of different neurologic diseases that classically involve dysfunction of the basal ganglia. Prototypic movement disorders, such as parkinsonism, chorea, or dystonia, commonly result from a variety of neurodegenerative or structural brain diseases, but movement disorders also can be presenting signs of cerebral involvement in a broad spectrum of systemic diseases, such as infectious, metabolic, endocrine, paraneoplastic, and autoimmune disorders (**Table 1**). A comprehensive review of all systemic conditions that may cause symptomatic movement disorders is beyond the scope of this article, and we refer the

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Table 1
Overview of common causes of movement disorders in systemic diseases

Etiology	Movement Disorders
Infectious diseases	
Whipple disease	Oculo-masticatory myorhythmia
Neurosyphilis	Parkinsonism, chorea
CNS-tuberculosis	Tremor, chorea, myoclonus, dystonia, and parkinsonism
HIV	Hemichorea, tremor, parkinsonism, dystonia
Toxoplasmosis	Hemichorea-hemiballism
Neurocysticercosis	Generally rare: parkinsonism, hemichorea
Lyme disease	Parkinsonism
Streptococcus infection	Parkinsonism, Sydenham -chorea (children)
Autoimmune disorders	
Systemic lupus erythematosus	Chorea. Parkinsonism rare
Sjögren syndrome	Parkinsonism
Antiphospholipid antibody syndrome	Rare: Parkinsonism, chorea
Stiff person syndrome	Hyperlordosis, ataxia
Neuro- Behçet	Chorea, ataxia
Celiac disease	Ataxia, parkinsonism, chorea
Paraneoplastic disorders	
Anti-Yo/APCA	Ataxia, tremor
Anti-NMDAR encephalitis	Dystonia, orofacial dyskinesias, ballism, myorhythmia
Amphiphysin	Stiff person syndrome (hyperlordosis, rigidity, ataxia)
Anti-Hu/ANNA-1	Dystonia, chorea, tremor, parkinsonism
CV2/CRMP5	Chorea, dystonia, ataxia
Ma1/Ma2	Parkinsonism
Hu/ANNA-2/VGKC	Myoclonus
Tr	Ataxia
Ri/ANNA-2	Dystonia, parkinsonism (PSP-like), opsoclonus-myoclonus
VGCC	Ataxia
Metabolic	
Wilson disease	Dystonia, parkinsonism, "wing-beating" tremor
Acquired hepatocerebral degeneration	Orobuccolingual dyskinesias, parkinsonism
Hemochromatosis	Ataxia, tremor, parkinsonism
Renal failure	Asterixis, restless legs syndrome. Parkinsonism rare
Endocrine	
Nonketotic hyperglycemia	Hemichorea- hemiballism, asterixis
Hypoglycemia	Paroxysmal chorea
Hyperthyroidism	Tremor, chorea
Hypothyroidism	Parkinsonism
Hypoparathyroidism	Parkinsonism, ataxia, tremor
Hematological	
Polycythemia rubra vera	Chorea

Chorea acanthocytosis	Chorea, feeding dystonia
McLeod syndrome	Chorea
Lysosomal storage disease	
Gaucher	Parkinsonism, dystonia
Niemann-Pick C	Parkinsonism, supranuclear vertical gaze palsy, dystonia
Metal and nonmetal systemic intoxication	
Carbon monoxide	Parkinsonism
Manganese	Parkinsonism
MPTP	Parkinsonism
Ephedrone	Parkinsonism
Carbon monoxide	Parkinsonism
Carbon disulfide	Parkinsonism
Cyanide	Parkinsonism, dystonia, apraxia of eyelid opening
Toluene	Parkinsonism
Ethanol	Ataxia, parkinsonism
Thallium	Chorea

Abbreviations: ANNA, antineuronal nuclear antibody; APCA, anti–Purkinje cell antibody; CNS, central nervous system; HIV, human immunodeficiency virus; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NMDAR, N-methyl-D-aspartate receptor; PSP, progressive supranuclear gaze palsy.

reader to recent monographs on the subject.[1] Here we mainly focus on those clinical settings in which systemic diseases can lead to movement disorders in adults.

INFECTIOUS DISEASES

Infectious diseases can induce movement disorders in the acute, subacute, and chronic stages, either via direct infection of the central nervous system (CNS), or by inducing parainfectious autoimmune processes, such as the acute onset of chorea in children with rheumatic fever due to streptococcus infection. Here we focus on those infectious etiologies that are commonly associated with movement disorders or should be borne in mind as differential diagnoses when there is a suspicion of a symptomatic movement disorder. These clinical scenarios include viral, bacterial, fungal, and protozoic infections, the latter 2 mainly in the setting of immunocompromised patients, and in some parts of the world also helminthic CNS infestations.

Whipple Disease

Whipple disease (WD) is a rare systemic infection caused by the anaerobic, gram-positive bacterium *Tropheryma whipplei*. It can affect multiple organs, including the brain, and is more common in men than women (87% vs 13%). The estimated annual incidence is fewer than 1 per 1,000,000 population.[2] Nevertheless, it is extremely important not to miss the diagnosis, as it is a curable condition that is potentially fatal if left untreated.

The prodromal stage lasts for approximately 6 years and is characterized by unspecific symptoms, such as arthralgia and arthritis. In the steady-state phase, patients may complain of abdominal cramping, weight loss, and diarrhea.[3] Neurologic complications occur in up to 60% of patients[3] and may even present in isolation without any signs of a systemic infection. Approximately 50% of patients develop a supranuclear

gaze palsy, which may resemble progressive supranuclear gaze palsy (PSP).[3] Hypophonia, reduced postural stability, and parkinsonism may occur. In approximately 20% of cases, convergence-divergence pendular oscillations, which are in synchrony with a 1-Hz oculo-masticatory myorhythmia, are seen.[4] Cognitive decline, which may progress to dementia, also is common.

The diagnosis is challenging and in some it may not be possible to obtain diagnostic proof in life. The classical findings in biopsies of the duodenum or the jejunum are periodic acid-Schiff (PAS)-positive macrophages in the lamina propria containing the bacteria. Polymerase chain reaction (PCR) of the cerebrospinal fluid (CSF) is confirmatory in patients with isolated CNS-WD.[5] MRI of the brain can show tumorlike or multifocal lesions in the midbrain, thalamus, and temporal lobe,[5] or signal abnormalities in the middle cerebellar peduncle (**Fig. 1**).

Patients require long-term antibiotic therapy. Initially, parenteral administration of ceftriaxone 2 g in combination with intramuscular injection of streptomycin 1 g per day for 14 days is recommended followed by oral administration of high doses of trimethoprim-sulfamethoxazole (160 mg/800 mg) three times a day (tds) for 1 to 2 years. Parkinsonism can improve under antibiotic therapy[6]; however, relapses can occur even several years after cessation of therapy.

Key points: Whipple disease	
Prevalence	Estimated annual incidence is <1 per 1,000,000 More common in men than women
Clinical presentation	50% supranuclear gaze palsy, 20% convergence-divergence pendular oscillations, 1-Hz oculo-masticatory myorhythmia
Diagnosis	Presence of PAS-positive macrophages in duodenal or jejunal biopsies; positive *Tropheryma whipplei* PCR in CSF
Therapy	Parenteral antibiotic therapy followed by oral antibiotics for 2 years

Tuberculosis

The frequency of movement disorders in tuberculous meningitis is approximately 17%.[7] Although dystonia, chorea, myoclonus, and parkinsonism also have been reported, tremor is the most common movement disorder and occurred in two-thirds of the cases in one study.[7,8] Neuroimaging in patients with tuberculous meningitis can be normal, but in 50% may show secondary vascular lesions in the basal ganglia or thalamus.[8]

Intracranial tuberculomas can cause movement disorders in up to 30% of cases.[7] Chorea and dystonia has been associated with deep intracranial tuberculomas, whereas tremor was observed in patients with surface lesions.[7] Apart from cerebral lesions, spinal tuberculomas also have been reported to cause tremor and myoclonus.[7] The therapy usually consists of isoniazid (plus pyridoxal phosphate), rifampin, pyrazinamide, ethambutol, and steroids.

Key points: Tuberculosis	
Etiology	Occurs in 1% of patients with systemic tuberculosis
Clinical presentation	All types of movement disorders, including tremor, chorea, myoclonus, dystonia, and parkinsonism
Diagnosis	CSF or culture isolating *Mycobacterium tuberculosis*
Therapy	Isoniazid (plus pyridoxal phosphate), rifampin, pyrazinamide, ethambutol, and steroids

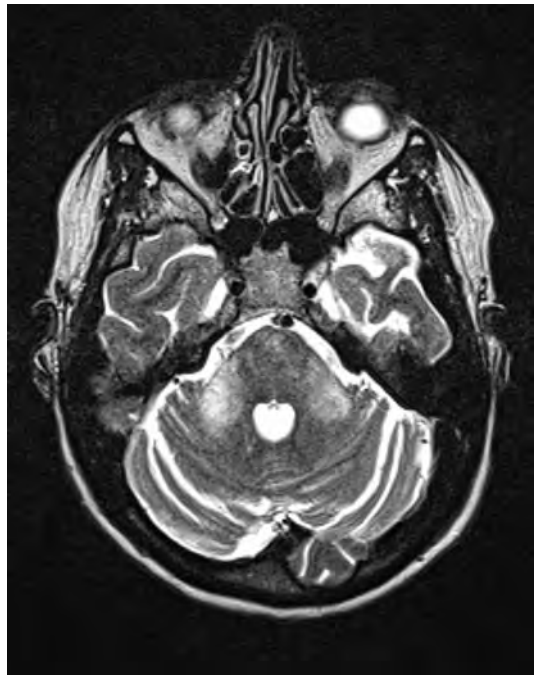

Fig. 1. T2-weighted MRI demonstrating signal abnormalities in the middle cerebellar peduncles bilaterally in a patient with WD.

Neurosyphilis

Although movement disorders are rare in patients with neurosyphilis, *Treponema pallidum* infections can cause symptoms mimicking corticobasal syndrome, with arm levitation, asymmetric bradykinesia, and myoclonus.[9] Parkinsonism, generalized chorea mimicking Huntington disease, hemichorea, ataxia, laryngeal dystonia, and myoclonus also have been described. Furthermore, neurosyphilis can cause PSP-like symptoms.[10] MRI findings may show infarction or inflammation of the midbrain and basal ganglia. Antibiotic use with parenteral penicillin G (3–4 million units tds for 14 days) remains gold standard therapy. Rigorous follow-up tests are necessary to assess whether the infection has vanished.

Key points: Neurosyphilis	
Etiology	Caused by *Treponema pallidum* infections
Clinical presentation	Movement disorder presentations (rare): parkinsonism, chorea, ataxia, corticobasal syndrome
Diagnosis	CSF and serum antibody test
Therapy	Antibiotic therapy with penicillin G

Human Immunodeficiency Virus–Related and AIDS-Related Movement Disorders

In 2012, the global prevalence of human immunodeficiency virus (HIV) infection was approximately 34 million with approximately 2.2 million new HIV infections.[11] The prevalence of movement disorders in patients with AIDS or HIV varies between 2%

and up to 44%.[7] Movement disorders may sometimes be the initial manifestation of AIDS,[12] of an HIV infection during serum conversion, or of an opportunistic infection[13] and generally increase with disease duration.

Hemichorea-hemiballism may be the most frequently seen movement disorders, although the prevalence is unclear. One study reported that 5 (1.4%) of 345 patients with AIDS suffered from hemichorea-hemiballism.[14] Onset of symptoms is generally subacute and unilateral.[12] Cerebral MRI commonly reveals multiple lesions, often caused by cerebral toxoplasmosis, affecting the contralateral striatum or subthalamic nucleus.[13] Pyrimethamine and sulfadiazine were effective in improving or resolving symptoms in some,[12,14] but not all, studies.[15]

Tremor can occur at all stages of the disease and increases up to 44% in patients with dementia.[16] Typically, patients exhibit a bilateral postural tremor but a rest tremor or a Holmes tremor also may occur.[13] Depending on the size of the study, estimates suggest that parkinsonism is seen in between 5% and up to 50% of patients with AIDS.[17] Often some atypical features, such as symmetric bradykinesia and rigidity and early postural instability occur. A classical resting tremor also may be absent.[13] Parkinsonism is commonly a result of HIV encephalopathy,[18] although it also may occur as a complication of opportunistic infections, such as cerebral toxoplasmosis, WD, progressive multifocal leukoencephalopathy, and CNS tuberculosis.[13] The therapeutic value of dopamine replacement therapy in HIV/AIDS parkinsonism is unclear and combined antiretroviral therapy (cART) is more likely to alleviate symptoms.

Dystonia, myoclonus, opsoclonus-myoclonus, and paroxysmal dyskinesias are rare complications and can be a complication of opportunistic infections.[13]

Finally, restless legs syndrome (RLS) was reported in 30% of HIV-positive patients in one series and was inversely correlated with the CD4+ cell count.[19] Ten of these patients were treated with levodopa and reported a significant alleviation of symptoms.[19]

Key points: HIV-related and AIDS-related movement disorders	
Etiology	Global estimated prevalence of HIV: 34 million Estimates of movement disorders in patients with HIV/AIDS vary between 2% and 44%
Clinical presentation	Common: hemichorea-hemiballism, parkinsonism, tremor, RLS Rare: dystonia, myoclonus, and paroxysmal dyskinesias
Diagnosis	HIV test, MRI imaging to screen for vascular and opportunistic infections
Therapy	cART Chorea induced by toxoplasmosis: pyrimethamine and sulfadiazine, dopamine receptor blockers Role of dopamine replacement therapy in patients with parkinsonism conflicting

Sydenham Chorea

Sydenham chorea (SC) is the most common cause of chorea in children.[20] It is caused by Group A beta-hemolytic *Streptococcus* and occurs in 25% of patients with acute rheumatic fever. Typical age of onset is 8 to 9 years, and girls are more commonly affected. Onset is abrupt and consists of orofacial movements, tics, chorea, and dysarthria. Chorea is generalized but may at times also be asymmetric or unilateral. Hypotonia is seen in most patients and, when severe, 2% of patients develop a flaccid quadriparesis often labeled as “chorea paralytica.”[21] Neuropsychiatric symptoms, such as obsessive compulsive disorder, are common. Despite strong indicators that

SC is an autoimmune process, a definitive autoantibody has not been found. Sixty percent to 80% of patients have cardiac involvement[22] and half of the patients still have chorea 2 years after onset of symptoms.[23]

Steroids alone or in combination with intravenous immunoglobulin are used in cases with severe chorea. Valproic acid or carbamazepine, rather than neuroleptic therapy, are preferred for symptomatic treatment.[21] Antibiotic prophylaxis following the acute rheumatic fever guidelines until the age of 21 is recommended to avoid rheumatic heart disease.[21]

Key points: Sydenham chorea	
Etiology	SC is the commonest cause of acute chorea in children
Clinical presentation	Orofacial movements, tics, chorea, and dysarthria are common Psychiatric side effects, such as obsessive compulsive behavior, may occur
Diagnosis	
Therapy	Antibiotic therapy Chorea: steroids, immunoglobulins, valproic acid or carbamazepine

Other Viral Infections Causing Movement Disorders

A variety of different viruses can cause movement disorders as a symptom of viral encephalitis. The most important are summarized in **Table 2**; a comprehensive review of these viral encephalitides is beyond the scope of this review.

Table 2
Common causes of viral infections causing movement disorders

Virus	Species	Movement Disorder
DNA		
Herpesviridae	Herpesvirus	Chorea, athetosis, tics, parkinsonism
	Epstein Barr	Chorea, opsoclonus-myoclonus, parkinsonism
	Cytomegalovirus	Chorea, parkinsonism
	Varicella zoster	Myoclonus, hemichorea, ataxia, parkinsonism
RNA		
Flaviviridae	West Nile	Opsoclonus-myoclonus, parkinsonism
	Japanese encephalitis	Parkinsonism, chorea, dystonia
	Tick-borne encephalitis	Chorea, tremor
Paramyxoviridae	Measles	Myoclonus, chorea, parkinsonism
Picornaviridae	Coxsackie virus	Parkinsonism
	Echo virus	Parkinsonism
	Polio virus	Parkinsonism
Orthomyxoviridae	Influenza virus	Chorea, parkinsonism
Bornaviridae	Borna disease virus	Parkinsonism
Togaviridae	Rubella virus	Chorea
Retrovirus	Human immunodeficiency virus (HIV)	Hemichorea/Hemiballism, parkinsonism, tremor (dystonia, myoclonus, opsoclonus, paroxysmal dyskinesias rare)

Adapted from Jang H, Boltz DA, Webster RG, et al. Viral parkinsonism. Biochim Biophys Acta 2009;1792(7):714–21. http://dx.doi.org/10.1016/j.bbadis.2008.08.001; with permission.

Fungal and Protozoal Infections

Cerebral toxoplasmosis almost always affects immunocompromised subjects, including those with HIV infections (see earlier in this article), and toxoplasmic abscesses commonly involve the basal ganglia, thalamus, and upper brain stem (Fig. 2), giving rise to a variety of movement disorders depending on anatomic location. Hemichorea-hemiballism is probably the most common and often relates to contralateral basal-ganglia or, rarely, thalamic lesions, but similar lesions also may produce focal or hemidystonia.[24] Parkinsonism can occur both with unilateral and bilateral basal ganglia abscesses, and generalized chorea also has been observed in patients with bilateral basal ganglia or thalamic lesions (Video 1).[14] Holmes tremor has been associated with toxoplasmic abscesses in the midbrain but also thalamus.

Movement disorders in CNS toxoplasmosis may respond to specific antitoxoplasmic therapy with sulfadiazine and pyrimethamine, but symptoms may persist even after resolution of abscesses, such that additional symptomatic therapy is required, including antidopaminergic agents to control chorea, levodopa or dopamine agonists to treat parkinsonism, or anticholinergics and focal botulinum toxin injections for dystonia.

Movement disorders in CNS toxoplasmosis at a glance

- Cerebral toxoplasmosis is almost exclusively seen in immunocompromised patients
- Clinical presentation: hemichorea-hemiballism, parkinsonism, focal dystonia
- Diagnosis: Neuroimaging may reveal contralateral basal ganglia lesion
- Therapy: Antitoxoplasmic treatment
- Dopamine blocking agents for hemichorea
- Dopamine replacement therapy for patients with parkinsonism

Similar to CNS toxoplasmosis, *fungal encephalitis* is usually associated with immunocompromised states and fungal abscesses may give rise to movement disorders depending on anatomic site. Parkinsonism has been observed in patients with *cryptococcal abscesses* in the basal ganglia[25,26] and hemichorea was associated with lesions in the contralateral head of the caudate.[27]

Helminthic Brain Infections

The most common parasitic worm infection invading the central nervous system is neurocysticercosis, which is endemic in Asia, Eastern Europe, and South America.[7] Neurocysticercosis is caused by the pork tape worm *Taenia solium*. Although neurocysticercosis is the most common cause for seizures in developing countries and the parasitic cysts affect the basal ganglia in 25%, movement disorders occur in only 3.5% of cases.[7,28] A few case reports have described levodopa-responsive akinetic-rigid parkinsonism[29,30]; however, in most cases, parkinsonism is secondary to hydrocephalus.[7] Further, dystonia, hemichorea, myoclonus, and hemifacial spasms have been described.[7,28] The proposed underlying mechanisms for movement disorders include a direct mass effect due to the cyst itself, ischemia in the basal ganglia due to vasculitis, and inflammatory processes.[7,28] In most cases, albendazole at 15 mg/kg per day for 3 days or 30 mg/kg per day for ventricular and subarachnoid cysts is effective. However, in some patients, surgical removal of the cyst or other drugs, such as praziquantel, phenobarbital, or primidone, are indicated.[7]

Key points: Helminthic brain infections	
Etiology	Neurocysticercosis is the most common helminthic infection
Clinical presentation	Movement disorders are rare, parkinsonism is mainly caused by hydrocephalus; case reports of dystonia, hemichorea, myoclonus, and hemifacial spasms
Diagnosis	MRI, serologic detection of antibodies to *Taenia solium*
Therapy	Antihelminthic therapy with albendazole or praziquantel

AUTOIMMUNE-MEDIATED MOVEMENT DISORDERS

Movement disorders occasionally may occur as presenting symptoms in patients with systemic autoimmune disease or may associate with antibodies directed to neuronal antigens, including neurotransmitter receptors. The latter is the case in patients with paraneoplastic movement disorders (see later in this article).

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) usually affects middle-aged women and has a prevalence that ranges between 20 and 150 cases per 100,000.[31] The disease, often called the "great imitator," affects various different organs. Antinuclear antibodies and anti–double-stranded DNA are diagnostic serologic markers.[31] Antiphospholipid syndrome (APS) is closely related and is characterized by recurrent vascular thrombosis (venous, small vessel, or arterial) associated with persistently positive antiphospholipid antibodies (lupus anticoagulant, cardiolipin antibodies, and β_2 glycoprotein antibodies).[32]

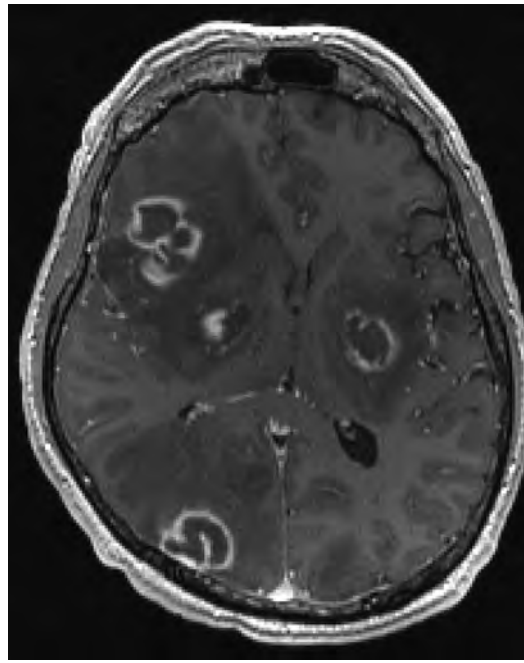

Fig. 2. Cerebral toxoplasmosis: T1-weighted MRI showing multiple gadolinium-enhancing lesions with perifocal edema.

Neurologic complications, which also are part of the diagnostic criteria, include seizures and psychosis,[31] but movement disorders also may occasionally dominate the clinical presentation. Chorea has been reported with a prevalence of 2% to 3%.[33] These patients are usually younger (mean age 20.6 years), of female predominance (84%–96%), and have a high prevalence of antiphospholipid antibodies.[33–35]

Parkinsonism is a rare complication of SLE and fewer than 40 cases have been reported since 1930, 10 with juvenile onset of parkinsonism.[36] Tremor was less frequently observed than bradykinesia and rigidity.[37] Patients may develop rapidly progressive apathy and bilateral bradykinesia.[38] Parkinsonism, probably triggered by thromboocclusive vasculopathy and white matter changes, also can be seen in patients with APS. In these patients, response to dopamine replacement therapy is generally poor.[37]

The diagnosis of movement disorders as a result of SLE is challenging. The presence of serologic markers typical for SLE or APS and exclusion of other causes, such as vascular chorea and Huntington disease, points toward an autoimmune process.

Most patients with chorea respond to either steroids or neuroleptic therapy. In some cases, intravenous immunoglobulin or plasma exchange has been described to alleviate symptoms.[34] All patients with SLE and parkinsonism improved either with dopamine replacement therapy alone or in combination with prednisolone, plasma exchange, and cyclophosphamide.[38]

Key points: Systemic lupus erythematosus

Prevalence	Ranges between 20 and 150 cases per 100,000
Clinical presentation	Chorea either generalized or hemichorea occurs in 3%; parkinsonism rare
Diagnosis	Apart from neurologic signs, presence of 4 of 11 symptoms (malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, kidney-blood and immunologic disorder, positive antinuclear antibodies
Therapy	Steroids, neuroleptics, immunotherapy Parkinsonism: dopamine replacement therapy, steroids

Sjögren Syndrome

Sjögren syndrome is characterized by lymphocytic infiltration of the lacrimal and salivary gland. Patients complain of xerostomia (dry mouth) and xerophthalmia (dry eyes). Antinuclear antibodies, such as SSA/Ro and SSB/La, may be positive.[39] Movement disorders, particularly parkinsonism, have been described in 2 distinct groups of patients: one group has abnormal white matter lesions on the T2-weighted cranial MRI scans and presents with an akinetic rigid form. Typically, these patients do not respond to dopamine replacement therapy.[40] The other group resembles idiopathic Parkinson disease (PD). These patients have a normal MRI scan, a good response to dopamine replacement therapy, and have motor fluctuations.[41] Other rarely seen movement disorders include chorea, dystonia, and dystonic tremor.

Key points: Sjögren syndrome

Clinical presentation	Parkinsonism; chorea, dystonia, tremor rare
Diagnosis	Antinuclear antibodies, such as SSA/Ro and SSB/La; salivary gland and labial biopsy; T2-weighted abnormalities in basal ganglia in patients with parkinsonism
Therapy	Steroids in combination with dopamine replacement therapy in patients with parkinsonism

A variety of other autoimmune disorders can cause movement disorders, the most common are listed in Table 3.

PARANEOPLASTIC MOVEMENT DISORDERS

Paraneoplastic movement disorders are very rare autoimmune complications that occur in patients with cancer, where the symptoms cannot be attributed to a direct invasion of the tumor, a metastasis, or side effects of the oncological therapy.[42] Often paraneoplastic symptoms may precede the diagnosis of the underlying tumor.[43] Usually immunologic cross reactions between the protein expressed by the tumor and the neuronal cells cause these symptoms. Clinically, symptoms progress more rapidly than in neurodegenerative disorders, CSF examination often shows pleocytosis, elevated protein levels, high immunoglobulin G index, and oligoclonal bands. Presence of antineuronal antibodies can point toward the underlying cancer.

Anti–N-Methyl-D-Aspartate Receptor Encephalitis

This rapidly progressive encephalitis, which predominantly affects women, was first described in 2005 in 4 young women with ovarian teratoma.[44] The underlying cause of this disease is an antibody against *N*-methyl-D-aspartate (NMDA) receptor, which affects children and young adults with and without teratoma.[45] In a case series of 100 patients, 91% were female with a mean age of 23 years (range 5–76 years).[46] Although an underlying tumor is rare in children and male patients, more than 50% of female patients aged 18 and older had an ovarian teratoma.[47,48] In contrast, only 5% of adult male patients with anti-NMDA receptor encephalitis had an underlying tumor.

Movement disorders are a prominent part of the clinical presentation of this condition. Characteristically, patients develop orofacial dyskinesias,[49,50] which can involve jaw opening and closing,[50] facial grimacing[49] or tongue protrusion, kissing, and frowning (Video 2).[48] In addition to stereotypies, many patients also have slow rest and postural rhythmic movements (myorhythmia). Psychiatric symptoms, such as psychosis, hallucinations, agitation, insomnia, and catatonia, are frequently seen[51–53] and epileptic seizures occur more commonly in children than adults.[45,48]

Table 3
Other common systemic autoimmune disorders causing movement disorders

Syndrome	Movement Disorder	Diagnostic Test
Steroid-responsive autoimmune encephalitis (Hashimoto)	Tremor (80%) Ataxia and gait disorder (66%) Myoclonus (37%) Cognitive impairment (36%) Psychiatric problems (30%) Strokelike episodes	Antithyroglobulin antibodies Antithyroperoxidase antibodies MRI brain scan
Celiac disease	Cerebellar ataxia Polyneuropathy Myelopathy Chorea Parkinsonism	Antigliadin antibodies Anti-TG2 antibodies Anti-TG6 antibodies
Behçet disease	Chorea Ataxia	MRI brain scan (basal ganglia hyperintensities) Cerebrospinal fluid

In 50% of patients, brain MRI shows hyperintensities in T2 or fluid attenuated inversion recovery signal in multiple brain areas, including the hippocampus, the cortex, the brainstem, the basal ganglia, and the cerebellum, and sometimes the spinal cord is involved as well.[47] CSF may reveal pleocytosis, elevated protein levels, and in some oligoclonal bands. In women, gynecological screening for an underlying ovarian teratoma is necessary.

In one large multicenter study with 577 patients (37% children younger than 18), immunotherapy with steroids, immunoglobulins, and plasma exchange, in combination with removal of tumor (if present), resulted in neurologic improvement in 81% of patients after a follow-up period of 2 years. In patients who did not respond to first-line immunotherapy, rituximab, cyclophosphamide, or both improved outcome compared with those who did not receive any therapy. Factors for good outcome included early initiation of therapy and lack of intensive care unit admission.[45]

Key points: Antibody against *N*-methyl-D-aspartate (NMDA) receptor encephalitis	
Prevalence	NMDA receptor encephalitis affects female more than male patients
	More than 50% of adult female patients had an ovarian teratoma
Clinical presentation	Orofacial dyskinesias and psychiatric complications
Diagnosis	Anti-NMDA receptor antibodies; detection of underlying teratoma; 50% of patients have brain MRI hyperintensities in multiple brain areas
Therapy	Immunotherapy in combination with removal of tumor

Paraneoplastic Cerebellar Degeneration

Paraneoplastic cerebellar degeneration is one of the most common paraneoplastic syndromes. Unspecific symptoms, such as vertigo, nausea, and flulike symptoms, are typical harbingers of the disease. Patients then develop rapidly progressing ataxia, dysarthria, and diplopia.[54] A high-amplitude tremor that can in some cases resemble essential tremor is often seen. In the early stages of the disease, cranial MRI imaging can be normal and PET scans may show hypermetabolism, but as the disease progresses, MRI scans reveal cerebellar atrophy and PET scans show hypometabolism.[54]

The most common underlying tumors are breast and gynecologic cancer,[55] small-cell lung cancer,[56] and Hodgkin lymphoma.[57] The corresponding antibodies for breast and gynecologic cancer are anti-Yo antibodies and anti-Tr antibodies associated with Hodgkin lymphoma, which both have a high specificity.[54] Forty-one percent of patients with small-cell lung cancer develop antibodies to voltage-gated calcium channels (with or without Lambert-Eaton myasthenic syndrome) and 23% develop anti-Hu antibodies.[54]

There is no standard treatment guideline for these patients. Treatment of the underlying tumor is necessary to stabilize the symptoms. The evidence for immune therapy, such as corticosteroids, plasma exchange, and administration of immunoglobulins, is conflicting.

Opsoclonus-Myoclonus Syndrome

This is a rare condition that was first described in 1962 in 6 children with ataxia, myoclonus, and opsoclonus.[58] Coexisting mild behavioral, cognitive, and mood changes may occur.

Although a neuroblastoma is found in 50% of children with opsoclonus myoclonus,[54] various types of other cancers, particularly breast and lung cell cancer, but also testicular and ovarian tumors, have been associated with opsoclonus myoclonus in adults.[59] Older age, a more severe clinical presentation, and a higher frequency of encephalopathy may point toward paraneoplastic causes.[60] Although anti-Ri antibodies may occur in patients with breast and ovarian cancer, most patients are antibody negative.[54]

A subgroup of patients with opsoclonus-myoclonus also develop truncal titubation and ataxia, termed opsoclonus-myoclonus ataxia (OMA) syndrome. Truncal ataxia and gait difficulties are common, and limb ataxia, tremor, and dysarthria are rarely seen. Typically, symptoms progress rapidly and, within a few weeks, may result in severe disability. Patients with OMA with paraneoplastic cause are older than patients with idiopathic OMA (mean age 66 vs 47 years).[60]

Cranial MRI with gadolinium enhancement is necessary to exclude structural abnormalities, such as thalamic infarction, multiple sclerosis, hydrocephalus, or metastasis. Most MRI scans are, however, normal. High-resolution chest and abdominal computed tomography (CT), as well as gynecologic screening and mammography in women, should be performed. If negative, a whole-body PET scan should be considered.[61]

Although in children with neuroblastoma, immunotherapies, such as corticosteroids, intravenous immunoglobulin, plasma exchange, cyclophosphamide, or rituximab, may be useful, in adults, immunotherapy is less effective and tumor therapy is more efficacious.[54]

Stiff Person Syndrome

Stiff person syndrome is a rare disorder presenting with thoracolumbar muscle stiffness, rigidity, and spasms triggered by emotional stimuli and stress. The estimated prevalence is 1 to 2 cases per million.[62] Although most patients have the classical autoimmune variant, approximately 15% of patients have an underlying cancer. The most common tumors are breast cancer and small cell lung cancer,[32] although cases with colon cancer, thymoma, and Hodgkin lymphoma have been described.[62]

Onset is typically an insidious, with painful spams and ataxia. Hyperlordosis because of abdominal and paraspinal muscular co-contraction is frequently seen.[62] Female gender and older age of disease onset are more commonly observed in paraneoplastic stiff person syndrome.[63] Type 1 diabetes can occur in 35% of patients with the autoimmune form.[64]

Stiff person syndrome is a clinical diagnosis based on the Dalakas criteria (**Box 1**).[64] Elevated antibodies against glutamic acid decarboxylase in serum and liquor can be detected in most cases.[62] Antiamphiphysin antibodies in serum or liquor can be found in 5% of patients with paraneoplastic stiff person syndrome. A CT chest scan, as well as gynecologic investigations and mammography is necessary and if negative then a whole-body PET scan is recommended.[63]

Muscle relaxants, such as benzodiazepines, gabapentin, baclofen, or immunotherapy, such as steroids, intravenous immunoglobulin, plasma exchange, or rituximab may alleviate symptoms.[62]

In patients with paraneoplastic stiff person syndrome, tumor extinction in combination with chemotherapy and steroids may be beneficial.[63] Typically, these patients respond poorly to diazepam.

A variety of different tumors are associated with onconeuronal antibodies causing movement disorders (**Table 4**). These paraneoplastic symptoms precede the cancer diagnosis in most cases.[65]

Box 1
Clinical diagnosis criteria of stiff person syndrome

- Stiffness in the axial muscles, prominently in the abdominal and thoracolumbar paraspinal muscle leading to a fixed deformity (hyperlordosis)
- Superimposed painful spasms precipitated by unexpected noises, emotional stress, tactile stimuli
- Confirmation of the continuous motor unit activity in agonist and antagonist muscles by electromyography
- Absence of neurologic or cognitive impairments that could explain the stiffness
- Positive serology for GAD65 (or amphiphysin) autoantibodies, assessed by immunocytochemistry, Western blot, or radioimmunoassay

Response to diazepam[a]

[a] Not part of the original criteria.

Adapted from Dalakas MC. Stiff person syndrome: advances in pathogenesis and therapeutic interventions. Curr Treat Options Neurol 2009;11(2):102–10; with permission.

Table 4
Common paraneoplastic movement disorders

Tumor	Associated Antibodies	Movement Disorder
Ovarian teratoma	NMDAR	Chorea
Small-cell lung cancer	CV2/CRMP5	
Small-cell lung cancer	Hu/ANNA-1	
Ovarian teratoma	NMDAR	Dystonia
Small-cell lung cancer	CV2/CRMP5	
Small-cell lung cancer	Hu/ANNA-1	
Small-cell lung cancer, breast, gyn	Ri/ANNA-2	
Testis, non–small-cell lung cancer	Ma1/Ma2	Atypical parkinsonism
Small-cell lung cancer, breast, gyn	Ri/ANNA-2	
B-cell lymphoma	Hu/ANNA-1	
Small-cell lung cancer, breast	Amphiphysin	Stiff person syndrome
Ovarian teratoma	NMDAR	Orofacial dyskinesia
Small-cell lung cancer, breast	Ri/ANNA-2	Opsoclonus-myoclonus
Breast	Hu/ANNA-2	Myoclonus
Various different tumors	VGKC	
Breast, gyn	Yo/APCA	Ataxia
Hodgkin lymphoma	Tr	
Small-cell lung cancer	VGCC	
Small-cell lung cancer	Amphiphysin	
Small-cell lung cancer	CV2/CRMP5	
Small-cell lung cancer	Hu/ANNA-1	Tremor
Ovarian, breast	Yo/APCA	

Abbreviations: ANNA, antineuronal nuclear antibody; APCA, anti–Purkinje cell antibody; gyn, gynecological tumors; NMDAR, N-methyl-D-aspartate receptor.

Adapted from Poewe W, Jankovic J. Movement disorders in neurologic and systemic disease. New York: Cambridge University Press; 2014. p. 39–51.

MOVEMENT DISORDERS IN METABOLIC DISORDERS

Most metabolic disorders may eventually affect brain function and thus also give rise to different types of movement disorders. Classical examples in adult neurology are movement disorders in the context of liver and renal disease, as well as late-onset types of lysosomal storage disorders.

Wilson Disease

Wilson disease is an autosomal recessive disorder of copper metabolism causing accumulation of copper chiefly in hepatocytes and other tissues, including the brain. Wilson disease has a prevalence of 1:30,000[66] and is caused by mutations in the ATP7B gene.[67]

Between 50% and up to 70% of patients with Wilson disease have neurologic or neuropsychiatric symptoms, such as anxiety, cognitive impairment, impulsivity, or apathy.[68] Patients who present with movement disorders are usually older than those with hepatic presentation and younger than those with psychiatric symptoms.[68] Two forms of neurologic Wilson disease have been described. The juvenile form is characterized by dystonia and rigidity, whereas the other pseudosclerotic form presents usually after the age of 20, with mainly ataxia and tremor. Parkinsonism, cranial involvement such as dysarthria, dysphagia, drooling, and a risus sardonicus are typical.[66] In some patients, the tremor can be of low frequency, when arms are raised with elbows bent, giving it a characteristic "wing beating" appearance.[66] Other movement disorders, such as myoclonus, tics, and oculogyric crisis are rare.

Patients with Wilson disease have a typical triad of a Kayser-Fleischer ring, low serum ceruloplasmin, and elevated 24-hour urinary copper levels. However, the absence of a Kayser-Fleischer ring does not exclude the diagnosis. MRI of the brain may reveal the "face of the giant panda" sign (**Fig. 3**), signal changes in the basal ganglia, thalamus, and brainstem.[69]

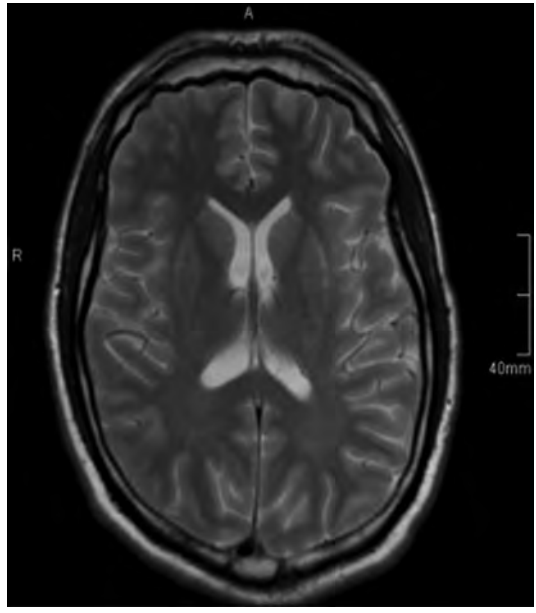

Fig. 3. T2-weighted MRI shows bilateral basal ganglia lesions in a patient with carbon monoxide poisoning.

Left untreated, Wilson disease leads to anarthria, liver failure, and inevitably to death. Treatment is targeted to reduce copper load. Increased copper secretion is achieved with the chelating agents trientine and D-penicillamine, which should be taken in combination with vitamin B6. Initially, both drugs (more common in D-penicillamine than with trientine) can cause worsening of symptoms, which may be due to a transient increase in free serum copper.[70] Zinc salt blocks absorption of copper but is less potent and sometimes used as a maintenance therapy. In patients with liver failure or decompensated cirrhosis, liver transplantation is indicated but bares the risk of operation, immunosuppression, and graft-versus-host reaction.

Key points: Wilson disease	
Prevalence	Prevalence of Wilson disease is 1:30,000
Etiology	Autosomal recessive disorder due to mutations in the *ATP7B* gene on chromosome 13
Clinical presentation	Dystonia (including risus sardonicus), tremor, ataxia, and parkinsonism; myoclonus, tics, and oculogyric crisis rare
Diagnosis	Triad of a Kayser-Fleischer ring, low serum ceruloplasmin, and elevated 24-hour urinary copper levels
Therapy	Chelating agents in combination with vitamin B6 Initial worsening may occur, less frequently seen with trientine Liver transplantation in patients with liver failure

Chronic Acquired Hepatolenticular Degeneration

This symptom may develop subacutely or insidiously, either within a few weeks or up to a decade. It is caused by portal-systemic shunting leading to excessive concentration of manganese in CSF and serum. The clinical course is usually progressive, although spontaneous remissions have been described. The prevalence rate is unknown. Survival after onset of symptoms ranges between a few weeks and up to 30 years.[71]

The most characteristic clinical features are orobuccolingual dyskinesias. Dystonia, apathy, dysarthria, bradyphrenia, chorea, ataxia, myelopathy, and parkinsonism also are common.[7,71] Although parkinsonism can closely resemble idiopathic PD, there are some atypical features, such as early postural instability, cognitive impairment, a bilateral tremor (more pronounced on action than at rest), and a faster disease progression.[72]

The diagnosis is challenging, as there are no reliable markers.[71] Cranial MRI, particularly in patients with cirrhosis, typically shows T1-weighted pallidal hyperintensities.[71]

No treatment guidelines have been established so far. Patients with orofacial dyskinesias or chorea may benefit from dopamine receptor blocking agents, such as tetrabenazine. The evidence for dopamine replacement therapies in patients with parkinsonism is conflicting, with some studies reporting improvement[72,73] and others reporting no benefit.[74,75]

Liver transplantation can improve all aspects of neurologic symptoms[71,75] but bares the risk of graft-versus-host reaction.[71]

Key points: Chronic acquired hepatolenticular degeneration	
Prevalence	Prevalence of chronic acquired hepatolenticular degeneration is unknown
Clinical presentation	Orobuccolingual dyskinesias, dystonia, dysarthria, and parkinsonism
Diagnosis	Pallidal hyperintensities on cranial MRI due to manganese deposition
Therapy	Chorea may respond to dopamine receptor blocking agents; evidence for dopamine replacement therapy in patients with parkinsonism is conflicting; liver transplantation is indicated in patients with liver failure

Hypermanganesemia with Dystonia, Polycythemia, and Cirrhosis

Hypermanganesemia with dystonia, polycythemia, and cirrhosis (HMDPC) is a rare syndrome of increased serum manganese, hepatomegaly, and polycythemia that predominantly presents during childhood but adult patients have been reported as well. Movement disorders are a prominent part of the syndrome because of manganese accumulation affecting the caudate and lentiform nuclei and dentate nuclei. The most common types of movement disorders described are parkinsonism and various forms of tremor.[76] A recently discovered mutation in the *SLC30A10* gene causes the syndrome, which is potentially treatable with oral chelation treatment and inhibitors of manganese absorption, leading to improvement of both movement disorders and hepatopathy.

Key points: Hypermanganesemia with dystonia, polycythemia, and cirrhosis (HMDPC)	
Prevalence	Rare multisystemic disease
Clinical presentation	Parkinsonism, dystonia, and tremor
Diagnosis	Mutation in *SLC30A10* gene; manganese accumulation in basal ganglia on MRI
Therapy	Chelation therapy to normalize manganese and iron levels

Renal Failure

Uremic encephalopathy is a manifestation of acute or chronic renal failure. Approximately 20% of patients with acute kidney failure who are admitted to the intensive care unit develop neurologic symptoms. In contrast, those with chronic renal failure often develop only subtle signs.[77] The spectrum of uremic encephalopathy ranges from mild inattention to severe confusion and coma. Asterixis and multifocal myoclonus, often found in acute liver failure and hepatic encephalopathy, are common.[7] Other movement disorders, such as parkinsonism[78] and chorea, are rare.

The prevalence of uremia-induced RLS in patients with renal failure is approximately 22% and increases to 38% in those who have concomitant polyneuropathy.[79] Dopamine replacement therapy has shown to be efficacious in alleviating symptoms.[77]

Another rare autosomal recessive disease is *action myoclonus renal failure syndrome*, which is a form of progressive myoclonus epilepsy. In contrast to uremic encephalopathy, these patients do not improve after kidney transplantation or dialysis. Clinically, patients present initially with a tremor at rest and on action. With disease progression, multifocal myoclonic jerks dominate the clinical picture.[80] The disease is caused by a loss-of-function mutation of the *SCARB2* gene encoding the lysosomal integral membrane protein type 2 (*LIMP-2*) gene.[81]

Key points: Renal failure	
Clinical presentation	Renal failure can cause a variety of movement disorders, typically asterixis, multifocal myoclonus, and RLS; parkinsonism is rare
Diagnosis	Patients with uremic encephalopathy can improve after dialysis or kidney transplantation

MOVEMENT DISORDERS IN IRON DYSREGULATION

Hereditary hemochromatosis is an autosomal recessive disorder and the most common cause of systemic iron overload. Excessive iron accumulates in many organs, including the brain.[82] Movement disorders are generally rare, among these, parkinsonism and

ataxia are the most common. Neuroimaging studies have shown iron deposition in the basal ganglia, although none of these patients had movement disorders.[83] The diagnosis is usually made by assessing serum iron levels, transferrin, and ferritin saturation. Iron overload should be removed by regular phlebotomy. Those few patients reported with parkinsonism responded well to dopamine replacement therapy.

Key points: Hereditary hemochromatosis	
Etiology	Iron overload is usually caused by hereditary hemochromatosis
Clinical presentation	Clinical presentation: rare: parkinsonism and ataxia
Diagnosis	Serum iron, transferrin levels, ferritin; basal ganglia lesions on MRI or CT
Therapy	Phlebotomy Parkinsonism: dopamine replacement therapy

A large group of heterogeneous disorders collectively termed neurodegeneration of brain iron accumulation (NBIA) can cause movement disorders. Accumulation of brain iron within the basal ganglia is usually seen on T2-weighted MRI images. Movement disorders usually present in childhood; however, adult-onset cases can exist (Table 5).[84]

MOVEMENT DISORDERS IN ENDOCRINE DISORDERS

Similar to metabolic disorders, the spectrum of endocrine conditions causing movement disorders is broad. Those with classical movement disorder presentations are summarized in the following paragraphs.

Nonketotic Hyperglycemia

Onset of symptoms is usually acute in adults with type 2 diabetes. Chorea and hemichorea-hemiballismus are the presenting movement disorders. Other movement

Table 5
Most common neurodegeneration of brain iron accumulation (NBIA) causing movement disorders

NBIA	MRI Sign	Movement Disorder	Genetics
Pantothenate kinase associated neurodegeneration (*PKAN*)	Eye of the tiger	Oromandibular dystonia, dysarthria, parkinsonism, ataxia, spasticity	Recessive (*PANK2* gene)
PLA2G6	Iron deposition in globus pallidus and substantia nigra	Dystonia-parkinsonism	Recessive (*PLA2G6*)
Neuroferritinopathy	Cystic changes and iron accumulation in basal ganglia	Chorea, dystonia, parkinsonism	Dominant (*FTL*)
Aceruloplasminemia	Iron accumulation in basal ganglia	Craniofacial dyskinesias, ataxia	Recessive (ceruloplasmin gene)
Kufor-Rakeb disease	Iron accumulation in basal ganglia may occur	Parkinsonism, supranuclear gaze palsy, mini-myoclonus	Recessive (*ATP13A2*)

disorders include asterixis, seizures, and altered levels of consciousness. T1-weighted MRI brain scans reveal hyperintensities in the contralateral putamen.[85] These signal abnormalities usually resolve within months after clinical improvement. The mechanisms of hemichorea-hemiballism in this syndrome are likely microvascular lesions,[86] and depletion of gamma-aminobutyric acid and acetylcholine in the putamen.

Treatment involves correction of glucose levels. Dopamine blocking agents, such as neuroleptics, sodium valproate, and benzodiazepines, may be useful.[85]

Key points: Nonketotic hyperglycemia	
Clinical presentation	Acute hemichorea-hemiballism in older adults with type 2 diabetes [asterixis, reduced level of consciousness, and seizures may occur]
Diagnosis	Hyperglycemia, T1-weighted hyperintensity of contralateral putamen
Therapy	Correction of glucose levels, dopamine-blocking agents
Prognosis	Chorea usually resolves within days

Hyperthyroidism

Tremor is the most common movement disorder in patients with hyperthyroidism and can resemble essential tremor. Clinically, tremor occurs on action and affects the upper limbs, but cases of orthostatic tremor have been reported.[87] Other movement disorders, such as chorea, athetosis, and ballism, have been reported in fewer than 2% of patients.[88] Chorea usually affects young woman with Graves disease. Other rare movement disorders include myoclonus, task-specific dystonia, and cervical dystonia.[89] The pathophysiology is unknown, but may involve an influence of thyroid hormone on motor excitability. Symptoms usually respond to correction of elevated thyroid levels. Beta-blockers also are effective in reducing tremor.

Key points: Hyperthyroidism	
Prevalence	Rare, no epidemiologic studies
Clinical presentation	Action-tremor common; chorea, athetosis, paroxysmal dyskinesias, and dystonia are rare
Diagnosis	Elevated thyroid function tests
Therapy	Correction of hormonal levels; beta-blockers

Other causes of movement disorders in endocrine diseases are listed in **Table 6**.

MOVEMENT DISORDERS IN HEMATOLOGICAL DISEASE

Neuro-Acanthocytosis

This heterogeneous disorder presents with chorea, psychiatric complications, such as compulsive behavior and a frontosubcortical type of dementia, and erythrocyte acanthocytosis.

Chorea-Acanthocytosis

Chorea-acanthocytosis is a rare autosomal recessive disease caused by mutation of the *VPS13A* gene.[90] The age of onset is typically between 25 and 45 years and manifests with buccolingual dyskinesias, tongue protrusions ("feeding dystonia"), mutilations of tongue and lips, generalized chorea, and peripheral

Table 6
Common causes of endocrine disorders causing movement disorders

Etiology	Movement Disorder
Hypothyroidism	Parkinsonism
Addison disease	Parkinsonism
Hypoparathyroidism	Parkinsonism, ataxia, tremor, chorea, myoclonus
Hyperparathyroidism	Parkinsonism
Hypoglycemia	Paroxysmal chorea

neuropathy.[91] Blood smears may show acanthocytes and elevation of CK levels is seen in most cases. Western blot is more specific and shows reduced chorein expression.

The disease is chronically progressive. Dopamine-blocking agents, such as neuroleptics, can reduce chorea.

Key points: Chorea-acanthocytosis

Prevalence	Rare, no epidemiologic studies
Etiology	Autosomal-recessive mutations of *VPS13A* gene on chromosome 9q21 (coding for chorein)
Age on onset	Mid adulthood (age ~25–45 years)
Clinical presentation	Progressive chorea, cognitive decline, buccolingual dyskinesias with tongue protrusion, mutilations of tongue and lips, peripheral neuropathies, psychiatric symptoms, epileptic seizures (rare)
Diagnosis	Acanthocytes in blood smears (>4%), CK elevation, reduced chorein expression
Therapy	Dopamine-blocking agents
Prognosis	Relentlessly progressive, reduced life-expectancy

McLeod Syndrome

McLeod syndrome is an X-linked disorder typically manifesting between 30 and 40 years. Cardiomyopathy (in 67%), myopathy, orofacial dyskinesias, and neuropathy are typically seen. In contrast to chorea-acanthocytosis, self-mutilation and the "feeding dystonia" are rare. Neuropsychiatric complications, such as obsessive compulsive disorders and psychosis, are common.[92] Therapy is symptomatic to reduce chorea.

Key points: McLeod syndrome

Prevalence	Prevalence of McLeod syndrome unknown
Etiology	X-linked disorder
Age on onset	Mid adulthood (age ~30–40 years)
Clinical presentation	Progressive chorea, cognitive decline with psychiatric symptoms, cardiomyopathy; self-mutilation and feeding dystonia rare
Diagnosis	Acanthocytes in blood smear, mutation in *XK* gene
Therapy	Dopamine-blocking agents
Prognosis	Progressive with reduced life-expectancy

Polycythemia Vera

Polycythemia vera is a sporadic myeloproliferative disorder of the hematopoietic stem cells. The annual incidence is 2 to 10 cases per million population.[93] Movement disorders are generally rare. Chorea is the most common and occurs in 0.5% and up to 5% of cases. Chorea can be unilateral or generalized with orofaciolingual involvement.[94] Mutation in the janus kinase 2 (*JAK2*) gene, which is necessary for apoptosis,[95] may be responsible for chorea. Excess of erythrocytes, which in turn lead to hyperviscosity, may lead to reduced cerebral flow in the basal ganglia, although this theory could not be confirmed in a case report.[96] Chorea usually respond to dopamine-blocking agents and benzodiazepines. Phlebotomy also has been also shown to improve chorea.[97]

Key points: Polycythemia vera	
Prevalence	Chorea occurs in up to 5% of patients with polycythemia vera
Clinical presentation	Chorea can be unilateral or generalized with orofaciolingual involvement
Diagnosis	Elevated red blood cell mass, splenomegaly, and arterial oxygen saturation $\geq$92%
Therapy	Dopamine-blocking agents, benzodiazepines, and phlebotomy

MOVEMENT DISORDERS IN SYSTEMIC INTOXICATIONS

Manganese

Manganese toxicity can cause an extrapyramidal syndrome with symmetric bradykinesia, a dystonic "cock" gait, postural instability, and dysarthria. These neurologic symptoms are collectively termed as manganism and are often seen ephedrone abusers[98,99] and have been also described in welders who work poorly ventilated places.[100] Symptoms are usually progressive despite cessation of manganese exposure. Diagnosis can be made by measuring manganese levels in pubic hair.[101] Furthermore, T1-weighted MRI brain imaging shows typical pallidal lesions, whereas dopamine transporter (DAT) scans are normal.[98,101] There is currently no effective treatment. Some cases responded to chelation therapy,[102] but in most cases there was no improvement of clinical symptoms.[101]

Key points: Manganese toxicity	
Prevalence	Typically seen in welders and ephedrone abusers
Clinical presentation	Dystonia, parkinsonism, "cock gait," and severe dysarthria ("pallidal speech"); usually progressive despite cessation of exposure
Diagnosis	High concentration of manganese in pubic hair; T1-weighted pallidal lesions on MRI
Therapy	Chelation therapy may alleviate symptoms in a minority of patients

Methanol

Methanol is widely used, for example as a fuel additive or for the production of plastic. Once ingested, it is metabolized in the liver to formic acid, which is neurotoxic.[103] Lethargy, nausea, and, in some, coma or death can occur. Movement disorders include parkinsonism, ataxia, and dystonia.[103,104] CT and MRI brain imaging typically show bilateral putaminal lesions with or without hemorrhage and subcortical white matter lesions.[105] Symptoms are usually progressive and unresponsive to therapy such as anticholinergic drugs. However, dopamine-replacement therapy may be effective in alleviating motor handicaps.[106]

Key points: Methanol toxicity	
Toxicity	Methanol becomes toxic after being metabolized in the liver
Clinical presentation	Parkinsonism, ataxia and dystonia; symptoms usually progressive
Diagnosis	Bilateral putaminal lesion with or without hemorrhage on neuroimaging
Therapy	Usually progressive, dopamine-replacement therapy may alleviate symptoms

Carbon Monoxide

Carbon monoxide poisoning is common, causing more than 50,000 emergency department visits in the United States each year.[107] Carbon monoxide is a fragrance-free, tasteless gas that has greater affinity to hemoglobin than oxygen. Acute intoxication can lead to movement disorders such as rigidity, tremor, chorea, and generalized dystonia.[108] Chronic low-dose exposure, seen in firefighters, has been suggested to cause parkinsonism in later life.[109] T2-weighted MRI brain imaging may show basal ganglia lesions (see **Fig. 3**).[107] Administration of normobaric 100% oxygen is recommended. The use of hyperbaric oxygen is still conflicting[107] and is not readily available everywhere.

Key points: Carbon monoxide poisoning	
Toxicity	Usually occurs in poorly ventilated rooms with fuel-burning heaters or gas stoves and in suicide attempts inhaling car exhaust fumes
Clinical presentation	Altered consciousness, seizures, and cardiac arrest are frequently seen; movement disorders include chorea, dystonia, tremor, and rigidity
Diagnosis	Clinical history, T2-weighted MRI brain scan may reveal lesions in the basal ganglia and the hippocampus
Therapy	Inhalation of normobaric 100% oxygen

Cyanide

Cyanide is a lethal mitochondrial toxin resulting in respiratory arrest. Once indigested in a dose above 3 mg per kg of body weight, it leads to coma and rapid death.[108] Chronic exposure in miners can lead to parkinsonism, dystonia, and apraxia of eye lid opening.[110,111] Parkinsonism is caused by lesions in the basal ganglia, particularly the globus pallidus and the putamen.[110] Anticholinergic therapy can improve apraxia of eyelid opening, and parkinsonism may respond to amantadine in combination with levodopa.[111]

Key points: cyanide toxicity	
Toxicity	Cyanide is one of the most lethal toxins
Clinical presentation	Death follows within minutes; chronic exposure: parkinsonism, dystonia, and apraxia of eyelid opening
Diagnosis	History; neuroimaging may reveal lesions in the globus pallidus and the putamen
Therapy	Anticholinergics and dopamine-replacement therapy may improve apraxia of eyelid opening and parkinsonism; botulinum toxin should be considered for dystonia

Table 7
Summary of common movement disorders in metal and nonmetal intoxications

Chorea	Dystonia	Parkinsonism
Psychostimulants	Manganese	Carbon monoxide
Ethanol	Ephedrone	Manganese
Thallium	Carbon monoxide	MPTP
	Cyanide	Ephedrone
		Carbon monoxide
		Carbon disulfide
		Cyanide
		Toluene
		Ethanol

Abbreviation: MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

An overview of the most common systemic intoxications can be found in Table 7.

SUMMARY

- Movement disorders are a common but still underrecognized complication of a wide spectrum of systemic diseases.
- A careful medical history and judicious use of laboratory tests are required to recognize or rule out symptomatic causes of movement disorders.
- In many conditions, MRI of the brain may provide important clues to movement disorder etiologies in the setting of systemic diseases.
- Recognizing the underlying medical cause has important therapeutic implications. Commonly, specific treatment of the underlying condition will improve the secondary movement disorder, but often additional symptomatic therapy is also necessary.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.ncl.2014.09.015.

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