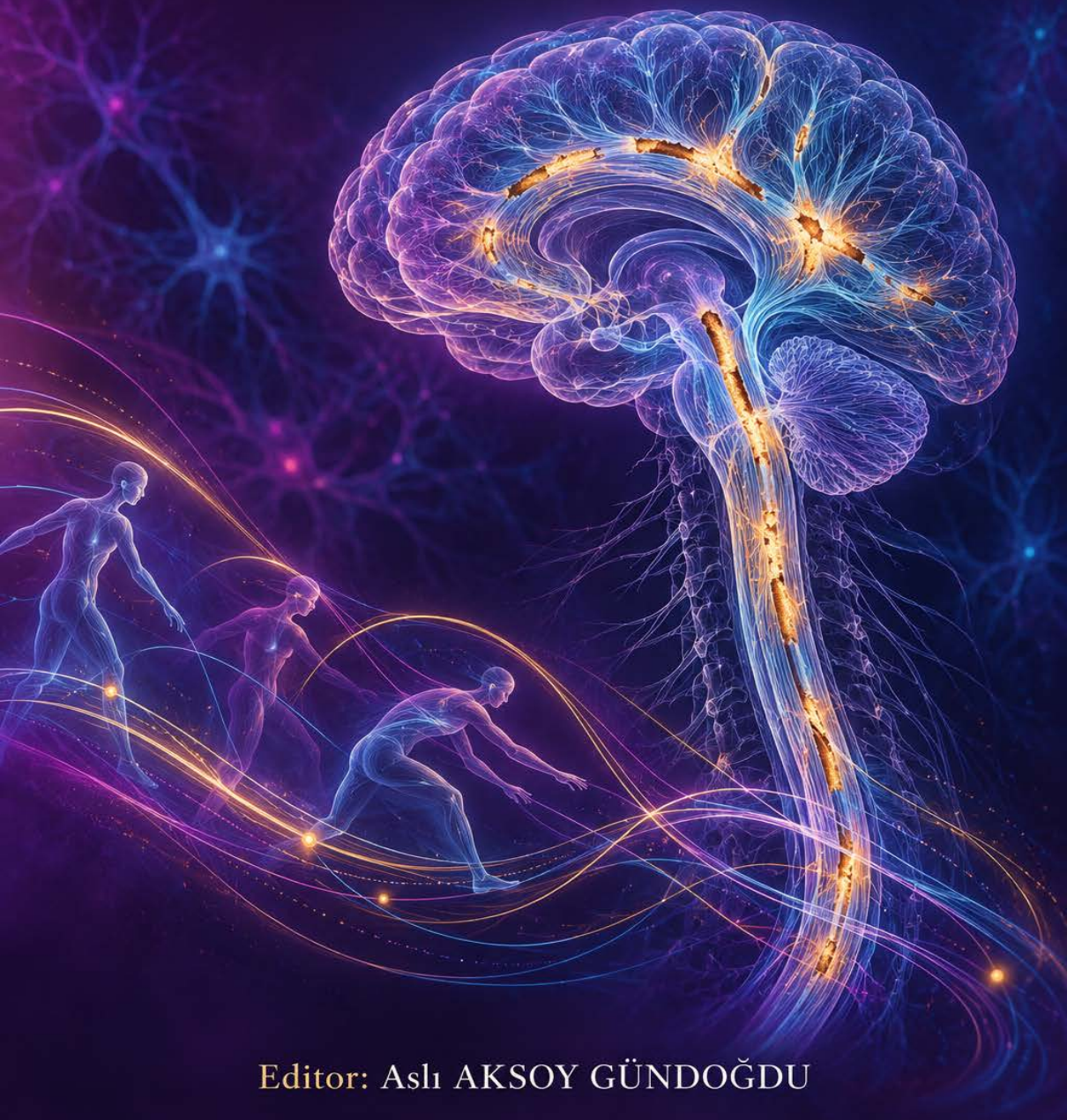
Movement Disorders in Central Nervous System Demyelinating Diseases



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Editor

Assoc. Prof. Dr. Aslı AKSOY GÜNDOĞDU

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Movement Disorders in Central Nervous System Demyelinating Diseases

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MOVEMENT DISORDERS IN INFLAMMATORY DEMYELINATING DISEASES OF THE CENTRAL NERVOUS SYSTEM: A DISEASE-COMPARATIVE DIAGNOSTIC APPROACH

Aslı AKSOY GÜNDOĞDU[1]

1. INTRODUCTION

Inflammatory demyelinating diseases of the central nervous system can cause motor manifestations beyond weakness, spasticity, and gait impairment. Tremor, ataxia, paroxysmal events, myoclonus, chorea, parkinsonism, facial movement phenomena, and restless legs syndrome (RLS) may appear at onset, during relapse or recovery, or after prior injury. A new abnormal movement may indicate active inflammation; a chronic symptom may reflect residual damage or unrelated disease.

Phenotype depends partly on lesion topography and affected motor networks, including cerebellar, brainstem, spinal, basal ganglia, thalamic, and midbrain pathways. Yet a movement disorder may reflect active demyelination, residual injury, or a coexisting primary disorder, epilepsy, medication effect, metabolic disturbance, structural lesion, or functional neurological disorder. Attribution requires precise phenomenology, a temporal relationship to disease activity, concordant magnetic resonance imaging (MRI), and assessment

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of competing explanations (Ghosh, Roy, Dubey, Das, & Benito-León, 2022; Kelly, Sun, Elkasaby, Wang, & Abboud, 2025).

Patterns differ among multiple sclerosis (MS), aquaporin-4 immunoglobulin G-positive neuromyelitis optica spectrum disorder (AQP4-IgG-positive NMOSD), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), and acute disseminated encephalomyelitis (ADEM). MS has the broadest reported spectrum. Painful tonic spasms and other paroxysmal events after myelitis are especially informative in AQP4-IgG-positive NMOSD. In MOGAD and ADEM, movement disorders may accompany multifocal inflammation, often in children, and must be interpreted with encephalopathy, lesion distribution, and antibody status (Abboud et al., 2024; Bringel et al., 2026; Kalampokini et al., 2026).

This chapter compares the diagnostic significance of movement disorders across these diseases. Dedicated chapters address MS-related tremor and ataxia, facial myokymia and hemifacial spasm, and secondary spinal dystonia in detail. Here, those phenotypes are discussed only when relevant to disease attribution, differential diagnosis, or recognition of inflammation. The focus is on clinical patterns, anatomical correlates, assessment, uncommon and sleep-related phenotypes, and the distinction between active disease, residual disability, and alternative diagnoses.

1.1. Scope and Terminology

The chapter covers acquired inflammatory demyelinating diseases of the central nervous system: MS, AQP4-IgG-positive NMOSD, MOGAD, and ADEM. Hereditary leukodystrophies, peripheral demyelinating neuropathies, progressive multifocal leukoencephalopathy, and osmotic demyelination syndrome lie outside its primary scope but merit consideration when the clinical or MRI presentation is atypical.

Movement disorders involve abnormal involuntary movement or impaired control of voluntary or automatic movement. Hyperkinetic phenomena include tremor, dystonia, chorea, ballism, myoclonus, tics, stereotypies, and paroxysmal dyskinesias; parkinsonism is the main hypokinetic syndrome considered here. Ataxia is included because cerebellar, sensory, vestibular, or mixed forms can arise in demyelinating disease. Cerebellar ataxia often accompanies tremor and can impair balance, gait, upper-limb function, and daily activities (Ghosh et al., 2022).

Phenomenology should precede anatomical or etiologic attribution. Tremor is involuntary rhythmic oscillation, described by distribution, activation condition, frequency when available, and associated signs. The International Parkinson and Movement Disorder Society recommends separating clinical features from etiology in a two-axis classification (Bhatia et al., 2018). Dystonia produces sustained or intermittent abnormal movements or postures that are usually patterned and repetitive, may be tremulous or jerky, and can worsen with action or overflow activation (Albanese et al., 2025).

Paroxysmal motor events are sudden, brief, stereotyped, recurrent episodes. Paroxysmal dyskinesia here denotes attacks dominated by dystonia, chorea, athetosis, or mixed movements. Painful tonic spasms are brief, stereotyped involuntary contractions associated especially with myelitis or spinal cord involvement; they serve mainly as diagnostic clues to spinal inflammation, particularly AQP4-IgG-positive NMOSD. Document awareness, triggers, duration, MRI correlation, and treatment response. Preserved awareness alone does not exclude focal aware seizures (Freiha et al., 2020).

Spasticity, paresis, and clonus may coexist with movement disorders but are distinct: velocity-dependent

increased tone, impaired voluntary power, and rhythmic stretch-induced motor responses, respectively. Each may resemble or amplify a paroxysmal event. Before attributing abnormal movement to demyelination, consider seizures, medication effects, functional disorders, metabolic disturbances, and coincidental primary movement disorders.

2. DISEASE-SPECIFIC CLINICAL PATTERNS AND EPIDEMIOLOGY

Movement-disorder frequency and phenotype vary across acquired inflammatory demyelinating diseases. Referral bias, inconsistent definitions, and case-report predominance for rare disorders limit direct comparisons. Clinical patterns should inform investigation, not serve as disease-specific diagnostic criteria.

MS has the broadest reported spectrum. In a prospective neuroimmunology-clinic cohort of 327 adults with relapsing or progressive MS, 64.5% had a movement disorder attributed to demyelination. Spinal phenotypes were most frequent, followed by brainstem-cerebellar patterns; striatal-thalamic disorders were uncommon. Tonic spasms and tremor led individual manifestations. This selected cohort does not provide population prevalence, but movement disorders occurred across the disease course and were more frequent with progressive disease or spinal lesions. In 6.4%, a movement disorder marked a new relapse or the first MS manifestation (Kelly et al., 2025).

AQP4-IgG-positive NMOSD has a distinctive spinal profile: painful tonic spasms and paroxysmal dystonia after myelitis suggest spinal involvement. A meta-analysis of 96 studies and 1,751 patients estimated pooled prevalences of 39% for tonic spasms or paroxysmal dystonia and 26% for ataxia in available study populations. In a prospective non-MS

demyelinating-myelopathy study, movement disorders were especially frequent in AQP4-IgG-positive NMOSD, and longitudinally extensive myelitis independently predicted spinal movement disorders (Abboud et al., 2024; Bringel et al., 2026). These symptoms aid diagnosis but cannot replace MRI correlation or antibody testing.

MOGAD epidemiology remains uncertain. A 2026 review identified 91 published patients with MOGAD and movement disorders; cerebellar ataxia was most common, followed by postural or kinetic tremor. Movement disorders were the initial manifestation in approximately 70% of these selected cases, particularly children; this is not a population frequency estimate. New ataxia, tremor, or mixed movements in a child or young adult with acute central nervous system inflammation should raise consideration of MOGAD, especially with an ADEM-like presentation (Kalampokini et al., 2026).

ADEM is usually a monophasic pediatric syndrome of encephalopathy and multifocal deficits. Cerebellar or brainstem involvement commonly produces acute ataxia; tremor, dystonia, chorea, and myoclonus occur less often with widespread brain inflammation. A reliable ADEM-specific prevalence estimate is unavailable. Myelin oligodendrocyte glycoprotein immunoglobulin G (MOG-IgG) testing matters in children with an ADEM phenotype because MOGAD may produce ADEM-like episodes and relapse (Lei et al., 2022; Wang, 2021).

Timing and context complement phenomenology. New symptoms may signal inflammation; persistent ones may reflect residual injury or comorbidity. Painful tonic spasms after longitudinally extensive myelitis favor AQP4-IgG-positive NMOSD, while ataxia with encephalopathy in a child suggests MOGAD or ADEM. These clues guide MRI, antibody testing,

and evaluation of alternative diagnoses. Table 1 summarizes the main patterns.

Table 1. Comparative Movement-Disorder Patterns in Inflammatory Demyelinating Diseases of the Central Nervous System

Disorder	More commonly reported patterns	Practical diagnostic clue
MS	Tremor, ataxia, RLS, paroxysmal motor events	New, clearly worsening, or stereotyped paroxysmal symptoms warrant assessment for relapse.
AQP4-IgG-positive NMOSD	Painful tonic spasms, paroxysmal dystonia, ataxia	Paroxysmal symptoms after myelitis favor spinal cord involvement.
MOGAD	Ataxia, postural or kinetic tremor	Consider in children or young adults with an acute inflammatory syndrome.
ADEM	Acute ataxia; less often tremor, dystonia, chorea, or myoclonus	Encephalopathy and multifocal deficits are important contextual clues.

Note: MS = multiple sclerosis; RLS = restless legs syndrome; AQP4-IgG = aquaporin-4 immunoglobulin G; NMOSD = neuromyelitis optica spectrum disorder; MOGAD = myelin oligodendrocyte glycoprotein antibody-associated disease; ADEM = acute disseminated encephalomyelitis. These patterns are not diagnostic in isolation. Information synthesized from Kelly et al. (2025), Abboud et al. (2024), Bringel et al. (2026), Kalampokini et al. (2026), Wang (2021), and Lei et al. (2022).

3. PATHOPHYSIOLOGY AND NEUROANATOMICAL CORRELATES

Movement disorders in inflammatory demyelinating disease reflect inflammation, disrupted motor networks, and accumulated axonal or tissue injury rather than damage to one structure alone. Lesion topography therefore helps interpretation: spinal lesions often accompany paroxysmal events, whereas

brainstem-cerebellar or deep gray matter lesions may underlie other phenotypes.

Cerebellar and brainstem lesions may cause gait or limb ataxia, action tremor, ocular motor abnormalities, and imbalance. Posterior column lesions may produce sensory ataxia, and vestibular involvement may add vertigo or postural instability. These mechanisms can coexist and complicate an apparently isolated tremor or gait disorder (Ghosh et al., 2022).

Myelitis may be accompanied or followed by painful tonic spasms, paroxysmal dystonia, or spinally generated jerks. Longitudinally extensive transverse myelitis is strongly associated with spinal movement disorders in AQP4-IgG-positive NMOSD (Abboud et al., 2024). Inflammation and demyelination may alter pathway conduction and excitability, although the mechanism of an individual attack is seldom directly established.

Less common basal ganglia, thalamic, or midbrain lesions may correlate with dystonia, chorea, ballism, or parkinsonism. Location alone does not establish causality. Temporal association with relapse or MRI activity and exclusion of vascular, toxic, metabolic, degenerative, and medication-related causes remain essential, especially in older patients or those with vascular risk factors.

Edema, conduction failure, and reversible network dysfunction may cause transient symptoms during acute inflammation. Persistent manifestations may reflect incomplete recovery, axonal injury, network reorganization, or chronic neurodegeneration. This distinction guides investigation for active disease versus management of residual deficits.

4. CLINICAL ASSESSMENT AND DIAGNOSTIC APPROACH

Assessment begins by describing the movement, not assuming demyelinating causation. Establish onset and course, episode duration and frequency, distribution, pain or sensory symptoms, triggers, and relation to other neurological symptoms or suspected relapse. Movement, touch, hyperventilation, position, fatigue, or sleep deprivation may trigger selected phenotypes. Record awareness, stereotypy, and post-event symptoms; obtain a typical-event video when episodes are brief or difficult to reproduce (Freiha et al., 2020).

Examine the movement at rest, during posture and action, and during gait. Rhythm, regularity, distribution, amplitude, activation, overflow, sensory tricks, distractibility, entrainment, and suppressibility help distinguish tremor, dystonia, myoclonus, tics, clonus, and functional phenomena. Also assess tone, weakness, reflexes, sensation, cerebellar and ocular motor signs, and gait. Functional movement disorders may coexist with inflammatory disease and require positive clinical signs; normal MRI alone does not establish the diagnosis (Park, 2024).

Interpret brain and spinal MRI against symptom timing, phenomenology, and prior studies. A new or enhancing lesion in a plausible motor network supports, but does not prove, inflammatory causation; stable lesions may represent chronic sequelae or incidental findings. Consider cervical and thoracic spinal MRI, with whole-cord coverage for suspected myelitis, in patients with paroxysmal events, spinal myoclonus, sensory symptoms, or pyramidal signs. Imaging also helps exclude vascular, neoplastic, infectious, degenerative, and structural causes (Jarius et al., 2023).

Consider serum AQP4-IgG and MOG-IgG testing when clinical or MRI findings are atypical for MS, particularly with

myelitis, brainstem or cerebellar syndromes, encephalopathy, or unusual relapsing movement phenomena. Prefer cell-based assays. Interpret MOG-IgG in context, especially with low titers or delayed testing. MOGAD diagnosis requires a compatible acquired demyelinating event, positive serum MOG-IgG, supportive clinical or MRI features when indicated, and exclusion of a likelier diagnosis (Banwell et al., 2023).

Electroencephalography (EEG) is useful when impaired awareness, behavioral arrest, evolving semiology, or postictal symptoms suggest seizures. A normal interictal EEG does not exclude focal epilepsy; capture events when feasible. Surface electromyography (EMG), accelerometry, and EEG-EMG polygraphy may differentiate tremor, cortical or spinal myoclonus, clonus, and functional jerks (Hallett et al., 2021). Guide metabolic tests, medication review, and assessment for infection, vascular disease, or primary movement disorders by the clinical phenotype.

Attribute a movement disorder to active demyelination only when timing, phenomenology, examination, MRI, and exclusion of competing causes form a coherent pattern. Treatment response can support, but does not independently establish, causation (Kelly et al., 2025).

5. PAROXYSMAL MOTOR EVENTS: CLINICAL FRAMING

Paroxysmal motor events are brief, recurrent, stereotyped episodes that may occur at onset, during relapse, or after myelitis. They are diagnostically important: MS events may accompany brainstem or spinal lesions, while painful tonic spasms and paroxysmal dystonia in AQP4-IgG-positive NMOSD are especially informative during or after recovery from longitudinally extensive myelitis. New or escalating attacks

warrant assessment for active spinal inflammation and review of MRI (Abboud et al., 2024; Bringel et al., 2026).

Stereotypy alone does not establish demyelinating causation. Focal seizures, clonus, spasticity-related spasms, medication effects, metabolic disturbances, and functional disorders may resemble paroxysmal events. Duration, awareness, associated symptoms, timing relative to myelitis or relapse, MRI, and EEG when indicated guide the differential (Freiha et al., 2020).

6. OTHER HYPERKINETIC AND HYPOKINETIC MOVEMENT DISORDERS

Chorea, athetosis, ballism, parkinsonism, myoclonus, tics, and stereotypies are uncommon in these diseases. Temporal coexistence with MS, NMOSD, MOGAD, or ADEM does not prove causation. Assess vascular, metabolic, toxic, infectious, degenerative, genetic, and functional causes before attributing an unusual movement to demyelination (Ghosh et al., 2022).

Chorea comprises irregular, unpredictable movements migrating across body regions; athetosis is slower and writhing, while ballism is high-amplitude proximal chorea. Striatal, pallidal, subthalamic, thalamic, or connecting-pathway lesions may be relevant. Acute hemichorea or hemiballism requires prompt exclusion of stroke, nonketotic hyperglycemia, medication effects, and infection. Such phenotypes are reported in MS, NMOSD, and MOGAD, but evidence comes mainly from cases and small series (Ghosh et al., 2022; Kalampokini et al., 2026).

Parkinsonism requires bradykinesia plus rigidity or rest tremor. It is rare in demyelinating disease and may be coincidental Parkinson disease, especially in older patients. Inflammatory

causation is more plausible with acute or subacute onset, concurrent disease activity, and a new basal ganglia, thalamic, midbrain, or nigrostriatal lesion. Steroid or dopaminergic response is supportive but inconclusive; longitudinal assessment and serial imaging are usually more informative (Ghosh et al., 2022).

Myoclonus comprises sudden, brief, shock-like movements from contraction or interruption of muscle activity. Distinguish cortical, subcortical, brainstem, segmental spinal, and propriospinal patterns when possible. EEG-EMG polygraphy may help identify cortical correlates and distinguish epileptic myoclonus from clonus, tremor, or functional jerks. Myoclonus is rarely reported in MS, NMOSD, or MOGAD. Concurrent encephalopathy, seizures, or prominent psychiatric symptoms should broaden investigation to autoimmune encephalitis and other inflammatory or metabolic disorders (van der Veen et al., 2022).

Premonitory urge and partial suppressibility support tics; stereotypies are generally more fixed, repetitive, and without urge. Reports in MS and pediatric MOGAD rarely establish demyelinating causation. In MOGAD and NMOSD, myoclonus, parkinsonism, chorea, and other rare hyperkinetic phenotypes appear much less often in published reports than ataxia or paroxysmal events (Bringel et al., 2026; Kalampokini et al., 2026). Table 2 summarizes anatomical correlates and alternative diagnoses.

Table 2. Rare Movement Disorders in Inflammatory Demyelinating Diseases: Potential Neuroanatomical Correlates and Essential Alternative Diagnoses

Phenotype	Potential neuroanatomical correlate	Essential alternative diagnoses
Chorea, athetosis, or ballism	Contralateral striatum, globus pallidus, subthalamic nucleus, thalamus, or related pathways	Acute ischemic or hemorrhagic stroke; nonketotic hyperglycemia; drug or toxic exposure; infection or autoimmune encephalitis
Parkinsonism	Basal ganglia, thalamus, midbrain, or nigrostriatal pathways	Idiopathic Parkinson disease; drug-induced or vascular parkinsonism; atypical neurodegenerative parkinsonism; structural lesions
Myoclonus	Cortical, subcortical, brainstem, segmental spinal, or propriospinal generators	Epileptic myoclonus; toxic, metabolic, or medication-related myoclonus; clonus; tremor; functional jerks; autoimmune encephalitis
Tics or stereotypies	No reliable focal lesion correlate	Primary tic disorder, including Tourette syndrome; functional tic-like behaviors; compulsions; neurodevelopmental disorders; medication-related movements

Note: A neuroanatomically plausible lesion supports, but does not independently establish, attribution to inflammatory demyelination. Temporal association with disease activity, MRI correlation, and exclusion of competing causes are required. MRI = magnetic resonance imaging. Information synthesized from Ghosh et al. (2022), van der Veen et al. (2022), and Kalampokini et al. (2026).

7. RESTLESS LEGS SYNDROME AND SLEEP-RELATED MOVEMENT DISORDERS

RLS causes an urge to move the legs, often with unpleasant sensations, that worsens at rest and in the evening or night and improves at least temporarily with movement. In MS,

it can disrupt sleep and contribute to fatigue, depressive symptoms, pain, and poorer quality of life. A meta-analysis of 75 studies found pooled RLS prevalence of 28% in MS versus 8% in controls; substantial heterogeneity limits application to individual settings (Zali et al., 2023).

Potential contributors to RLS in MS include spinal lesions, altered motor or sensory pathways, iron deficiency, medications, insomnia, sleep-disordered breathing, and comorbidities. Studies of spinal-lesion association conflict (Baba, Ozdogar, Ozcelik, Kaya, & Ozakbas, 2022; Eskut, Koskderelioglu, Gedizlioglu, & Onder, 2023). Evidence is less extensive for NMOSD and insufficient for MOGAD or ADEM (Ozdogar et al., 2025; Shaygannejad et al., 2020).

Distinguish RLS from cramps, spasticity-related discomfort, akathisia, neuropathy, radiculopathy, positional discomfort, and painful tonic spasms. Document circadian timing, relation to rest and movement, sleep disruption, daytime effects, family history, and exacerbating drugs or substances. Assess ferritin, transferrin saturation, renal function when appropriate, medication use, and coexisting insomnia or sleep-disordered breathing.

Periodic limb movements during sleep (PLMS) may accompany RLS and fragment sleep. A polysomnography review found higher periodic limb movement and arousal indices in MS than controls (Zhang et al., 2023). PLMS alone do not establish periodic limb movement disorder. Reserve polysomnography for diagnostic uncertainty or suspected PLMS, sleep-disordered breathing, or another sleep disorder.

First address iron deficiency, exacerbating medications, sleep disruption, and comorbidities. Guidance supports iron replacement when indicated and gabapentinoids for many patients with persistent clinically significant RLS. Dopamine

agonists suit selected patients but require caution about augmentation with long-term use (Winkelman et al., 2025). Assess benefit through sleep quality, daytime function, fatigue, and patient-reported burden, not attack frequency alone.

8. TREATMENT AND REHABILITATION

First determine whether a movement disorder reflects active inflammation, residual deficit, or unrelated disease. New or rapidly worsening symptoms with clinical or MRI evidence of relapse require prompt disease-directed treatment; symptomatic therapy must not delay acute attack care. Follow established acute-treatment and relapse-prevention strategies for the underlying disease, especially AQP4-IgG-positive NMOSD, whose attacks often leave substantial disability (Kümpfel et al., 2024).

Once active inflammation is excluded or treated, base symptomatic care on phenotype and functional impact. For chorea, parkinsonism, myoclonus, tics, or stereotypies, first address possible medication, metabolic, vascular, epileptic, or primary movement-disorder causes. Consider standard symptomatic treatment when demyelinating causation remains plausible, ideally with movement-disorder specialist input.

Begin individualized rehabilitation once medically stable. Physical therapy addresses balance, gait, coordination, endurance, transfers, and falls; occupational therapy addresses daily and work activities, aids, and home safety. Speech and language therapy may help dysarthria, dysphagia, or communication problems from brainstem or cerebellar disease. Plans should account for fatigue, pain, spasticity, sensory or visual loss, sleep disturbance, mood, and cognition.

Task-specific, sufficiently intensive rehabilitation can improve MS mobility and balance, though optimal treatment depends on disability and goals (Corrini et al., 2023). Evidence for NMOSD, MOGAD, and ADEM is limited. Combine disease-specific expertise with cautious extrapolation from MS studies and reassess safety, independence, participation, and caregiver burden (Abboud et al., 2022).

9. CONCLUSION

Movement disorders in inflammatory demyelinating disease may mark onset or active inflammation, persist after tissue injury, or represent unrelated comorbidity. Attribution requires coherent phenomenology, symptom course, examination, lesion topography, MRI activity, antibody status, and exclusion of alternatives; coexistence alone is insufficient.

Disease patterns refine but do not establish attribution. Painful tonic spasms or paroxysmal dystonia after myelitis suggest spinal involvement, especially in AQP4-IgG-positive NMOSD. Acute ataxia or mixed movements in a child with central nervous system inflammation suggest MOGAD or ADEM. In MS, a new, clearly worsening, or stereotyped paroxysmal movement disorder may indicate relapse, whereas persistent symptoms may reflect established injury or disability (Abboud et al., 2024; Bringel et al., 2026; Kalampokini et al., 2026; Kelly et al., 2025).

Active inflammation needs timely disease-directed treatment and relapse prevention. Residual movement disorders need phenotype-guided symptomatic care, rehabilitation, and support for mobility, upper-limb function, communication, sleep, and daily participation. This approach helps avoid delayed attack treatment and unwarranted demyelinating attribution.

Evidence is stronger for common MS manifestations than for rare hyperkinetic and hypokinetic phenotypes or disorders in NMOSD, MOGAD, and ADEM. Prospective studies need standardized phenomenology, video-supported assessment, longitudinal MRI, and patient-centered outcomes. Pending stronger evidence, careful characterization, cautious attribution, and individualized multidisciplinary care remain central.

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ATAXIA IN MULTIPLE SCLEROSIS: CLINICAL FEATURES AND TREATMENT APPROACHES

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1. INTRODUCTION

Multiple sclerosis (MS) is a chronic disease characterised by inflammation, demyelination and neuroaxonal damage of the central nervous system, with a course of heterogeneous clinical manifestations. Involvement of the cerebellum and its connecting pathways is among the common and disabling features of the disease; up to 80% of patients develop tremor or ataxia at some point during the disease course (Mills, Yap, & Young, 2007). Cerebellar dysfunction may emerge during an acute relapse or may also show persistent or progressive features, and it restricts the patient's independence in daily life by impairing motor coordination and postural control (Wilkins, 2017).

Ataxia is a coordination disorder arising from impairments in the timing, speed, amplitude and accuracy of voluntary movements. In MS, ataxia is mostly associated with involvement of the cerebellum or cerebellar connections; however, involvement of the proprioceptive, vestibular and pyramidal pathways may also contribute to the clinical picture (Wilkins, 2017). Evidence regarding ataxia-specific pharmacological treatments is limited; management encompasses control of disease activity, symptomatic treatment and rehabilitation together (Mills et al., 2007). This chapter addresses the neuroanatomical and pathophysiological basis, clinical

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features and assessment methods of ataxia in MS, and evaluates pharmacological, rehabilitative and interventional treatment approaches in the light of the current literature.

2. NEUROANATOMICAL AND PATHOPHYSIOLOGICAL BASIS OF ATAXIA IN MULTIPLE SCLEROSIS

The cerebellum can be examined functionally in three regions. The vestibulocerebellum (flocculonodular lobe) plays a role in the control of balance and eye movements. Within the spinocerebellum, the vermis regulates the coordination and muscle tone of trunk and proximal limb movements, whereas the paravermal region regulates those of distal limb movements. The cerebrocerebellum (lateral hemispheres) is involved in the planning and initiation timing of movements. Therefore, vestibulocerebellar and vermal involvement leads to nystagmus, truncal instability and wide-based gait, whereas hemispheric involvement leads to dysmetria, dysdiadochokinesia and intention tremor (Unverdi & Alsayouri, 2023). Since information flow to and from the cerebellum is conveyed via the superior, middle and inferior cerebellar peduncles, demyelination of these pathways in MS may cause ataxia even when the cerebellar cortex is relatively preserved (Wilkins, 2017).

In MS, cerebellar pathology is not limited to white matter plaques. Kutzelnigg and colleagues showed that, particularly in primary and secondary progressive MS, on average 38.7% of the cerebellar cortex is demyelinated (reaching 92% in some cases) and that most cortical lesions develop independently of adjacent white matter lesions (Kutzelnigg et al., 2007). Redondo and colleagues, in turn, reported Purkinje cell loss, spheroids in Purkinje axons and changes in neurofilament phosphorylation, predominantly in areas of leucocortical demyelination (Redondo

et al., 2015). These findings indicate that cerebellar dysfunction is associated with neuronal and axonal damage in addition to myelin loss.

Advanced neuroimaging studies can detect microstructural changes even in connecting pathways in which no lesion is seen on conventional magnetic resonance imaging (MRI). In a meta-analysis including eleven studies (623 patients with relapsing–remitting MS [RRMS] and 416 healthy controls), reduced fractional anisotropy and increased mean diffusivity in the cerebellar peduncles were reported on diffusion tensor imaging (DTI); however, marked heterogeneity was found between studies (Broomand Lomer, Saberi, AmirAshjei Asalemi, & Sarlak, 2025). Regional cerebellar volume loss has also been associated with motor and cognitive outcomes in longitudinal follow-up (Parmar et al., 2022). Nevertheless, these measures are not validated biomarkers indicating the severity of ataxia in the individual patient.

3. CLINICAL FEATURES OF ATAXIA IN MULTIPLE SCLEROSIS

In MS, ataxia manifests as impaired limb coordination, postural instability and walking difficulty. In limb ataxia, dysmetria, dysdiadochokinesia and impaired timing of movements predominate, whereas truncal ataxia causes difficulty with postural control while sitting and standing. The clinical picture may be accompanied by intention and postural tremor, cerebellar dysarthria, nystagmus and saccadic dysmetria. As the motor, sensory and cerebellar systems are frequently affected together, the clinical presentation often reflects the effect of more than one mechanism (Kenyon et al., 2023).

Gait ataxia is characterised by a wide base of support, irregularity in step length and rhythm, increased trunk sway and

instability during turns. In a cohort of 204 patients with MS who underwent instrumented gait analysis, 14.2% of patients were classified into the ataxic gait pattern group according to functional system scores, and reduced walking speed together with increased step variability was found in this group. The resemblance of the pyramidal pattern to the ataxic pattern shows that assessment should consider not only walking speed but also spatiotemporal features such as step variability (Trentzsch, Schriefer, Stölzer-Hutsch, Inojosa, & Ziemssen, 2025).

Cerebellar involvement may be subclinical in the early period. Cerebellar involvement was detected by eye movement recordings in 16 of 29 patients with clinically isolated syndrome at high risk of conversion to MS; the Nine-Hole Peg Test (9HPT) distinguished patients from healthy controls but could not differentiate between patients with and without cerebellar involvement (Moroso et al., 2017).

Early cerebellar signs, including ataxia, may have prognostic importance. In a cohort of 10,513 patients from the MSBase registry, a cerebellar presentation in the first two years was associated with a higher risk of disability progression, whereas a brainstem presentation was associated with a lower risk (Le et al., 2021). Early cerebellar involvement should therefore be considered in prognostic assessment and treatment planning.

Unlike persistent coordination impairment, paroxysmal dysarthria-ataxia follows a course of brief, sudden-onset, stereotyped and recurrent attacks; the neurological examination may be normal between attacks. Distinguishing this presentation from chronic cerebellar ataxia is important for the choice of treatment (Freiha et al., 2020).

4. CLINICAL ASSESSMENT OF ATAXIA IN MULTIPLE SCLEROSIS

In the neurological examination, limb coordination, truncal stability, gait, speech and oculomotor functions should be assessed together. Dysmetria, dysdiadochokinesia, intention tremor and impaired tandem gait are the core signs of cerebellar involvement. Since concurrent involvement of the pyramidal, proprioceptive and vestibular systems may mimic these signs, cerebellar signs need to be distinguished from impairments originating from other systems. Describing limb coordination, postural balance and tremor separately in the clinical record makes it easier to monitor which function a treatment modifies (Kenyon et al., 2023).

The Scale for the Assessment and Rating of Ataxia (SARA) and the International Cooperative Ataxia Rating Scale (ICARS) are used for the quantitative assessment of ataxia severity (Table 1). The eight-item SARA assesses gait, stance, sitting, speech and limb coordination on a scale of 0–40 points, whereas the 19-item ICARS assesses posture and gait, kinetic functions, speech and oculomotor disorders on a scale of 0–100 points. As SARA has no oculomotor section, eye movements should be examined separately. In the Turkish adaptation study, the inter-rater and test–retest reliability of both scales was found to be high in 80 patients with MS who had cerebellar signs and mild pyramidal involvement, and the correlation of ICARS with the Expanded Disability Status Scale (EDSS) and the cerebellar functional system score was found to be stronger than that of SARA. The generalisability of the findings to patients with moderate or severe pyramidal involvement is limited (Salcı, Fil, Keklicek, et al., 2017). The International Parkinson and Movement Disorder Society (MDS) has also classified ICARS as the recommended scale for the assessment of cerebellar symptoms in MS (Perez-Lloret et al., 2021).

Although the EDSS contains a subscore relating to cerebellar functions, it does not measure the components of ataxia in detail. The 9HPT, timed walking tests and balance scales provide complementary information on functional impairment; however, they are not specific to cerebellar dysfunction (Feys et al., 2017; Kenyon et al., 2023). Indeed, in the Turkish adaptation study, no significant correlation was found between the Berg Balance Scale and SARA or ICARS (Salcı, Fil, Keklicek, et al., 2017). Therefore, ataxia severity and functional performance should be monitored together, and improvement in one domain should not be interpreted as improvement in the other domains as well.

Table 1. Scope and Interpretive Limitations of the Tools Used in the Assessment of Ataxia in MS

Tool	Main domain assessed	Interpretive limitation
SARA	Trunk, gait, speech and limb coordination; 0–40	No oculomotor section; an MS-specific threshold for clinically meaningful change has not been established.
ICARS	Posture–gait, kinetic function, speech and eye movements; 0–100	More detailed; in MS, its factor structure does not fully match the original subscales.
EDSS and cerebellar functional system score	Overall disability and cerebellar involvement	Does not measure the components of ataxia in detail.
9HPT	Manual dexterity and task performance	Not specific to ataxia; does not distinguish cerebellar involvement on its own.
Balance and timed walking tests	Postural control, mobility and walking performance	Improvement should not be interpreted as a reduction in ataxia severity.
Quantitative eye movement and gait analysis	Subtle oculomotor disorders and spatiotemporal gait characteristics	Differences in devices and protocols limit generalisability.

Note: Compiled by the author from data in Salcı, Fil, Keklicek, et al. (2017), Perez-Lloret et al. (2021), Feys et al. (2017), Moroso et al. (2017) and Trentzsch et al. (2025).

In new-onset or worsening ataxia, causes other than MS should also be excluded. Drug-induced ataxia is a cause that may be overlooked. The most common responsible drug groups are antiepileptics (e.g. carbamazepine, oxcarbazepine, gabapentin) and benzodiazepines. Symptoms usually appear within days or weeks after starting a new drug or increasing the dose and generally resolve when the drug is discontinued (van Gaalen, Kerstens, Maas, Härmark, & van de Warrenburg, 2014). Alcohol use and vitamin B12 deficiency may also lead to ataxia. Since sensory and vestibular ataxia may mimic cerebellar ataxia, they should be considered in the differential diagnosis (Hafiz & De Jesus, 2023).

5. TREATMENT OF ATAXIA IN MULTIPLE SCLEROSIS: GENERAL PRINCIPLES AND PHARMACOLOGICAL APPROACHES

The treatment of ataxia in MS is planned according to the pattern of symptom onset and its effect on daily functioning. Persistent cerebellar ataxia, acute cerebellar relapse, paroxysmal dysarthria-ataxia and predominant upper limb tremor require different approaches (Table 2). Since weakness, spasticity, sensory loss and vestibular disorders may coexist, the aim of treatment is to enable the patient to move safely and to support their independence in daily activities (Kenyon et al., 2023; Wilkins, 2017).

In new-onset or increasing ataxia, a distinction should be made between relapse, pseudorelapse and progression. Infection, fever and a rise in body temperature may temporarily worsen existing symptoms. In a true relapse affecting daily functioning, a high-dose corticosteroid course is recommended. Oral methylprednisolone 500 mg daily for 5 days is a standard regimen; intravenous methylprednisolone 1 g daily for 3–5 days

is an alternative when oral treatment is unsuitable, relapse is severe, or hospital monitoring is needed (National Institute for Health and Care Excellence [NICE], 2026; Ramo-Tello et al., 2022). Plasma exchange may be considered in severe relapses with an inadequate response (Ramo-Tello et al., 2022). Corticosteroids accelerate recovery from a relapse but do not correct persistent ataxia. New disease activity may require a review of disease-modifying therapy; control of disease activity and symptomatic management of existing ataxia are separate goals (NICE, 2026).

Evidence on the pharmacological treatment of persistent cerebellar ataxia is limited. In the Cochrane review, no reliable treatment recommendation could be made owing to methodological problems and differing outcome measures (Mills et al., 2007), and the NICE evidence review likewise found insufficient evidence to develop a recommendation for or against any specific drug for ataxia and tremor (NICE, 2022). This does not indicate that the drugs are ineffective, but rather that their benefits and risks are uncertain.

In a double-blind, placebo-controlled crossover study of 48 patients evaluating levetiracetam, 9HPT performance of the more affected hand improved during the three-week treatment periods; however, the other clinical and kinematic outcomes did not improve consistently. The short follow-up and a primary outcome focused on manual dexterity limit the generalisability of the findings to truncal and gait ataxia (Solaro et al., 2020).

Fampridine is a potassium channel blocker approved for improving walking in adult patients with MS who have walking disability; response to treatment is assessed within the first 2–4 weeks, and the drug is discontinued if no benefit is observed (European Medicines Agency [EMA], n.d.). In a meta-analysis of 18 studies, most of which were non-placebo-controlled before–

after studies, improvement in walking measures was reported (Ghorbanpour, Rahimibarghani, Rohani, Rastkar, & Ghajarzadeh, 2023); however, there are no controlled data on the ataxia-specific efficacy of fampridine.

In paroxysmal dysarthria-ataxia, a good response to antiepileptics, particularly carbamazepine, has been reported; however, the evidence is based largely on case reports (Freiha et al., 2020). In attacks occurring for the first time, inflammatory activity should also be evaluated (Ramo-Tello et al., 2022).

Evidence for the pharmacological treatment of accompanying tremor is also limited. A systematic review reported inconsistent results for 5-HT3 receptor antagonists and levetiracetam, and limited benefit and significant adverse effects for isoniazid; cannabis-based products were not recommended. Botulinum toxin A may reduce tremor, but post-injection muscle weakness limits functional gain (Pourmohammadi, Riahi, Hosseini, & Adibi, 2022). NICE (2022) did not find sufficient evidence to make a recommendation on botulinum toxin. A reduction in tremor should not be equated with an improvement in global ataxia severity.

Table 2. Treatment Options and Limitations of the Evidence for Ataxia and Associated Symptoms in MS

Clinical presentation	Option	Evidence and limitations
Acute cerebellar relapse	High-dose corticosteroids; plasma exchange if the response is inadequate	Consensus recommendations; does not correct persistent ataxia.
Persistent cerebellar ataxia	Individualised rehabilitation; no approved ataxia-specific drug	Insufficient pharmacological evidence (Cochrane, NICE).
Limb ataxia affecting manual dexterity	Levetiracetam (investigational)	Single randomised crossover study (n=48); short follow-up, inconsistent secondary outcomes.
Walking impairment	Fampridine; response assessed at 2–4 weeks	Approved for walking; no controlled ataxia-specific data.
Paroxysmal dysarthria-ataxia	Antiepileptics, particularly carbamazepine	Case reports.
Drug-resistant tremor	Botulinum toxin A; deep brain stimulation (DBS) or thalamotomy in selected cases	Small and heterogeneous studies; risk of weakness; does not correct ataxia.
Loss of balance and walking ability	Task-oriented training, trunk stabilisation; neuromodulation at the research stage	Small randomised studies; lack of long-term follow-up.

Note: Compiled by the author from data in Mills et al. (2007), NICE (2022), Ramo-Tello et al. (2022), Solaro et al. (2020), EMA (n.d.), Freiha et al. (2020), Pourmohammadi et al. (2022), Zali et al. (2021) and Chasiotis et al. (2023).

6. REHABILITATION OF ATAXIA IN MULTIPLE SCLEROSIS

Rehabilitation forms the cornerstone of ataxia management in MS and aims to reduce the impact of coordination impairment on daily life and to support safe movement. The

programme should be individualised on the basis of limb and trunk control, balance, gait and the daily activities prioritised by the patient. Accompanying weakness, spasticity, sensory loss and fatigue determine the content and intensity of exercise (Chasiotis et al., 2023).

Evidence specific to MS-related cerebellar ataxia is promising but limited. In a systematic review evaluating three randomised controlled studies and three pilot studies including a total of 145 patients, post-treatment gains were reported in most of the neurodevelopmental (Bobath) therapy, robotic and visual feedback training, and functional rehabilitation programmes. However, small samples, differing interventions and a lack of long-term follow-up made it difficult to establish a common protocol (Chasiotis et al., 2023).

Trunk stabilisation and task-oriented training are approaches that have been investigated directly in patients with MS and ataxia. In the study by Salcı and colleagues, which enrolled 42 patients, gains in ICARS and the composite balance score were greater in the groups in which lumbar stabilisation or task-oriented training was added to balance training than in the group receiving balance training alone. However, the fact that session duration was twice as long in the additional training groups (90 versus 45 minutes) makes this difference difficult to interpret (Salcı, Fil, Armutlu, et al., 2017). In another study including 45 patients with ataxic RRMS, task-oriented training added to conventional balance training was found to be superior to the control group in all balance measures, whereas the group with added trunk stabilisation did not differ from the control group (Ali, Darwish, Shalaby, Abbas, & Soubhy, 2021).

In a pilot study investigating the addition of local vibration to eight weeks of spinal stabilisation training in 30 ambulatory patients with ataxic MS, postural control improved in all groups.

Paraspinal vibration provided additional gains in the Berg Balance Scale, and gastrosoleus vibration in step length and gait variability; no additional benefit of vibration on ataxia severity (ICARS) was shown (Özvar Şenöz, Onursal Kılınç, Doğan, & Kılınç, 2026).

In clinical practice, exercise should start with movements the patient can perform safely; daily tasks such as rising from sitting, reaching, carrying objects, changing direction and walking should be selected according to the individual's functional loss, and rest intervals and exercise load should be adjusted according to fatigue (Ali et al., 2021; NICE, 2022). Occupational therapy and speech therapy for dysarthria are also among the treatment options in the management of ataxia (Zengin, 2024). Reducing the risk of falls is one of the important goals of rehabilitation. In a systematic review evaluating 16 studies in MS, exercise interventions improved balance moderately, with the greatest gains achieved through gait, balance and functional training. However, the reduction in falls risk was small and not statistically significant (Gunn, Markevics, Haas, Marsden, & Freeman, 2015). In monitoring treatment response, ataxia severity, balance and mobility should be measured separately, and the transfer of gains to daily life and their durability should be questioned (Chasiotis et al., 2023; Kenyon et al., 2023).

7. INTERVENTIONAL TREATMENTS AND NEUROMODULATION

Interventional treatments may be considered in selected patients with drug-resistant tremor that markedly restricts daily life. In a meta-analysis including 17 studies and 168 patients, improvement in tremor was reported in 73% of patients after deep brain stimulation (DBS); however, heterogeneity between studies

was high (Zali et al., 2021). Tremor may also decrease after lesional procedures such as thalamotomy; however, the durability of the effect is variable, and neither method corrects accompanying ataxia. Therefore, the contributions of tremor and ataxia to functional loss should be assessed separately before intervention (Wilkins, 2017).

Non-invasive neuromodulation methods are being investigated as complementary approaches that may enhance the effect of rehabilitation. In this field, the most studied method in patients with MS and ataxia is cerebellar high-frequency repetitive transcranial magnetic stimulation (rTMS); however, the results are inconsistent. In a randomised study involving 30 patients with ataxia, balance improved in both the rTMS and sham groups receiving physiotherapy, and the gains were maintained at six-week follow-up. The absence of a difference between the groups indicates that rTMS provides no additional benefit over physiotherapy (Mohamed, Elwishy, Shalaby, Shehata, & Ali, 2025). By contrast, in another study of 40 patients, greater improvement in ICARS, postural balance and gait measures was reported in the real stimulation group compared with the sham group (Fawaz et al., 2026). Owing to small samples, differing application protocols and short follow-up periods, neuromodulation cannot yet be recommended for routine use.

8. CONCLUSION

Ataxia develops in a substantial proportion of people with multiple sclerosis and can contribute to disability. Early cerebellar involvement, which may include ataxia, is associated with an unfavourable prognosis. The following points stand out for clinical practice:

- In new or worsening ataxia, a distinction should be made between relapse, pseudorelapse, progression and adverse drug effects.
- In assessment, cerebellar signs should be distinguished from sensory, pyramidal and vestibular contributions; ataxia severity should be monitored with SARA or ICARS, and functional performance separately with the 9HPT and balance and walking tests.
- Corticosteroid treatment in acute relapse and individualised rehabilitation in persistent ataxia are the main approaches.
- Evidence for pharmacological and interventional treatments is limited; gains in tremor or balance measures should not be equated with global improvement in ataxia.

Future studies need to evaluate MS-specific ataxia measures together with daily life and participation outcomes, and to establish the durability of treatment effects with larger samples and long-term follow-up.

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FACIAL MYOKYMIA AND HEMIFACIAL SPASM IN DEMYELINATING DISEASES

Asude ÇOLAKOĞLU ÇİL[1]

1. INTRODUCTION

Central demyelinating diseases include multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), acute disseminated encephalomyelitis (ADEM), and osmotic demyelination syndrome (ODS). Movement disorders may precede, accompany, or follow an attack (Singh & Pandey, 2022); Table 1 lists reported forms and frequencies in MS and related diseases (Singh & Pandey, 2022). Facial manifestations include myokymia, hemifacial spasm (HFS), and spastic paretic hemifacial contracture (SPHC) (Ghosh, Roy, Dubey, Das, & Benito-León, 2022).

2. OVERVIEW OF MOVEMENT DISORDERS IN DEMYELINATING DISEASES

Movement disorders may reflect brain or spinal networks; some persist after corticosteroid-responsive symptoms remit or coexist coincidentally with MS (Singh & Pandey, 2022; Ghosh et al., 2022). Table 1 summarizes movement-disorder frequencies across demyelinating diseases (Singh & Pandey, 2022). Rare ADEM eyelid-myokymia case reports supplement its source review (Singh & Pandey, 2022).

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Table 1. Frequency of Movement Disorders in Demyelinating Diseases

Movement disorder	MS	NMOSD	MOGAD	ADEM	ODS
Tremor	+++	+/−	+	−	+
Dystonia	+	−	−	+/−	−
Paroxysmal dyskinesia	+	+++	+	−	−
Myoclonus	+	−	−	+/−	−
Myokymia	+	−	−	−	+/−
Hemifacial spasm	+/−	−	−	−	−
Tics	+	−	−	−	−
Chorea	+	−	−	−	−
Restless legs syndrome	++	−	−	−	−
Parkinsonism	+	−	−	−	+++
Ocular manifestations	+	−	−	−	−

Note: Adapted from Singh and Pandey (2022). +: occasional; ++: frequent; +++: very frequent; −: not reported; +/−: insufficient evidence. MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorder; MOGAD: myelin oligodendrocyte glycoprotein antibody-associated disease; ADEM: acute disseminated encephalomyelitis; ODS: osmotic demyelination syndrome.

3. CLINICALLY RELEVANT NEUROANATOMY OF THE FACIAL NERVE

Facial fibers loop around the abducens nucleus before exiting at the pontomedullary junction. Their postnuclear, postgenu dorsolateral pontine course localizes continuous myokymia (Clay & Villamar, 2020; Ghosh et al., 2022); an ipsilateral pontine case supports this pattern (Salavisa, Serrazina, Pires, & Correia, 2021). Proximal facial-nerve segments are attached, root-detachment, proximal cisternal, and distal cisternal; the first three are relatively fixed; in the attached segment, fibers are covered only by arachnoid and lack epineurium or interfascicular septa. The proximal cisternal oligodendroglial-to-Schwann-cell myelin transition is vulnerable to injury, demyelination, and ephaptic transmission (Jesuthasan,

Natalwala, Davagnanam, Saifee, & Zrinzo, 2025; Marin Collazo & Tobin, 2018).

4. EPIDEMIOLOGY

Most of the data on facial movement disorders in demyelinating diseases derive from MS. In a cross-sectional study in which 2,260 patients with MS were screened at an MS clinic in Isfahan, Iran, between March 2021 and March 2022, MS-related facial involvement was identified in 122 patients (approximately 5.4%). When calculated for the entire cohort, the frequencies of facial palsy, facial myokymia, and HFS were 3.27%, 1.28%, and 0.84%, respectively, and the mean ages at onset of facial symptoms were 30.74, 29.07, and 31.37 years, respectively (Etemadifar, Sabouri, Zarepour, Akhavan Sigari, & Salari, 2022). In the same study, the facial sign was the first clinical manifestation of MS in 51.70% of patients with facial myokymia, whereas in 57.90% of patients with HFS the facial sign emerged after the diagnosis of MS. Nevertheless, no statistically significant association was found between the type of facial involvement and age, sex, MS subtype, affected side of the face, or time of presentation (Etemadifar et al., 2022).

An early series observed myokymia in 3 of 103 newly diagnosed MS cases (approximately 2.9%, or 1 in 34; de Silva & Pearce, 1972). Another study found HFS in 0.6% of 733 patients, with onset at 23–44 years (Nociti et al., 2008, as cited in Etemadifar et al., 2022). A Mayo Clinic review (1996–2015) identified 35 patients: 28 with myokymia and 7 with HFS. Of these, 24 were women; median age was 40 years (17–66). Median MS-diagnosis-to-onset intervals were 4 and 2 years, respectively (Marin Collazo & Tobin, 2018).

General-population HFS prevalence is about 14.5 per 100,000 women versus 7.4 per 100,000 men. Finnish age-

standardized annual incidence was 1.53 per 100,000; women were affected twice as often, with onset usually in the fourth to sixth decades (Jesuthasan et al., 2025). In one 252-patient series, about 79% had primary and 21% secondary HFS (Tambasco, Filidei, Nigro, Parnetti, & Simoni, 2021). MS-related facial movements begin younger.

5. FACIAL MYOKYMIA

5.1. Definition and Clinical Features

Myokymia causes fine undulating movements and affects the face more often than limbs in MS (Clay & Villamar, 2020; Marin Collazo & Tobin, 2018; Singh & Pandey, 2022). Myokymia may present MS (Ghosh et al., 2022): 11 of 28 patients had clinical or radiological relapse, and three first underwent MS evaluation for this symptom (Marin Collazo & Tobin, 2018). Acute continuous myokymia can localize active disease (Clay & Villamar, 2020).

5.2. Pathophysiology and Lesion Localization in Facial Myokymia

Facial myokymia usually localizes to dorsolateral pontine postnuclear fascicles (Ghosh et al., 2022; Singh & Pandey, 2022). Jacobs et al. (1994, as cited in Marin Collazo & Tobin, 2018) found ipsilateral postnuclear, postgenu lesions in 11 of 12 patients. Magnetic resonance imaging (MRI) changes paralleling symptoms support a lesion–symptom link; demyelination may trigger ectopic motor discharges (Singh & Pandey, 2022).

During myokymia, ipsilateral pontine lesions appeared in 12 of 19 MRI scans, only 7 new (Marin Collazo & Tobin, 2018). Most lacked visible intra-axial facial-nerve lesions; small demyelinating lesions remain possible (Clay & Villamar, 2020; Marin Collazo & Tobin, 2018).

5.3. Electrophysiological Features of Facial Myokymia

On electromyography (EMG), myokymic bursts may recur at approximately 2–10 Hz, while motor-unit discharges within a burst may fire at roughly 5–150 Hz as doublets, triplets, or multiplets (Singh & Pandey, 2022; Jesuthasan et al., 2025). The electrophysiological differential diagnosis includes synkinesis, fasciculation, post-paralytic facial spasm (bursts occurring at irregular intervals and increasing in intensity with voluntary facial contraction), cryptogenic facial spasm, facial Jacksonian epilepsy or epilepsia partialis continua, blepharospasm, neuromyotonia, myotonic discharges, and complex repetitive discharges (Singh & Pandey, 2022). In clinical practice, the diagnosis is largely based on clinical observation; indeed, in the series by Marin Collazo and Tobin (2018), EMG was performed in only two patients, both of whom had confirmed orbicularis oris myokymia.

5.4. Natural Course of Facial Myokymia

MS-related myokymia lasts two weeks to six months (Singh & Pandey, 2022); 27 of 28 cases resolved in 3 days to 1 year (median 21 days), irrespective of treatment (Marin Collazo & Tobin, 2018). Pontine case reports describe recovery after intravenous methylprednisolone or spontaneously (Clay & Villamar, 2020; Salavisa et al., 2021). Progressive or >6-month myokymia warrants evaluation for MS and other causes; lower motor neuron facial palsy can follow (Ghosh et al., 2022). Consider autoimmune disease and image for brainstem lesions, including pontine glioma (Etemadifar et al., 2022).

6. HEMIFACIAL SPASM

6.1. Definition, Classification, and Clinical Features

HFS usually begins near the eye and spreads downward (Jesuthasan et al., 2025; Marin Collazo & Tobin, 2018). Eye-opening difficulty, typewriter-like tinnitus, sleep-time spasm, stress exacerbation, and increased anxiety or depression have been reported (Xiang et al., 2024). Table 2 compares its phenotype with myokymia and SPHC. Primary HFS usually reflects facial root vascular compression; secondary causes include cerebellopontine masses, vascular malformations, brainstem lesions including demyelination, infections, posterior-fossa anomalies, parotid tumors, and Bell's palsy (Tambasco et al., 2021). Of 125 patients, 63.2% were idiopathic; Bell's palsy accounted for 17.6%, vascular compression 14.4%, with tumors and MS also identified (Herrero-Infante, Rodríguez-Sanz, Máñez-Miró, & Vivancos-Matellano, 2021). Treat secondary causes (Tambasco et al., 2021).

6.2. Hemifacial Spasm Associated With Multiple Sclerosis

Among 60 MS patients, 58.3% had demyelination-related movement disorders and two had HFS secondary to pontine demyelination (Ghosh et al., 2022). Lower pontine HFS lesions were also reported (Telischi et al., 1991, as cited in Ghosh et al., 2022). In seven cases, three had ipsilateral brainstem lesions and three relapse; trigeminal or glossopharyngeal neuralgia sometimes coexisted (Marin Collazo & Tobin, 2018). Platysma involvement favors idiopathic HFS; simultaneous upper and lower facial contraction suggests secondary disease (Ghosh et al., 2022). MS-to-HFS interval averaged 2.78 ± 4.14 years, longer than other facial manifestations without statistical significance (Etemadifar et al., 2022).

6.3. Pathophysiology of Hemifacial Spasm

MS-related HFS may reflect ephaptic transmission at demyelinated cranial-nerve transitions or facial-nucleus hyperexcitability from peripheral irritation (Ghosh et al., 2022; Marin Collazo & Tobin, 2018). Root-zone kindling, antidromic impulses, and nuclear reorganization are proposed mechanisms (Singh & Pandey, 2022).

Exploratory primary-HFS research implicates APOE ε4–related myelin repair and SCN10A-encoded Nav1.8 excitability, but small-study and rat findings cannot be extrapolated directly to demyelination-associated HFS (Jesuthasan et al., 2025; Xiang et al., 2024).

6.4. Natural Course of Hemifacial Spasm

MS-related HFS may outlast myokymia: five of seven cases resolved within four years, but two persisted for at least two and five years despite botulinum toxin (Marin Collazo & Tobin, 2018); about 71% resolve irrespective of treatment (Ghosh et al., 2022). Primary HFS is usually chronic (Duarte et al., 2020; Tambasco et al., 2021), although 41.3% of 104 patients followed mean 12 years had little or no spasm untreated (Jesuthasan et al., 2025).

7. SPASTIC PARETIC HEMIFACIAL CONTRACTURE

Spastic paretic hemifacial contracture (SPHC) combines sustained ipsilateral contraction with paresis, unlike myokymia (Singh & Pandey, 2022). Initially linked to brainstem tumors, two cases were found among 500 MS patients (Koutsis et al., 2008, as cited in Ghosh et al., 2022). Resting EMG lacks myokymic discharges; voluntary recruitment is reduced (Singh & Pandey, 2022). Table 2 gives electrophysiological details. SPHC lesions

may involve dorsolateral pontine or corticofacial pathways (Ghosh et al., 2022). Two of nine reported cases had MS; most resolve spontaneously. Gabapentin, baclofen, and carbamazepine have been used (Singh & Pandey, 2022).

8. NEUROIMAGING

Contrast-enhanced MRI evaluates new facial movements in demyelinating disease, excluding brainstem lesions or masses in HFS (Tambasco et al., 2021) and brainstem pathology in persistent myokymia (Etemadifar et al., 2022). All MS patients with facial involvement had periventricular lesions; brainstem involvement was second most common (Etemadifar et al., 2022). It affected 55.17% with myokymia and 57.89% with HFS, chiefly pons then middle cerebellar peduncle (Figure 1).

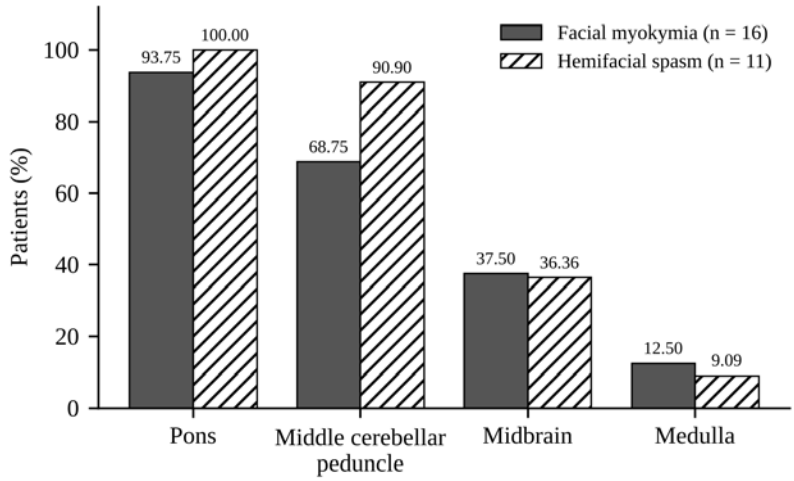


Figure 1. Regional distribution of brainstem lesions in patients with MS and facial myokymia or hemifacial spasm

Note: Created by the author from the data of Etemadifar et al. (2022). Percentages were calculated among patients with brainstem lesions on MRI (facial myokymia, n = 16; hemifacial spasm, n = 11).

Pontine case lesions may enhance or lie dorsolaterally (Clay & Villamar, 2020; Salavisa et al., 2021); others occur contralaterally or outside classic postnuclear fascicles (Marin Collazo & Tobin, 2018).

High-resolution T2 MRI and angiography assess neurovascular conflict (NVC), masses, and vascular anomalies. Combined 3D time-of-flight MR angiography (3D-TOF MRA) and fast imaging employing steady-state acquisition (3D-FIESTA) at 3 Tesla is recommended (Jesuthasan et al., 2025). In 330 HFS patients, NVC appeared on 97.9% of symptomatic and 38.8% of asymptomatic sides; correlate clinically (Jesuthasan et al., 2025). MS lesions do not exclude NVC: one spasm resolved after ipsilateral facial microvascular decompression (MVD) (Marin Collazo & Tobin, 2018). Exploratory primary-HFS diffusion tensor imaging shows lower affected-side fractional anisotropy, higher mean diffusivity, and reduced inferior fronto-occipital and inferior longitudinal fasciculus integrity in chronic cases; applicability to demyelination is unknown (Xiang et al., 2024).

9. ELECTROPHYSIOLOGICAL EVALUATION

The abnormal muscle response (AMR), or lateral spread response (LSR), is recorded in muscles supplied by one facial branch about 10 ms after stimulation of another branch and guides MVD, though it may be absent preoperatively (Xiang et al., 2024). As summarized in Table 2, EMG can exclude denervation (Tambasco et al., 2021) and distinguish myokymia, HFS, and SPHC patterns (Ghosh et al., 2022; Singh & Pandey, 2022; Xiang et al., 2024).

10. DIFFERENTIAL DIAGNOSIS

Table 2 compares clinical, EMG, and imaging features of myokymia, HFS, and SPHC.

Table 2. Comparison of Facial Myokymia, Hemifacial Spasm, and Spastic Paretic Hemifacial Contracture in Demyelinating Diseases

Feature	Facial myokymia	Hemifacial spasm	SPHC
Clinical appearance	Continuous, undulating, vermicular fine muscle movements	Intermittent or sustained paroxysmal clonic/tonic contractions	Sustained tonic contraction accompanied by facial paresis
Typical distribution	Periorbital or perioral; strictly unilateral perioral involvement suggests a structural lesion	Begins in the orbicularis oculi and spreads downwards; upper and lower face may be involved simultaneously in secondary cases	Ipsilateral facial muscles
EMG	Rhythmic/semi-rhythmic motor unit bursts recurring at 2–10 Hz	Abnormal muscle response (AMR/LSR) in the primary form	Irregular continuous resting activity; no myokymic discharges; low amplitude and incomplete interference on voluntary contraction
Lesion	Postnuclear-postgenu fascicular lesion in the dorsolateral pontine tegmentum; no lesion on MRI in some patients	Ipsilateral pontine lesion in some patients; NVC may coexist	Ipsilateral dorsolateral pontine tegmentum; demyelinated corticofacial fibers
Reported frequency in MS cohorts	1.28%	0.84%	2 cases among 500 patients
Course	Usually self-limiting (2 weeks–6 months)	Longer and more refractory; resolution in ~71% of cases	Usually resolves spontaneously

Note: The 1.28% and 0.84% frequency values come from one MS clinic cohort of 2,260 patients (Etemadifar et al., 2022); the two SPHC cases among 500 patients come from a separate series (Koutsis et al., 2008, as cited in Ghosh et al., 2022). Compiled by the author from the data of Clay and Villamar (2020), Etemadifar et al. (2022), Ghosh et al. (2022), Marin Collazo and Tobin (2018), Singh and Pandey (2022), and Xiang et al. (2024). AMR: abnormal muscle response; LSR: lateral spread response; NVC: neurovascular conflict; SPHC: spastic paretic hemifacial contracture.

Table 3 summarizes mimics (Xiang et al., 2024). Focal seizures occur (Tambasco et al., 2021); electroencephalography (EEG) helps when uncertain (Jesuthasan et al., 2025).

Table 3. Main Craniofacial Hyperkinesias in the Differential Diagnosis of Facial Myokymia and Hemifacial Spasm

Condition	Distinguishing features
Blepharospasm	Increased blinking frequency, gradually progressing to bilateral, synchronous eyelid contractions
Oromandibular dystonia / Meige syndrome	Involuntary contraction of the masticatory and/or tongue muscles; in Meige syndrome, eyelid spasm is combined with involvement of the lower jaw muscles
Synkinesis after facial palsy	History of facial palsy and persistent facial weakness; polyphasic reinnervation potentials on needle EMG 4–10 months after the lesion
Psychogenic (functional) facial spasm	Early onset, asymmetric bilateral movements, downward pull of the ipsilateral corner of the mouth, isolated involvement of the lower face; absence of the "other Babinski sign" (elevation of the eyebrow due to frontalis contraction ipsilateral to the spasm)
Tardive dyskinesia	History of antipsychotic use; bilateral irregular movements extending beyond the face
Facial myoclonus / myorhythmia	May be associated with anti-NMDA receptor encephalitis (seizures, psychiatric symptoms, altered consciousness) or Whipple's disease
Hemimasticatory spasm	Mainly involves the masticatory muscles; connective tissue features such as facial hemiatrophy and morphea may coexist
Facial motor tics	Sudden, brief movements that increase with negative emotions; often accompanied by a premonitory sensation
Benign eyelid myokymia	Associated with fatigue, stress, caffeine overuse, lack of sleep, or eye irritation; no preceding sensory symptoms; no structural correlate

Note: Adapted from Xiang et al. (2024) and expanded with data from Ghosh et al. (2022) and Salavisa et al. (2021).

In clinical practice, certain findings should raise suspicion of an underlying structural or demyelinating lesion and prompt a detailed evaluation:

- Continuous myokymia that is strictly unilateral and involves the perioral muscles (Ghosh et al., 2022; Salavisa et al., 2021).
- Myokymia persisting for more than six months or progressing, and myokymia accompanied by facial paresis (Ghosh et al., 2022; Singh & Pandey, 2022).

- HFS with simultaneous involvement of the upper and lower facial muscles (Ghosh et al., 2022).
- Onset in young adulthood (Etemadifar et al., 2022) and coexisting cranial neuralgias (Marin Collazo & Tobin, 2018).

Atypical Bell's palsy warrants assessment and follow-up for MS clues (Etemadifar et al., 2022).

11. TREATMENT APPROACHES

Evidence comes mainly from small series and case reports. Individualized treatment (Marin Collazo & Tobin, 2018) may address demyelination, symptoms, or use procedures (Singh & Pandey, 2022).

11.1. Management of the Underlying Demyelinating Process

When facial myokymia or HFS accompanies a clinically significant relapse affecting daily function, relapse treatment may be indicated (National Institute for Health and Care Excellence [NICE], 2026). New MRI activity without a clinical relapse should prompt assessment and a review of disease-modifying therapy rather than routine acute corticosteroids (NICE, 2026). In the series by Marin Collazo and Tobin (2018), 12 of 28 patients with facial myokymia were treated with oral prednisone or intravenous methylprednisolone, and corticosteroid treatment was associated with symptomatic improvement in most patients with myokymia. However, because symptoms resolved within months in both treated and untreated patients, the true effect of corticosteroids on the clinical course remains unclear, and the authors emphasize that symptomatic treatment may not always be necessary in facial myokymia. Singh and Pandey (2022) likewise note that there is no clear evidence for the efficacy of

corticosteroids in myokymia. On the other hand, resolution of facial myokymia and HFS after methylprednisolone or immunotherapy has been reported even in patients without evidence of a new brainstem lesion (Marin Collazo & Tobin, 2018).

In the case reported by Clay and Villamar (2020), the myokymia resolved after intravenous methylprednisolone, and dimethyl fumarate, which the patient had discontinued on her own, was restarted. A newly developing facial hyperkinesia may signal disease activity and should prompt assessment for relapse; disease-modifying therapy should be reviewed if new activity is confirmed. Marin Collazo and Tobin (2018), on the other hand, found no association between the development of facial myokymia or HFS and the use of disease-modifying therapies or dalfampridine.

11.2. Symptomatic Pharmacological Treatment

Reported myokymia treatments include corticosteroids, gabapentin, carbamazepine, and botulinum toxin (Ghosh et al., 2022), including toxin after methylprednisolone or carbamazepine failure (Singh & Pandey, 2022). Gabapentin, baclofen, or carbamazepine have been used for SPHC (Singh & Pandey, 2022). MS-related HFS therapies include corticosteroids, oxcarbazepine, carbamazepine, gabapentin, pregabalin, or toxin; remission in one series required drug changes or combinations (Marin Collazo & Tobin, 2018). Primary-HFS oral drugs include carbamazepine, gabapentin, clonazepam, levetiracetam, and baclofen, but evidence is mainly case reports and benefit uncommon (Jesuthasan et al., 2025; Xiang et al., 2024). A four-week double-blind trial found no clonazepam benefit; drugs suit early or mild disease (Xiang et al., 2024). Carbamazepine, baclofen, pizotifen, and clonazepam may cause somnolence, dizziness, ataxia, or weakness, especially in older patients;

gabapentin and levetiracetam may be better tolerated (Jesuthasan et al., 2025).

11.3. Botulinum Toxin Type A

Botulinum toxin type A (BoNT-A) blocks acetylcholine release by cleaving presynaptic SNARE proteins and is preferred for HFS despite limited high-quality trials (Tambasco et al., 2021). Across 1991–2021 studies, efficacy was 73%–98.4%, mean effect 12 weeks, without waning or formulation differences (Tambasco et al., 2021). A 35-study meta-analysis estimated single-arm effectiveness at 0.882 (95% CI 0.830–0.926), reported improvement in anxiety and depression scores, and found ptosis most common (Wang et al., 2024). Cochrane found no parallel-group placebo-controlled BoNT-A trial, precluding randomized conclusions. Observational data associate treatment with improvement and favorable safety, supporting common first-line use (Duarte et al., 2020).

Among 125 BoNT-A recipients (1993–2019), benefit and injection interval averaged 12.3 weeks, dose 21.53 units, with 96% good response. Secondary HFS needed 5.8 more units; 47.2% had adverse effects, mainly transient ptosis or weakness resolving within weeks (Herrero-Infante et al., 2021). Both forms respond (Tambasco et al., 2021). Three-monthly botulinum injections gave partial-to-good responses in persistent MS-related HFS (Marin Collazo & Tobin, 2018); myokymia may also benefit (Marin Collazo & Tobin, 2018; Singh & Pandey, 2022). Orbicularis oculi is injected most often; pretarsal injection may last longer and satisfy patients more than preseptal injection (Tambasco et al., 2021; Xiang et al., 2024). Immunoresistance is rare, but injections recur every 3–6 months (Jesuthasan et al., 2025). Unaffected-side injection may correct long-term asymmetry (Tambasco et al., 2021).

11.4. Surgical and Interventional Treatments

Microvascular decompression is potentially curative in primary HFS, benefiting up to 90% (Jesuthasan et al., 2025). A meta-analysis found 90.5% spasm-free at last follow-up; complications included cranial-nerve deficits, hearing loss, facial weakness, or cerebrospinal-fluid leak (Tambasco et al., 2021). Benefit can be delayed in up to 30% (Jesuthasan et al., 2025); MVD may be considered when a vascular mechanism is suspected after specialist assessment (Jeon, Kim, Lee, Kong, & Park, 2023). MS-associated HFS intervention remains uncertain. HFS resolved once each after ipsilateral facial MVD, trigeminal MVD for neuralgia, or ipsilateral trigeminal radiofrequency rhizotomy (Marin Collazo & Tobin, 2018). HFS treatment did not relieve neuralgia, but neuralgia treatment relieved movement symptoms; selected surgery may help.

Pulsed radiofrequency has been described only in an isolated case report, so its efficacy and safety remain uncertain. Conventional thermal radiofrequency ablation can relieve primary HFS: complete symptom resolution was reported in 48 of 53 patients (91%), although facial weakness is an important risk and long-term evidence is limited (Jesuthasan et al., 2025; Xiang et al., 2024). Electroacupuncture has also been reported only in isolated cases. The role of these methods in demyelinating disease is undefined.

12. CLINICAL APPROACH

Figure 2 outlines phenotype assessment, imaging for demyelination, NVC, or mass, and treatment guided by activity and persistence.

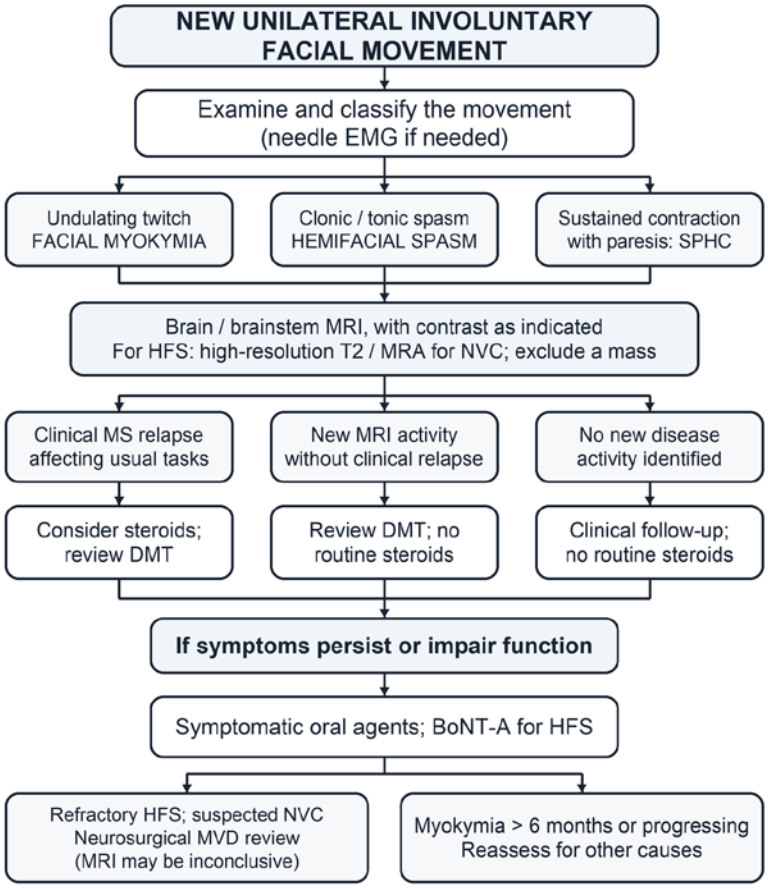


Figure 2. Clinical approach to unilateral facial hyperkinesia in the setting of demyelinating disease

Note: Developed from Ghosh et al. (2022), Jeon et al. (2023), Jesuthasan et al. (2025), Marin Collazo and Tobin (2018), NICE (2026), and Singh and Pandey (2022). BoNT-A: botulinum toxin type A; DMT: disease-modifying therapy; EMG: electromyography; HFS: hemifacial spasm; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; MVD: microvascular decompression; NVC: neurovascular conflict; SPHC: spastic paretic hemifacial contracture.

13. CONCLUSION

In one MS clinic cohort, myokymia and HFS were observed in about 1.3% and 0.8% of patients, respectively, at younger ages than primary HFS (Etemadifar et al., 2022). Facial myokymia was the first MS manifestation in about half of patients with facial myokymia (Etemadifar et al., 2022). Continuous unilateral perioral myokymia or upper- and lower-face HFS in young adults warrants brainstem MRI.

Clinically significant relapses may warrant corticosteroids; new clinical or MRI activity calls for review of disease-modifying therapy (NICE, 2026). Oral antiepileptic agents and, particularly for HFS, BoNT-A can relieve persistent symptoms. MVD may be considered for refractory HFS with suspected neurovascular compression after specialist assessment (Jeon et al., 2023). Evidence for demyelination-associated facial hyperkinesia remains limited to case reports, small series, and primary-HFS studies. Prospective multicenter work with standardized electrophysiological and imaging protocols is needed to establish frequency, natural history, and treatment response.

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THE RELATIONSHIP BETWEEN SECONDARY SPINAL DYSTONIA AND DEMYELINATING DISEASE

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1. INTRODUCTION

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions that produce abnormal, often repetitive movements, postures, or both. Its clinical expression involves distributed motor networks, including the basal ganglia, cerebellum, cerebral cortex, and brainstem (Balint et al., 2018). Clinical observations in patients with myelopathy have challenged the view that dystonic posturing must always arise from structures above the spinal cord. Lesions of the cervical and thoracic spinal cord have been associated with focal, segmental, and, in some reports, more widespread dystonic postures, sometimes before the underlying spinal disease is recognized. These observations support including spinal motor pathways in the assessment of unusual or newly developed dystonic postures. Nevertheless, a spinal lesion alone does not establish the anatomical generator of the movement, and contributions from supraspinal motor networks must also be considered (Sarin, Lawal, & Abboud, 2023).

Practical difficulties in recognizing spinal dystonia arise because it can resemble other manifestations of spinal motor dysfunction. Published reports have not always distinguished clearly among paroxysmal dystonia, painful tonic spasms, and the

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broader category of paroxysmal dyskinesias. These episodic movement phenomena may also be mistaken for epileptic seizures, but paroxysmal dyskinesia should not be treated as synonymous with an epileptic or functional seizure disorder (Sarin et al., 2023). This chapter therefore examines clinical phenomenology, possible neurological substrates, etiological settings, and treatment options. Its methodological approach is a source-based narrative synthesis of selected literature; it is neither a systematic review nor a new pooled analysis. Accordingly, clinical associations and proposed mechanisms are discussed with attention to their evidential limitations.

2. CLINICAL RECOGNITION AND DIFFERENTIAL DIAGNOSIS

Clinical assessment should begin with direct observation of the movement and posture. A dystonic phenotype is suggested by sustained or intermittent patterned muscle contractions that produce abnormal postures or repetitive movements. Agonist–antagonist co-contraction may be present, but it is not independently diagnostic. The resulting posture may include flexion, extension, adduction, or combinations of these movements; these directional descriptions do not establish dystonia or its cause. Events may be brief and paroxysmal, or abnormal posturing may persist between episodes. Even when a fixed posture is found on examination, it cannot by itself establish a structural spinal abnormality. The examiner should assess clinical variability, distractibility, other positive functional signs, and the anatomical correspondence between the phenotype and neuroimaging findings (Batla, 2018; Sarin et al., 2023).

Tonic spasms generally produce brief, stereotyped contractions with flexor, extensor, adductor, or isometric patterns. An isometric spasm may occur without visible joint displacement,

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whereas other spasms can produce conspicuous posturing. Although pain frequently accompanies these attacks, tonic spasms can also be painless, and pain alone does not distinguish them from dystonia. Terminology and clinical complexity overlap across reports; consequently, the movement should be described before a diagnostic label or presumed spinal generator is assigned (Sarin et al., 2023).

Spinal myoclonus produces sudden, shock-like muscle activations. Depending on the form, these may be focal or involve muscles supplied by adjacent spinal segments. Propriospinal myoclonus involves axial jerks with broader rostrocaudal recruitment, although functional presentations are common and the recruitment pattern alone is insufficient to establish an organic spinal cause. Tremor is an oscillatory, rhythmic movement that may be observed during posture, action, or stance, depending on the syndrome. Clonus consists of rhythmic contractions and commonly accompanies pyramidal tract dysfunction. Pseudoathetosis reflects impaired proprioceptive feedback and an inability to maintain limb position, rather than primary dystonic activation of the involved muscles. Tables 1 and 2 summarize the clinical and electrophysiological characteristics of these spinal and related movement phenomena (Sarin et al., 2023; Termsarasab, Thammongkolchai, & Frucht, 2015; van der Salm et al., 2014).

A thorough medical history should establish the duration and frequency of each attack, its stereotypy, and whether movement or sensory stimulation provokes it. The history should also document the presence or absence of pain, accompanying sensory disturbances, awareness during the event, and the temporal relationship to a recent myelitic episode. These details help distinguish recurrent dystonic posturing from tonic spasms, seizures, and other episodic motor events. Physical examination should assess overall muscle tone, hyperreflexia, proprioceptive

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deficits, sensory levels, and weakness, as well as the ability to reproduce the abnormal posture. Examination findings should be interpreted together rather than using a single sign to assign a spinal origin. When attacks occur intermittently, video recordings can provide additional information about their distribution, sequence, triggers, and consistency, and can support subsequent phenomenological review (Sarin et al., 2023; Termsarasab et al., 2015).

Spinal magnetic resonance imaging (MRI) is particularly useful when a newly identified movement disorder coexists with long-tract signs or other clinical features suggesting myelopathy. Brain imaging and additional investigations should be guided by the distribution of symptoms and the wider neurological examination. Focal epileptic seizures and functional movement disorders remain important differential diagnoses, especially when episodic posturing is the presenting complaint. Multichannel electromyography (EMG), with electroencephalography (EEG) when indicated, may help characterize ambiguous events. These investigations support clinical interpretation but do not provide a single confirmatory test for spinal dystonia (Sarin et al., 2023; Zafar & Almajid, 2016).

Table 1. Clinical and Electrophysiological Comparison of Spinal Dystonia and Myoclonus

Feature	Spinal dystonia / dystonic posturing	Spinal segmental myoclonus	Propriospinal myoclonus
Core phenomenology	Sustained or intermittent patterned contractions with abnormal postures	Repetitive, usually rhythmic or semirhythmic jerks	Brief axial flexion jerks, often arrhythmic
Distribution	Focal or segmental; may affect limbs or trunk	Muscles linked to one or a few adjacent spinal segments	Trunk/abdomen with possible spread to hips and limbs

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Feature	Spinal dystonia / dystonic posturing	Spinal segmental myoclonus	Propriospinal myoclonus
Temporal pattern	Sustained or episodic; often posture/action-related	Repetitive; typically ~1–2 Hz	Intermittent bursts, often while supine
EMG findings	Prolonged patterned activity and possible agonist–antagonist co-contraction; nonspecific	Rhythmic/semi-rhythmic bursts in segmentally related muscles	Polymyography may show rostrocaudal recruitment; pattern alone is not diagnostic
Clinical clues	Consistent patterned posture; examine for structural lesion and other dystonia causes	Segmental topography; often stimulus-insensitive	Axial jerks; assess variability, distractibility and functional signs
Key investigations	MRI of relevant spinal levels; EMG for phenomenology; broader work-up by context	Spinal MRI, with contrast when indicated; multichannel EMG	Multichannel EMG; EEG–EMG back-averaging for a readiness potential when indicated; spinal MRI
Etiologic considerations	Rare descriptive phenotype; spinal lesions or disinhibited motor circuits may contribute	Structural, inflammatory, vascular, infectious or other cord pathology	Functional presentations common; structural spinal causes uncommon
Management principles	Treat cause; selected use of baclofen, benzodiazepines or focal botulinum toxin	Treat cause; clonazepam or antiseizure agents in selected cases	Etiology-specific; rehabilitation for functional cases; selected symptomatic therapy

Note: Author's synthesis based on Termsarasab et al. (2015), van der Salm et al. (2014), and Sarin et al. (2023). Abbreviations: EMG, electromyography; EEG, electroencephalography; MRI, magnetic resonance imaging; GAD65, glutamic acid decarboxylase 65.

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Table 2. Clinical and Electrophysiological Comparison of Tonic Spasms and Related Syndromes

Feature	Paroxysmal tonic spasms	Stiff-person spectrum	Painful legs–moving toes
Core phenomenology	Brief, stereotyped tonic contractions; may be painful or painless	Persistent rigidity with superimposed painful spasms	Slow, irregular, writhing or flexion–extension toe movements
Distribution	Often unilateral limb or hemibody; may involve trunk	Axial and proximal limbs (classic); focal limb variants	Distal toes/feet, sometimes fingers
Temporal pattern	Paroxysms lasting seconds to minutes	Continuous stiffness; episodic exacerbations	Often persistent or fluctuating
EMG findings	Sustained activation during tonic episode	Continuous motor-unit activity at rest; spasmodic co-contraction	Irregular bursts of distal muscle activity
Clinical clues	Often triggered by movement or sensory stimuli; consider demyelination	Stimulus-sensitive spasms, exaggerated startle, hyperlordosis	Pain frequently precedes or accompanies toe movements
Key investigations	Brain/spinal MRI for demyelinating or structural disease	EMG; GAD65/glycine-receptor antibodies as clinically appropriate	Peripheral nerve/radicular assessment; spinal MRI when indicated
Etiologic considerations	Multiple sclerosis, NMOSD, and other spinal cord insults	Autoimmune spectrum, including GAD65-associated disease	Neuropathy, radiculopathy, trauma; occasionally central pathology
Management principles	Treat underlying disease; carbamazepine sometimes used symptomatically	Benzodiazepines/baclofen; immunotherapy in selected confirmed cases	Pain-directed therapy; individualized symptomatic treatment

Note: Author's synthesis based on Termsarasab et al. (2015), van der Salm et al. (2014), and Sarin et al. (2023). Abbreviations: EMG, electromyography; EEG, electroencephalography; MRI, magnetic resonance imaging; GAD65, glutamic acid decarboxylase 65.

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3. A PATHOPHYSIOLOGICAL FRAMEWORK

Although no single mechanism has been established for spinal dystonia, axonal hyperexcitability after demyelination has been proposed as one explanation for paroxysmal motor phenomena. Demyelinated axons may be more susceptible to ectopic impulse generation and ephaptic coupling. Ephaptic coupling describes an interaction in which activity in one axon influences a neighboring axon without conventional synaptic communication. Such electrical cross-talk could contribute to episodic symptoms arising during or after spinal cord demyelination. However, the link between these mechanisms and a clinically defined dystonic posture remains uncertain. General evidence concerning symptom production in demyelination and computational evidence concerning ephaptic interactions should therefore be distinguished from direct clinical proof that a particular lesion generates an individual patient's movement disorder (Sarin et al., 2023; Schmidt, Hahn, Deco, & Knösche, 2021; Smith & McDonald, 1999).

An alternative, potentially complementary explanation involves impaired integration of sensory information and motor output. Spinal cord damage can disrupt proprioceptive feedback and descending signals that normally modulate agonist and antagonist muscle activity. Injury to corticospinal and related pathways may contribute to spasticity, altered reciprocal inhibition, and other abnormal motor patterns. These changes can produce spasticity-associated involuntary movements, including spastic dystonia (Abboud, Macaron, et al., 2019; Sarin et al., 2023). In this context, spastic dystonia refers to sustained involuntary muscle activity associated with an upper motor neuron syndrome. It should not be used as a synonym for dystonia as a movement-disorder phenotype. Both phenomena may be present in the same patient, making careful examination and

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explicit terminology essential when interpreting the clinical and mechanistic literature.

These proposed mechanisms are not mutually exclusive. The phenotypic expression of the clinical syndrome may depend on the location and severity of spinal cord damage, the specific tracts affected, the stage of the disease, and the interaction between the damaged spinal circuits and larger motor networks. This framework also helps explain why similar lesions need not produce identical motor manifestations in different patients. An MRI lesion that corresponds anatomically to the abnormal movement should therefore be regarded as suggestive evidence of an association, rather than conclusive evidence that the spinal lesion independently generates the observed movement pattern. Clinical evolution and possible supraspinal contributions should remain part of the interpretation (Sarin et al., 2023).

4. DEMYELINATING DISEASE AS A CLINICAL SETTING

4.1. Multiple Sclerosis

Movement disorders occur in multiple sclerosis (MS), and published reports describe cervical dystonia, limb dystonia, writer's cramp, hemidystonia, and paroxysmal posturing associated with cervical spinal cord plaques. Some manifestations arise before MS is recognized and may initially be misdiagnosed as epilepsy or a primary movement disorder (Rüegg et al., 2004; Sarin et al., 2023; Zafar & Almajid, 2016). In a prospective observational study, 11 of 60 patients with early MS and related demyelinating diseases (18.3%) had focal paroxysmal dystonia. Eight of these 11 presentations followed a spinal relapse, one followed a brainstem relapse, one was attributed to a thalamic lesion, and one had an undetermined origin (Abboud, Yu, Knusel, Fernandez, & Cohen, 2019). Thus, approximately 73% of the

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dystonic presentations were associated with a spinal relapse. These observations came from a selected mixed cohort, rather than an unselected MS population or a cohort consisting entirely of patients with dystonia. The reported proportion should not be interpreted as the general prevalence or incidence of dystonia in MS.

4.2. Neuromyelitis Optica Spectrum Disorder

Neuromyelitis optica spectrum disorder (NMOSD) can damage the spinal cord through extensive inflammatory lesions. Paroxysmal dystonic posturing and tonic spasms have both been reported during recovery from attacks, but the terms have not been applied consistently across publications (Abboud, Fernandez, Mealy, & Levy, 2016; Kim, Go, Sung, Park, & Lee, 2012; Sarin et al., 2023). In a retrospective study, painful tonic spasms were identified in 10 of 40 patients in the NMO group (25.0%), compared with 1 of 35 patients with MS (2.9%) and 1 of 41 patients with antibody-negative idiopathic acute transverse myelitis (2.4%). These figures describe painful tonic spasms, not the frequency of a separately established paroxysmal dystonia phenotype (Kim et al., 2012). Interpretation requires attention to the original diagnostic criteria, the extent of spinal cord involvement, and the phenomenological definitions used. Differences between selected clinical groups also limit generalization of these percentages to all patients with NMOSD or MS.

A second retrospective study of 37 patients with NMO identified spinal movement disorders in 16 patients (43.2%). Two patients (5.4% of the entire cohort) had focal nonparoxysmal dystonia affecting the neck or arm (Abboud et al., 2016). These findings support specifically asking about abnormal involuntary postures after myelitis, particularly when attacks cause pain, interfere with daily activities, or impair function. They also

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illustrate the importance of documenting whether posturing is persistent or episodic and whether pain or a stimulus accompanies it. The reported frequency of spinal movement disorders should not be equated with the frequency of dystonia, and these data do not imply that all tonic spasms in NMOSD represent dystonic movements.

4.3. Other Inflammatory Myelopathies

Movement phenomena have also been described after idiopathic myelitis and in association with myelin oligodendrocyte glycoprotein antibodies. Earlier literature contained less evidence on these conditions than on MS and NMOSD, supporting their inclusion in the differential diagnosis while discouraging unsupported comparisons of frequency (Sarin et al., 2023). The evidence base has since expanded. A 2024 prospective observational study examined 63 patients with NMOSD, myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), or idiopathic transverse myelitis who had current or previous myelitis. Spinal movement disorders were identified in 46 patients (73%); tonic spasms occurred in 36 (57%) and focal dystonia in 16 (25%). The cohort included only seven patients with MOGAD, limiting estimates for this subgroup (Abboud et al., 2024). These observations support actively assessing movement phenomena across inflammatory myelopathies, while preserving the distinction between tonic spasms and focal dystonia. Recruitment from a tertiary neuroimmunology clinic, the requirement for spinal cord involvement, small diagnostic subgroups, and differences in ascertainment from earlier studies limit direct comparisons. The reported percentages should therefore be interpreted as findings within the study cohort rather than population prevalence estimates. They also do not establish that each diagnostic category shares the same pathophysiology or risk of a particular movement phenotype.

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5. STRUCTURAL AND INFILTRATIVE SPINAL LESIONS

Although demyelination has received considerable attention in discussions of spinal dystonia, the phenomenon is not restricted to inflammatory disease. Torticollis, abnormal limb postures, and dystonia–athetosis have also been reported in association with cervical neoplasms, intramedullary tumors, syringomyelia, and other structural or infiltrative lesions (Hill et al., 1999; Kumandaş et al., 2006; Sarin et al., 2023). The interpretation of torticollis requires particular care because pain, mechanical restriction, and compensatory positioning can mimic a dystonic posture. A tumor-associated abnormal posture should therefore not automatically be classified as dystonia. Most supporting reports are individual cases or small series and cannot establish the comparative likelihood of different spinal lesions. Their clinical importance lies in showing that an apparently isolated movement disorder can occasionally be the initial manifestation of a potentially treatable structural abnormality. Clinical assessment should therefore address both movement phenomenology and the possibility of an underlying spinal lesion.

6. THERAPEUTIC CONSIDERATIONS

The treating physician should first determine the underlying cause of the symptoms and characterize the specific movement disorder. If abnormal posturing accompanies an active inflammatory demyelinating attack, treatment directed at the acute relapse may also improve the associated motor manifestations. The expected response depends on the underlying diagnosis, the patient's clinical status, and the relationship between inflammation and the observed movement pattern (Sarin et al., 2023). Tonic spasms may also arise during recovery without a new inflammatory event, so their appearance alone should not

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be assumed to indicate a relapse (Kim et al., 2012). Persistent involuntary movements and other residual deficits, such as weakness, may require separate symptomatic management and rehabilitation. Disease activity, residual disability, and the movement phenotype should therefore be evaluated individually when treatment goals are defined.

For selected patients with focal or segmental dystonia, botulinum toxin injections into the muscles contributing to the dystonic pattern may be useful. Cervical dystonia is one example in which the distribution of abnormal muscle activity can guide the choice of injection targets. Treatment planning should also consider baseline weakness and the functional consequences of further reducing muscle activity. However, controlled trial evidence specific to spinal dystonia is limited. Reported practice is largely informed by individual clinical observations and extrapolation from the wider literature on dystonia, rather than by trials establishing efficacy across different spinal etiologies (Abboud et al., 2016; Balint et al., 2018; Sarin et al., 2023). Clinical response should therefore be monitored against the patient's original symptoms and functional goals.

Some patients with MS or NMOSD have experienced a reduction in paroxysmal tonic spasms or dystonic episodes after carbamazepine treatment. Acetazolamide has also been used in reported cases of paroxysmal dystonia associated with central demyelinating disease. Although these reports can inform treatment selection, they do not provide sufficient evidence for a universally applicable regimen (Kim et al., 2012; Sarin et al., 2023; Sethi, Hess, Huffnagle, & Adams, 1992). Anticholinergic agents such as trihexyphenidyl, benzodiazepines, and oral or intrathecal baclofen may be useful for selected dystonic or spasticity-associated syndromes. Their use should reflect the phenotype being treated and the patient's overall clinical condition. Adverse effects differ by agent: anticholinergic

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treatment may cause cognitive and other anticholinergic effects, whereas benzodiazepines and baclofen may cause sedation or weakness. Falls, impaired balance, and interactions with concomitant medication also require consideration. These risks should be weighed against the expected reduction in pain or functional limitation (Balint et al., 2018; Sarin et al., 2023). Coexisting spasticity should be assessed separately because improvement in muscle tone does not necessarily eliminate dystonic posturing or other involuntary movements.

Given the limited evidence for managing dystonia associated with chronic neurological disability, each case requires an individualized approach. The clinician should characterize the phenomenon, determine whether active disease is present, identify target muscles or attack patterns, and establish how the symptoms affect function. Treatment should then be selected according to the degree of disability, the anticipated benefit, and the patient's tolerance of adverse effects. Follow-up should assess both the response to treatment and the continuing accuracy of the diagnosis. An unexpected or incomplete response should prompt reconsideration of the movement phenotype and of coexisting spasticity or other contributors, rather than automatic escalation of symptomatic medication.

7. EVIDENCE LIMITATIONS AND RESEARCH PRIORITIES

The available evidence has been assembled from case reports, retrospective cohorts, and prospective observational studies. Diagnostic terminology, particularly for tonic spasms and paroxysmal dystonia, has varied across publications. Studies also differ in how they determine whether a specific lesion is associated with a patient's symptoms. These differences make comparisons among MS, NMOSD, MOGAD, and structural

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myelopathy difficult, even when similar labels are used. Prospective data provide a broader basis for interpretation but remain subject to referral patterns, small subgroups, and differences in ascertainment (Abboud et al., 2024; Sarin et al., 2023). Future research would benefit from standardized video-based phenotyping, explicit and consistent diagnostic definitions, and longitudinal assessment linking MRI findings with symptom evolution. Treatment reports should document the phenotype treated, the intervention, clinical response, functional outcomes, and adverse effects. Mechanistic studies should also distinguish local generation of motor activity within spinal circuits from altered feedback within distributed sensorimotor networks. This distinction is necessary before an anatomical association can be interpreted as evidence of a specific causal generator.

8. CONCLUSION

Spinal dystonia should be considered in the differential diagnosis of patterned involuntary movements or postures that accompany signs of myelopathy or follow an inflammatory spinal cord event. Distinguishing dystonia from tonic spasms, spasticity-associated phenomena, myoclonus, and other abnormal spinal movements is important for both clinical interpretation and treatment decisions. Functional presentations and focal seizures should also be considered when appropriate. Demyelinating disease is an important clinical setting, but structural spinal lesions may provide other potentially treatable explanations. Further research is needed to establish consistent diagnostic criteria and clarify the contribution of spinal circuits and supraspinal motor networks to these presentations. Current evidence supports careful phenomenological assessment and individualized management, while avoiding an assumption that

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every abnormal posture associated with a spinal lesion shares the same mechanism.

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TREMOR IN MULTIPLE SCLEROSIS

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1. INTRODUCTION

Tremor is a common, potentially disabling manifestation of multiple sclerosis (MS) (Makhoul, Ahdab, Riachi, Chalah, & Ayache, 2020). Charcot described it among the cardinal clinical features of MS (Zalc, 2018). This chapter reviews its frequency, clinical phenotypes, proposed cerebellar and network mechanisms, assessment, and evidence for medication, botulinum toxin type A, rehabilitation, deep brain stimulation (DBS), and thalamotomy.

2. EPIDEMIOLOGY OF TREMOR IN MULTIPLE SCLEROSIS

In the studies summarized by Makhoul et al. (2020), reported tremor prevalence in MS ranged from 25% to 58%; estimates vary with definitions and assessment methods. This wide range in prevalence may reflect variability in tremor type, severity, frequency, onset, and progression; overlap with other symptoms, such as spasticity, ataxia, and weakness; potential underreporting by patients with mild symptoms; and differences in the sensitivity of the methods used to assess tremor (Makhoul et al., 2020). In a 100-patient cohort, tremor was reported by 37 patients but detected on clinical examination in 58 (Alusi, Worthington, Glickman, & Bain, 2001). This gap between self-

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report and examination, together with varied definitions and methods, complicates prevalence estimates and assessment of functional impact.

3. CLINICAL MANIFESTATIONS

In MS, tremor may affect the head, neck, vocal cords, trunk, and extremities. The tongue and jaw are not typically affected, whereas palatal and oculopalatal tremor have been described in rare cases of MS (Makhoul et al., 2020). MS classically causes a large-amplitude tremor with a frequency of 2.5–7 Hz, characterized by postural or intention components and generally classified as an action tremor. Phenotype proportions depend on how tremor components are defined. In one 100-patient MS cohort, 44 had a postural component, whereas six had isolated intention tremor (Alusi et al., 2001). Although parkinsonism has been reported in MS, isolated rest tremor has rarely been described (Ayache et al., 2015). Furthermore, Holmes tremor (rubral tremor) is also relatively rare in patients with MS (Koch, Mostert, Heersema, & De Keyser, 2007). In a selected cohort of 32 patients with MS and manual clumsiness, combined accelerometry and EMG identified true rhythmic activity in only one patient; clinically apparent tremor in this cohort frequently corresponded to pseudorhythmic activity (Ayache et al., 2015).

Although the relationship between tremor and MS severity and progression has not been systematically investigated, epidemiological data suggest that tremor may be a progressive symptom that worsens over the course of the disease (Alusi et al., 2001; Hohol, Orav, & Weiner, 1995; Pittock, McClelland, Mayr, Rodriguez, & Matsumoto, 2004).

4. PATHOPHYSIOLOGICAL MECHANISMS

The pathophysiology of tremor in MS remains poorly understood and is challenging to investigate, as its occurrence cannot be attributed to a single anatomical region due to the multifocal nature of the disease. Action tremor, which is commonly observed in MS, suggests that the cerebellum and its connections may represent a potential source of tremor generation (Koch et al., 2007). Furthermore, the coexistence of other signs and symptoms, such as dysarthria, dysmetria, and dysdiadochokinesia suggests that lesions involving the cerebellum, cerebellar peduncles, or cerebello-thalamo-cortical pathways may contribute to tremor generation in MS (Makhoul et al., 2020). Several clinical studies have suggested a correlation between upper limb dystonic features and MS-related tremor, supporting the hypothesis that dysfunction of the cerebello-pallido-thalamo-cortical network plays a role in the pathophysiology of MS-related tremor (Van der Walt et al., 2015). The effects of peripheral cooling on intention tremor also suggest a role for the cerebellum in its pathophysiology. Intention tremor is thought to be modulated through increased long-latency stretch reflexes. Cooling reduced intention tremor in Feys et al. (2005). Quintern et al. (1999) found less postural finger sway after cooling, without improvement in pointing-movement amplitude or speed. Cooling may alter peripheral sensory input and long-latency reflexes, although the mechanism of clinical benefit remains uncertain.

In recent years, neuroimaging (tractography) data obtained from patients undergoing deep brain stimulation (DBS) for tremor, including patients with MS, together with structural and functional magnetic resonance imaging studies, have highlighted the role of the dentato-rubro-thalamic tract and cerebello-thalamo-cortical pathways (Boonstra et al., 2020; Coenen et al., 2020).

Despite the available evidence, the role of the cerebellum in MS-related tremor has never been conclusively established. Responses in selected patients to DBS targeting the ventral oralis posterior (VOP) and ventral intermediate (VIM) thalamic nuclei support a role for distributed cerebello-thalamic and thalamocortical circuits; they do not establish a basal-ganglia generator. The rarity of resting tremor and limited response to antiparkinsonian medication argue against a dominant nigrostriatal mechanism. Variable responses to DBS may reflect differences in patient selection, tremor phenotype, stimulation targets, and associated neurological impairment; treatment response alone does not establish the anatomical generator of tremor. Some researchers have attributed action tremor to a pathological oscillator located at the supraspinal level. In addition, in certain tremor syndromes, such as palatal tremor, symptom severity has been associated with lesions involving the Guillain–Mollaret triangle, and a similar relationship has been reported in some patients with MS (Makhoul et al., 2020).

Overall, the pathophysiology of tremor in patients with MS is thought to be associated with the interplay of multiple connectivity abnormalities within cortico-cerebello-subcortical networks, rather than damage confined to a single anatomical region.

5. ASSESSMENT OF TREMOR

Assessing tremor in patients with MS can be challenging because of the variability in tremor phenotypes. Several methods have been used to evaluate tremor in this population, including neurological examination (finger-to-nose testing, spiral drawing, and handwriting assessment), visual tracking techniques, accelerometry, electromyography (EMG) and its combined use with accelerometry, the Stewart–Holmes maneuver, and digital

spirography (Makhoul et al., 2020). In addition, several scales have been used to assess tremor, including the Bain Score for Tremor Severity (BSTS), the Tremor and Coordination Scale (TACS), the Fahn Tremor Rating Scale (FTRS), and the Multidimensional Assessment of Tremor (MAT) (Alusi, Worthington, Glickman, Findley, & Bain, 2000; Daudrich, Hurl, & Forwell, 2010; Hooper, Taylor, Pentland, & Whittle, 1998; Marrie & Goldman, 2011). The assessment scales used evaluate parameters such as tremor severity (e.g., absent, mild, moderate, or severe, or using a numerical rating from 0 to 10) and its impact on functional abilities (e.g., performance during activities such as dressing, eating, and pouring water). However, inter-rater variability may affect the reliability of these assessments. Although accelerometry and neurophysiological methods provide more objective data, they may assess only a single component of the movement disorder and may be insufficient to evaluate associated impairments (Koch et al., 2007). Furthermore, neurophysiological assessment techniques have been shown to be useful in identifying patients who may benefit from specialized therapeutic interventions, such as thalamotomy (Liu et al., 2000).

Although a wide range of assessment tools is available, no universally accepted scale or method has been established for routine clinical assessment. Therefore, there is a need to develop a standardized assessment method with established validity and reliability that can be widely implemented in clinical practice to ensure consistency in the evaluation of tremor in MS.

6. MEDICAL TREATMENT OF TREMOR IN MULTIPLE SCLEROSIS

There is no definitive therapeutic approach for the medical management of MS-related tremor. The available evidence is derived primarily from case reports, uncontrolled open-label

studies, and a limited number of randomized controlled trials involving small patient populations. Agents investigated for MS-related tremor or related cerebellar symptoms include primidone, glutethimide, 4-aminopyridine, intrathecal baclofen, isoniazid, propranolol, ethanol, carbamazepine, levetiracetam, topiramate, cannabis, ondansetron, and dolasetron (Koch et al., 2007; Makhoul et al., 2020). Studies have also investigated the treatment of tremor through immunomodulation. In a retrospective questionnaire study, patients receiving natalizumab more frequently reported subjective tremor improvement and showed less worsening in Tremor-Related Activities of Daily Living scores than the comparison groups. These findings do not establish a causal or tremor-specific treatment effect (Rinker, Salter, & Cutter, 2014).

Botulinum toxin type A has been studied for MS-related upper-limb tremor. In a double-blind, placebo-controlled crossover trial, tremor severity, handwriting, and spiral-drawing scores improved. Temporary limb weakness occurred after 42.2% of treated limbs versus 6.1% after placebo and resolved within two weeks (Van der Walt et al., 2012). Table 1 summarizes the investigated agents and limitations of the evidence.

Table 1. Studies of Agents Investigated for Multiple Sclerosis-Related Tremor

Medication	Evidence	Reported signal	Main limitation
Isoniazid	Open-label and placebo-controlled crossover studies	Mild improvement in 10/13 on at least one measure; one pilot found a 2–3-fold goniometric reduction	Clinical and objective results conflict; small samples; adverse effects.
Levetiracetam	Open-label and placebo-controlled crossover studies	Transient benefit in one 20-patient open-label series; controlled results mixed, including a negative trial	No consistent clinically meaningful benefit.

Medication	Evidence	Reported signal	Main limitation
Topiramate	Case report; small open-label mixed cohort	Clinical and neurophysiological improvement reported	Mixed MS/non-MS cohort; three discontinuations.
Cannabis/cannabinoids	Case report; blinded placebo-controlled trials	Early benefit reports; controlled trials showed no consistent tremor benefit	Large trial focused on spasticity, not tremor.
Ondansetron	Placebo-controlled crossover; MS open-label pilot	Initial mixed-cohort improvement; MS pilot negative	Not replicated; initial cohort included non-MS patients.
Primidone	Two-patient case series; 10-patient open-label pilot	Clinical improvement reported	Very small uncontrolled samples.
4-Aminopyridine	Single case report	Improvement in one patient	Case-level evidence only.
Glutethimide	Open-label mixed MS/TBI cohort (n = 8)	Functional benefit in 6/8	No control group; mixed diagnoses.
Propranolol	Double-blind crossover (n = 3)	No significant benefit	Extremely small trial.
Carbamazepine	Single-blind placebo-controlled study (n = 10; 7 MS)	Clinical and accelerometric tremor improvement in all 10	Mixed cohort; functional benefit unclear.
Ethanol	Small double-blind crossover	No significant benefit	Balance and coordination risks in MS.
Intrathecal baclofen	Single case report	Dose-related amplitude reduction; abolished at 250 µg/day	Single invasive-treatment case.
Dolasetron	Small cerebellar-ataxia study	No significant ataxia benefit	Tremor-specific efficacy was not assessed.

Note: Adapted from Koch et al. (2007) and Makhoul et al. (2020). MS: multiple sclerosis; TBI: traumatic brain injury. Studies vary in design, sample size, and outcomes. Dolasetron was assessed for cerebellar ataxia rather than tremor.

7. SURGICAL TREATMENT OF TREMOR IN MULTIPLE SCLEROSIS

Considering that evidence-based algorithms for the pharmacological treatment of MS tremor have not yet been sufficiently established and that treatment-related complications may occur, surgical treatment options may be considered in selected patients, with deep brain stimulation (DBS) being one of the principal options. Although DBS is a surgical intervention, it offers the advantage of allowing stimulation parameters to be adjusted according to tremor severity and the patient's clinical response; however, the need for frequent reprogramming in some patients may complicate long-term treatment management. DBS should be considered in patients with severe tremor or tremor that significantly restricts activities of daily living and is refractory to medical treatment, who do not have sensory or motor deficits limiting the functionality of the target limb, whose disease course is stable before surgery, and whose cognitive functions are relatively preserved (Wishart et al., 2003).

The optimal target for electrode placement in DBS for MS tremor has not yet been definitively established. The ventral intermediate (VIM) nucleus of the thalamus is one of the primary targets used for this purpose. Studies have reported that tremor improvement is more pronounced in proximal components than in distal components and that postural tremor may respond better than intention tremor. Individualization of target selection according to the phenomenological characteristics of the tremor has been recommended. Accordingly, stimulation of the VIM or ventral oralis posterior (VOP) nucleus of the thalamus has been suggested to be more beneficial for distal, single-frequency hand tremor, whereas stimulation of the VOP–zona incerta (ZI) combination may be more beneficial for tremor characterized by a broader frequency range and involving both proximal and distal components (Geny et al., 1996; Nandi & Aziz, 2004).

Thalamotomy is one of the surgical treatment options for MS-related tremor and is primarily used to treat severe intention tremor affecting the upper limbs. However, the heterogeneity of outcome measures, limited sample sizes, and reports of serious postoperative complications in existing studies complicate the assessment of its clinical efficacy and safety (Makhoul et al., 2020).

Studies on the surgical treatment of MS-related tremor indicate that both thalamotomy and deep brain stimulation (DBS) can reduce tremor severity. Tremor reduction beyond one year has been reported in approximately 70% of patients following thalamotomy, whereas 69%–100% of patients in three DBS studies with follow-up beyond one year experienced some tremor reduction. Although comparative studies have reported more favorable outcomes with thalamotomy for certain tremor measures, the higher risk of adverse effects limits the clinical interpretation of these findings. Preliminary data on gamma knife thalamotomy are also promising; however, further studies are required to confirm its efficacy. Overall, the available evidence should be interpreted cautiously because of small sample sizes and methodological limitations. Given the higher complication risk associated with thalamotomy compared with DBS, bilateral thalamotomy is not recommended. For patients requiring bilateral treatment, bilateral DBS or unilateral thalamotomy followed by contralateral DBS may be considered as alternative approaches (Koch et al., 2007).

In a study evaluating the long-term outcomes of surgical treatment, Hassan, Ahlskog, Rodriguez, and Matsumoto (2012) followed nine patients for 12 years, including three who underwent deep brain stimulation (DBS) and six who underwent thalamotomy. Although tremor control was initially achieved in all patients following surgery, tremor recurred within a median of 3 months. However, tremor suppression persisted for 5 years in

two patients who underwent DBS. At the 12-year follow-up, all four surviving patients had severe disability. The progressive nature of MS and its multifocal, multisymptomatic clinical course complicate the assessment of the long-term efficacy of surgical interventions and limit the ability to distinguish treatment outcomes from the effects of the natural disease progression.

Overall, the pharmacological management of MS-related tremor should be individualized according to patient characteristics and clinical judgment. Further studies are needed to establish the efficacy of available agents across different tremor phenotypes. When pharmacological treatment is unsuccessful, botulinum toxin type A injections may be considered at specialized centers with expertise in tremor assessment and management. For patients with persistent, disabling tremor despite these interventions, DBS may be considered as a further treatment option in experienced centers capable of selecting appropriate stimulation targets.

8. REHABILITATION OF TREMOR IN MULTIPLE SCLEROSIS

Although rehabilitation plays an important role in the management of multiple sclerosis (MS) and tremor, research specifically investigating rehabilitation interventions for MS-related tremor remains limited. Upper limb intention tremor can contribute substantially to disability in individuals with MS, potentially affecting their ability to perform activities of daily living (ADLs), including eating, writing, dressing, and bathing. A review of eight studies investigating noninvasive interventions for upper limb intention tremor in MS reported that these approaches were generally associated with transient reductions in tremor amplitude and short-term improvements in functional performance. However, the available evidence remains

insufficient to draw firm conclusions regarding their long-term efficacy. Further research may help clarify the effectiveness of these interventions in reducing tremor-related disability and improving functional independence and quality of life in individuals with MS (McCreary, Rogers, & Forwell, 2018).

Occupational therapy can address eating, writing, and dressing through task adaptation, assistive devices, and compensatory strategies; physical therapy can address mobility and balance. Weighted utensils, limb loading, and task-oriented exercise may help some patients function, but evidence that these approaches directly and durably reduce MS-related tremor remains limited (McCreary et al., 2018).

9. CONCLUSION

Tremor can substantially impair function in multiple sclerosis. Its varied phenotypes and distributed cerebellar and thalamocortical mechanisms complicate assessment and treatment. No single clinical measure or medication has established reliable benefit across patients. Botulinum toxin type A may help selected patients but can cause transient weakness; deep brain stimulation and thalamotomy may be considered for severe, refractory tremor after careful assessment of disability, associated neurological deficits, and procedural risk. Rehabilitation should target daily function. Larger controlled studies using consistent outcome measures are needed to define durable treatment benefit and identify patients most likely to respond.

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MOVEMENT DISORDERS IN CENTRAL NERVOUS SYSTEM DEMYELINATING DISEASES

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