



Ataxia in Patients with Multiple Sclerosis: A Brief Review

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Abstract

Ataxia is a significant and often debilitating symptom characterized by the impaired coordination of voluntary muscle movements. It frequently occurs in patients with multiple sclerosis (MS) and profoundly impacts their quality of life. This comprehensive review explores the multifaceted nature of ataxia, including its diverse etiologies such as central nervous system lesions, medication side effects, nutritional deficiencies, and hereditary conditions, as well as its association with various diseases. A detailed examination of ataxia's correlations with neuroanatomy revealed its complex relationship with cerebellar pathology. This emphasized the critical role of the cerebellum and its associated pathways in coordinating voluntary movements. The manifestation of ataxia in MS were examined, highlighting its prevalence, impact on disability and life quality, and the pathological underpinnings within cerebellar structures. Diagnostic approaches, including the International Cooperative Ataxia Rating Scale, Scale for the Assessment and Rating of Ataxia, and nine-hole peg test for assessing upper limb dexterity, were discussed. Furthermore, the treatment strategies were critically reviewed. Although long-term effective options are currently lacking, specific pharmacological agents and rehabilitation techniques have demonstrated some benefits. The review findings indicate that further studies are required to better understand ataxia's dynamics, treatment efficacy, and overall impact on patients with MS. Additionally, there is a pressing need for advancements in management and therapeutic approaches.

Keywords: Ataxia, movement disorders, multiple sclerosis, review

Introduction

Traditionally, movement disorders were considered to be uncommon in multiple sclerosis (MS) (1). However, the true prevalence and incidence of movement disorders in MS remain unknown because most previous reports have been retrospective studies, small case series, or review articles (2,3).

Ataxia, which is characterized by impaired coordination of voluntary muscle movements, may be the main complaint of the patient or one of several accompanying symptoms. It is often caused by cerebellar dysfunction or pathologies in the vestibular or proprioceptive afferent pathways to the cerebellum. However, when considered in more detail, ataxia is a coordination disorder caused by abnormalities in different components of the nervous system, including the brain, spinal cord, peripheral nerves, and nerve roots (4). In addition, hypomyelination with atrophy of the basal ganglia and cerebellum, a recently defined and incompletely understood disorder, has been associated with the development of dystonia,

ataxia, rigidity, choreoathetosis and tremor (6). Different types of ataxia can often occur in the same patient due to similar or overlapping causes (5). The following are the possible causes of ataxia: Focal lesions of the central nervous system (such as tumor, stroke, and MS), alcohol, antidepressants, antiepileptic drugs, intoxication, radiation, vitamin B12 deficiency, thyroid diseases, head trauma, celiac disease (gluten ataxia), hereditary disorders (such as Friedreich ataxia, ataxia-telangiectasia, Niemann-Pick disease, and fragile X-related ataxia/tremor syndrome), Arnold-Chiari malformation, Wilson's disease, and metabolic disorders (such as succinic semialdehyde dehydrogenase deficiency).

Localization of Lesion Associated with Ataxia

Establishing a direct relationship between the clinical features of cerebellar pathologies and the cerebellar anatomy can be challenging (7,8). Lesions located in the midline of the cerebellum typically cause gait ataxia, truncal ataxia, and titubation. However, involvement of the paravermian region is associated with speech disturbances. Lesions in the posterior cerebellum

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or the flocculonodular lobe can induce vertigo, ataxia, and eye movement abnormalities. Furthermore, lesions in the ipsilateral cerebellar hemispheres have been associated with limb ataxia (7-10). A crucial aspect of coordinating voluntary movements is the cerebellum's role in integrating sensory pathways. Thus, demyelinating lesions affecting either the central or peripheral sensory pathways, as well as the vestibular system, can lead to sensory ataxia (7,8,11). The clinical findings of ataxia and their correlation with neuroanatomy have been described in Table 1.

Symptoms of Ataxia

Patients may present with different forms of ataxia such as postural/balance disorder, ataxic gait, sensory ataxia, truncal ataxia, limb ataxia, dysdiadokinesia (dysrhythmokinesia), intrinsic tremor, dysmetria, dysarthria, nystagmus, paroxysmal ataxia and dysarthria (PAD), and ataxic hemiparesis. A healthy individual can maintain a stable standing position if their feet are placed less than 12 cm apart. Furthermore, they can remain in a fixed position with their feet together or in tandem for >30 seconds. However, a patient with posture/balance issues cannot maintain these positions. An abnormal posture without motor weakness or involuntary movements may be indicative of cerebellar ataxia or sensory ataxia.

Gait ataxia, which is a lack of coordination in the lower limbs, is caused by cerebellar pathologies or decreased proprioceptive

inputs. Individuals may experience a feeling of unsteadiness, a desire to hold on to walls or furniture, or need to keep their feet wide apart, causing an unsteady gait. A worsening in gait disturbance without visual cues (such as walking with eyes closed or in the dark) is indicative of sensory or vestibular ataxia. In patients with cerebellar pathologies, the gait ataxia is similar regardless of visual cues (5).

Patients may present with truncal ataxia, a swaying sensation while sitting or standing (especially with arms extended forward), and titubation. Intentional tremors are caused by an instability in the proximal part of the limb, and its amplitude increases toward the end of a voluntary movement. This is usually evaluated by finger-to-nose and heel-to-shin tests. MS-related tremors have postural and intrinsic components. Furthermore, because these features significantly affect the daily functioning of patients with MS-related tremors, these patients are more likely to be unemployed or retired (12).

Ataxia-associated oculomotor disturbances may present as saccadic dysmetria (eye movements exceeding or lagging behind the target), nystagmus (rapid and involuntary eye movements, especially during lateral gaze) and saccadic intrusions during slow pursuit eye movements (13).

PAD was first proposed by Parker in 1946 (14). It is characterized by short-term stereotypical episodes of speech impairment

Table 1. Correlation between neuroanatomy and the clinical features of ataxia (5)

| Neuroanatomy | Function | Ataxia or ataxia-like features arising due to damage of the particular region |
|--|---|---|
| Cerebellar hemisphere, including dentate nuclei | Integration of sensory input and motor planning for the coordination of complex tasks | Ipsilateral limb ataxia, dysdiadochokinesia, dysmetria, intention tremor, and scanning speech |
| Midline cerebellar structures (vermis, fastigial and interposed nuclei, vestibulocerebellum, and paravermis) | Motor execution, rapid and slow eye movements, balance, lower extremity coordination, and vestibular function | Gait ataxia and imbalance, truncal ataxia, dysmetria, ocular findings, head bobbing, and vertigo |
| Posterior lobe (flocculonodular lobe) | Integration of information from the vestibular nuclei | Nystagmus, postural instability, and gait ataxia |
| Cerebral cortex (frontal lobe) | Planning and initiation of gait | Frontal ataxia (Bruns apraxia), and magnetic gait (different from ataxic gait). Associated pathology in this region can worsen the ataxia |
| Brainstem (vestibular nuclei, inferior olivary nuclei, pontine nuclei, and cerebellar peduncles) | Relay of signals in and out of the cerebellum | Ataxia associated with cranial nerve dysfunction and motor-sensory deficits |
| Spinal cord [cuneate fasciculus, gracile fasciculus, and spinocerebellar tracts (mossy fibers)] | Conduction of sensory pathways | Sensory ataxia |
| Musculoskeletal system (gluteal muscles) | Stabilization of the weight-bearing hip | Waddling gait rather than ataxia. Associated pathology in this region can worsen the ataxia |
| Peripheral sensation system and visual system | Proprioception and visual cues, respectively | Sensory ataxia with Romberg sign can worsen cerebellar ataxia |
| Vestibular system (labyrinth of the inner ear, vestibular nerve, and vestibular nuclei) | Sense of balance and special orientation and maintaining equilibrium | Disequilibrium, loss of balance associated with dizziness and vertigo, tinnitus, hearing impairment, and nystagmus |

that may be accompanied by clumsiness in the extremities, feeling of lightheadedness, and unsteady gait. PAD is one of the paroxysmal symptoms in patients with MS. The other symptoms include tonic spasms, trigeminal neuralgia, Lhermitte's sign, paroxysmal pruritus, and other sensory symptoms. These symptoms are usually of sudden onset and short duration (5-15 s), and they may manifest more than one time per hour. In most of the reported cases of PAD, the lesion responsible has been detected in the midbrain, in or near the red nucleus, and in the cerebellum or cerebellar peduncles. Thus, PAD appears to develop due to pathologies of the cerebello-thalamo-cortical pathways (15-18).

Multiple Sclerosis and Ataxia

Ataxia is a common symptom in demyelinating diseases. It manifests in different forms at any time during the disease course in approximately 80% of the patients, and it significantly affects the patients' quality of life (5,19). A recent retrospective analysis of 123 patients with demyelinating disease-related movement disorders identified ataxia as the predominant movement disorder (20). The presence of cerebellar dysfunction significantly exacerbates disability rates, diminishes mobility, and compromises the quality of life (21). Furthermore, the development of cerebellar dysfunction within the first two years after disease onset is associated with a 20% increase in overall future disability (22).

MS-associated cerebellar pathology can arise from alterations in the microstructure of the cerebellar cortex, cerebellar nuclei, and the white matter of the cerebellar peduncles (23-26). Infratentorial lesions have been associated with persistent disability (27). Recent studies have demonstrated that lesions are more prevalent in the pons and cerebellar peduncles than in the other areas among individuals with clinically isolated syndrome (CIS), which often precedes MS (28,29). Furthermore, autopsies have revealed that 38.7% of the cerebellar cortical area can undergo demyelination in patients with MS. In severe cases of MS, >90% of the area may be involved (30). Cerebellar dysfunction may present during acute relapses or, more frequently, as a result of progressive decline in advanced MS (31). The development of cerebellar symptoms in MS is associated with a heightened risk of transitioning to a progressive disease trajectory (32). Furthermore, a reduced cerebellar volume and increased T2 lesion load are associated with greater cognitive and motor challenges, as well as increased clinical disability as determined by the Expanded Disability Status Scale (33). T2 lesions in the middle and superior cerebellar peduncles are commonly found in patients with MS, and they are associated with disease severity and upper limb functionality (31). Furthermore, the cerebellar cortex undergoes demyelination, which becomes more pronounced in individuals with progressive MS (30). However, patients with earlier stages of MS and CIS, exhibit reduced cerebellar white

matter and overall brain volume when compared with healthy individuals (34).

Clinical manifestations of cerebellar dysfunction, such as tremors, limb and gait ataxia, and dysarthria, tend to persist following a relapse more frequently than sensory alterations (21,35). This poses a significant challenge to the management and contributes to increased morbidity.

Any injury that interferes with the communication pathways between the cerebellum and higher cortical regions may partially account for the cognitive impairments in patients with MS. These clinically present as executive dysfunction, decline in memory, and language capabilities (36).

Assessment of Ataxia

Clinical scales are essential for the initial assessment and scoring of disease severity, monitoring of progression, and quantification of therapeutic outcomes. Several scales exist for the clinical assessment of cerebellar symptoms. Some scales have been specifically designed and validated for particular cerebellar disorders such as Friedreich ataxia. Other scales effectively identify cerebellar symptoms, irrespective of the underlying causes (37).

Ataxia is a prevalent issue among patients with MS, necessitating the use of appropriate scales to comprehensively evaluate this condition. When evaluating ataxia-related symptoms in patients with MS, the International Cooperative Ataxia Rating Scale (ICARS) and Scale for the Assessment and Rating of Ataxia (SARA) are reliable (37). ICARS rates ataxia-related symptoms on the basis of 19 items under four subscales (posture and gait disturbances, kinetic functions, speech disturbances, and oculomotor disturbances). Although semi-quantitative, ICARS depends on the subjective grading of clinicians (38). Similarly, SARA is a semi-quantitative assessment tool. However, it is much simpler and less time consuming than ICARS (39). The upper limb dexterity and effects of ataxia can be effectively and directly assessed in individuals with MS via the nine-hole peg test (9HPT) (40). This test can accurately differentiate between controls and people with MS with varying degrees of impairment. As part of the MS functional composite, the 9HPT is commonly included with tasks related to walking, visual abilities, and cognition (41).

Treatment of Ataxia

The treatment of ataxia is symptomatic and multidisciplinary. The treatment options include pharmacological drugs, occupational therapy, speech therapy, and rehabilitation. However, despite the numerous treatment-related studies, no single treatment has proved efficacious. In a Cochrane-collaborative systematic review of several randomized controlled trials (including placebo-controlled or drug-controlled trials), the results of 172 patients with ataxia or tremor were included. In this review, the methods of only

ten studies were appropriate. Furthermore, a wide range of therapeutic drugs, including baclofen, pyridoxine, isoniazid, and cannabis, were investigated. The review revealed that no treatment modality, including thalamotomy, deep brain stimulation, physiotherapy and neurorehabilitation, was effective against MS-related ataxia in the long-term. However, the included studies had significant limitations, including their small sample size and inability to quantify treatment benefits (19). In a randomized controlled study conducted in 2020, which included 48 patients with upper extremity ataxia, levetiracetam significantly improved the upper extremity symptoms and dexterity, which was assessed via the 9PHT (38) (Table 2).

In a comprehensive review by Chasiotis et al. (38) in 2023, six non-pharmacological interventional studies on the rehabilitation of cerebellar ataxia in patients with MS were analyzed (39). Of the six studies, three were randomized controlled trials that included two rehabilitation protocols. One protocol was task-oriented training (kinematic exercises involving routine daily life tasks) (40,41), and the other was functional rehabilitation training (42). The remaining three studies were pilot studies with small sample sizes (10-20 participants) that examined the following protocols: combination of NDT-Bobath approach and traditional physiotherapy (43), reeducation using robotic and visual biofeedback (a physiotherapy technique that helps patients control their muscles by visualizing muscle activity in real time) (44), functional rehabilitation (45). The review by Chasiotis et al. (38) revealed that the patient’s symptoms and quality of life improve when a combination of different rehabilitation techniques is used to treat ataxia. Furthermore, the symptoms significantly improved when evenly distributed external torso weights and dynamic plasters were used for the treatment of trunk and extremity tremors (46,47).

In conclusion, although ataxia is very common in patients with any stage of MS and throughout the disease course, studies in this field are insufficient. Ataxia typically manifests a few months after a spinal or brainstem/cerebellar relapse. However, they may occasionally be the presenting symptom of a relapse. Failure to recognize MS as a potential cause of new-onset movement disorder can lead to delays in the diagnosis and initiation of disease modifying therapy (47). Therefore, more studies on the

frequency, pattern and severity of ataxia, associated factors, MRI features, and treatment modalities of MS-related ataxia are required.

Ethics

Conflict of Interest: The author declare no conflict of interest.

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| Treatment modality | Options |
|--------------------|--|
| Physical | Balance-based torso weighting and task-oriented and core-stability exercises |
| Pharmacological | Carbamazepine, levetiracetam, phenytoin, acetazolamide, lacosamide, and fingolimod |
| Surgical | Thalamic deep brain stimulation and thalamotomy |

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