Chapter

Ataxia in Multiple Sclerosis: From Current Understanding to Therapy

Bilal El-Mansoury, Jawad Laadraoui, Abdelaati El Khiat, Omar El Hiba, Arumugam R. Jayakumar, Abdessalam Ferssiwi and Abdelali Bitar

Abstract

Ataxia is a type of neurological disorder that affects the ability to coordinate voluntary movements, such as walking, balance, and speech. In people with multiple sclerosis (MS), ataxia is a common symptom, affecting around 80% of people with the condition. The cause of ataxia in MS is still unknown; however, it is thought to be due to damage to the part of the central nervous system (CNS) that controls balance, coordination, and movement, especially the cerebellum. Symptoms of ataxia in people with MS can range from mild to severe, and can include a lack of coordination, difficulty speaking, difficulty walking, and gait. Ataxia management in MS typically involves pharmacotherapy to improve coordination, physiotherapy to enhance strength and balance, surgical procedures to alleviate tremor as well as occupational therapy to help with everyday activities.

Keywords: ataxia, tremor, multiple sclerosis, neurodegeneration, treatment

1. Introduction

Multiple sclerosis (MS) is an immune-mediated neurodegenerative disease of the central nervous system (CNS), which primary affects young adults [1–3]. The large immune response to putative CNS antigens is thought to be driven by an interplay between environmental and genetic factors [4]. There are four different forms of MS that can be distinguished based on the clinical disease pattern, namely: relapsing–remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive relapsing MS (PRMS) [5]. Clinically, RRMS is the most common form of MS, with more than 85% of patients initially present with such form.

Multiple sclerosis is believed to be associated with a wide range of neurological abnormalities, which often interact to cause mobility difficulties, while the impairment in balance is thought to be significant factor in these mobility difficulties [6]. A body line of evidence shows that 85% of MS patients may experience mild ataxia at some point in time, while 32% of MS patients exhibits a severe form that can decline their functional abilities [7–9]. The word ataxia (from the Greek) literally means the

absence of order, disorder, or confusion and is characterized by a loss of coordination of the body's limbs, the trunk, and the gait and it can be brought on by sensory system's dysfunction (sensory ataxia), cerebellum's dysfunction (cerebellar ataxia), or dysfunction of the vestibular system (vestibular ataxia) [10, 11], which may also arise from thalamic and parietal- and frontal-lobe injuries [8].

Clinically, ataxia refers to a collection of abnormal movements, of which tremor is the main symptom. Other clinical manifestations include dysmetria, dysdiadochokinesia, incoordination, and movement delays [8]. It is rarely seen as a single symptom and usually occurs with muscle weakness and spasticity [7]. Nevertheless, severe ataxia may occur alone but it is usually combined with brainstem signs [12]. A range of interventions aimed at enhancing balance in standing and walking are used in clinical practice, including pharmacotherapy, surgical therapies, and the most common is physiotherapy. This chapter provides an overview of different types of ataxia, the current understanding of ataxia in MS, and the currently available therapeutic approaches.

2. Clinical features of cerebellar dysfunction in MS

Cerebellar dysfunction is a typical feature of MS, which results in a wide range of neurological manifestations. The clinical signs of cerebellar involvement in MS include gait ataxia, dysmetria when performing the finger-to-nose and heel-to-shin tests, and the inability to perform tandem gait [4]. Cerebellar involvement in MS results from both vermian and hemispheric lesions. Up to 50% of MS patients may experience intention tremor and limb ataxia [4]. Indeed, MS frequently causes coordination issues, which are mostly brought on by pathology in the cerebellum itself or dysfunction in cerebellar connections, including proprioceptive afferent inputs. Depending on the exact location of the lesion, cerebellar dysfunction can cause limb, gait, and truncal ataxia as well as other cerebellar characteristics including dysarthria, and tremor [13]. MS patients exhibit signs of either chronic cerebellar abnormalities in a progressing disease or acute cerebellar impairment related to an acute relapse [13]. A higher incidence of cerebellar involvement during successive relapses appears to be linked to cerebellar relapse in the early stages of the disease [14].

It is believed that injury to the anterior lobe of the cerebellum is the primary cause of gait ataxia [15]. Cerebellar dysarthria is a rare symptom at disease initiation but is common in people with secondary progressive diseases that have worsened [13]. Although paroxysmal MS symptoms are rare, paroxysmal dysarthria with ataxia has been documented in MS and is thought to be related to midbrain pathology [16, 17]. Sensory evaluation (sensory ataxia) based on as scoring from 0 to 4, shows minimal sensory impairment in MS patients. The minimal sensory impairment detected clinically was found to be more prominent in the electrophysiological studies [7].

A recent database research of over 15,000 patients found that there were nearly 50,000 total relapses. Cerebellar relapses made up about 10% of those, and they were more common in men and in people who had had the disease for a longer period of time [18]. Poor relapse recovery is also linked to cerebellar/brainstem relapses, which are linked to an earlier onset of progressive disease [13].

Likewise, tremor is a common symptom of MS and has been found in more than half of MS patients who visit specialized clinics [11]. Clinical studies have revealed that tremor was clinically detected in 18 MS patients and absent in 14 patients. While

MS patients who had a visible tremor had an ataxia score that was more severe and showed clinical symptoms of cerebellar dysfunction [19]. It is worth mentioning that cerebellar ataxia is generally associated with tremor, which typically happens during voluntary movements or while maintaining a position [11]. MS tremor is believed to be mostly brought on by cerebellar and/or thalamic dysfunction [20]. Otherwise, tremor can occur in the head, limbs, vocal cords, and trunk. Though rest and rubral tremors are uncommon, intention and postural tremors are the most prevalent types [21, 22]. Whereas, severe tremor, which is thought to affect 3% of MS patients, is a very uncommon but severely debilitating MS complication [22]. The pathophysiology of tremor in MS is complex and is thought to involve connections between the cerebellum, cerebral cortex, and basal ganglia [13]. Given the significance of cerebellar connections in motor control, it may not be surprising that the involvement of the cerebellum is associated with higher impairment and a worse prognosis.

3. Classification of ataxia

Based on the location, there are different forms of ataxia: cerebellar, sensory, and vestibular ataxia. It can be further divided into three categories: acquired (caused by structural or demyelinating conditions, toxicity, paraneoplastic, inflammatory or infectious diseases, and autoimmune conditions), hereditary (caused by a gene defect and manifesting in childhood), and sporadic (patients have no family history of ataxia and present in adulthood) [23]. The most prevalent of the genetic types of ataxias is Friedreich's ataxia (FRDA), which is autosomal recessive.

3.1 Primary ataxia

Ataxias that affect the primary cerebellum can also be considered as sporadic and inherited. The latter includes episodic ataxias, X-linked cerebellar ataxias, mitochondrial ataxias, autosomal dominant cerebellar ataxias, also known as spinocerebellar ataxias (SCAs), and autosomal recessive cerebellar ataxias (ARCAs). The cerebellar variant of multiple system atrophy (MSA-C) and idiopathic late-onset cerebellar ataxias are examples of idiopathic degenerative cerebellar ataxias [24–31].

3.2 Congenital ataxia

Cerebellar malformations or pontocerebellar hypoplasia can produce congenital ataxias, which manifest as cerebellar ataxias. The uncommon autosomal recessive condition, Joubert's syndrome, whose most well-known manifestation is the "molar tooth sign" on MRI, is defined by a congenital hind-brain abnormality. The clinical picture includes multiple organ involvement, cerebellar ataxia, respiratory dysregulation, ocular motor apraxia, and neonatal hypotonia. Till now, more than 20 causal genes have been found, the majority of which encode proteins for the main cilium, and an organelle found within cells that plays a key role in many cellular processes. The genetic condition known as ciliopathies, which is a new class, includes Joubert's syndrome **Figure 1** [32, 33].

3.3 Inherited ataxia

The vast set of clinically and genetically diverse, complicated neurodegenerative disorders known as inherited cerebellar ataxias is brought on by several genetic

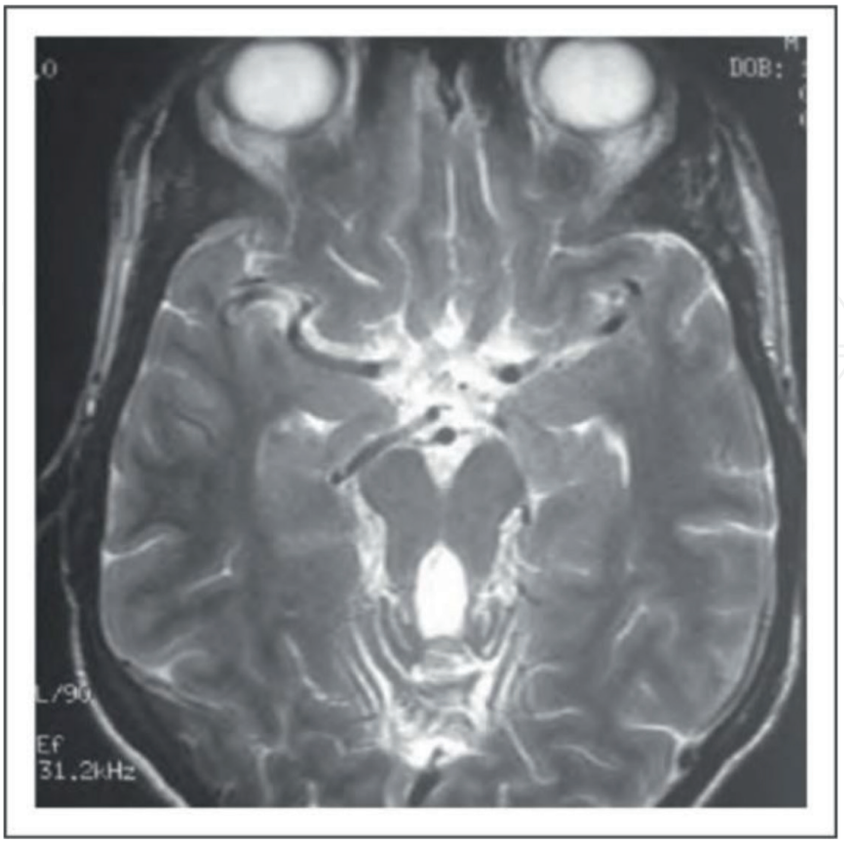

Figure 1.
T2-weighted, axial image of a brain MRI in a patient presenting Joubert's syndrome and the molar tooth sign [23].

abnormalities. There are two X-linked ataxias, more than 30 ARCAs, almost 40 SCA forms, and several mitochondrial ataxias among the hereditary cerebellar ataxias [24, 25, 31, 34].

3.4 Mitochondrial ataxia

Cerebellar and sensory ataxias, which are caused by defects in mitochondrial DNA, are frequently coupled with additional symptoms in mitochondrial ataxias [35]. These ataxias include maternally inherited hereditary ataxias caused by deletions or duplications of mitochondrial DNA or point mutations in the genes encoding for RNAs and respiratory chain components [35, 36]. A mutation in the mitochondrial DNA polymerase subunit gamma (POLG) gene results in mitochondrial recessive ataxia syndrome [35, 36]. With cerebellar and afferent/sensory ataxia, POLG-related ataxia is a mixed ataxia that manifests with a variety of non-ataxia symptoms, including sensory neuropathy, external ophthalmoplegia, ptosis, epilepsy, and hyperkinetic movement abnormalities [35, 36].

3.5 Idiopathic degenerative ataxia

As well as being referred to as sporadic adult-onset ataxia (SAOA) of unknown etiology or even idiopathic sporadic cerebellar ataxia, MSA-C and idiopathic late-onset cerebellar ataxia are two examples of the diseases with unknown etiology that fall within the category of idiopathic cerebellar degeneration [26, 27, 29, 30, 37, 38].

3.6 Secondary ataxia

Ataxias caused by exogenous or endogenous nongenetic factors, such as those that are toxic, paraneoplastic, immune-mediated, nutritional, and infectious in character, as well as localized damage to the cerebellum, fall under the category of secondary or acquired ataxias [26, 29, 30]. When characterizing localized lesions in the cerebellum and its connections due to conditions including neoplastic, inflammatory, demyelinating, and vascular illnesses, neuroimaging investigations are crucial [26, 29, 30]. The unfavorable effects of some medications might also cause ataxia [39]. Whereas, antiepileptic drugs like oxcarbazepine, lamotrigine, and phenytoin, benzodiazepines like nitrazepam and triazolam, and antineoplastic/immunosuppressive medications like cytarabine, tacrolimus, and cyclosporine are the most prevalent causes of drug-induced cerebellar ataxia [39]. Ataxia can also be brought on by chemicals including alcohol, lithium, and toluene [39, 40]. Otherwise, cerebellar ataxia can result from a number of infectious diseases, including syphilis, Whipple's disease, the mumps, and infectious mononucleosis [26, 29, 30]. It can also be a symptom of endocrine disorders, notably hypothyroidism. Hashimoto's encephalopathy, also known as a steroid-responsive encephalopathy, is associated with autoimmune thyroiditis (Thomas [26, 29, 30]). Whereas, it has been reported that people who do not get enough vitamins including thiamine, tocopherol, and cobalamin may develop cerebellar and afferent/sensory ataxias [26, 29, 30]. While antibodies against glutamic acid decarboxylase (GAD), which were first identified in individuals with stiff-person syndrome, have also been linked to cerebellar ataxia [26, 29, 30, 41, 42]. A body of evidence sustain a sex dimorphism of such immune-mediated cerebellum condition, with women being more likely to have anti-GAD ataxia, which can also coexist with thyroid disorders and insulin-dependent diabetic mellitus. While intravenous immunoglobulins and steroids have varying effects on anti-GAD ataxia. Otherwise, gluten ataxia is another immune-mediated condition brought on by gluten consumption in people with a genetic predisposition [43]. The disease is characterized by adult-onset, progressive gait ataxia with gaze-evoked nystagmus and peripheral neuropathy symptoms. In all cases, the anti-gliadin antibody is positive and an anti-gluten diet can enhance gluten ataxia [43].

3.7 Autosomal recessive cerebellar ataxia

Autosomal recessive cerebellar ataxias (ARCAs) are a part of the diverse category of hereditary ataxias. They often start young and are marked by degeneration of the cerebellum and spinal cord [24, 26, 29–31]. **Table 1** displays the most typical ARCAs that have been genetically identified, wherein we note that ataxia telangiectasia and FRDA are the two most prevalent forms in white children [24, 31, 44, 45].

3.8 Friedreich's ataxia

Since the identification of the FRDA gene and the GAA trinucleotide expansion that causes FRDA, phenotypic variants of this ataxia have been regularly reported in individuals with pathogenic mutations [44, 46]. Some of these variations do not correspond to how this sickness is usually described. Atypical phenotypes include movement abnormalities, pyramidal signals, preserved reflexes, late-onset and very-late-onset ataxia, minor GAA expansions, and ataxia [47, 48].

Autosomal recessive cerebellar ataxia types	Locus	Gene	Protein
Friedreich's ataxia	9q13	*FXN*	Frataxin
Ataxia with vitamin E deficiency	8q12.3	*TTPA*	α-Tocopherol transfer protein
Autosomal recessive spastic cerebellar ataxia of Charlevoix-Saguenay	13q12	*SACS*	Sacsin
Ataxia telangiectasia	11q22.3	*ATM*	Serine protein kinase
Ataxia telangiectasia-like disorder	11q21	*MRE11*	Meiotic recombination 11
Ataxia with oculomotor apraxia type 1	9p13	*APTX*	Aprataxin
Ataxia with oculomotor apraxia type 2	9q34	*SETX*	Senataxin
Mitochondrial recessive ataxia syndrome	15q25	*POLG1*	DNA polymerase subunit g-1
Marinesco-Sjogren syndrome	5q31	*SIL1*	Nucleotide exchange factor SIL1
Autosomal recessive cerebellar ataxia type 1	6q25	*SYNE1*	Nesprin-1
Autosomal recessive cerebellar ataxia type 2	1q42.2	*CABC1*	Chaperone activity of bc1 complex like
Autosomal recessive cerebellar ataxia type 3	3p22.1	*ANO10*	Anoctamin-10

Table 1.
The most prevalent kinds of autosomal recessive cerebellar ataxias with genetic definition.

Friedreich's ataxia is largely an ataxia of the efferent and sensory nerves where neuropathological investigations and more recent neuroimaging studies have both verified the existence of a cerebellar component (**Figure 2**) [44, 46, 49]. Nevertheless, antioxidants like coenzyme Q10 and its derivatives, such as idebenone, have been employed, despite the lack of agreement on a cure. Although it is ineffective for neurological disorders, idebenone has demonstrated notable advantages for hypertrophic cardiomyopathy [50, 51]. Deferiprone and epigenetic treatment for Friedreich's ataxia have both recently undergone testing, as have other novel medications [52, 53].

3.9 Ataxia telangiectasia

More than 200 potentially harmful mutations affecting virtually all of the ataxia telangiectasia-mutated (ATM) gene's coding exons have been identified since the ATM gene was initially characterized [54]. In addition to the typical phenotype with cerebellar ataxia and oculocutaneous telangiectasia, many instances of ataxia telangiectasia with milder phenotypes have been documented (**Figure 3**). These phenotypes involve later diagnosis, lower progression of the disease, longer life expectancy, an affinity for movement disorders such as dystonia, myoclonus, and chorea instead of cerebellar ataxia, an absence of ocular telangiectasia, decreased levels of chromosomal instability and cellular radiosensitivity, as well as the absence of ocular telangiectasia [45, 54]. Actually, ataxia telangiectasia is a multisystem disorder with a range of neurological and systemic symptoms. A more appropriate name for this condition has been suggested: as ATM syndrome.

3.10 Spinocerebellar ataxia

Spinocerebellar ataxias (SCAs) are a sizable and intricate collection of diverse autosomal dominant degenerative illnesses that affect several parts of the

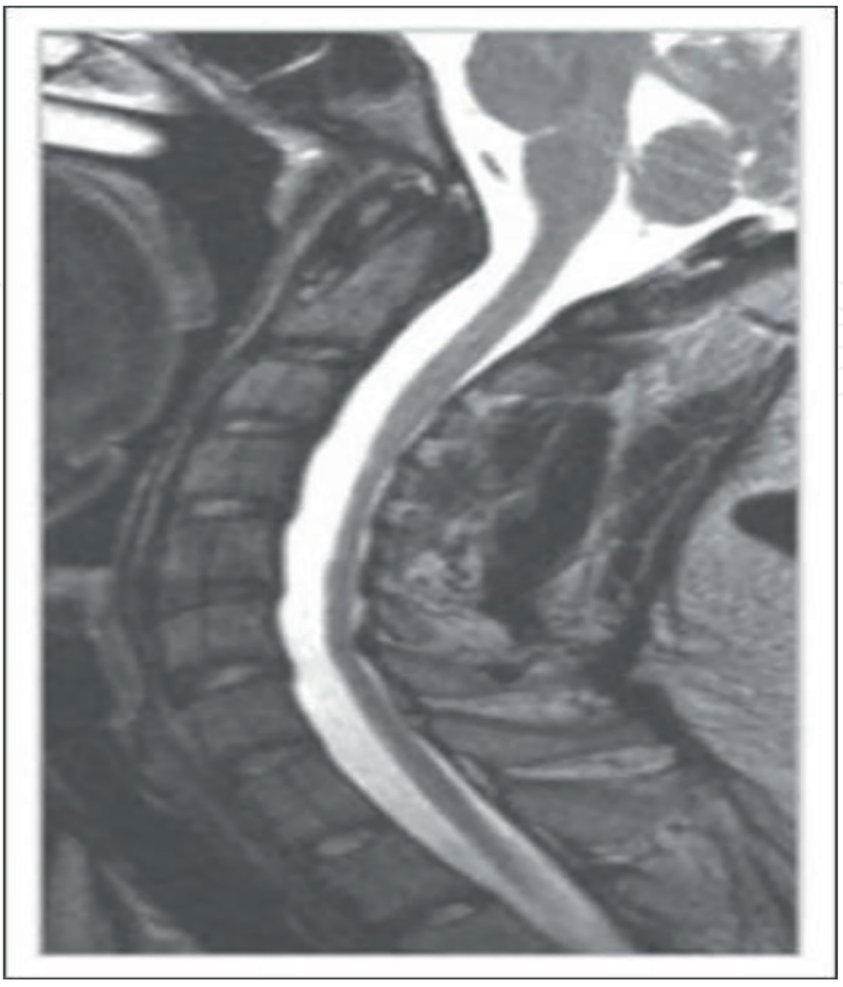

Figure 2.
Sagittal image of a T2-weighted MRI of the spinal cord of patient presenting Friedreich's ataxia with cervical spinal cord atrophy [23].

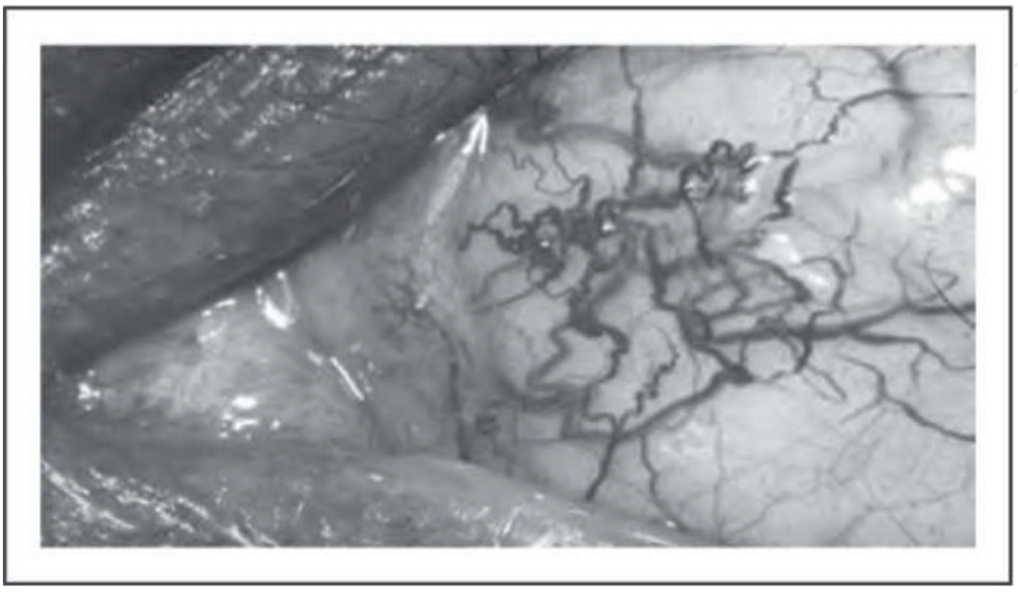

Figure 3.
A patient with ataxia telangiectasia with conjunctival telangiectasia [23].

neurological system, including the cerebellum and its efferent and afferent connections [25, 26, 28–30, 34, 55–57]. **Table 2** lists the most common SCA subtypes along with the genetic locations, mutations, and proteins linked to each condition from SCA type 1 through SCA type 40. The most prevalent form of SCA is type 3, while types 1, 2, 6, and 7 have significantly different prevalence depending on the racial makeup of the population [25–30, 34, 57]. The genetic etiology of illness is still unknown in roughly 40–50% of ARCAs, despite great progress in the discovery of ARCA genes [58–64]. With the exception of ataxia brought on by a vitamin E shortage and a set of ataxias linked to a coenzyme Q10 deficiency, there is no known therapy for these ataxias [26, 29, 30, 58, 63].

Entity	Locus	Gene	Mutation	Potential identifying clinical characteristics
SCA1 (spinocerebellar ataxia type 1)	6p22–23	*ATXN1*	CAG expansion	Hypermetric saccades, corticospinal tract signs
SCA2	12q23–24.1	*ATXN2*	CAG expansion	Slow saccades, areflexia
SCA3 (Machado-Joseph diseases)	14q32.1	*ATXN3/ DMJ*	CAG expansion	Bulging eyes, fasciculations
SCA4	16q22.1	*SCA4*		
SCA5	11q13.2	*SPTBN2*	Deletion, point mutation	Downbeat nystagmus
SCA6	19p13	*CACNA1A*	CAG expansion	Coarse nystagmus and saccadic intrusions
SCA7	3p21.1-p12	*ATXN7*	CAG expansion	Visual loss due to retinal degeneration
SCA8	13q21	*ATXN8OS*	CAG/CTG expansion	Reduced penetrance
SCA10	22q13.31	*ATXN10*	ATTCT expansion	Seizures
SCA11	15q15.2	*TTBK2*	Deletion	Downbeat nystagmus
SCA12	5q32	*PPP2R2B*	CAG expansion	Action tremor in midlife
SCA13	19q13.33	*KCNC3*	Point mutation	Absent eye findings
SCA14	19q13.4	*PRKCG*	Deletion, point mutation	Tremor, myoclonus, facial myokymia
SCA15/ SCA16	3p26.1	*ITPR1*	Duplication	Postural and kinetic tremor, psychiatric symptoms or dementia
SCA17	6q27	*TBP*	CAG	Huntington's disease like (dysarthria before gait ataxia)
SCA20	11p11.2-q13.3	*SCA20*	Multiple gene duplication	Spasmodic dysphonia, palatal tremor
SCA27	13q34	*FGF14*	Point mutation	Mental retardation and tremor
SCA28	18p11	*AFG3L2*	Point mutation	
SCA29	3p26.1	*ITPR1*	Allelic to SCA15, 16	Congenital nonprogressive ataxia

Entity	Locus	Gene	Mutation	Potential identifying clinical characteristics
SCA30	4q34.3-q35.1	*SCA30*		
SCA31	16q22	*SCA31*	TGGAA	
SCA32	7q32-q33	*SCA32*		
SCA34	6q12.3-q16.1	*AFG3L2*	Point mutation	Erythrokeratodermia
SCA35	20p13	*TGM6*		
SCA36	20p13	*NOP56*	GGCCTG expansion	Myoclonus, choreoathetosis, dementia (Huntington's disease like)
SCA37	1p32	*SCA37*		
SCA38	6p12.1	*ELOVLE5*		
SCA40	14q32	*CCDC88C*		
Dentatorubral-pallidoluysian atrophy (DRPLA)	12p13.31	*ATN1*	CAG expansion	Hyperkeratosis, multiple system atrophy-cerebellar type-like (Huntington's disease like)
Episodic ataxia type 1		*KCNA1*		Episodic, lasts seconds to minutes, interictal fasciculations
Episodic ataxia type 1		*CACNA1Q*		Episodic, lasts from hours to days, interictal nystagmus

Table 2.
Genetic characteristics of spinocerebellar ataxias.

Other SCAs cover a wide range of clinical symptoms. As opposed to the normal phenotype, which comprises of cerebellar ataxia and epilepsy, the major phenotype seen in the latter is pure cerebellar [29, 30]. It is worth mentioning that several additional SCAs with novel loci and gene mutations have been described more recently and SCA patients have a relatively high number of mutations, however, many patients (30–40%) still lack a genetic or molecular diagnosis [34, 57].

3.11 Secondary ataxias

Secondary or acquired ataxias include ataxias arising from exogenous or endogenous nongenetic origins, including those naturally caused toxins, paraneoplastic, immune-mediated agents, and infections, as well as focal injury to the cerebellum [26, 65, 66]. In MS, inflammation attacks and damages nerve fibers and myelin, a protective tissue around the nerves of the brain and spinal cord. Eventually, nerve cells that control body movements by sending and receiving electrical signals are damaged, which leads to abnormalities in body movement. In patients with MS, three types of ataxias are cerebellar, sensory (proprioceptive ataxia), and vestibular ataxia. Cerebellar ataxia is a syndrome that encompasses gait ataxia, nystagmus, dysarthria, tremor, and cognitive dysfunction, among others [67]. It is caused by damage to the cerebellum, leading to disruptions in the actions of different nerves that control muscle and movements on one or both sides of the body. Vestibular ataxia causes loss of balance, vertigo, dizziness, nausea, and vomiting, among others. Some people with

MS develop vestibular ataxia slowly, so they just have a loss of balance or equilibrium, not other severe symptoms. Vestibular ataxia is caused by damage to the vestibular system (i.e., inner ear structures and fluid-filled ear canals that control the sense of balance) and it might also be caused by lesions in the brainstem, or if MS pathology affects nerves that connect tiny organs in the inner ear that control balance. In this setting, neuroimaging studies are of great importance in determining focal lesions in the cerebellum and its connections as well as other affected parts of the brain [67].

4. Diagnosing patients with ataxia

The history should provide information on the kind of ataxia or vestibular dysfunction, the body areas affected, any concomitant signs, and the underlying etiology. Neurologists will be able to anticipate the results of the physical examination with a high degree of accuracy if they take a thorough history. Any unexpected physical discoveries should be cause for rethinking the past.

Numerous concomitant signs and symptoms of ataxia may appear, allowing the neurologist to focus on the differential diagnosis. Postural problems in case of cerebellar ataxia can be assessed objectively and subjectively. An accurate assessment of clinical symptoms serves as the foundation for qualitative evaluations. Cerebellar ataxia is indicated by postural instability and a stumbling, jerky gait. Since instruction regarding gait and gait disorders is rarely given much attention in medical colleges, an accurate examination of clinical symptoms is frequently overlooked [68].

- **Mental status examination:** There is growing understanding of the cerebellum's function in cognition. Along with being the location of motor coordination, the cerebellum also interacts closely with the cerebrum to perform higher-order cortical tasks, such as frontal executive functions, spatial orientation, motor memory, language skills, and the ability to recognize and express emotions [68].

- **Cranial nerve examination:** Examining extraocular movements typically shows aberrant pursuit and saccades, ocular dyskinesia such as square-wave jerks, ocular flutter, and opsoclonus in a variety of cerebellar illnesses. A cerebellar mass lesion may cause papilledema, particularly in people with hydrocephalus. The ipsilateral loss of the corneal reflex and impairment of the eighth cranial nerve may be signs of a cerebellopontine angle tumor. SCA3 symptoms include facial and tongue fasciculations, and SCA36 symptoms include significant tongue atrophy and fasciculations.

- **Vestibular signs:** The majority of the time, ataxia from the vestibular system is accompanied by vertigo and sluggish nystagmus with or without change in posture. When trying to walk straight, affected patients frequently deviate to the ipsilateral side. To rule out problems with the inner ear, hearing loss should be further assessed.

- **Cerebellar signs:** Often, the gait is impacted first. They are unable to stand with their feet together. Walking or adopting a tandem posture is a more sensitive test. Patients frequently lean in the same direction. With titubation, the gait is wide based. A localized cerebellar lesion frequently causes dysmetria of the limbs, intention tremor, loss of control, hypotonia, and dorsal spooning (hyperextension

of interphalangeal joints) of the hand, in addition to dysarthria and nystagmus. In addition to appendicular ataxia, which should be assessed by looking at limb movements, and upright ataxia, which should be assessed by looking at posture, gait, and truncal ataxia, physical examinations should also look for ocular dyskinesias, speech abnormalities, proprioceptive loss, and vestibular dysfunction.

- **Extrapyramidal symptoms:** It is typical for extrapyramidal symptoms to be accompanied by persistently increasing ataxia. Extrapyramidal symptoms are frequently a clue that a neurodegenerative process is moving beyond the cerebellum and brainstem in inherited ataxias. For instance, whereas MSA and certain SCAs may also have linked Parkinsonism, most SCAs often impact gait first. Levodopa frequently alleviates the symptoms of Parkinsonism in SCA2, SCA3, and SCA17; however, when the striatum is affected, patients frequently have Parkinsonism and are not sensitive to levodopa. In these individuals receiving levodopa medication, dyskinesia can be brought on; nevertheless, involuntary movements, including dystonia, may be a symptom of SCAs. To find them, the inspection may need careful attention.

- **Strength:** It is critical to determine whether muscular weakness may account for the severity of ataxia. The examiner might ask the patient to rise up from a sitting posture and to stand on their toes and heels in order to assess the functional proximal and distal muscular strength while compensating for ataxia. Myopathy is suggested by symmetrically proximal muscle weakness. Generalized neuropathy is suggested by distal muscular weakness. In addition to ataxia, muscular weakness may also be indicated by abnormal gait. For instance, waddling gait, which should not be confused with ataxic gait, is caused when the hip girdle is weak owing to myopathy, which causes the pelvis to have a tendency to move toward the side.

- **Proprioceptive sensory system:** Sensory ataxia may result from a loss of sensory information from spinocerebellar pathways to the cerebellum. Any proprioceptive pathway impairment, including Friedreich's ataxia, ataxia with vitamin E deficiency, acquired sensory ataxias linked to ataxic polyneuropathies (e.g., paraneoplastic sensory neuronopathy), Sjögren's syndrome, diabetes mellitus, vitamin B6 toxicity, and Miller Fisher syndrome, may result in sensory loss. Proprioception and vibration at the great toe can be used to evaluate this. In contrast to cerebellar ataxia, where there is no change in the severity of ataxia with and without the eyes closed, the ataxia often gets worse when the visual signals are removed. Additionally, these individuals struggle to stand with their feet together and their eyes closed (Romberg sign).

5. Neuroanatomy and neuropathology of ataxia

Ataxia is a condition that affects the cerebellum and its afferent and efferent connections, the vestibular system, and the proprioceptive sensory pathway (**Figure 4**). The cerebellum is often divided into the cerebellar hemispheres and the midline cerebellum. A separate form of ataxia may manifest after lesions in any of these areas. For instance, injury to the unilateral cerebellar hemisphere typically results in ipsilateral cerebellar ataxia, whereas damage to the midline cerebellar structures typically manifests as gait impairment and truncal ataxia.

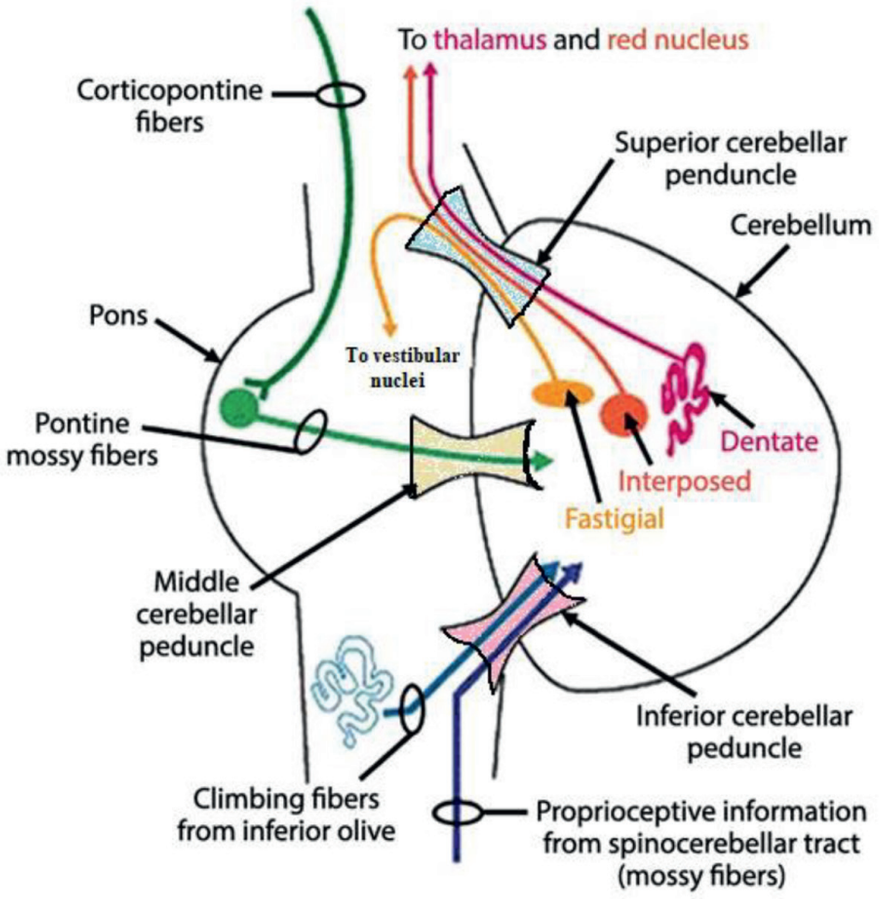

Figure 4.
The cerebellum's afferent and efferent connections. Climbing fibers from the inferior olives pass through the inferior cerebellar peduncles to link to the cerebellum, whereas pontine mossy fibers pass through the middle cerebellar peduncles. The superior cerebellar peduncles receive cerebellar outputs from the dentate nucleus and other deep cerebellar nuclei.

A lesion that disrupts the sensory transmission to the cerebellum may be the cause of ataxia. Spinal ataxia or sensory ataxia may result from this disease. Cerebellar ataxia is brought on by a break in the cerebellum's cortical impulses. Both of the aforementioned disorders can lead to spinocerebellar ataxias. They are caused by chromosomal CAG repetition and are autosomal dominant. Characteristic findings vary depending on where the lesion is located and include:

- Diffuse lesions result in widespread symptoms, whereas lesions in the lateral cerebellum only induce symptoms on the side of the lesion (ipsilateral).
- Ataxia of the limbs is brought on by cerebellar hemisphere lesions.
- Truncal, gait ataxia is caused by vermis lesions that spare the limbs.
- Vertigo, imbalance, and gait ataxia are all symptoms of vestibulo-cerebellar lesions, chromosomes [69].

Localization can be aided by comprehension of this neuroanatomy and its relationship to coordination. Despite the fact that there is considerable clinical overlap among them, the relationships are presented in **Table 3**.

Neuroanatomy	Function	Ataxia or ataxia-like presentation arising from damage of the region
Cerebellar hemisphere, including dentate nuclei	combining motor planning with sensory information to coordinate difficult tasks	Ipsilateral limb ataxia, dysdiadochokinesia, dysmetria, intention tremor, and scanning speech
Midline cerebellar structures (vermis, fastigial and interposed nuclei, the vestibulocerebellum, and the paravermis)	Balance, coordination of the lower extremities, fast and slow eye movements, and vestibular function	Gait ataxia and imbalance, truncal ataxia, dysmetria, ocular findings, head bobbing, and vertigo
Posterior lobe (flocculonodular lobe)	including information on vestibular nuclei	Nystagmus, postural instability, and gait ataxia
Cerebral cortex (frontal lobe)	Planning and initiating gait	Frontal ataxia (Bruns apraxia), magnetic gait (not the same as ataxic gait), although damage in this area that is related to the ataxia might make it worse.
Brainstem (vestibular nuclei, inferior olivary nuclei, pontine nuclei, and cerebellar peduncles)	Relay 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])	Sensory pathways conduction	Sensory ataxia
Musculoskeletal system (gluteal muscles)	Stabilizing the weight-bearing hip	Waddling gait rather than ataxia, however disease in this area that is connected to it can make ataxia worse
Peripheral sensation system and visual system	Proprioception, visual cues	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, equilibrium	Unsteadiness, loss of balance brought on by vertigo, and a feeling of heaviness, tinnitus, and hearing loss, as well as nystagmus

Table 3.
Clinical characteristics and neuroanatomical relationships in ataxia.

6. Management of ataxia in MS

Management of ataxia and tremor encompasses a variety of available treatments, ranging from pharmacological approaches, surgical strategies to neurorehabilitation [10, 70]. The effectiveness and safety of treatments for ataxia in MS are not well understood; however, neurosurgery and rehabilitation procedures may be at least somewhat helpful [8]. Ataxia and tremor are challenging symptoms for management and treatments are supportive only [10, 11, 71]. Broadly speaking, the management of MS is based either on symptomatic treatments for established symptoms and/or disease-modifying therapies (DMTs), which aim to alleviate the impact of this condition [13].

Surgical procedures like deep brain stimulation (DBS) may be useful for some patients and prior to invasive procedures, a team examination of each individual is

necessary [10]. The most popular non-pharmacological treatment for MS ataxia is physiotherapy, which is used frequently. Exercises designed specifically for balance that facilitate somatosensory and motor strategies are typically used, albeit to various degrees [72]. Task-oriented training also improves ambulation and postural control in MS patients by fostering motor learning [73]. Combinations of these physiotherapy techniques are generally considered to be highly beneficial for MS patients [74].

Finding new treatment approaches will be aided by a better understanding of the pathophysiology of cerebellar disease in MS which will help to treat its related ataxia and tremor. Hence, treating cerebellar disorders and offering neuroprotection inside the cerebellum are urgently needed while newer treatments are being tested, like stem cell therapy. The possibility of stem cell therapies for MS cerebellar pathology is particularly alluring, given the revelation that Purkinje cell fusion is a potential neurorestorative mechanism [13]. A summary of treatment modalities and options for the ataxia of MS patients is provided in **Table 4** [75–77].

6.1 Pharmacological treatment

Pharmacological treatment for cerebellar ataxia also remains challenging. Case report studies and small studies offer little support for certain treatments. Although recommendations are difficult to make for the treatment of ataxia and tremor, a variety of medications have been shown to have advantages in small open-label studies or case reports. Several treatments have been used including propranolol [78], isoniazid [76, 77], topiramate [79], carbamazepine [80], clonazepam, and levetiracetam [81] and reported only little success [10]. In a small pilot research involving 14 MS patients, levetiracetam was also found to dramatically lessen tremor and ataxia [82]. Moreover, topiramate has shown significant functional improvement in a sustained, dose-dependent manner [79]. Additionally, fingolimod may have added benefits in MS patients with ataxia [75]. Other drugs tested including glutethimide [83], cannabinoids [84], and dolasetron mesylate [85]. Cannabis extracts have been the subject of several randomized controlled trials, and the results have shown that cannabinoids do not seem to reduce MS tremor [84, 86, 87]. There is some evidence that paroxysmal ataxia and dysarthria may respond to carbamazepine in a manner comparable to other paroxysmal symptoms of MS, such as tonic spasm [88].

Although isoniazid, propranolol, and levetiracetam have been investigated, the findings are inconclusive, and these drugs are not frequently used (the patients included in these trials were typically very small, allowing for few generalizations) [76, 78, 81, 89–91]. Whereas, isoniazide in high doses, carbamazepine, propranolol,

Treatment Modality	Options
Physical	Balance-based torso weighting, task oriented, and core-stability exercises
Pharmacologic therapy	Carbamazepine, topiramate, Isoniazide, levetracetam, phenytoin, acetazolamide, lacosamide, fingolimod[#]
Surgical approches[*]	Deep brain stimulation, thalamotomy

[*] *Adverse effects such as dysarthria and ataxia disability scores not improved.*
[#] *To be used with caution as it has significant immunosuppressive effects.*

Table 4.
Treatment modalities and options for the ataxia of multiple sclerosis (MS) patients.

glutethimide, 4-aminopyridine, and topiramate have been reported to provide some benefit in the treatment of ataxia and tremor [20, 79, 92]. As ataxia constitutes a difficult symptom to treat, medications like isoniazid and carbamezepine must be used in high amounts for the treatment to be effective. Since these medications have hepatotoxic effects, many patients are unable to receive the maximum dosage, which limits their ability to be used for extended periods of time [7]. Indeed, pharmacological approaches used to improve ataxic symptoms are generally disappointing, necessitating the need for innovative treatments. In a meta-analysis study performed by Mills et al. [70], the authors have reviewed six randomized placebo-controlled trials (pharmacotherapy) of treatments for ataxia in MS. They concluded that there is insufficient information regarding absolute and comparative efficacy and tolerability of pharmacotherapies [70]. As a result, no recommendations could be given to guide in prescribing these medications [70].

It is worth mentioning that a patient-centered strategy is critical to the efficacy of pharmacological treatment, which is a crucial part of managing MS symptoms. To maximize compliance, particularly with invasive interventions, doctors must properly inform patients, discuss their priorities and expectations, and assist them in making the right treatment decisions [11]. With oral medications, the first dose should be low and gradually increased based on response and tolerability. If one medication is insufficient due to its ineffectiveness or unacceptable side effects, it is advised to combine several medications—possibly at lower doses [11].

6.2 Surgical interventions

Tremors can be both kinetic and postural, and they can be very challenging to manage. In case of tremor resistance to treatment, thalamotomy or thalamic stimulation has been tried to some degree of success [93]. Carefully selected patients with localized tremor with minimum disability could benefit from stereotactic thalamotomy, which targets the nucleus ventralis lateralis and nucleus ventralis intermedius, or DBS, which targets the nuclei ventralis lateralis and nucleus ventralis intermedius, ventralis oralis posterior nucleus, and zona incerta [94–96]. Tremor was abolished by both thalamotomy and thalamic stimulation in all patients immediately postsurgery [97]. However, tremor returned in almost all MS patients after 6 months, albeit of less severity than preoperative levels. Stereotactic thalamotomy seems to be more effective for intractable tremor, but the consequent functional improvement is variable and the intervention is associated with a higher risk of neurological deficit [11].

It is believed that distal tremor with good proximal stability and limb function are particularly responsive to DBS [11]. Successful alleviation of tremor in patients with MS has been achieved using DBS of the ventralis intermedius (VIM) thalamic nucleus [98]. Indeed, DBS is likely to improve tremor, but the effect might be reduced over time. Functional improvement is more often reported after DBS than after stereotactic thalamotomy, and DBS can be better tolerated. It has been reported that both procedures initially suppressed tremor in over 90% of patients, although functional improvement was seen only in 47.8% of those who underwent thalamotomy as opposed to 85.2% of those who had DBS [99]. However, the choice between interventions should be made on an individual basis in consultation with the specialist neurosurgical team [11], and larger trials that compare these two interventions and assess the efficacy are needed.

6.3 Rehabilitation approaches

Beyond pharmacological and surgical approaches, many physiotherapy approaches are used in balance therapy and tremor. Physiotherapy, orthoses, and limb cooling may be beneficial [20]. Indeed, in MS, rehabilitation programs may be helpful to enhance core stability in individuals with balance issues, lumbar stabilization exercises that strengthen the core trunk muscles and have an impact on postural control, ambulation, and skilled motor function [100]. A systemic review of trials with physical therapies showed some beneficial effect [101]. Additionally, Armutlu et al. [72] reported that physiotherapy approaches were effective to decrease the ataxia [7]. There is some evidence, according to a systematic review of research looking into the benefits of treadmill or robot-assisted training, that people with severe disabilities can see improvements in their quality of life and gait [102]. Two of the eight studies that were considered were modest single-group studies that only included individuals with progressing MS in their sample [103, 104]. Using weights and heavy walkers may decrease ataxic movements; however, they may increase fatigue [7, 105–107]. Patients with MS who were randomly assigned to physiotherapy showed improved scores on the Expanded Disability Status Scale (EDSS) and the Rivermead Mobility Index [7, 108]. An improvement in the Rivermead Mobility Index was seen in a different study on 42 randomly selected patients when home and outpatient therapy groups were compared to no therapy. However, mobility returned to pretreatment levels after 2 months of follow-up [109]. In MS patients, balance-based torso-weighting has been shown to improve cerebellar ataxia patients [110]. In 45 ataxic relapsing–remitting MS patients, the addition of core stability exercises and task-oriented training to typical balance training was found to potentially enhance stability [111]. Similar to this, task-oriented training and lumbar stabilization enhanced the efficacy of balance therapy in a group of 42 MS patients [74], exhibiting a considerable improvement in the International Cooperative Ataxia Rating Scale and composite balance scores. As measured by the International Cooperative Ataxia Rating Scale, the Mini-Balance Evaluation Systems Test, the smoothness of movement on both sides in a 5-m walk, and balance in a step-to-stand task before and after the intervention, a targeted ballet program aimed at reducing MS-associated ataxia and improving balance in women demonstrated significant clinical improvement [112]. These studies collectively demonstrate the positive effects of physiotherapy in MS-related ataxia [75]. In another study, it was determined that physiotherapy approaches were effective to decrease ataxia and that the combination of suitable physiotherapy techniques is effective in MS rehabilitation [7]. Even though physiotherapy has been shown to improve function in ataxia modestly, its long-term benefits in MS patients remain unclear.

Following task-specific rehabilitation, neural plasticity is enhanced [113, 114]. Thus, it is believed that balance and mobility interventions offer the proper task-specific stimuli to promote neural reorganization of central sensory integration, resulting in improved stability [6]. Despite the fact that neuroplasticity and motor learning are commonly considered to be more beneficial in the initial stages of MS, they seem to remain even in those with more severe disability [114]. Future research should establish whether or not those with progressive MS, and at different levels of disability, respond differently to these interventions, and if so whether and when interventions should be refocused on compensatory rather than restorative strategies.

7. Conclusion

Ataxia is a common symptom of MS that can dramatically impact the patient's quality of life. The underlying pathophysiology of ataxia in MS is not fully understood, but it is believed to be related to demyelination and neurodegeneration in specific areas of the brain. There are currently no specific therapies approved for the treatment of ataxia in MS; however, several promising therapeutic approaches are being investigated, including the use of disease-modifying therapies, rehabilitative interventions, and symptomatic treatments.

8. Final remarks

This study demonstrates the complexity of understanding and targeting ataxia in MS. It provides a comprehensive overview of the most recent research and the current therapeutic strategies for managing ataxia in individuals with MS. It also highlights the multifactorial nature of the complex involvement of various brain regions, such as the cerebellum, brainstem, and spinal cord, in motor incoordination and impaired balance which might make their diagnosis and management difficult. There is still a lack of appropriate strategy in the treatment of ataxia in MS and in order to treat the complex character of ataxia, a multimodal strategy is urgently required. Finally, in order to better understand ataxia in MS and develop more effective treatments for this condition, ongoing research efforts and collaborative initiatives are of great importance.

Author details

Bilal El-Mansoury[1*], Jawad Laadraoui[2], Abdelaati El Khiat[3,4], Omar El Hiba[1], Arumugam R. Jayakumar[5], Abdessalam Ferssiwi[1] and Abdelali Bitar[1]

1 Laboratory of Anthropogenic, Biotechnology and Health, Team Physiopathology Nutritional, Neurosciences and Toxicology, Faculty of Sciences, Chouaib Doukkali University, El Jadida, Morocco

2 Laboratory of Pharmacology, Neurobiology, Anthropology and Environment, Faculty of Sciences, Semlalia, Cadi Ayyad University, Marrakech, Morocco

3 Laboratory of Clinical and Experimental Neurosciences and Environment, Faculty of Medicine and Pharmacy, Cadi Ayyad University, Marrakech, Morocco

4 Biological and Health Sciences Team, Higher Institute of Nursing Professions and Health Techniques, Ministry of Health, Ouarzazate, Morocco

5 University of Miami School of Medicine, Miami, FL, USA

*Address all correspondence to: elmansoury1995bilal@gmail.com

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