ABSTRACT

Background: Multiple sclerosis (MS), a subset of chronic primary inflammatory demyelinating disorders of the central nervous system, is closely associated with various movement disorders. These disorders may be due to MS pathophysiology or be coincidental. This review describes the full spectrum of movement disorders in MS with their possible mechanistic pathways and therapeutic modalities.

Methods: The authors conducted a narrative literature review by searching for ‘multiple sclerosis’ and the specific movement disorder on PubMed until October 2021. Relevant articles were screened, selected, and included in the review according to groups of movement disorders.

Results: The most prevalent movement disorders described in MS include restless leg syndrome, tremor, ataxia, parkinsonism, paroxysmal dyskinesias, chorea and ballism, facial myokymia, including hemifacial spasm and spastic paretic hemifacial contracture, tics, and tourettism. The anatomical basis of some of these disorders is poorly understood; however, the link between them and MS is supported by clinical and neuroimaging evidence. Treatment options are disorder-specific and often multidisciplinary, including pharmacological, surgical, and physical therapies.

Discussion: Movements disorders in MS involve multiple pathophysiological processes and anatomical pathways. Since these disorders can be the presenting symptoms, they may aid in early diagnosis and managing the patient, including monitoring disease progression. Treatment of these disorders is a challenge. Further work needs to be done to understand the prevalence and the pathophysiological mechanisms responsible for movement disorders in MS.
INTRODUCTION

Resources appraising movement disorders in multiple sclerosis (MS) differ in clinical characteristics and accurate prevalence data [1-3]. This variation could stem from the retrospective nature of the studies, small sample size, and consideration of coexisting non-MS-related movement disorders, among others. Neuroinflammation and neurodegeneration are the two processes that pathophysiologically define MS [2]. Although movement disorders are common in MS, their accurate pathobiological basis remains elusive [2]. The interrelation between these two might be either causal or coincidental [4]. Some movement disorders present with symptoms highly suggestive of MS, which should prompt immediate diagnosis and treatment. The most prevalent movement disorders in MS include restless leg syndrome (RLS), tremor, ataxia, parkinsonism, paroxysmal dyskinesias, dystonia, chorea and ballism, facial myokymia, including hemifacial spasm and spastic paretic hemifacial contracture, tics, and tourettism [1-6].

Our aim with this review is: 1) to describe the entire spectrum of movement disorders associated with MS; 2) to discuss possible pathophysiological mechanisms responsible for movement disorders in MS and; 3) to discuss the therapeutic modalities of the various movement disorders in MS.

METHODS

We conducted a narrative literature review by searching for the keywords ‘multiple sclerosis’ and the specific movement disorder on PubMed until October 2021. The search terms are outlined in Supplementary Table 1. Relevant articles were screened, selected, and included in the review according to groups of movement disorders.

We undertook a descriptive analysis, where the movement disorders were separated into groups and discussed according to their prevalence, causal relation with MS, pathophysiology, and treatment modalities. After searching databases and initial screening titles and abstracts, two separate reviewers (R.G. and D.R.) extracted the relevant papers to screen full-text manuscripts. We omitted duplicate publications during this process. Search results were further augmented by bibliographic searches and studies familiar to the authors. The included studies were case reports, case series, literature reviews including systematic reviews and meta-analysis, population-based studies, and clinical trials related to any movement disorder associated with MS. Studies were excluded if they did not include human subjects. We extracted the data from the included publications.

RESULTS

1) RESTLESS LEGS SYNDROME

There is a significant association between MS and RLS, especially in cases with severe sensory and motor disabilities [7-16]. RLS prevalence rates in patients with MS are significantly higher than in the general population, especially in women [7-12]. A recent meta-analysis reported a prevalence of RLS of 27.5% (13.2–65.1) in patients with MS [17].

RLS negatively impacts sleep quality and causes excessive daytime sleepiness [7-16, 18]. Moreover, this resultant sleep impairment may be one of the causes of the cognitive decline associated with MS [9]. Therefore, a search for RLS should be done in patients with MS having insomnia.

The pathophysiologic link between MS and RLS is yet to be established, and several theories have been proposed [15, 16, 19]. The presence of cervical cord lesions is more common in patients with MS having RLS symptoms than in those who do not [20, 21]. MS-related inflammatory damage may also induce secondary forms of RLS [11]. Iron deficiency anemia is a known risk factor for RLS with or without MS [20]. RLS is particularly found in premenopausal MS women because they have a higher likelihood of worse iron stores due to menstrual loss [22]. Ferritin level, when lower than 50 μg/L, should be considered a candidate for iron replacement in patients with RLS with or without MS [23].

Dopamine agonists, i.e., pramipexole, ropinirole, transdermal rotigotine, effectively manage RLS [24]. Clonazepam, gabapentin, and levodopa/carbidopa are the other options [25]. Therapy-related augmentation of RLS symptoms is an important clinical problem reported in up to three-fourths of patients treated with levodopa and, to a lesser extent, with dopamine agonists [26]. Co-activation of functionally different dopamine receptor subtypes or interactions with other receptors may have a role in augmentation [27]. Therefore, newer treatment options should consider these dynamic changes in the dopaminergic system. A recent clinical trial has provided preliminary evidence that a 16-week physical activity can effectively reduce RLS severity and improve sleep outcomes in MS patients [9].

2) TREMOR

Tremor was included in the original triad of MS symptoms postulated by Charcot, i.e., tremor, scanning speech, and nystagmus [28, 29]. The estimated prevalence of tremor is between 25% and 58% of the patients with MS, with 3–15% having severe MS-related tremors [28]. Patients with MS who have tremor of any severity retire early or become unemployed because of disability [28, 29]. Typically a combination of postural and intention tremors may be
observed in patients with MS [28, 29]. Tremor in MS is often bilateral and involves the upper limbs more than the lower limbs, but can affect the head, neck, and even vocal cords [28–30]. The pathophysiological basis of tremor in MS is elusive, as it seldom occurs in isolation [28–30]. Because of the preponderance of mixed (postural and intentional) tremors and scarcity of rest tremor syndromes in MS, it likely originates from and is mediated by cerebellar connections [28–30]. The intensity of MS tremors can be reduced by cooling of extremities, likely due to a reduction in muscle excitability and neuronal conduction, causing reduced input to the cerebellar circuitry [28–31]. The severity of upper limb tremors is strongly associated with high degrees of ataxia, dysmetria, and dysdiadochokinesia, which may be due to an aberrant cerebellar-thalamocortical network [5, 28–30, 32]. Recently, this involvement has been supported by imaging studies. Increased lesion load and cerebellar and thalamic atrophy were observed on the ipsilateral side of the tremor than on the side without tremor in MS patients [33, 34]. Other studies have found significant associations between tremor amplitude and increased contralateral pontine lesion load highlighting the role of pontine components in MS-tremor [35].

Holmes’ tremor (also termed “rubral” or “midbrain”) [5, 36, 37], a combination of kinetic, postural, and resting tremor, predominantly involving the proximal limbs, is uncommon in MS [38]. It appears due to cerebellothalamic and nigrostriatal pathway dysfunction, and it is partially responsive to levodopa [37].

Figure 1 summarizes the treatment modalities for the tremor in MS. Isoniazid, one of the first-line anti-tubercular agents, has shown promising results in a few randomized controlled trials in MS-related tremors (Figure 1) [39–45]. However, several adverse effects have limited its use [39–42]. Results with cannabis/cannabinoids have not been remarkably successful [46–48]. 4-aminopyridine positively impacts MS-related tremors as it presumably improves the excitability of the cerebellar Purkinje neurons [49]. Anecdotal reports claim that topiramate may be helpful at low doses to control MS-tremor and enhance functionality [50]. Type-A botulinum toxin was also found to be effective in the treatment of MS-related tremors [51–53]. Other medications such as levetiracetam, ondansetron, primidone, propranolol, baclofen pump, and carbamazepine have shown conflicting results [51–61].

![Figure 1: Treatment modalities in multiple sclerosis-associated tremors.](image-url)
For the last 3–4 decades, surgical treatment for relieving tremor in MS have been tried with mixed success rates [30, 55, 62–64, 64–76, 77]. Surgical options include deep brain stimulation (DBS) and stereotactic thalamotomy [63–76]. As most studies are small, retrospective, and observational, they are insufficient to provide data on the efficacy of these interventions on post-intervention functional status, post-intervention residual disability, and long-term follow-up status of adverse events [63–76]. It is difficult to demonstrate an improvement in health-related quality of life with such interventions as it is difficult to differentiate between tremor-related and MS-related disabilities [78]. Overall, thalamic stimulation with DBS and thalamotomy had comparable effects in controlling tremors in MS [79]. Permanent reduction in MS-related tremors following DBS can also be attributed to the natural progression of the disease, where limb weakness prevents the expression of the tremor [80, 81–85]. Recently, MRI-guided focused ultrasound thalamotomy was successfully used to treat a medically refractory tremor in a 28-year-old female [81]. The procedure is minimally invasive and has yielded positive results in patients with essential tremor [86]. However, in the reported case [81], the patient developed dysarthria that took nearly 12 months to resolve [81]. Imaging-guided thalamotomy, although proven to help manage tremors in MS, may be associated with neurological side effects, which may require a longer time to resolve. However, direct evidence of “off-target” damage in neuroaxis was not evident in earlier cases, demanding more rationale and further pragmatism in patient selection [81]. For treatment-resistant tremors in MS such as Holmes’ tremor, simultaneous DBS involving ventralis intermedius with globus pallidus internus pallidotomy may be efficacious due to the synergistic effect [87].

3) ATAXIA

In isolation or associated with other neurological deficits, ataxia is a common manifestation (almost 80% of patients) in demyelinating disorders and significantly impacts health-related quality of life [25, 88]. It is caused by dysfunction of the cerebellar connections with the cerebral cortex, brainstem, thalamus, and spinal cord [25, 88].

It can be difficult to directly correlate clinical manifestations of cerebellopathies with cerebellar anatomy [89, 90]. Midline cerebellar lesions result in gait and truncal ataxia and titubation, while paravermian area involvement affects speech. Posterior cerebellar lesion or flocculonodular lobe involvement is known to cause vertigo, ataxia, and eye movement abnormalities [89, 90, 91]. Limb ataxia is associated with ipsilateral cerebellar hemispheric lesions [89, 90]. The lesions associated with these tremors may also involve the cerebellum-rubro-thalamocortical tract beyond the cerebellar cortex (the long-loop pathway) [89, 90]. Sensory integration is another significant component of the coordination of voluntary movements. Hence, demyelinating lesions involving the central or peripheral sensory tracts and the vestibular system can cause sensory ataxia [89, 90, 92].

In a recent retrospective study involving 123 patients with movement disorders and demyelinating diseases, ataxia was the most common movement disorder, followed by an isolated tremor [6]. In a study involving five MS patients who developed limb ataxia/intention tremor, a contralateral cortical MRI lesion became visible on an average of 22.3 months before the development of limb ataxia [93]. Lesions involving the contralateral thalamus and internal capsule have also been reported in MS in the form of ataxic hemiparesis, almost indistinguishable from a vascular syndrome [94]. Episodic ataxia may also be present in demyelinating diseases [95]. A recent case report revealed a coincidental occurrence of type 2 episodic ataxia and MS in a patient with previously unidentified heterozygous mutation in the gene coding for the voltage-gated calcium channel subunit alpha 1A [96]. These cases highlight the various anatomical regions that can be affected in demyelinating lesions, resulting in ataxia and the long-term disability of ataxia in patients with MS.

Ataxia in MS is often associated with paroxysmal dysarthria (PDA) [97]. An episode of PDA is usually accompanied by slurring of speech and gait ataxia that may last seconds and recur throughout the day [97]. Sensory symptoms, such as numbness, burning sensations, and paresthesia of the face, tongue, or limbs, may follow and can be provoked by physical or emotional stress [95, 97–99]. PDA can be attributed mainly to midbrain lesions at or below the level of the red nucleus but has also been described in dorsolateral pons and cerebellar lesions [95, 99–105]. More than 60 cases of PDA in MS have been documented to date [99, 103, 105–108]. Furthermore, paroxysmal limb hemiataxia with crossed facial paresthesia may also occur in MS, albeit rarely [109, 110]. The causative lesion is localized in the upper part of the pons, affecting the ventral central trigeminal tract, brachium conjunctivum, and lateral spinothalamic tract [110].

The treatment for ataxia is symptomatic and often multidisciplinary. The treatment options range from pharmacologic to physical, occupational, and speech therapy and rehabilitation. Multiple trials have been carried out with varied results [67, 88, 111–113], but ultimately failed to show conclusive evidence of a singular effective therapy. A systematic study comprised of 10 randomized controlled trials investigated a wide range of therapeutics,
including baclofen, pyridoxine, isoniazid, cannabis, thalamotomy, DBS, physiotherapy, and neurorehabilitation in MS, none of which proved to be effective against ataxia in the long-term [88]. However, the assessment of outcomes in these studies was possibly affected by the different methods used to measure tremors and the small sample size [88]. Thalamic DBS and thalamotomy have shown initial promise in medication-resistant tremors in MS, but on follow-up, not only did the treatment group suffer from other adverse effects such as dysarthria and ataxia, but disability scores did not improve [67].

Even though physiotherapy has been shown to improve function in ataxia modestly, its long-term benefits in MS patients are unclear. Two different trials revealed an improved Expanded Disability Status Scale score and Rivermead Mobility index in patients with MS randomized to physiotherapy [111, 113]. Another study on 42 randomized patients initially showed improvement in Rivermead Mobility Index for home and outpatient therapy groups compared to no therapy. However, after two months of follow-up, mobility regressed to pretreatment levels [112]. Balance-based torso-weighting has been beneficial in standing stability, cadence, gait velocity, and percentage of the gait cycle in single-limb support in MS patients [114–116] and in cerebellar ataxia patients [117]. Ali et al [118], added core stability exercises and task-oriented training to traditional balance training in 45 ataxic relapsing-remitting patients with MS and concluded that this technique might improve stability.

Similarly, in a group of 42 patients with MS, task-oriented training and lumbar stabilization improved the success of balance rehabilitation [119], showing significant improvement in composite balance scores and the International Cooperative Ataxia Rating Scale. Finally, a targeted ballet program aimed at mitigating MS-associated ataxia and improving balance in women showed significant clinical improvement, as observed by the International Cooperative Ataxia Rating Scale, the Mini-Balance Evaluations Systems Test, the smoothness of movement on both sides in a five-meter walk, and balance in a step-to-stand task before and after the intervention [120]. All these studies point towards the promising benefits of physiotherapy in MS-related ataxia.

Pharmacologic treatment for cerebellar ataxia also remains challenging. Benzodiazepines and barbiturates (e.g., clonazepam, primidone), although effective in improving tremors, can cause worsening of balance and coordination in the long term [121]. Episodic ataxia can be effectively treated by acetazolamide and calcium-channel blockers [122]. Topiramate has shown significant functional improvement in a sustained, dose-dependent manner [50]. Levetiracetam has also been shown to significantly improve tremor and ataxia in a small pilot study of 14 patients with MS [56]. Standard antiepileptics, such as carbamazepine [99, 100], levetiracetam [105], lacosamide [102], phenytoin [110], and acetazolamide [108] have been effective in PDA related to episodic events in MS. Goodwin and Carpenter [105] reported PDA in a 37-year-old woman approximately three months after a multifocal MS relapse. The lesions were in the posterior midbrain and the right posterior internal capsule [105]. Levetiracetam (500 mg twice daily) was administered, which reduced her attack frequency [105]. The attacks completely stopped when the dose was increased to 750 mg [105]. Similarly, a 49-year-old MS patient who developed PDA due to a midbrain lesion responded well to carbamazepine [101]. In another case [103], the PDA attacks resolved after fingolimod treatment. Fingolimod may have added benefits in MS patients with ataxia. However, immunosuppressive side effects must be weighed against potential benefit [123].

A summary of ataxia in MS and possible treatment options is provided in Tables 1 and 2.

| PRESENTATION                        | LOCALIZED LESION                                                                 |
|-------------------------------------|----------------------------------------------------------------------------------|
| Gait ataxia; truncal ataxia; titubation | Midline of the cerebellum, including the vermis; cerebellar peduncle.          |
| Gait ataxia; nystagmus; balance problems | Posterior cerebellum, including the flocculonodular lobe; cerebellar peduncle. |
| Limb ataxia                         | Cerebellar hemisphere; cerebello-rubro-thalamocortical tract.                  |
| Sensory ataxia                      | Vestibular system; central or peripheral sensory tracts.                        |
| Ataxic tremor                       | Cerebello-rubro-thalamocortical tract                                           |
| Ataxic hemiparesis                  | Internal capsule                                                                |
| Paroxysmal dysarthria               | Midbrain; dorsolateral pons                                                     |
| Paroxysmal limb hemiataxia          | Upper pons; ventral central trigeminal tract; brachium conjunctivum; lateral spinothalamic tract |

Table 1 Clinical presentation and anatomical correlates of ataxia in multiple sclerosis.
Another type of focal dystonia, writer’s cramp, can affect the face, arm, and leg and be precipitated by hyperventilation, tactile stimulation, or repetitive and patterned twisted movements [162]. An unpleasant sensory aura (ipsilateral or contralateral) can precede the episodes [124, 137, 138]. The pathophysiology has been attributed to axonal inflammation, axonal hypersensitivity, potassium channel alteration, decreased ionized calcium, and demyelination of theafferent inhibitory neuroanatomic pathways [130, 135, 136]. Demyelinating lesions lead to an ephaptic activation of secondary axons, especially where the motor fibers run closely together [109, 134]. In the reported cases, lesions are detected in the midbrain, cerebral peduncle, thalamus, basal ganglia, contralateral posterior limb of the internal capsule, brainstem, and cervical spinal cord [125, 131, 135–149]. In a recent retrospective voxel-wise symptom mapping analysis of 25 patients with MS, paroxysmal dystonia was causally associated with basal ganglia lesions adjacent to the thalamus, the internal capsule, and the periventricular occipital area of the posterior thalamic radiations [150]. Thus, lesions in various regions may contribute to paroxysmal dystonia in MS. Generally, a normal electroencephalogram can exclude the possibility of the misdiagnosis of a focal onset seizure [124, 135, 149, 151].

Tonic spasms are sudden, involuntary movements usually lasting seconds, manifesting with abnormal posturing of limbs or part of a limb and precipitated by voluntary movements, emotional stress, and specific sensory stimulation. Paroxysmal tonic spasm is rarely observed in demyelinating disorders like MS and neuromyelitis optica spectrum disorder [152]. Abnormal sensory integration in the thalamus, which may also stem from the ephaptic activation of neurons in the spinal cord, and related dopamine level fluctuations in basal ganglia are thought to be the basic underpinning mechanisms [152].

Focal dystonia cases that have been reported in MS include oromandibular [127, 128], writer’s cramp [153], and pharyngeal forms [133]. Another type of focal dystonia, infrequently reported in MS, is cervical dystonia [154–161], which usually appears a few years after the onset of MS [3, 147, 162, 163]. The association between cervical dystonia and MS was thought to be coincidental [148]. However, a causal association has also been implicated [146, 158–160], in the form of high cervical spinal lesions on MRI, lesions in the left posterior putamen, and the patient’s response to corticotropin. Indeed, lesions in the cervical spinal cord can cause interruptions of afferent fibers responsible for the proprioception of head posture [164]. The treatment for cervical dystonia in MS varies depending on whether the attacks are related or not to an MS relapse [3, 159, 165].

A few MS-associated choreoathetosis cases have been reported [166–173]. In these cases, the lesions have been found in varied areas, such as the basal ganglia circuitry and mesencephalon [166–168, 172, 174], thalamo-striatal network [166, 167], posterior part of the internal capsule [167], medial longitudinal fasciculi [169], and cervical cord [173].

Regarding treatment, paroxysmal dyskinesias in MS may be self-limiting and without the need for any therapeutic intervention. Classically, use steroids, alone or in combination with symptomatic treatments, are the treatment of choice [126, 132, 134, 136, 161]. Symptomatic treatment is necessary when movements persist despite

### Table 2: Treatment modalities for the ataxia of multiple sclerosis patients.

| TREATMENT MODALITY | OPTIONS |
|--------------------|---------|
| Physical           | Balance-based torso weighting, task-oriented, and core-stability exercises |
| Pharmacologic      | Carbamazepine, levetiracetam, phenytoin, acetazolamide, lacosamide, fingolimod* |
| Surgical*          | Thalamic 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.
immunosuppressive treatments [97]. Carbamazepine is one of the best options [130, 147, 151]. Other useful drugs are acetazolamide [132, 175], clonazepam [175], levetiracetam [175], valproate [134], and oxcarbazepine [136]. For cervical dystonia, corticosteroids are the first line, whether there is an MS-relapse manifestation [3, 163]. For gradual-onset attacks unrelated to MS exacerbation or persistent symptoms despite high-dose corticosteroids, botulinum toxin is the optimal treatment [159].

For MS-related choreoathetosis, therapeutic evidence is not well documented. However, corticosteroids, antiepileptics such as carbamazepine, oxcarbazepine, phenytoin, valproate, lacosamide, and neuroleptics such as haloperidol, risperidone, and olanzapine are among the options [97, 121, 176].

5) MYOCLONUS
The “Guillain Mollaret” triangle (GMT) (or myoclonic triangle) is formed by the red nucleus and inferior olive ipsilaterally connected to the contralateral cerebellar dentate nucleus. The red nucleus in the midbrain connects with the ipsilateral inferior olive in the medulla through the central tegmentum tract, traversing through the pons. This triangle includes almost the whole of the brain stem, which is packed with white matter tracts, and thus vulnerable to be affected by a demyelinating disease like MS. This brainstem and deep cerebellar nucleus connection modulate the spinal cord motor activities, thereby heralding varied neurological manifestations once acted. Only a handful of cases of myoclonus have been reported in MS [177–187]. The palatal type is the most commonly encountered [147], usually associated with nystagmus. Palatal myoclonus is a form of segmental myoclonus [147]. It can be of two types: essential and symptomatic. Symptomatic or secondary cases are associated with structural brain lesions ranging from demyelinating to space-occupying lesions involving GMT. Ear clicks are an important clinical correlate seen in essential palatal myoclonus due to the involvement of the tensor vali palatini muscle, which helps differentiate it from symptomatic palatal myoclonus where there are no ear clicks [147]. The lesions in the palatal myoclonus are thought to be localized to the dentato-rubro-olivary pathway [147, 185]. Other types of myoclonus reported in patients with MS are intention myoclonus [178, 182, 187], middle ear myoclonus [183], and spinal myoclonus [180, 181]. It is controversial whether middle ear myoclonus is different or is a part of palatal myoclonus. Middle ear myoclonus is associated with tinnitus and ear clicks [183]. Tensor tympani contractions, two walls of Eustachian tube collision, and stapedius contractions are proposed mechanisms underlying middle ear myoclonus [183].

Intention myoclonus is rarely seen in MS [178] and has been related to neuronal loss contributed by demyelination in the red nuclei [178]. Myoclonic jerks may resemble flexor spasms, a frequent finding in patients with spasticity and MS. Hence, a careful clinical distinction between the two may aid in correct clinical interpretation and treatment. Spinal segmental myoclonus, characterized by involuntary, semirhythmic contractions of skeletal muscle groups innervated by a limited spinal cord region, poses a diagnostic challenge at the time of presentation. It is usually precipitated by fatigue, stress, and relieved in sleep. Among six cases of demyelinating disorder associated with myoclonus, Jankovic and Pardo [186] reported one with spinal myoclonus and five others with brainstem myoclonus. Due to demyelinating lesions at the cervical roots, upper limb myoclonus has been reported [180, 181, 184]. The possible pathophysiological mechanisms include axonal hyperexcitability and spontaneous discharge, leading to the disinhibition of alpha-motor neurons and disrupted spinal interneuronal circuitry [180, 188].

Commonly used therapeutics that can be effective are valproic acid, clonazepam, tizanidine, and levetiracetam [121, 182, 187]. Botulinum toxin could prove beneficial in palatal myoclonus in MS [189]. Medical management was unsuccessful in an MS case of bilateral middle ear myoclonus causing incapacitating tinnitus [183], which was successfully treated with bilateral sectioning of tensor tympani and stapedial tendons.

6) BALLISM
Several reports of hemiballismus in patients with MS have been reported [147, 190–194]. In two reports, MS defining demyelinating plaques were observed in the contralateral subthalamic nucleus [191, 194]. The treatment options for ballism are almost the same as chorea, except it may be reasonable to start with corticosteroids. Neuroleptics may also be used. However, neuroleptics should be used with caution in patients with MS in general, as they have been reported to cause, albeit rarely, adverse reactions [195].

7) FACIAL MYOKYMIA
Facial myokymia is frequently reported as the presenting feature in patients with MS [196–211]. The lesion is usually attributed to the postnuclear facial fascicular involvement in the dorsolateral pontine tegmentum [212]. Strictly unilateral myokymia involving peri-oral muscles warrants a search for underlying structural/demyelinating lesion over pons in contrast to eyelid myokymia, which is usually benign without any structural correlations [206].

Facial myokymia is often resolved spontaneously. A descriptive study showed that most facial myokymia in MS remits regardless of treatment received [208]. When it
does not resolve, it may progress into a lower motor neuron type facial palsy [97, 209]. Thus, a progressive or persistent myokymia (more than six months) should also raise the suspicion of secondary causes such as MS. Most patients respond to corticosteroids, gabapentin, carbamazepine, and botulinum toxin [52, 202, 208].

8) HEMIFACIAL SPASM

A prospective observational study in a cohort of 60 patients with MS revealed that 58.3% had demyelination-related movement disorders. Two of them were found to have hemifacial spasms secondary to pontine demyelination [1]. In a descriptive study of clinical features and treatment outcomes involving 35 patients with MS, seven had hemifacial spasm [208]. In another case series of six patients with MS who developed hemifacial spasm, two had unilateral lower pontine lesions visible in brain MRI [197]. The involvement of the platysma is characteristic of the idiopathic variety, whereas in secondary causes, the upper and lower facial muscles are simultaneously involved [97, 213].

Spastic paretic hemifacial contracture, associated initially with brainstem tumors, has also been described in a few cases of MS [211, 214–216]. Koutsis et al. [214] screened 500 patients with MS and found two cases of spastic paretic hemifacial contracture, which were characterized by continuous resting activity by irregular motor unit firing potentials on electromyogram and the absence of myokymic discharges. The lesions have been attributed to the involvement of ipsilateral dorsolateral pontine tegmentum [211, 216] and demyelinated corticofacial fibers [216].

Several theories exist regarding the pathophysiology of hemifacial spasms in MS. Demyelination can cause ephaptic transmission, leading to abnormal firing [217]. The cranial nerves’ transition zones (i.e., root-exit zones) are susceptible to injury. Irritative feedback from peripheral lesions can also cause hyperexcitability of the facial nerve nucleus. Consequently, microvascular decompression (for facial palsy and trigeminal neuralgia) and radiofrequency rhizotomy (trigeminal neuralgia) could benefit [208]. Most hemifacial spasm cases in MS resolve (almost 71%), regardless of treatment [208].

9) TICS AND TOURETTISM

The coexistence of MS with tics and tourettism is extremely rare, with two reports of tourettism [218], one report of complex vocal tic [219], and another one with simple phonic tics [220]. In Nociti et al. [218], the tourettism was presumed secondary to progressive MS. The anatomical localization of tics has not been established. Involvement of the cortico-striatal-thalamocortical circuit and basal ganglia is supported by clinical evidence, as demyelinating lesions were observed disrupting the basal ganglia and thalamus circuits [218–220].

The patient with secondary progressive MS and tourettism was successfully treated with quetiapine [218]. The one with simple phonic tics presented with paroxysmal throat-clearing sounds recovered with pimozide [220]. Available treatment options include typical neuroleptics (e.g., haloperidol, pimozide), α-adrenergic receptor agonists (e.g., clonidine), and atypical neuroleptics (e.g., clozapine, risperidone), tetrabenazine, and carbamazepine, among others [121, 221]. Finally, DBS may be helpful as a third-line treatment in patients who are refractory to medical treatment [222].

10) PARKINSONISM

Parkinsonism is a rare phenomenon in MS [147, 172, 223–243]. The association may be coincidental [147], or caused by MS [226, 231]. Evidence supporting a causal relationship includes the lesions of basal ganglia or midbrain on neuroimaging and improvement with corticosteroids [225, 226, 231, 240, 243]. Demyelinating plaques involving the basal ganglia and thalamus are quite common in patients with MS [244], and involvement of nigrostriatal pathway may lead to features of parkinsonism [244, 245]. The reports with either documented evidence of lesions on neuroimaging (i.e., MRI) or therapeutic response to corticosteroids are summarized in Table 3.

The frequency of basal ganglia lesions on MRI of patients with MS and the rarity of parkinsonism in the setting of MS and normal MRI in the presence of parkinsonian features also suggests that these lesions may not be causal [223, 239]. Any such correlating features are absent in coincidental association, and those cases are responsive to levodopa [223, 224, 227]. Indeed, a nationwide historical prospective study on a Danish cohort did not find any increased risk of Parkinson’s disease in MS (standardized incidence ratio 0.98, 95% CI 0.67–1.44), which suggests the absence of a causal association [246].

However, recent genetic evidence may indicate a possible relationship between the two disorders. The increased expression of α-synuclein has been observed in astrocytes in normal-appearing white matter adjacent to MS lesions in secondary progressive MS [247]. Neuronal loss was observed in both white matter and grey matter structures (e.g., thalamus), suggesting that immune-mediated demyelinating diseases may share some standard features with other neurodegenerative conditions such as parkinsonism. In addition, increased cerebrospinal fluid (CSF) α-synuclein in patients with MS may suggest axonal injury around inflammatory lesions [248]. PARK2 gene, associated with young-onset parkinsonism, is...
highly expressed in acute plaques in patients with MS [205]. Similarly, PTEN-induced kinase 1, which has a protective role against stress-induced mitochondrial dysfunction, showed marked astrocytic immunostaining in demyelinating lesions of MS [249]. The genetic variability of HLA-DRB5 is also evidence in favor of a possible genetic relationship between MS and parkinsonism as it has a role in the inflammatory processes in both diseases [250].

**CONCLUSION**

MS is a debilitating disease with severe implications for its sufferers' health-related quality of life. Movement disorders are relatively common in MS but have varied manifestations, underlying pathomechanisms, and treatment modalities. In many instances, movement disorders are presenting features, indicating the importance of these pathologies in the early diagnosis of MS. The most prevalent movement disorders in MS include RLS, tremor, ataxia, parkinsonism, paroxysmal dyskinesias, dystonia, chorea and ballism, facial myokymia, including hemifacial spasm and spastic paretic hemifacial contracture, tics, and tourettism.

A multidisciplinary approach including pharmacologic, surgical, and physical therapy is usually necessary for MS-associated tremor and ataxia. Newer methods such as focused ultrasound thalamotomy may be appropriate for MS-tremor management because they are cost-effective, time-saving, minimally invasive, and have reduced infection risk, however, further studies are needed. Treatment options are based on previous case studies and expert opinions rather than high-quality clinical and epidemiological evidence. Advancement of our understanding of movement disorders in MS regarding their prevalence, impact on the patient population, and management options are only possible when these issues are addressed in large cohorts. Until then, awareness among clinicians may aid in avoiding delays in the management of these patients.

| AUTHOR, YEAR | CASES (AGE, SEX) | MRI LESIONS IN MS-RELATED TO PARKINSONISM | L-DOPA RESPONSE | CORTICOSTEROID RESPONSE |
|--------------|------------------|----------------------------------------|-----------------|------------------------|
| Vieregge et al. 1992 [225] | 2 cases (55/M; 60/F) | M: periventricular white matter, left lateral thalamus, globus pallidus F: periventricular white matter, lateral thalamus | – | M: Yes F: Yes |
| Federlein et al. 1997 [226] | 1 case (61/M) | Substantia nigra | – | Yes |
| Folgar et al. 2003 [231] | 1 case (48/F) | Periventricular white matter | – | Yes |
| Wittstock et al. 2001 [243] | 1 case (58/F) | Periventricular region, substantia nigra | – | Yes |
| Burn and Cartlidge 1996 [240] | 1 case (45/F) | Paraventricular areas | – | Yes |
| Tranchant et al. 1995 [147] | 1 case (46/F) | Cerebral peduncle near substantia nigra | – | – |
| Maranhao et al. 1995 [237] | 1 case (48/M) | Cerebral peduncles, thalamus, globus pallidus | – | – |
| Ozturk et al. 2002 [228] | 1 case (39/F) | Substantia nigra | Yes | – |
| Barun et al. 2008 [227] | 2 cases (38/F; 53/F) | 1st: F: Basal ganglia 2nd: F: periventricular white matter | Yes | Yes |
| Valkovic et al. 2007 [223] | 1 case (25/M) | Subthalamic region | Yes | – |
| Kreisler et al. 2004 [239] | 1 case (38/F) | Substantia nigra | Yes | – |
| Saidha et al. 2010 [232] | 1 case (53/M) | Substantia nigra, thalamus, globus pallidus | Yes | Yes |
| Schultheiss et al. 2011 [230] | 1 case (82/M) | Basal ganglia, periventricular white matter | – | – |
| Etemadifar et al. 2014 [236] | 8 cases (5F: 32.6 ± 7; 3M: 34.6 ± 6.8) | Basal ganglia (four cases), thalamus (two cases), midbrain (five cases) | Yes (all) | – |
| Bougea et al. 2015 [235] | 1 case (55/F) | Periventricular white matter, thalamus | Yes | – |
| Delalic et al. 2020 [234] | 1 case (52/F) | White matter | Yes | Yes (initially) |
| Shaygannejad et al. 2016 [233] | 1 case (21/F) | Periventricular | Yes | Yes (initially) |

Table 3 Reported cases having parkinsonism in multiple sclerosis with either brain MRI lesions related to Parkinson’s disease or a positive response to corticosteroids.

The age is mentioned according to the onset of multiple sclerosis. F = Female; M = Male. MRI = magnetic resonance imaging.
ADDITIONAL FILE

The additional file for this article can be found as follows:

- Supplementary Table 1. Search terms used on PubMed platform, October 2021. DOI: https://doi.org/10.5334/tohm.671.s1

COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

RG and DR had equal contributions, and hence they should be considered conjointly as the first authors.

AUTHOR AFFILIATIONS

Ritwik Ghosh, MD  orcid.org/0000-0002-8192-0807
Department of General Medicine, Burdwan Medical College & Hospital, Burdwan, West Bengal, India

Dipayan Roy, MD, DNB  orcid.org/0000-0002-3429-1470
Department of Biochemistry, All India Institute of Medical Sciences (AIIMS), Jodhpur, Rajasthan, India; Indian Institute of Technology (IIT), Madras, Tamil Nadu, India; School of Humanities, Indira Gandhi National Open University, New Delhi, India

Souvik Dubey, MD, DM  orcid.org/0000-0003-1733-3429
Department of Neumroedicine, Bangur Institute of Neurosciences, IPGME&R, Kolkata, West Bengal, India

Shambaditya Das, MD, DM  orcid.org/0000-0001-9075-2000
Department of Neumroedine, Bangur Institute of Neurosciences, IPGME&R, Kolkata, West Bengal, India

Julién Benito-León, MD, PhD  orcid.org/0000-0002-1769-4809
Department of Neurology, University Hospital “12 de Octubre”, Madrid, Spain; Centro de Investigación Biomédicaen Red sobre Enfermedades Neuropedagenerativas (CIBERNED), Madrid, Spain; Department of Medicine, Complutense University, Madrid, Spain

REFERENCES

1. Abboud H, Yu XX, Knusel K, et al. Movement disorders in early MS and related diseases: A prospective observational study. Neurol Clin Pract., Feb 2019; 9(1): 24–31. Epub ahead of print. DOI: https://doi.org/10.1212/CPJ.0000000000000560

2. Potulska-Chromik A, Rudzinska M, Najszewska M, et al. Clinical and neuroimaging correlation of movement disorders in multiple sclerosis: case series and review of the literature. Folia Neuropathol., 2014; 52: 92–100. DOI: https://doi.org/10.5114/fn.2014.41747

3. Mehanna R, Jankovic J. Movement disorders in multiple sclerosis and other demyelinating diseases. J Neurol Sci., 2013; 328: 1–8. DOI: https://doi.org/10.1016/j.jns.2013.02.007

4. Nociti V, Bentivoglio AR, Frisullo G, et al. Movement disorders in multiple sclerosis: Causal or coincidental association? Mult Scler., Nov 2008; 14(9): 1284–7. DOI: https://doi.org/10.1177/1352458508094683

5. Alusi SH, Worthington J, Glickman S, et al. A study of tremor in multiple sclerosis. Brain., Apr 2001; 124(Pt 4): 720–30. DOI: https://doi.org/10.1093/brain/124.4.720

6. Suarez-Cedeno G, Mehanna R. Movement Disorders in Multiple Sclerosis and Other Demyelinating Diseases: A Retrospective Review From a Tertiary Academic Center. Neuralogist., Sept 2021; 26(5): 161–166. Epub ahead of print. DOI: https://doi.org/10.1097/NRL.0000000000000333

7. Zecca C, Manconi M, Fulda S, et al. Restless legs syndrome in multiple sclerosis. CNS Neurol Disord Drug Targets., Dec 2012; 11(8): 1061–9. DOI: https://doi.org/10.2174/1871512711211080017

8. Giannaki CD, Aristotelous P, Stefanakis M, et al. Restless legs syndrome in Multiple Sclerosis patients: a contributing factor for fatigue, impaired functional capacity, and diminished health-related quality of life. Neurol Res., Jul 2018; 40(7): 586–592. DOI: https://doi.org/10.1080/01616421.2018.1454719

9. Cederberg KLJ, Jeng B, Sasaki JF, et al. Restless legs syndrome and health-related quality of life in adults with multiple sclerosis. J Sleep Res., Jun 2020; 29(3): e12880. Epub ahead of print. DOI: https://doi.org/10.1111/jsr.12880

10. Liu G, Feng X, Lan C, et al. Restless leg syndrome and multiple sclerosis: a case-control study in China. Sleep Breath., Dec 2015; 19(4): 1355–60. DOI: https://doi.org/10.1007/s11325-015-1201-3

11. Group IREMSS, Manconi M, Ferini-Strambi L, et al. Multicenter case-control study on restless legs syndrome in multiple sclerosis: the REMS study. Sleep., Jul 2008; 31(7): 944–52.

12. Manconi M, Fabbrini M, Bonanni E, et al. High prevalence of restless legs syndrome in multiple sclerosis. Eur J Neurol; May 2007; 14(5): 534–9. DOI: https://doi.org/10.1111/j.1468-1331.2007.01740.x

13. Miri S, Rohani M, Sahebian MA, et al. Restless legs syndrome in Iranian patients with multiple sclerosis. Neurol Sci., Jul 2013; 34(7): 1105–8. Epub ahead of print. DOI: https://doi.org/10.1007/s10072-012-1186-7

14. Aydar G, Kurt S, Karaer Unaldi H, et al. Restless legs syndrome in multiple sclerosis. Eur Neurol., 2011; 65: 302–6. DOI: https://doi.org/10.1159/000327315

15. Sieminski M, Losy J, Partinen M. Restless legs syndrome in multiple sclerosis. Sleep Med Rev., 2015; 22: 15–22. DOI: https://doi.org/10.1016/j.smrv.2014.10.002
16. Douay X, Waucquenier N, Hautecoeur P, et al. G-SEP (Groupe Septentrional d’Etudes et de Recherche sur la Sclérose en Plaques). Prévèlèance élevée du syndrome des jambes sans repos dans la sclérose en plaques [High prevalence of restless legs syndrome in multiple sclerosis. Rev Neurol (Paris)., Feb 2009; 165(2): 194–6. DOI: https://doi.org/10.1016/j.neurol.2008.06.001

17. Ozdogar AT, Kalron A. Restless legs syndrome in people with multiple sclerosis: An updated systematic review and meta-analyses. Mult Scler Relat Disord., Nov 2021; 56: 103275. DOI: https://doi.org/10.1016/j.msard.2021.103275

18. Monschein T, Schestak C, Schillerwein-Kral C, et al. Restless Legs Syndrome in Multiple Sclerosis: Risk factors and effect on sleep quality – a case-control study. Mult Scler Relat Disord., Jun 2021; 51: 102916. DOI: https://doi.org/10.1016/j.msard.2021.102916

19. Trenkwalder C, Allen R, Högö B, et al. Restless legs syndrome associated with major diseases: A systematic review and new concept. Neurology; 5 2016; 86(14): 1336–1343. DOI: https://doi.org/10.1212/WNL.0000000000002542

20. Sünter G, Kilinç Ö, Berk A, et al. Restless Legs Syndrome/Willis-Ekbom Disease in Multiple Sclerosis Patients with Spinal Cord Lesions., March 2019; 57(4): 299–302. DOI: https://doi.org/10.29399/npa.23351

21. Baba C, Ozdogar AT, Ozcelik S, et al. Relationship between presence of spinal cord lesion and restless legs syndrome in multiple sclerosis. Somatosens Mot Res, 2022; 18: 1–5. DOI: https://doi.org/10.1080/08990220.2022.2027360

22. Li Y, Munger KL, Batool-Anwar S, et al. Association of multiple sclerosis with restless legs syndrome and other sleep disorders in women. Neurology., May 2012; 78(19): 1500–6. DOI: https://doi.org/10.1212/WNL.0b013e3182553c5b

23. Chenini S, Delaby C, Rassu AL, et al. Hecipadin and ferritin levels in restless legs syndrome: a case-control study. Sci Rep., July 2020; 10(1): 11914. DOI: https://doi.org/10.1038/s41598-020-68851-0

24. Comella CL. Treatment of restless legs syndrome. Neurotherapeutics., Jan 2014; 11(1): 177–87. DOI: https://doi.org/10.1007/s13311-013-0247-9

25. Ashizawa T, Continuum XGA. Ataxia. Continuum (Movement Disorders.), Aug 2016; 1208–26. DOI: https://doi.org/10.1212/CON.0000000000000362

26. García-Borreguero D, Benitez A, Kohen R, et al. Augmentation of restless leg syndrome (Willis-Ekbom disease) during long-term dopaminergic treatment. Postgrad Med., 2015; 127: 716–25. DOI: https://doi.org/10.1080/00325481.2015.1058140

27. Earley CJ, Uhl GR, Clemens S, et al. Connectome and molecular pharmacological differences in the dopaminergic system in restless legs syndrome (RLS): plastic changes and neuroadaptations that may contribute to augmentation. Sleep Med., 2017; 31: 71–77. DOI: https://doi.org/10.1016/j.sleep.2016.06.003

28. Mokhoul K, Ahdab R, Riachi N, et al. Tremor in Multiple Sclerosis—An Overview and Future Perspectives. Brain Sci., October 2020; 10(10): 722. Epub ahead of print. DOI: https://doi.org/10.3390/brainsci10100722

29. Koch M, Mostert J, Heerserra D, et al. Tremor in multiple sclerosis. J Neurol., Feb 2007; 254(2): 133–45. DOI: https://doi.org/10.1007/s00415-006-0296-7

30. Labiano-Fontcuberta A, Benito-León J. Understanding tremor in multiple sclerosis: prevalence, pathological anatomy, and pharmacological and surgical approaches to treatment. Tremor Other Hyperkinet Mov (N Y)., 2012; 2: tre-02-109-765-2. DOI: https://doi.org/10.7916/D8Z60MR3

31. Christogianni A, Bibb R, Davis SL, et al. Temperature sensitivity in multiple sclerosis: An overview of its impact on sensory and cognitive symptoms. Temperature (Austin., 5 September 2018; 5(3): 208–223. DOI: https://doi.org/10.1080/23328940.2018.1475831

32. Walt AV, KB, SS, et al. The occurrence of dystonia in upper-limb multiple sclerosis tremor. Mult Scler., Dec 2015; 21(14): 1847–55. DOI: https://doi.org/10.1177/1352458515577690

33. Boonstra FM, Noffs G, Perera T, et al. Functional neuromodulation in response to cerebellar-thalamic injury underpins the clinical presentation of tremor in multiple sclerosis. Mult Scler. May 2020; 26(6): 696–705. DOI: https://doi.org/10.1177/1352458519837706

34. Boonstra F, Florescu G, Evans A, et al. Tremor in multiple sclerosis associated with cerebello-thalamic pathology. J Neural Transm (Vienna)., Dec 2017; 124(12): 1509–1514. DOI: https://doi.org/10.1007/s00702-017-1798-4

35. Fews P, Moes F, Nuttlin B, et al. Relationship between multiple sclerosis intention tremor severity and lesion load in the brainstem. Neuroreport., August 2005; 16(12): 1379–82. DOI: https://doi.org/10.1097/01.wnr.0000176521.26971.58

36. Yerdelen D, Karatas M, Aydin M. Generalized Chorea Associated With Nonketotic Hyperglycemia: Cerebral MRL and SPECT Findings. Neurosurgery Quarterly., 2008; 18: 72–3. DOI: https://doi.org/10.1097/WNQ.0b013e3181644eec

37. Alqwaifly M. Treatment responsive Holmes tremor: case report and literature review. Int J Health Sci (Qassim)., Oct; 10(4): 558–562. DOI: https://doi.org/10.12816/0048905

38. Yerdelen D, Karatas M, Goksel B, et al. A patient with multiple sclerosis presenting with Holmes’ tremor. Eur J Neurol., Jan 2008; 15(1): e2–3. DOI: https://doi.org/10.1111/j.1468-1331.2007.01984.x

39. Francis DA, Grundy D, Heron J. The response to isoazid of action tremor in multiple sclerosis and its assessment using polarised light goniometry. J Neurol Neurosurg Psychiatry., Jan 1986; 49(1): 87–9. DOI: https://doi.org/10.1136/jnnp.49.1.87
40. Morrow J, McDowell H, Ritchie C, et al. Isoniazid and action tremor in multiple sclerosis. J Neurol Neurosurg Psychiatry, Mar 1985; 48(3): 282–3. DOI: https://doi.org/10.1136/jnnp.48.3.282

41. Sabra AF, Hallett M, Sudovsky L, et al. Treatment of action tremor in multiple sclerosis with isoniazid. Neurology, Aug 1982; 32(8): 912–3. DOI: https://doi.org/10.1212/00005390-000000000-00009

42. Duquette P, Pleines J, Souich P. Isoniazid for tremor in multiple sclerosis: a controlled trial. Neurology, Dec 1985; 35(12): 1772–5. DOI: https://doi.org/10.1212/00005390-000000000-00009

43. Hart FM, Bainbridge J. Current and emerging treatment of multiple sclerosis. Am J Manag Care, Jun 2016; 22(Suppl): s159–70. PMID: 27356025.

44. Prieto González JM. Tratamiento sintomático y del brote de esclerosis múltiple [Treatment of multiple sclerosis symptoms and exacerbations]. Med Clin (Barc.), 2014; 143 Suppl 3: 39–43. DOI: https://doi.org/10.1016/S0025-7753(15)30009-9

45. Sailer M, Lindquist S, Sickert A, et al. Multiple Sklerose: Neurorehabilitation und symptomatische Therapie [Multiple Sclerosis: Neurorehabilitation and Symptomatic Treatment]. Rehabilitation (Stuttg.), 2019; 58(5): 339–50. DOI: https://doi.org/10.1055/a-0755-1398

46. Fox P, Bain PG, Glickman S, et al. The effect of cannabis on tremor in patients with multiple sclerosis. Neurology, 13 2004; 62(7): 1105–9. DOI: https://doi.org/10.1212/01.WNL.0000118203.67138.3E

47. Zajicek JP, Apostu V. Role of cannabinoids in multiple sclerosis. CNS Drugs, Mar 2011; 25(3): 187–201. DOI: https://doi.org/10.2165/11539000-000000000-00000

48. Nielsen S, Germanos R, Weier M, et al. The Use of Cannabis and Cannabinoids in Treating Symptoms of Multiple Sclerosis: A Systematic Review of Reviews. Curr Neurol Neurosci Rep, Feb 2018; 18(2): 8. DOI: https://doi.org/10.1007/s11910-018-0814-x

49. Schniipp R, Jakl V, Wuehr M, et al. Treatment with 4-aminopyridine improves upper limb tremor of a patient with multiple sclerosis: a video case report. Mult Scler., Apr 2013; 19(4): 506–8. DOI: https://doi.org/10.1177/1352458512461394

50. Schroeder A, Linker RA, Lukas C, et al. Successful treatment of cerebellar ataxia and tremor in multiple sclerosis with topiramate: a case report. Clin Neuropharmacol., 2010; 33(6): 317–9. DOI: https://doi.org/10.1097/WNF.0b013e3181f84a39

51. Mittal SO, Lenka A, Jankovic J. Botulinum toxin for the treatment of tremor. Parkinsonism Relat Disord., 2019; 63: 31–41. DOI: https://doi.org/10.1016/j.parkreldis.2019.01.023

52. Habek M, Karni A, Balash Y, et al. The place of the botulinum toxin in the management of multiple sclerosis. Clin Neurol Neurosurg., Sep 2010; 112(7): 592–6. DOI: https://doi.org/10.1016/j.clineuro.2010.04.010

53. Van Der Walt A, Sung S, Spelman T, et al. A double-blind, randomized, controlled study of botulinum toxin type A in MS-related tremor. Neurology., July 2012; 79(1): 92–9. DOI: https://doi.org/10.1212/WNL.0b013e31825dcd9

54. Feys P, D’hooghe MB, Nagels G, et al. The effect of leviteracetam on tremor severity and functionality in patients with multiple sclerosis. Mult Scler., Mar 2009; 15(3): 371–8. DOI: https://doi.org/10.1177/135245850809142

55. Chitsaz A, Mehrbod N, Etemadifar M, et al. Does leviteracetam decrease of the rubral tremor in patients with multiple sclerosis. J Res Med Sci., Mar 2013; 18(Suppl 1): S78–80.

56. Striano P, Coppola A, Vacc G, et al. Leviteracetam for cerebellar tremor in multiple sclerosis: an open-label pilot tolerability and efficacy study. J Neurol., Jun 2006; 253(6): 762–6. DOI: https://doi.org/10.1007/s00415-006-0112-4

57. Solaro C, Sire A, Messmer Uccelli M, et al. Efficacy of leviteracetam on upper limb movement in multiple sclerosis patients with cerebellar signs: a multicenter double-blind, placebo-controlled, crossover study. Eur J Neurol., Nov 2020; 27(11): 2209–2216. DOI: https://doi.org/10.1111/ene.14403

58. Gbadamosi J, Buhmann C, Moench A, et al. Failure of ondansetron in treating cerebellar tremor in MS patients–an open-label pilot study. Acta Neurol Scand., 2001 Nov; 104(5): 308–11. DOI: https://doi.org/10.1034/j.1600-0404.2001.00075.x

59. Naderi F, Javadi SA, Motamedi M, et al. The efficacy of primidone in reducing severe cerebellar tremors in patients with multiple sclerosis. Clin Neuropharmacol. Sep–Oct 2012; 35(5): 224–6. DOI: https://doi.org/10.1097/WNF.0b013e31826249bb

60. Sechi GP, Zuddas M, Piredda M, et al. Treatment of cerebellar tremors with carbamazepine: a controlled trial with long-term follow-up. Neurology., Aug 1989; 39(8): 1113–5. DOI: https://doi.org/10.1212/WNL.39.8.1104

61. Koller WC. Pharmacologic trials in the treatment of cerebellar tremor. Arch Neurol., Mar 1984; 41(3): 280–1. DOI: https://doi.org/10.1001/archneur.1984.04050150058017

62. Deuschl G. Movement disorders in multiple sclerosis and their treatment. Neurodegener Dis Manag., Dec 2016; 6(6s): 31–35. DOI: https://doi.org/10.2217/nmt-2016-0053

63. Bittar RG, Hyam J, Nandi D, et al. Thalamotomy versus thalamic stimulation for multiple sclerosis tremor. J Clin Neurosci., Aug 2005; 12(6): 638–42. DOI: https://doi.org/10.1016/j.jocn.2004.09.008
64. Matsumoto J, Morrow D, Kaufman K, et al. Surgical therapy for tremor in multiple sclerosis: an evaluation of outcome measures. Neurology., November 2001; 57(10): 1876–82. DOI: https://doi.org/10.1212/WNL.57.10.1876

65. Alusi SH, Aziz TZ, Glickman S, et al. Stereotactic lesional surgery for the treatment of tremor in multiple sclerosis: a prospective case-controlled study. Brain., Aug 2001; 124(Pt 8): 1576–89. DOI: https://doi.org/10.1093/brain/124.8.1576

66. Niranjan A, Kondzialka D, Baser S, et al. Functional outcomes after gamma knife thalamotomy for essential tremor and MS-related tremor. Neurology., August 2000; 55(3): 443–6. DOI: https://doi.org/10.1017/S00415-003-1067-3

67. Schuurman PR, Bosch DA, Bossuyt PM, et al. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. N Engl J Med., February 2000; 342(7): 461–8. DOI: https://doi.org/10.1056/NEJM20000217317420703

68. Nandi D, Aziz TZ. Deep brain stimulation in the management of neuropathic pain and multiple sclerosis tremor. J Clin Neurophysiol., Jan–Feb 2004; 21(1): 31–9. DOI: https://doi.org/10.1097/00004691-200401000-00005

69. Schuler M, Sernas TJ, Karimi R. Thalamic stimulation in patients with multiple sclerosis: long-term follow-up. Stereotact Funct Neurosurg., 2003; 80: 48–55. DOI: https://doi.org/10.1159/000075160

70. Wishart HA, Roberts DW, Roth RM, et al. Chronic deep brain stimulation for the treatment of tremor in multiple sclerosis: review and case reports. J Neurol Neurosurg Psychiatry., Oct 2003; 74(10): 1392–7. DOI: https://doi.org/10.1136/jnnp.74.10.1392

71. Berk C, Carr J, Sinden M, et al. Thalamic deep brain stimulation for the treatment of tremor due to multiple sclerosis: a prospective study of tremor and quality of life. J Neurosurg., Oct 2002; 97(4): 815–20. DOI: https://doi.org/10.3171/jns.2002.97.4.0815

72. Nandi D, Chir M, Liu X, et al. Electrophysiological confirmation of the zona incerta as a target for surgical treatment of disabling involuntary arm movements in multiple sclerosis: use of local field potentials. J Clin Neurosci., Jan 2002; 9(1): 64–8. DOI: https://doi.org/10.1054/jocn.2001.1012

73. Hooper J, Taylor R, Pentland B, et al. A prospective study of thalamic deep brain stimulation for the treatment of movement disorders in multiple sclerosis. Br J Neurosurg., Apr 2002; 16(2): 102–9. DOI: https://doi.org/10.1080/026886902020131769

74. Loher TJ, Gutbrod K, Fravi NL, et al. Thalamic stimulation for tremor. Subtle changes in episodic memory are related to stimulation per se and not to a microthalamotomy effect. J Neurol., Jun 2003; 250(6): 707–13. DOI: https://doi.org/10.1007/s00415-003-1067-3

75. Krauss JK, RK S, Jr., Ondo WG, et al. Concepts and methods in chronic thalamic stimulation for treatment of tremor: technique and application. Neurosurgery., 2001 Mar; 48(3): 535–41, 541–3. DOI: https://doi.org/10.1097/00006123-200103000-00015

76. Matsumoto J, Morrow D, Kaufman K, et al. Surgical therapy for tremor in multiple sclerosis: an evaluation of outcome measures. Neurology., November 2001; 57(10): 1876–82. DOI: https://doi.org/10.1212/WNL.57.10.1876

77. Schuurman PR, Bosch DA, Bossuyt PM, et al. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. N Engl J Med., February 2000; 342(7): 461–8. DOI: https://doi.org/10.1056/NEJMM20000217317420703

78. Oliveria SF, Rodriguez RL, Bowers D, et al. Safety and efficacy of dual-lead thalamic deep brain stimulation for patients with treatment-refractory multiple sclerosis tremor: a single-centre, randomised, single-blind, pilot trial. Lancet Neurol., Sep 2017; 16(9): 691–700. DOI: https://doi.org/10.1016/S1474-4422(17)30166-7

79. Yap L, Kouyialis A, Varma TR. Stereotactic neurosurgery for disabling tremor in multiple sclerosis: thalamotomy or deep brain stimulation? Br J Neurosurg., Aug 2007; 21(4): 349–54. DOI: https://doi.org/10.1080/02688690701544002

80. Hyam JA, Aziz TZ, Bain PG. Post-deep brain stimulation—gradual non-stimulation dependent decrease in strength with attenuation of multiple sclerosis tremor. J Neurol., Jul 2007; 254(7): 854–60. DOI: https://doi.org/10.1007/s00415-006-0433-3

81. Móñez-Miró JU, Martínez-Fernández R, Del Alamo M, et al. Focused ultrasound thalamotomy for multiple sclerosis-associated tremor. Mult Scler., Jun 2020; 26(7): 855–858. DOI: https://doi.org/10.1177/1352458519861597

82. Mathieu D, Kondzialka D, Niranjan A, et al. Gamma knife thalamotomy for multiple sclerosis tremor. Surg Neurol., Oct 2007; 68(4): 394–9. DOI: https://doi.org/10.1016/j.surneu.2006.11.049

83. Hosseini H, Mandat T, Waubant E, et al. Unilateral thalamic deep brain stimulation for disabling kinetic tremor in multiple sclerosis. Neurosurgery., Jan 2012; 70(1): 66–9. DOI: https://doi.org/10.1227/NEU.0b013e31822da55c

84. Hassan A, Ahlskog JE, Rodríguez M, et al. Surgical therapy for multiple sclerosis tremor: a 12-year follow-up study. Eur J Neurol., May 2012; 19(5): 764–8. DOI: https://doi.org/10.1111/j.1464-1337.2011.03626.x

85. Moore GR, Vitali AM, Leung E, et al. Thalamic stimulation in multiple sclerosis: evidence for a ‘demyelinating thalamotomy’. Mult Scler. 2009; 15(11): 1311–21. DOI: https://doi.org/10.1177/1352458509345914

86. Benito-León J, Louis ED. Movement disorders: New hope for medically-refractory essential tremor? Nat Rev Neurol., October 2016; 12(11): 618–619. DOI: https://doi.org/10.1038/nrneurol.2016.162
87. Lim DA, Khandhar SM, Heath S, et al. Multiple target deep brain stimulation for multiple sclerosis related and poststroke Holmes’ tremor. Stereotact Funct Neurosurg., 2007; 85: 144–9. DOI: https://doi.org/10.1159/000099072

88. Mills RJ, Yap L, Young CA. Treatment for ataxia in multiple sclerosis. Cochrane Database Syst Rev., 2007; (1): CD005029. DOI: https://doi.org/10.1002/14651858.CD005029.pub2

89. Pandolfi M, Manto M. Cerebellar and afferent ataxias. Continuum (Minneap Minn). Oct 2013; 19(S Movement Disorders): 1312–43. DOI: https://doi.org/10.1212/01.CON.0000436158.39285.22

90. Mitoma H, Buffo A, Gelfo F, et al. Consensus Paper. Cerebellar Reserve: From Cerebellar Physiology to Cerebellar Disorders. Cerebellum., Feb 2020; 19(1): 131–153. DOI: https://doi.org/10.1007/s12311-019-01091-9

91. Vidalhiet M, Jedynak CP, Pollak P, et al. Pathology of symptomatic tremors. Mov Disord., 1998; 13 Suppl 3: 49–54. DOI: https://doi.org/10.1002/mds.870131309

92. Zhang Q, Zhou X, Li Y, et al. Clinical Recognition of Sensory Ataxia and Cerebellar Ataxia. Front Hum Neurosci., 2021 Apr 1; 15: 639871. DOI: https://doi.org/10.3389/fnhum.2021.639871

93. Karmon Y, Morrow SA, Weinstock A, et al. Limb ataxia originating from peri-central sulcus demyelinating lesion in multiple sclerosis. J Neural Sci., September 2012; 320(1–2): 136–40. Epub ahead of print. DOI: https://doi.org/10.1016/j.jns.2012.05.039

94. Gorman MJ. Multiple sclerosis presenting as ataxic hemiparesis. J Neurol Sci., May 2002; 197(1–2): 85–7. Epub ahead of print. DOI: https://doi.org/10.1016/S0022-510X(02)00045-X

95. Marcel C, Anheim M, Flamand-Rouvière C, et al. Symptomatic paroxysmal dysarthria-ataxia in demyelinating diseases. J Neural., Aug 2010; 257(8): 1369–72. DOI: https://doi.org/10.1007/s00415-010-5534-3

96. Batum M, Kısabay Ak A, Çetin G, et al. Coincidental occurrence of episodic ataxia and multiple sclerosis: a case report and review of the literature. Int J Neurosci., 2020; 20: 1–6. DOI: https://doi.org/10.1080/00207454.2020.1835896

97. Freiha J, Riachi N, Chalah MA, et al. Paroxysmal Symptoms in Multiple Sclerosis-A Review of the Literature. J Clin Med., September 2020; 9(10): 3100. DOI: https://doi.org/10.3390/jcm9103100

98. Twomey JA, Espir ML. Paroxysmal symptoms as the first manifestations of multiple sclerosis. J Neural Neurosurg Psychiatry., Apr 1980; 43(4): 296–304. DOI: https://doi.org/10.1136/jnnp.43.4.296

99. Iorio R, Capone F, Plantone D, et al. Paroxysmal ataxia and dysarthria in multiple sclerosis. J Clin Neurosc., Jan 2014; 21(1): 174–5. DOI: https://doi.org/10.1016/j.jcn.2013.01.031

100. Li Y, Zeng C, Luo T. Paroxysmal dysarthria and ataxia in multiple sclerosis and corresponding magnetic resonance imaging findings. J Neurol., Feb 2011; 258(2): 273–6. DOI: https://doi.org/10.1007/s00415-010-5748-4

101. Papastergios C, Shaker A, Schiopu-Mariean BL, et al. Paroxysmal dysarthri och axati – en ovanlig manifestation vid MS [Paroxysmal dysarthria and ataxia – an unusual MS manifestation]. Lakartidningen., 2021; 118: 21022.

102. Lilleker JB, Gull C, Dayanandan R, et al. Paroxysmal dysarthria ataxia syndrome responds to lacosamide. Mult Scler., Feb 2015; 21(2): 256. DOI: https://doi.org/10.1177/1352458514546792

103. Rossi S, Studer V, Motta C, et al. Paroxysmal dysarthrioataxia syndrome resolving after fingolimod treatment. J Neural Sci., March 2015; 350(1–2): 101–2. DOI: https://doi.org/10.1016/j.jns.2015.01.023

104. Gorard DA, Gibberd FB. Paroxysmal dysarthria and ataxia: associated MRI abnormality. J Neural Neurosurg Psychiatry., Dec 1989; 52(12): 1444–5. DOI: https://doi.org/10.1136/jnnp.52.12.1444

105. Goodwin SJ, Carpenter AF. Successful treatment of paroxysmal ataxia and dysarthria in multiple sclerosis with levetiracetam. Mult Scler Relat Disord., Nov 2016; 10: 79–81. Epub ahead of print. DOI: https://doi.org/10.1016/j.msard.2016.09.003

106. Klaas JP, Burkholder DB, Singer W, et al. Harry Lee Parker and paroxysmal dysarthria and ataxia. Neurology., 2013; 80(3): 311–4. DOI: https://doi.org/10.1212/WNL.0b013e31827dec0f

107. Zovalishin IA, Nevaskaia OM, Niizbekova AS. Parokszimal’nye pristupy dizartrii i ataksii pri rasseiannom skleroze [Paroxysmal attacks of dysarthria and ataxia in multiple sclerosis]. Zh Neivropatol Psikhiatr Im S S Korsakova., 1978; 78(11): 1645–9.

108. Shah S, Klassen BT, Flanagan EP. Teaching Video NeuroImages: Paroxysmal Dysarthria-Ataxia in Multiple Sclerosis. Neurology., 27 2021; 96(17): e2245–e2246. DOI: https://doi.org/10.1212/WNL.0b013e31827dec0f

109. Osterman PO, Westerberg CE. Paroxysmal attacks in multiple sclerosis and corresponding magnetic resonance abnormality. J Neurol Sci., 27 2021; 96(17): e2245–e2246. DOI: https://doi.org/10.1016/j.jns.2015.01.023

110. Skillrud DM, Goldstein NP. Paroxysmal limb hemiataxia with crossed facial paresthesias in multiple sclerosis. JAMA., 250(20): 2843–4. DOI: https://doi.org/10.1001/jama.250.20.2843

111. Armutlu K, Karabudak R, Nurul G. Physiotherapy approaches in the treatment of ataxic multiple sclerosis: a pilot study. Neurehabil Neural Repair., 2001; 15: 203–11. DOI: https://doi.org/10.1177/154596830101500308

112. Wiles CM, Newcombe RG, Fuller KJ, et al. Controlled randomised crossover trial of the effects of physiotherapy on mobility in chronic multiple sclerosis. J Neural Neurosurg...
113. Lord SE, Wade DT, Halligan PW. A comparison of two physiotherapy treatment approaches to improve walking in multiple sclerosis: a pilot randomized controlled study. Clin Rehabil., Dec 1998; 12(6): 477–86. DOI: https://doi.org/10.1097/01.CHR.00000686375863456

114. Gibson-Horn C. Balance-based torso-weighting in a patient with ataxia and multiple sclerosis: a case report. J Neurol Phys Ther., Sep 2008; 32(3): 139–46. DOI: https://doi.org/10.1097/NPT.0b013e318185558f

115. Crittendon A, O’Neill D, Widener GL, et al. Standing data disproves biomechanical mechanism for balance-based torso-weighting. Arch Phys Med Rehabil., Jan 2014; 95(1): 43–9. DOI: https://doi.org/10.1016/j.apmr.2013.08.235

116. Gorgas AM, Widener GL, Gibson-Horn C, et al. Gait changes with balance-based torso-weighting in people with multiple sclerosis. Physiother Res Int., Mar 2015; 20(1): 45–53. DOI: https://doi.org/10.1002/pri.1595

117. Widener GL, Conley N, Whiteford S, et al. Changes in standing stability with balance-based torso-weighting with cerebellar ataxia: A pilot study. Physiother Res Int., Jan 2020; 25(1): e1814. DOI: https://doi.org/10.1002/pri.1814

118. Ali AS, Darwish MH, Shaloby NM, et al. Efficacy of core stability versus task oriented trainings on balance in ataxic persons with multiple sclerosis. A single blinded randomized controlled trial. Mult Scler Relat Disord., 2021; 50: 102866. DOI: https://doi.org/10.1016/j.msard.2021.102866

119. Salci Y, Fil A, Armutlu K, et al. Effects of different exercise modalities on ataxia in multiple sclerosis patients: a randomized controlled study. Disabil Rehabil., Dec 2017; 39(26): 2626–2632. DOI: https://doi.org/10.1080/09638288.2016.1236411

120. Scheidler AM, Kinnett-Hopkins D, Learmonth VC, et al. Targeted ballet program mitigates ataxia and improves balance in females with mild-to-moderate multiple sclerosis. PLoS One., October 2018; 13(10): e0205382. DOI: https://doi.org/10.1371/journal.pone.0205382

121. Oakes PK, Srivatsal SR, Davis MY, et al. Movement disorders in multiple sclerosis. Phys Med Rehabil Clin N Am., 2013; 24(4): 639–51. DOI: https://doi.org/10.1016/j.pmr.2013.06.003

122. Perlman SL. Cerebellar Ataxia. Curr Treat Options Neurol., May 2000; 2(3): 215–224. DOI: https://doi.org/10.1007/s11940-000-0004-3

123. Bourdette D, Gilden D. Fingolimod and multiple sclerosis: four cautionary tales. Neurology, November 2012; 79(19): 1942–3. DOI: https://doi.org/10.1212/WNL.0b013e3182735edf

124. Berger JR, Sheremota WA, Melamed E. Paroxysmal dystonia as the initial manifestation of multiple sclerosis. Arch Neurol., Jul 1984; 41(7): 747–50. DOI: https://doi.org/10.1001/archneur.1984.0405018069020

125. Machado C, Amorim JM, Rodrigues M, et al. Paroxysmal dystonia as a manifestation of multiple sclerosis. Neurologist., May 2015; 19(5): 132–4. DOI: https://doi.org/10.1097/NRL.0000000000000025

126. Yilmaz S, Serdaroglu G, Gokben S, et al. Paroxysmal dystonia as a rare initial manifestation of multiple sclerosis. J Child Neurol., Dec 2011; 26(12): 1564–6. DOI: https://doi.org/10.1177/088307381140882

127. Rajabally YA, Farrell D, Messios N. Oro-mandibular dystonia in a case of multiple sclerosis with capsular plaque. Eur Neurol., 2003; 49: 190–1. DOI: https://doi.org/10.1159/000069084

128. Thompson PD, Obeso JA, Delgado G, et al. Focal dystonia of the jaw and the differential diagnosis of unilateral jaw and masticatory spasm. J Neurol Neurosurg Psychiatry., Jun 1986; 49(6): 651–6. DOI: https://doi.org/10.1136/jnnp.49.6.651

129. Coleman RJ, Quinn NP, Marsden CD. Multiple sclerosis presenting as adult onset dystonia. Mov Disord., 1988; 3: 329–32. DOI: https://doi.org/10.1002/mds.870030408

130. Fontoura P, Vale J, Guimarães J. Symptomatic paroxysmal hemidystonia due to a demyelinating subthalamic lesion. Eur J Neurol., Sep 2000; 7(5): 559–62. DOI: https://doi.org/10.1046/j.1468-1331.2000.00110.x

131. Demirkiran M, Jankovic J. Paroxysmal dyskinesias: clinical features and classification. Ann Neurol., Oct 1995; 38(4): 571–9. DOI: https://doi.org/10.1002/ana.410380405

132. Woubant E, Alizé P, Toubah A, et al. Paroxysmal dystonia (tonic spasm) in multiple sclerosis. Neurology., December 2001; 57(12): 2320–1. DOI: https://doi.org/10.1212/WNL.57.12.2320

133. Restivo DA, Solaro C, Maimone D, et al. Pharyngeal painful tonic spasms: paroxysmal painful swallowing. Ann Intern Med., Nov 2011; 155(9): 649–50. DOI: https://doi.org/10.7326/0003-4819-155-9-201111010-00024

134. Andrade C, Massano J, Guimarães J, et al. Stretching the limbs? Tonic spasms in multiple sclerosis. BMJ Case Rep., November 2012; 2012: bcr2012007513. DOI: https://doi.org/10.1136/bcr-2012-007513

135. Maimone D, Reder AT, Finocchiaro F, et al. Internal capsule plaque and tonic spasms in multiple sclerosis. Arch Neurol., Apr 1991; 48(4): 427–9. DOI: https://doi.org/10.1001/archneur.1991.00530160097021

136. Aguirregomozcorta M, Ramió-Torrentà L, Gich J, et al. Paroxysmal dystonia and pathological laughter as a first manifestation of multiple sclerosis. Mult Scler., Mar 2008; 14(2): 262–5. DOI: https://doi.org/10.1177/1352458507082053

137. Aladro Benito Y, Villagrosa Cocco P, Carrillo Padilla F. Distonia paroxística como primera manifestación de esclerosis múltiple. Rev Neurol., May 2000; 30(5): 827–9. DOI: https://doi.org/10.1016/S0306-0463(00)00044-0

138. Lord SE, Wade DT, Halligan PW. A comparison of two physiotherapy treatment approaches to improve walking in multiple sclerosis: a pilot randomized controlled study. Clin Rehabil., Dec 1998; 12(6): 477–86. DOI: https://doi.org/10.1097/01.CHR.00000686375863456
multiple [Paroxysmal dystonia as the first manifestation of multiple sclerosis. Rev Clin Esp., Jun; 193(2): 64–6.

138. Uca AU, Aitag M. Paroxysmal Dystonia as the First Manifestation of Multiple Sclerosis with Internal Capsular Plaque. Noro Psikiyar Ars., Sep 2014; 51(3): 295–296. DOI: https://10.4274/npa.y7515

139. Honig LS, Wasserstein PH, Adornato BT. Tonic spasms in multiple sclerosis. Anatomic basis and treatment West J Med., Jun 1991; 154(6): 723–6.

140. El Otmani H, Benmansour Y, Araqui-Houssaini A, et al. Dystonie paroxystique et sclérose en plaques [Paroxysmal dystonia and multiple sclerosis]. Rev Neurol (Paris), Feb 2014; 170(2): 119–23. DOI: https://10.1016/j.neurology.2013.07.031

141. Trompetto C, Avanzino L, Bove M, et al. Investigation of paroxysmal dystonia in a patient with multiple sclerosis: a transcranial magnetic stimulation study. Clin Neurophysiol., Jan 2008; 119(1): 63–70. DOI: https://10.1016/j.clinph.2007.09.123

142. Zenzola A, De Mari M, De Blasi R, et al. Paroxysmal dystonia with thalamic lesion in multiple sclerosis. Mov Disord., Oct 2001; 22(5): 391–4. DOI: https://10.1007/s100720100070

143. Burguera JA, Catalá J, Casanova B. Thalamic demyelination and paroxysmal dystonia in multiple sclerosis. Mov Disord., 1991; 6: 379–81. DOI: https://10.1002/mds.870060423

144. Ehling R, Bsteh G, Di Pauli F, et al. Rethinking the importance of paroxysmal and unusual symptoms as first clinical manifestation of multiple sclerosis: They do matter. Mult Scler Relat Disord., 2016; 9: 150–4. DOI: https://10.1016/j.msard.2016.07.014

145. Lugaresi A, Uncini A, Gambi D. Basal ganglia involvement in multiple sclerosis with alternating side paroxysmal dystonia. J Neurol., 1993; 240: 257–8. DOI: https://10.1007/BF00818716

146. Verheul GA, Tyssen CC. Multiple sclerosis occurring with paroxysmal unilateral dystonia. Mov Disord., 1990; 5: 352–3. DOI: https://10.1002/mds.870050421

147. Tranchant C, Bhatia KP, Marsden CD. Movement disorders in multiple sclerosis. Mov Disord., Jul 1995; 10(4): 418–23. DOI: https://10.1002/mds.870100403

148. Gatto EM, Zurrú MC, Rugilo C. Medullary lesions and unusual bilateral paroxysmal dystonia in multiple sclerosis. Neurology., Mar; 46(3): 847–8.

149. Shibasaki H, Kuroiwa Y. Painful tonic seizure in multiple sclerosis. Arch Neurol., Jan 1974; 30(1): 47–51. DOI: https://10.1001/archneur.1974.00490310049008

150. Fröhlich K, Winder K, Linker RA, et al. Lesion correlates of secondary paroxysmal dyskinesia in multiple sclerosis. J Neurol., Oct 2018; 265(10): 2277–2283. DOI: https://10.1007/s00415-018-8989-2

151. Espir ML, Millac P. Treatment of paroxysmal disorders in multiple sclerosis with carbamazepine (Tegretol). J Neural Neurosurg Psychiatry., Aug 1970; 33(4): 528–31. DOI: https://10.1136/jnnp.33.4.528

152. Sinkha CS, Patil KB. Paroxysmal tonic spasms as an initial manifestation of neuromyelitis optica. Neuro India., May–Jun 2017; 65(3): 631–632. DOI: https://10.4103/neuroindia.NI_865_16

153. Kim JS, Guak TH, Ahn JY, et al. Writer’s cramp as a manifestation of cervical demyelinating lesions. Eur Neurol., 2007; 58: 54–6. DOI: https://10.1159/000102169

154. Jost WH, Hefter H, Stenner A, et al. Rating scales for cervical dystonia: a critical evaluation of tools for outcome assessment of botulinum toxin therapy. J Neural Transm (Vienna). Mar 2013; 120(3): 487–96. DOI: https://10.1007/s00702-012-0887-7

155. Milanov I, Georgiev D. Spasmodic torticollis and tremor due to multiple sclerosis: a case report. Funct Neurol., Nov-Dec 1995; 10(6): 281–5. PMID: 8837992.

156. Svetel M, Sternic N, Filipovic S, et al. Spasmodic torticollis associated with multiple sclerosis: report of two cases. Mov Disord., Nov 1997; 12(6): 1092–4. DOI: https://10.1002/mds.870120645

157. Minagar A, Sheremata WA, Weiner WJ. Transient movement disorders and multiple sclerosis. Parkinsonism Relat Disord., Dec 2002; 9(2): 111–3. DOI: https://10.1016/S1353-8030(02)00009-3

158. Ruegg SJ, Bühlmann M, Renaud S, et al. Cervical dystonia as first manifestation of multiple sclerosis. J Neurol., Nov 2004; 251(11): 1408–10. DOI: https://10.1007/s00415-004-0544-7

159. Cavallieri F, Godeiro C, Lino JC Jr., et al. Cervical dystonia in a case of long-standing secondary progressive multiple sclerosis. Rev Neurol (Paris)., Apr 2019; 175(4): 269–71. DOI: https://10.1016/j.neurol.2018.05.005

160. Rozza L, Bortolotti P, Sica A, et al. Kinesigenic dystonia as the first manifestation of multiple sclerosis. J Neurol., Nov-2016; 102169

161. Berger B, Rijntjes M, Stehlin L, et al. Corticosteroid-responsive torticollis as a presenting symptom of multiple sclerosis. J Neurol Sci., 2013.07.031

162. Moore CE, Lees AJ, Schady W. Basal ganglia involvement and brainstem lesions. Mov Disord., 1990; 5: 352–3. DOI: https://10.1002/mds.870050421

163. Roth LM, Bosticott P, Sica A, et al. Kinesigenic dystonia as the first manifestation of multiple sclerosis with cervical and brainstem lesions. Eur Neurol., 1993; 33: 331–2. DOI: https://10.1159/000116964

164. Milano I, Georgiev D. Spasmodic torticollis and tremor due to multiple sclerosis: a case report. Funct Neurol., Nov-Dec 1995; 10(6): 281–5. PMID: 8837992.

165. Svetel M, Sternic N, Filipovic S, et al. Spasmodic torticollis associated with multiple sclerosis: report of two cases. Mov Disord., Nov 1997; 12(6): 1092–4. DOI: https://10.1002/mds.870120645

166. Minagar A, Sheremata WA, Weiner WJ. Transient movement disorders and multiple sclerosis. Parkinsonism Relat Disord., Dec 2002; 9(2): 111–3. DOI: https://10.1016/S1353-8030(02)00009-3

167. Ruegg SJ, Bühlmann M, Renaud S, et al. Cervical dystonia as first manifestation of multiple sclerosis. J Neurol., Nov 2004; 251(11): 1408–10. DOI: https://10.1007/s00415-004-0544-7

168. Cavallieri F, Godeiro C, Lino JC Jr., et al. Cervical dystonia in a case of long-standing secondary progressive multiple sclerosis. Rev Neurol (Paris)., Apr 2019; 175(4): 269–71. DOI: https://10.1016/j.neurol.2018.05.005

169. Rozza L, Bortolotti P, Sica A, et al. Kinesigenic dystonia as the first manifestation of multiple sclerosis with cervical and brainstem lesions. Eur Neurol., 1993; 33: 331–2. DOI: https://10.1159/000116964

170. Berger B, Rijntjes M, Stehlin L, et al. Corticosteroid-responsive torticollis as a presenting symptom of multiple sclerosis. J Neurol Sci., May 2014; 340(1–2): 239–40. DOI: https://10.1016/j.jns.2014.02.021

171. Moore CE, Lees AJ, Schady W. Multiple sclerosis leading to blepharospasm and dystonia in a sibling pair. J Neurol., Sep 1996; 243(9): 667–70. DOI: https://10.1007/ BF00878668

172. Shneyder N, Harris MK, Minagar A. Movement disorders in patients with multiple sclerosis. Handb Clin Neurol. 2011; 100: 307–14. DOI: https://10.1016/B978-0-444-52014-2.00023-9
164. Tolosa E, Montserrat L, Bayes A. Blink reflex studies in focal dystonias: enhanced excitability of brainstem interneurons in cranial dystonia and spasmodic torticollis. Mov Disord., 1988; 3: 61–9. DOI: https://doi.org/10.1002/mds.870030108

165. Klostermann W, Vieregge P, Kömpf D. Spasmodic torticollis in multiple sclerosis: significance of an upper cervical spinal cord lesion. Mov. Disord., Apr 1993; 8(2): 234–6. DOI: https://doi.org/10.1002/mds.870080227

166. Zittel S, Bester M, Gerloff C, et al. Symptomatic paroxysmal kinesigenic choreoathetosis as primary manifestation of multiple sclerosis. J. Neurol., Mar 2012; 259(3): 557–8. DOI: https://doi.org/10.1007/s00415-011-6188-5

167. de Seze J, Stojkovic T, Destée M, et al. Paroxysmal kinesigenic choreoathetosis as a presenting symptom of multiple sclerosis. J. Neurol., Jun 2000; 247(6): 478–80. DOI: https://doi.org/10.1007/s004150070184

168. Roos RA, Wintzen AR, Vielvoye G, et al. Paroxysmal kinesigenic choreoathetosis as presenting symptom of multiple sclerosis. J. Neurol Neurosurg Psychiatry., Jul 1991; 54(7): 657–8. DOI: https://doi.org/10.1136/jnnp.54.7.657-a

169. Toff I, Sabato UC, Lehrer G. Choreoathetosis in multiple sclerosis. Clin. Neurol Neurosurg., 1985; 87: 41–3. DOI: https://doi.org/10.1016/0303-8467(85)90065-4

170. Bachman DS, Lo-Vélez C, Estanol B, et al. Dystonia and choreoathetosis in multiple sclerosis. Arch. Neurol., Aug 1976; 33(8): 590. DOI: https://doi.org/10.1001/archneur.1976.00500080068016

171. Sarkari NB. Involuntary movements in multiple sclerosis. Br Med J., June 1968; 2(5607): 738–40. DOI: https://doi.org/10.1136/bmj.2.5607.738

172. Mao CC, Gancher ST, Herndon RM. Movement disorders in multiple sclerosis. Mov. Disord., 1988; 3: 109–16. DOI: https://doi.org/10.1002/mds.870030202

173. Uncini A, Di Muzio A, Thomas A, et al. Hand dystonia secondary to cervical demyelinating lesion. Acta Neurol Scand., Jul 1994; 90(1): 51–5. DOI: https://doi.org/10.1111/j.1600-0404.1994.tb02679.x

174. Pop R, Kipfer S. Paroxysmal kinesigenic dyskinesia-like phenotype in multiple sclerosis. Mult. Scler., 2017; 23(13): 1795–7. DOI: https://doi.org/10.1177/1352458517702535

175. Ciampi E, Uribe-San-Martín R, Godoy-Santín J, et al. Secondary paroxysmal dyskinesia in multiple sclerosis: Clinical-radiological features and treatment. Case report of seven patients. Mult. Scler., 2017; 23(13): 1791–5. DOI: https://doi.org/10.1177/1352458517702968

176. Plant G. Focal paroxysmal kinesigenic choreoathetosis. J. Neurol Neurosurg Psychiatry., Apr 1983; 46(4): 345–8. DOI: https://doi.org/10.1136/jnnp.46.4.345

177. Gauthier S, Young SN, Baxter DW. Myoclonies du voile associées à une diminution de l’acide 5-hydroxy-indole-acétique céphalo-rachidien et répondant au clonazépam [Palatal myoclonus associated with a decrease in 5-hydroxy-indole acetic acid in cerebrospinal fluid and responding to clonazepam. Can J Neurol Sci., Feb; 8(1): 51–4. DOI: https://doi.org/10.1017/S0317167100042840

178. Hassler R, Bronisch F, Mundinger F, et al. Intention myoclonus of multiple sclerosis, its patho-anatomical basis and its stereotactic relief. Neurochirurgia. (Stuttg.), May 1975; 18(3): 90–106. DOI: https://doi.org/10.1055/s-0028-109435

179. Hassler R, Schmidt K, Riechert T, et al. Stereotactic treatment of action myoclonus in a case of combined status marmoratus and multiple sclerosis. A contribution to the pathophysiology of basal ganglia with multiple lesions in both the striatum and the substantia nigra. Confin. Neurol., 1975; 37: 329–56. DOI: https://doi.org/10.1159/000102769

180. Alroughhani RA, Ahmed SF, Khan RA, et al. Spinal segmental myoclonus as an unusual presentation of multiple sclerosis. BMC Neurol., Feb 2015; 15: 15. DOI: https://doi.org/10.1186/s12883-015-0271-y

181. Khafizova IF, Zalialova ZA, Baranova EA, et al. Spinal’naia segmentarnaia miokloniia pri rasseiannom skleroze (nabliudenie iz praktiki). [Spinal segmental myoclonus in multiple sclerosis (case report)] Zh Nevrul Psikhiatr Im S S Korsakova., 2014; 114: 48–54.

182. Mukand JA, Giunti EJ. Tizanidine for the treatment of intention myoclonus: a case series. Arch Phys Med Rehabil., Jul 2004; 85(7): 1125–7. DOI: https://doi.org/10.1016/j.apmr.2003.09.006

183. Zipfel TE, Kaza SR, Greene JS. Middle-ear myoclonus. J Laryngol Otol., 2000; 114(3): 207–209. DOI: https://doi.org/10.1258/0022215001905120

184. Kapoor R, Brown P, Thompson PD, et al. Propiospinal myoclonus in multiple sclerosis. J. Neurol Neurosurg Psychiatry., 1992; 55(11): 1086–8. DOI: https://doi.org/10.1136/jnnp.55.11.1086

185. Revol A, Vighetto A, Confavreux C, et al. Myoclonies oculo-vélo-palatines et sclérose en plaques [Oculo-palatal myoclonus and multiple sclerosis. Rev Neurol (Paris)., 1990; 146: 518–21.

186. Jankovic J, Pardo R. Segmental myoclonus. Clinical and pharmacologic study. Arch Neurol., Oct 1986; 43(10): 1025–31. DOI: https://doi.org/10.1001/archneur.1986.00520100039012

187. Smith CR, Scheinberg L. Coincidence of myoclonus and multiple sclerosis: dramatic response to clonazepam. Neurology., Oct 1990; 40(10): 1633–4. DOI: https://doi.org/10.1212/WNL.40.10.1633

188. Rasmisky M. Hyperexcitability of pathologically myelinated axons and positive symptoms in multiple sclerosis. Adv Neurol., 1981; 31: 289–97.
189. Penney SE, Bruce IA, Saeed S. Botulinum toxin is effective and safe for palatal tremor: a report of five cases and a review of the literature. J Neurol., Jul 2006; 253(7): 857–60. DOI: https://doi.org/10.1007/s00415-006-0039-9

190. Mouren P, Tatossian A, Toga M, et al. Etude critique du syndrome hémbalilaque. (A propos d’une observation anatomo-clinique de sclérose en plaques avec hypercinésie monoballistique terminale) [Critical study of the hemiballistic syndrome]. (Apropos of an anatomo-clinical case of multiple sclerosis with terminal monoballistic hyperkinesia). Encephale., May–Jun 1966; 55(3): 212–74.

191. Riley D, Long AE. Hemiballism in multiple sclerosis. Mov Disord., 1988; 3: 88–94. DOI: https://doi.org/10.1002/mds.870120644

192. Giroud M, Semana D, Proadeux L, et al. Hemiballismus revealing multiple sclerosis in an infant. Childs Nerv Syst., Jun 1990; 6(4): 236–8. DOI: https://doi.org/10.1007/BF01850982

193. Masucci EF, Saini N, Kurtzke JF. Bilateral ballism in multiple sclerosis. Neurology., Dec 1989; 39(12): 1641–2. DOI: https://doi.org/10.1212/WNL.39.12.1641

194. Waubant E, Simonetto-Moreau M, Clanet M, et al. Left arm monoballism as a relapse in multiple sclerosis. Neurology., Jun 1990; 37(6): 583–8. DOI: https://doi.org/10.1212/WNL.0000000000000163

195. Iuppa CA, Diefenderfer LA. Risperidone-induced Pisa syndrome in MS: resolution with lurasidone and recurrence with Chlorpromazine. Ann Pharmacother., Sep 2013; 47(9): 1223–8. DOI: https://doi.org/10.1177/1060028013503132

196. Palasi A, Martínez-Sánchez N, Bau L, et al. Unilateral eyelid myokymia as a form of presentation of multiple sclerosis. Neurologia., Apr 2013; 28(3): 187–9. DOI: https://doi.org/10.1016/j.nrl.2011.09.010

197. Telisch FF, Grobman LR, Shermata WA, et al. Hemifacial spasm occurrence in multiple sclerosis. Arch Otolaryngol Head Neck Surg., May 1991; 117(5): 554–6. DOI: https://doi.org/10.1001/archotol.1991.01870170100022

198. Dupeyron A, Chaury F, Guiraud-Chaumeil C, et al. Hémicontracture et mykymies faciales continues révélatrices d’une sclérose en plaques [Hemicontracture and facial myokymia as the first manifestation of multiple sclerosis]. Rev Neurol (Paris), Mar 2001; 157(3): 315–7.

199. Tenser RB. Myokymia and facial contraction in multiple sclerosis. Arch Intern Med., Jan; 136(1): 81–3. DOI: https://doi.org/10.1001/archinte.136.1.81

200. Radü EW, Skorpil V, Kaeser HE. Facial myokymia. Eur Neurol., 1975; 13(6): 499–512. DOI: https://doi.org/10.1159/000114706

201. De Silva KL, Pearce J. Facial myokymia: a clue to the diagnosis of multiple sclerosis. Postgrad Med J. 1972; 48(565): 657–62. DOI: https://doi.org/10.1136/pgmj.48.565.657

202. Sedano MJ, Trejo JM, Macarrón JL, et al. Continuous facial myokymia in multiple sclerosis: treatment with botulinum toxin. Eur Neurol., 2000; 43: 137–40. DOI: https://doi.org/10.1159/00008152

203. Gold R, Kappos L. Faziale Myokymie durch pontine Läsionen und zentrales Fieber bei multipler Sklerose-Kasuistik [Facial myokymia caused by pontine lesions and central fever in multiple sclerosis–case report]. Schweiz Rundsch Med Prax., 19; 80(47): 1327–9.

204. Scioli V, Savoiardo M, Bussone G, et al. Brain-stem auditory evoked potentials (BAEPs) and magnetic resonance imaging (MRI) in a case of facial myokymia. Electroencephalogr Clin Neurophysiol., Mar–Apr 1988; 71(2): 153–6. DOI: https://doi.org/10.1016/0168-5597(88)90075-5

205. Kojima S, Yagishita T, Kita K, et al. Nuclear magnetic resonance imaging in a case of facial myokymia with multiple sclerosis. No To Shinkei. 1985 Jun; 37(6): 583–8. Japanese. PMID: 4041289.

206. Salavisa M, Serrazina F, Pires P, et al. Teaching Video NeuroImages: Infratentorial Multiple Sclerosis Relapse Presenting as Continuous Hemifacial Myokymia. Neurology., 6 July 2021; 97(1): e111–e112. DOI: https://doi.org/10.1212/WNL.0000000000012052

207. Clay JL, Villamar MF. Continuous facial myokymia in multiple sclerosis. Cln Case Rep., 16 July 2020; 8(11): 2326–2327. DOI: https://doi.org/10.1002/ccr3.3135

208. Marin Collazo IV, Tobin WO. Facial Myokymia and Hemifacial Spasm in Multiple Sclerosis: A Descriptive Study on Clinical Features and Treatment Outcomes. Neurologist., Jan 2018; 23(1): 1–6. DOI: https://doi.org/10.1097/NRL.0000000000000163

209. Hertz R, Espinosa J, Lucerna A, et al. Multiple Sclerosis Presenting with Facial Twitching (Myokymia and Hemifacial Spasms). Case Rep Neurol Med., 2017; 2017: 7180560. DOI: https://doi.org/10.1155/2017/7180560

210. London F, Hadhoun M, Zéphir H, et al. Continuous hemifacial myokymia as the revealing symptom of demyelinating disease of the CNS. Mult Scler Relat Disord., 2017; 2017: 7180560

211. Koutsis G, Breza M, Evangelopoulos ME, et al. Spastic paretic hemifacial contracture as a presenting feature of multiple sclerosis. Mult Scler Relat Disord., 2017; 13: 112–115. DOI: https://doi.org/10.1016/j.msard.2017.02.017

212. Jacobs L, Kaba S, Pullicino P. The lesion causing continuous facial myokymia in multiple sclerosis. Arch Neurol., Nov 1994; 51(11): 1115–9. DOI: https://doi.org/10.1001/archneur.1994.00540230053012

213. Colosimo C, Bologna M, Lamberti S, et al. A comparative study of primary and secondary hemifacial spasm. Arch Neurol., Mar 2006; 63(3): 441–4. DOI: https://doi.org/10.1001/archneur.63.3.441
214. Koutsis G, Kokotis P, Sarriigiannis P, et al. Spastic paretic hemifacial contracture in multiple sclerosis: a neglected clinical and EMG entity. Mult Scler., Aug 2008; 14(7): 927–32. DOI: https://doi.org/10.1177/1352458508090668

215. Fastré S, Hanson P, London F. Spastic paretic hemifacial contracture related to multiple sclerosis: a rare and under-recognized entity. Acta Neurol Belg., Dec 2017; 117(4): 927–929. DOI: https://doi.org/10.1007/s13760-017-0817-4

216. Sarriigiannis P, Tsakanicas C, Anagnostostouli M, et al. Spastic paretic hemifacial contracture (SPHC) in a patient with multiple sclerosis. A clinical, EMG and neuroimaging study. Neurophysiol Clin., Oct 2004; 34(3–4): 147–51. DOI: https://doi.org/10.1016/j.neucli.2004.07.006

217. Chaudhry N, Srivastava A, Joshi L. Hemifacial spasm: The past, present and future. J Neurol Sci., September 2015; 356(1–2): 27–31. Epub ahead of print. DOI: https://doi.org/10.1016/j.jns.2009.07.009

218. Nociti V, Fasano A, Bentivoglio AR, et al. Tourettism in multiple sclerosis: a case report. J Neurol Sci., December 2009; 287(1–2): 288–90. DOI: https://doi.org/10.1016/j.jns.2009.07.009

219. Deutsch SI, Rossie RB, Connor JM, et al. Current status of cannabis treatment of multiple sclerosis with dronabinol. CNS Spectr., Apr 2011; 17(2): 245–9. DOI: https://doi.org/10.1016/j.jocn.2009.09.026

220. Lano-Peixoto MA, Teixeira AL. Brazilian Committee for Treatment and Research in Multiple Sclerosis. Simple phonic tic in multiple sclerosis. Mult Scler., Dec 2002; 8(6): 510–1. DOI: https://doi.org/10.1191/1352458502ms829ao

221. Nomura Y. Pharmacological therapy for Tourette syndrome: What medicine can do and cannot do. Biomed J., September 2021; 18: S2319–4170(21)00114–1. Epub ahead of print. DOI: https://doi.org/10.1016/j.bj.2021.09.002

222. Billnitzer A, Jankovic J. Current Management of Tics and Tourette Syndrome: Behavioral, Pharmacologic, and Surgical Treatments. Neurotherapeutics., Oct 2020; 17(4): 1681–1693. DOI: https://doi.org/10.1007/s13311-020-00914-6

223. Valkovic P, Krastev G, Mako M, et al. A unique case of coincidence of early onset Parkinson’s disease and multiple sclerosis. Mov Disord., November 2007; 22(15): 2278–81. DOI: https://doi.org/10.1002/mds.21642

224. Pedemonte E, Trabucco E, Cella M, et al. Parkinsonism in multiple sclerosis patients: a casual or causal association? Parkinsonism Relat Disord. Epub., Apr 2013; 19(4): 492–3. DOI: https://doi.org/10.1016/j.parkreldis.2012.11.021

225. Vieregge P, Klostermann W, Brückmann H. Parkinsonism in multiple sclerosis. Mov Disord., Oct 1992; 7(4): 380–2. DOI: https://doi.org/10.1002/mds.870070416

226. Federlein J, Postert T, Allgeier A, et al. Remitting parkinsonism as a symptom of multiple sclerosis and the associated magnetic resonance imaging findings. Mov Disord., Nov 1997; 12(6): 1090–1. DOI: https://doi.org/10.1002/mds.870120643

227. Barun B, Brinar VV, Zadro I, et al. Parkinsonism and multiple sclerosis—is there association? Clin Neurol Neurosurg., Nov 2008; 110(9): 958–61. DOI: https://doi.org/10.1016/j.clineuro.2008.03.019

228. Ozturk V, Idiman E, Sengun IS, et al. Multiple sclerosis and parkinsonism: a case report. Funct Neurol. Jul–Sep 2002; 17(3): 145–7.

229. Domášio J, Ramos C, Valdemar L, et al. A coincidental case of young-onset Parkinson disease and multiple sclerosis. Neurologist., Sep 2011; 17(5): 286–8. DOI: https://doi.org/10.1097/NRL.0b013e318224ed84

230. Schultheiss T, Reichmann H, Ziemssen T. Rapidly progressive course of very late onset multiple sclerosis presenting with Parkinsonism: case report. Mult Scler., Feb 2011; 17(2): 245–9. DOI: https://doi.org/10.1177/1352458510384306

231. Folgar S, Gatto EM, Raina G, et al. Parkinsonism as a manifestation of multiple sclerosis. Mov Disord., Jan 2003; 18(1): 108–10. DOI: https://doi.org/10.1002/mds.10317

232. Saidho S, Mok TH, Butler M, et al. Multiple sclerosis exceptionally presenting as parkinsonism responds to intravenous methylprednisolone. J Clin Neurosci., May 2010; 17(5): 654–5. DOI: https://doi.org/10.1016/j.jocn.2009.09.026

233. Shaygannejad V, Shirmandi M, Dehghani L, et al. Co-occurrence of multiple sclerosis and Parkinson disease. Adv Biomed Res., Apr 2016; 5: 75. DOI: https://doi.org/10.4103/2277-9175.180993

234. Delalíć S, Rus T, Horvat Ledinek A, et al. Parkinson’s disease in a patient with multiple sclerosis and heterozygous glucocerebrosidase gene mutation. Clin Park Relat Disord., Apr 2020; 3: 100055. DOI: https://doi.org/10.1016/j.prdoa.2020.100055

235. Bougea A, Kapoki E, Paraskevas GP, et al. Multiple sclerosis and Parkinson's disease: the two faces of neurodegeneration. Report of the first Greek case and a review on the literature. Clin Neurologist, Sep 2011; 17(5): 286–8. DOI: https://doi.org/10.1016/j.prdoa.2020.100055

236. Bougea A, Kapoki E, Paraskevas GP, et al. Multiple sclerosis and Parkinson's disease: the two faces of neurodegeneration. Report of the first Greek case and a review on the literature. Clin Neurologist, Sep 2011; 17(5): 286–8. DOI: https://doi.org/10.1016/j.prdoa.2020.100055

237. Maranhão-Filho PA, Moraes Filho L, Camara LS, et al. Fulminant form of multiple sclerosis simulating brain tumor: a case with parkinsonian features and pathologic study. Arq Neuropsiquiatr., Sep 1995; 53(3–A): 503–8. DOI: https://doi.org/10.1016/j.prdoa.2020.100055
238. Fog T, Linnemann F. The course of multiple sclerosis in 73 cases with computer-designed curves. Acta Neurol Scand., 1970; 47: 3–175.

239. Kreisler A, Stankoff B, Ribeiro MJ, et al. Unexpected aggravation of Parkinson’s disease by a mesencephalic multiple sclerosis lesion. J Neurol., Dec 2004; 251(12): 1526–7. DOI: https://doi.org/10.1007/s00415-004-0570-5

240. Burn DJ, Cartlidge NE. A case of parkinsonism associated with multiple sclerosis. Mov Disord., Jul 1996; 11(4): 460–1. DOI: https://doi.org/10.1002/mds.870110426

241. Sadnicka A, Sheerin UM, Kaplan C, et al. Primary progressive multiple sclerosis developing in the context of young onset Parkinson’s disease. Mult Scler., Jan 2013; 19(1): 123–5. DOI: https://doi.org/10.1177/1352458512445942

242. Delgado S, Boez S, Singer C, et al. Parkinsonism/dystonia syndrome secondary to multiple sclerosis with anti-basal-ganglia antibodies. Mov Disord., Jan 2009; 24(2): 309–11. DOI: https://doi.org/10.1002/mds.22331

243. Wittstock M, Zettl UK, Grossmann A, et al. Multiple sclerosis presenting with parkinsonism. Parkinsonism Relat Disord., Jan 2001; 7: S74–S74.

244. Zivadinov R, Cox JL. Neuroimaging in multiple sclerosis. Int Rev Neurobiol., 2007; 79: 449–74. DOI: https://doi.org/10.1016/S0074-7742(07)79020-7

245. Kamphorst W, Ravid R. Movement disorders with multiple sclerosis. Mov Disord., Sep 1997; 12(5): 818. Epub ahead of print. DOI: https://doi.org/10.1002/mds.870120537

246. Nielsen NM, Pasternak B, Stenger E, et al. Multiple sclerosis and risk of Parkinson’s disease: a Danish nationwide cohort study. Eur J Neurol., Sept 2014; 21(1): 107–11. DOI: https://doi.org/10.1111/ene.12255

247. Papadopoulos D, Ewans L, Pham-Dinh D, et al. Upregulation of alpha-synuclein in neurons and glia in inflammatory demyelinating disease. Mol Cell Neurosci., Apr 2006; 31(4): 597–612. Epub ahead of print. DOI: https://doi.org/10.1016/j.mcn.2006.01.007

248. Evangelou N, Konz D, Esiri MM, et al. Regional axonal loss in the corpus callosum correlates with cerebral white matter lesion volume and distribution in multiple sclerosis. Brain., Sep 2000; 123( Pt 9): 1845–9. DOI: https://doi.org/10.1093/brain/123.9.1845

249. Witte ME, Bol JG, Gerritsen WH, et al. Parkinson’s disease-associated parkin colocalizes with Alzheimer’s disease and multiple sclerosis brain lesions. Neurobiol Dis., Dec 2009; 36(3): 445–52. DOI: https://doi.org/10.1016/j.nbd.2009.08.009

250. International Parkinson Disease Genomics Consortium, Nalls MA, Plagnol V, et al. Imputation of sequence variants for identification of genetic risks for Parkinson’s disease: a meta-analysis of genome-wide association studies. Lancet., Feb 2011; 377(9766): 641–9. DOI: https://doi.org/10.1016/S0140-6736(10)62345-8