Movement Disorder in Demyelinating Disease: Tracing the Charcot's Foot Print

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Abstract

Movement disorders may be one of the neurological manifestations of demyelinating disorders. They can manifest in Parkinsonism or a wide spectrum of hyperkinetic movement disorders including tremor, paroxysmal dyskinesia, dystonia, chorea, and ballism. Some of these disorders occur during an acute episode of demyelination, whereas others can develop later or even may precede the onset of the demyelinating disorders. The pathophysiology of movement disorders in demyelination is complex and the current evidence indicates a wide involvement of different brain networks and spinal cord. Treatment is mainly symptomatic and oral pharmacological agents are the mainstay of the management. Botulinum toxin and neurosurgical interventions may be required in selected patients.

Keywords: Corticosteroids, multiple sclerosis, NMOSD

Introduction

Movement disorders (MDs) may be one of the important clinical manifestations of demyelinating disorders.[1] But the detailed description of different types of MDs has been rarely reported. Also, the dilemma of whether or not to include some features like spasticity, fasciculation, ataxia, tonic seizures, nystagmus, and saccades in MDs and reporting of new conditions like clumsy hand syndrome complicate the condition even more.[1] The rarity of MDs in demyelinating disorders is surprising, considering that there is relatively frequent involvement of basal ganglia and subthalamic nucleus by multiple sclerosis (MS) plaques. Also, the persistence of MDs in some cases after remission of other symptoms by the corticosteroids are unsolved questions that lead to more aberrations.[2-4] Further, most of the studies conducted in the past are on a small number of patients as case series and case reports. However, in the recent era, more knowledge of causal association and better management of the symptoms have led to a better understanding of the disease.

Methods

We reviewed English-written articles published in PubMed till 31st December 2021 using the combination of "Medical Subject Headings (MeSH)" ["Multiple sclerosis" OR "Neuromyelitis Optica Spectrum Disorders (NMOSD)" OR anti-aquaporin-4 (AQP4) antibody OR "Anti-myelin oligodendrocyte antibody disease (MOG-Ab disease)" OR "Acute disseminated encephalomyelitis" OR "Osmotic demyelination syndrome"] AND ["Movement disorders"]. We retrieved 2415 articles, and after removing duplication and non-English articles, 199 articles were selected for the final review [Table 1]. Based on the review of literature, frequency [Table 2] and treatment [Table 3] of different MDs in different types of demyelinating disorders have been summarized.

Tremor

Tremor is known to occur in MS from the very past. Joseph coats discussed tremor in his patient with disseminated sclerosis in 1879, but despite being one among Charcot's triad (intention tremor, dysarthria, nystagmus), it was not much discussed.[5,6] Prevalence of tremors in MS is variable, ranging from 58% to 77%. Tremor is moderate to severe in 15%, severe disabling in 3–15%, and may rarely be a presenting feature in only 0.3% of cases.[7-10] Tremors most frequently occur in arms and hands with frequency ranging from 1–10 Hz, but may also be seen in the head, neck, vocal cords, trunk, and limbs.[9,11] In most MS patients, tremor is postural and intention; rest tremor is rare (1–3.33% cases only). Holmes, task-specific and orthostatic tremors have also been described in a few case studies.[9,10,12]

According to Pittock, relapsing-remitting MS (RRMS) patients are more likely to have tremors as compared to secondary progressive MS (SPMS).[9] The localization of tremors in MS and other demyelinating lesions has been

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illustrated from the thalamus to the spinal level, which includes the basal ganglia, zona incerta, subthalamic nuclei, centromedian thalamic nuclei, cerebellum, cerebellothalamic connections in the pons, brain-stem, and spinocerebellar tracts in the spinal cord.[9,13,14] Different authors have correlated the severity of tremors to various anatomic lesions. Boonstra *et al*.[15] correlated tremor severity in MS with thalamic volume and superior cerebellar peduncle. Other studies have attributed it to pontine and cerebellar lesion load.[12,14-17] The mechanism of tremor genesis in MS is not clear yet, and most hypotheses are made taking into account animal studies illustrating the dentate nucleus transmitting impulses to the thalamus via the superior cerebellar peduncle and red nucleus.[18] Tremor is also modulated at the level of the muscle spindle and can be decreased by cooling, decreasing the sensitivity of the muscle spindle and thence peripheral nerve conduction, therefore, decreasing the input in the cerebellar circuits.[14,19] A trial of stereotactic surgery in tremor ridden MS patients ascribed the ventralis-oralis-posterior (VOP) nucleus rather than the ventral intermediate nucleus (VIM) for causing the tremor, but this was not supported by other authors who attributed this to the edema and plaques induced disruption of the normal morphology of the brain leading to such aberration.[20,21] The clinical improvement is being assessed by different scales, including accelerometry and polarized light goniometry in various studies.[17,20,22-26]

Table 1: Results of PubMed search (on 31st December 2021)

Search terms	Number of hits
Multiple sclerosis AND Movement disorders	2268
Neuromyelitis optica spectrum disorders AND Movement disorders	66
anti-aquaporin-4 (AQP4) antibody and movement disorders	4
Acute disseminated encephalomyelitis AND Movement disorders	48
Osmotic demyelination syndrome AND Movement disorders	24
Anti-myelin oligodendrocyte antibody disease AND Movement disorders	5

Table 2: Spectrum of movement disorders in demyelinating disorders

Movement disorders	Multiple sclerosis	Neuromyelitis optica spectrum disorders	Myelin oligodendrocyte glycoprotein (MOG) antibody disease	Acute disseminated encephalomyelitis	Osmotic demyelination syndrome
Tremor	+++	+/-	+	–	+
Dystonia	+	–	–	+/–	–
Paroxysmal dyskinesia	+	+++	+	-	-
Myoclonus	+	-	-	+/-	-
Myokymia	+	–	–	-	+/-
Hemifacial spasm	+/-	-	–	-	–
Tics	+	–	-	–	-
Chorea	+	-	-	–	-
Restless leg syndrome	++	–	-	-	-
Parkinsonism	+	-	–	-	+++
Ocular manifestations	+	-	-	-	-

+ : Occasional; ++ : Frequent; +++ : Very frequent; – : Absent; +/– : Lack of evidence

Table 3: Different types of treatment in demyelinating disorders

Movement disorders	Corticosteroids	Isoniazid	Anti-epileptic drugs	Tetrahydrocannabinol	Botulinum toxin	Levodopa	Thalamo-tomy	DBS/ Thalamic stimulation
Tremor	+	++	+	+	+/–	+/–	++	+++
Dystonia			+	+	+		+	
PD			+	+	+		+	
Myoclonus			+/–	+				+
Myokymia	+/–		+-		+			
HFS			+		+			
Tics				+/–	+			
Chorea	+							+
RLS			+					
Parkinsonism	+/-					+/-		+++
Ocular manifestations			+/–		+			

+ : Mild benefit; ++ : Moderate benefit; +++ : Significant benefit; – : No benefit; +/– : No clear evidence of efficacy

A tremor in MS is one of the most difficult symptoms to treat and imposes significant functional disability. Various medications, including isoniazid, topiramate, benzodiazepines, beta-blockers, ethanol, antiemetics, mood stabilizers, levetiracetam, antispasmodics, and dementia medications, have been tried to produce an effect on the magnitude of action tremor.[23,27-30] Overall, among these, isoniazid is the most evaluated and shown to provide improvement in 60–80% of cases.[27] According to the The North American Research Committee on Multiple Sclerosis (NARCOMS) trial in 2016, moderate to severe tremor is more likely to respond to the medications acting via the Gamma-aminobutyric acid (GABA)ergic pathway compared to mild and disabling tremor.[25] In the late '90s, various drugs from oral cannabis, nabiximol spray, phenobarbital, topiramate, and glutathione to intrathecal baclofen were used, some of which showed improvement by their sedative, anticon vulsive, and anticholinergic effect, but due to their nonspecific nature and side-effects, the American Academy of Neurology guidelines are against their use.[31,32] Vagus nerve stimulation has also been tried successfully in postural cerebellar tremors with dysphagia in MS patients. Few trials available showed up to 67% improvement over three months.[33,34] The unilateral thalamotomy of VIM or VOP is considered the treatment of choice and has shown to be effective in postural tremors (50%) and intention tremors (72%). The response remains for more than one to five years. Due to higher chances of complications like subdural hematoma and intracerebral hemorrhage with thalamotomy, and the comparatively reversible nature of complications with thalamic deep brain stimulation (DBS), the latter is considered the preferable approach.[7,20,35,36] The mean improvement with DBS is reported to be 39% which can be a maximum of up to 100%.[37,38] But due to the fluctuating/progressing nature of the disease in MS, unlike steady deterioration in Parkinson's disease, the regression in improvement cannot be precisely expected.[37]

Due to different disease courses and tremor characteristics, the stimulation site varies in MS compared to other causes of tremor.[7,34,39] VOP/VIM for distal single frequency tremor and VOP and Zona inserta (ZI) for mixed proximal and distal joint tremor with broader frequency are generally considered.[40] Postoperative complications like epilepsy, sensory disturbances, hemiparesis, aphasia, dysphagia, transient bladder disturbances, depression, confusion, lethargy, and somnolence were also reported.[9,41-44] Magnetic resonance-guided focussed ultrasound has also been used for unilateral tremors in MS patients.[45] Keeping all the contraindications in the concern like weakness of the tremulous extremity, psychiatric comorbidity, and other neurosurgical contraindications, DBS is effective for bilateral tremors.[46] Besides this, upcoming technologies like exoskeleton may be another treatment option for tremor management in patients with MS, but they are still in the rootlet stage.[47]

Paroxysmal Dyskinesia

Paroxysmal dyskinesia (PD) remained hidden under the cloak of epilepsy (reflex) owing to its paroxysmal nature and the responsiveness to the anti-epileptic drugs and had not got a separate name until the 1940s when Mount and Reback used the term "paroxysmal choreoathetosis" instead of epilepsy due to intactness of consciousness.[48] PD was further classified by Kertesz into kinesogenic (PKD) and non-kinesogenic (PNKD), and later, three more variants evolved based on relation to sleep, exercise, and childhood dystonic form, i.e., paroxysmal hypnagogic choreoathetosis (PHC), paroxysmal exercise-induced dyskinesia (PED), and paroxysmal dystonic choreoathetosis (PDC).[48-52] But confusion persisted about the paroxysmal dystonia, and tonic spasm/tonic seizure. Later, tonic seizure (TS), and paroxysmal dystonia were established under "other episodic disorders that can be confused with a paroxysmal MD" separating it from PD.[49,53] However, in MS, the three forms mostly discussed are PKD, PNKD, and PED (paroxysmal exertion induced dystonia). PKD is a major form of primary origin, and secondary PKD (structural and other recognizable causes) accounts for 7.6% of cases only.[54] Primary and secondary PKD have also been differentiated based on the duration of each episode in which the primary lasts for <5 minutes (usually 30–90 seconds) and the secondary PD lasts longer (>5 minutes). However, some authors are not much supportive of this statement.[54,55]

The tonic seizure is the second most common MD reported in MS.[50] It was initially described by the Gullian in NMOSD but later illustrated by Mathews in MS, as abrupt onset transient painful extensor or flexor spasm in one or more limbs with or without trunk or face or lingual involvement of brief duration with frequency up to 200 per day.[50,56-61] The incidence is found at 3.8% to 17% in MS and often presents as an initial symptom.[58,62-65] In some studies, autonomic symptoms like ipsilateral sweating have also been reported.[50,58,66] Isometric, complex, and adductor/inversion TS have also been described in NMOSD.[5,67-69] Hyperventilation is the most common trigger, followed by spinal flexion, sudden exertion, sexual intercourse, anxiety, fatigue, ingestion of alcohol, exposure to noises, and moving into a cold environment.[55,70-72] The lesion can be localized anywhere in the motor pathway from the spinal cord (cervical cord), brain-stem, cerebral peduncle, thalamus, posterior limb of the internal capsule, and corpus callosum. But the spinal cord is likely to be the most common, where the motor and sensory fibers are situated close to each other.[55,73,74] As the knowledge evolved, it seems that not the lesion per se causes the spasm, as the TS was found to be present even before the appearance of spinal cord lesion {Cervical and brain-stem >dorsal} on magnetic resonance imaging (MRI) and sometimes may appear during the treatment phase also, when other symptoms start disappearing.[75,76]

Being more associated with a spinal lesion, it is not surprising that TSs are more commonly found in NMOSD (3–98%), which is also more associated with Longitudinal extensive transverse myelitis (LETM) than MS.[76,77] Kim *et al*.[75] depicted the sensitivity and specificity of myelitis for TS as 80% and 63.3%, respectively, in NMOSD, and has no association with the length and location of the spinal cord lesion. Besides

this, it can also be found in the thalamocapsular lesion in MS patients.[73,78] TS has a localizing and predictive value also in suspected cases of transverse myelitis with NMOSD.[59,79,80] Few cases of TS have been described in Acute disseminated encephalomyelitis (ADEM) as well.[81] In one comparative study, the association of TS was found to be higher for NMOSD than Myelin oligodendrocyte glycoprotein (MOG) antibody disease, which can be obvious by the fact that MOG-Ab disease is associated with more of the caudal (conus) spinal cord, whereas TS is found to be more in the cervical spinal cord.[82] Various case series and case reports have shown the association between the two, and sometimes, TS may present as an initial symptom.[61-63,70]

TS is managed by anticonvulsant drugs like carbamazepine, phenytoin, valproate, primidone, phenobarbitone, levetiracetam, clonazepam, gabapentin, and in refractory cases, topiramate, lidocaine, mexiletine, and tiagabine, acetazolamide, cannabis, and botulinum toxin have also been tried successfully.[10,82-87]

Hemidystonia

Several cases of hemi-dystonia secondary to the lesions in the caudate, lentiform nucleus, thalamus, and subthalamus were commonly reported in MS, but most of them had paroxysmal symptoms.[74,88] A few cases of sustained hemi-dystonia have also been reported, but the causative lesion has not been found.[88,89]

Pharyngeal Tonic Spasm

Like other dystonia in MS, pharyngeal tonic spasm also is a rare entity, and two cases have been reported proven by electromyography, which illustrated the hypertonic activity of the cricopharyngeal muscle; however, no anatomical lesion was described.[90,91]

Spasmodic Torticollis

Spasmodic torticollis (ST) has been rarely reported with demyelinating lesions. A case report has been traced back to Guillain, who first reported ST in a patient with an 11-year history of having MS.[92] Later other studies also linked ST with MS lesions involving basal ganglia, periventricular to subcortical regions, cerebral peduncle, ponto-mesencephalic junction, cerebellum, and upper cervical spinal cord.[55,92-96] One case of painless torticollis has also been reported in ADEM patients.[96] Unlike PD, no specific correlation or causal mechanism (except anti-basal ganglia antibody) has been illustrated and has long been considered a coincidental finding.[97]

Cases of MS with initial presentation as torticollis has been reported, implying the need for MRI and other evaluation studies in patients with focal dystonia.[93] There are case reports of ST precipitating with exacerbation of MS and recovering on its own. Some of these patients got remitted with steroids, and in others, botulinum toxin was the only rescuer.[98] One study demonstrated the resolution of symptoms with ACTH.[99]

Catatonia

Catatonia is characterized by catalepsy, that is, maintaining abnormal posture for a prolonged duration, waxy flexibility (retention of the limbs for an indefinite period), mutism, negativism, and bizarre behavior.[99-102] In MS patients with catatonia, MRI findings have documented demyelinating lesions in frontal, supplemental motor areas, basal ganglia, and amygdala.[101]

Myoclonus

In MS, the most commonly reported myoclonus is the palatal myoclonus.[103-105] One case of propriospinal myoclonus has also been described by Kapoor *et al*., and a few cases of branchial/spinal myoclonus due to demyelinating lesion have been described by Jankovic in his study of the spinal myoclonus.[105,106] Foschi *et al*.,[107] in their review article, purred about the existence of propriospinal myoclonus in sleep due to intramedullary demyelinating plaque, but no case has been reported. There are case reports of spinal myoclonus in ADEM and opsoclonus myoclonus syndrome in MOG-Ab disease.[108,109] It has been postulated that the myoclonus in demyelinating disorders is likely to be due to a loss of inhibition from the suprasegmental pathway or the overactivity of the anterior horn cell with hyper-excitability of the demyelinated axons.[104,105,110]

There is no definitive treatment for myoclonus in demyelinating disorders. Various drugs, including carbamazepine, primidone, clonazepam, tizanidine, levetiracetam, baclofen, cannabis, and dimethyl fumarate, have been tried with no significant benefit.[32,111-114]

Myokymia

Buzzard first described it as “fibrillotonic facial spasm”. Later, Bernhardt (1902) coined the term “Facial Myokymia” and Oppenheim (1916) proposed its association with MS.[115] Myokymia has been classified based on the region involved, i.e., focal and generalized. The focal myokymia is primarily localized to the facial region, and generalized is used interchangeably with limb myokymia. Continuous facial myokymia (eyelid myokymia) is more commonly seen in MS as compared to limb myokymia.[115,116] Facial myokymia is more likely to be associated with demyelinating lesions in MS localizing to the post-genu position of the facial nerve in the dorsolateral pontine tegmentum.[117] Recognizing this phenomenon is of clinical significance in making the diagnosis of MS, as facial myokymia due to MS is usually transient, lasting from two weeks to six months.[117] On Electromyography (EMG), it presents as short bursts of ectopically generated motor neuron unit potentials firing at a frequency of 2–10 Hz in a rhythmic or semi rhythmic fashion. The differential diagnosis of EMG includes synkinesis, fasciculation (giant voltage, simple, solitary action potential, firing at random), post-paralytic facial spasm (burst at irregular interval, increased intensity following voluntary facial contraction), cryptogenic

facial spasm (irregular in rhythm, region, and degree), facial jacksonian epilepsy or epilepsia partialis continua (absence of wavy character and clonic type spasm of brief duration), blepharospasm, neuromyotonia, myotonic discharges, and complex repetitive discharges.[118] Radu and Jacob, in their respective studies, tried to prove the correlation between myokymia and the demyelinating lesion.[119] The MRI lesion emergence and evanesce with myokymia were used as evidence to prove the simultaneity. Similarly, Kojima also presented a case of MS with initial presentation as facial myokymia with the lesion in the lateral tegmentum pontine plaque/infranuclear area of the facial nerve.[120] In comparison to MS, the lesion is infranuclear, and it is the deafferentation of the nerve that leads to myokymia in Guillain-Barré syndrome (GBS).[118,120] Cases that initially present with facial myokymia due to MS are usually self-limited.[114,121] If methylprednisolone and carbamazepine are not effective, botulinum toxin can be tried.[122] Besides MS only a few case reports have been reported regarding the presence of eyelid myokymia in other demyelinating disorders like ADEM.[123] Spastic paretic hemifacial contracture (SPHC) is the sustained contraction of the ipsilateral facial muscles with facial paresis, which differentiates it from myokymia. SPHC is also caused by the pontine (dorsolateral) lesions and recovers spontaneously.[124] EMG findings are suggestive of low amplitude, incomplete interference, and impaired recruitment pattern during voluntary contraction. To date, only nine cases have been reported, and two were associated with MS. The underlying mechanism was postulated as hyperexcitability of the facial neurons due to the absence of inhibitory action of the corticobulbar fibers.[125] Patients were treated with gabapentin, baclofen, and carbamazepine.[125]

Hemifacial Spasm

Hemifacial spasm (HFS) is a short, continuous, spontaneous paroxysmal contraction of facial muscles supplied by the facial nerve, caused by the *kindling effect* where the damaged root entry zone acts as a trigger, generating the impulses and transmitting them both anti and orthodromically. The antidromic impulses activating the facial motor nucleus send the impulses down the facial nerve, thereby generating the HFS. An alternate theory has also been proposed of ephaptic transmission and malfunction with rearrangement of facial nucleus, respectively.[126,127] The association with trigeminal neuralgia has also been suggested, but researchers have not found much evidence. Besides typical anticonvulsive drugs, baclofen, botulinum toxin, microvascular decompression, and other surgical approaches have been used.[122]

Choreo-Athetosis

Only a few cases of chorea and ballism in MS have been discussed so far.[128-134] Management available varies, as in some cases, it improves with typical drugs (like chorea due to other causes). Proving the causal association between the two, some cases showed improvement with anti-inflammatory drugs and recovery with resolution of the lesion.[55,131] However, few cases did not suggest coincidence.[134] DBS has also been tried with successful results in a few studies.[129,135]

Tics

Tics in demyelinating disorder are unheard entity, and only a few cases so far have been described with controversy regarding their coexistence as a causal association or incidental finding.[136,137] Tics are more specific to the RRMS rather than SPMS.[8] It occurs due to disinhibition of the frontal subcortical thalamocortical circuitry controlling voluntary movement.[136,137] Other than that, lesions of the cortices and corpus callosum and thinning of sensorimotor areas (a ventral portion of the homunculus) have also been found.[74,138]

Various treatments, including clonidine, antipsychotics, and botulinum toxin, have been tried in motor tics with dystonic features. As there is a male preponderance (male: female; 4:1), androgen receptor blocker flutamide has also been tried in placebo-controlled cross-over trials.[139] The use of cannabis is also reported but controversial.[32,140]

Restless Legs Syndrome

Restless leg syndrome (RLS) usually occurs in MS patient with a long evolution time and should be differentiated from pseudo-RLS [Table 4].[141,142] The frequency of RLS is found to be more in patients with MS (RRMS > PPMS) than without it.[142] No association with age has been established.[143] RLS in MS is also associated with the prognosis, the quality of life,

Table 4: Differences between restless legs syndrome and pseudo-restless legs syndrome

Clinical features	Restless legs syndrome (RLS)	Pseudo-RLS
Major symptoms	Neurosensory disorder, characterised by discomforting leg sensations like dys/paraesthesia and pain.	Dysesthesia, paresthesia, and spasticity in limbs mimicking RLS.
Relationship with sleep	Classically appearing at night before going to sleep	Worst when subjects wake up
Urge	Causes the urge to move	Do not cause the urge to move
Frequency	Dysesthesia is more or less intermittent	Dysesthesia is relatively constant
Relationship with leg-movement	The decrease in moving the affected limb	Do not decrease on moving the limb
Site	Usually occur in the calf region and aggravate to thighs and lower leg	Characterized by ankle involvement
Association with periodic leg movement syndrome	Present	No such association present

and cognitive impairment (affecting the quality of sleep), as subjects with RLS are found to have a higher disability and risk of depression than subjects without RLS.[144] For the assessment of severity, the International Restless Legs Syndrome Study Group (IRLSSG) criteria has been used.[145,146]

There is not much difference in the management of RLS in patients with MS, and iron, dopamine agonist, and anti-epileptic drugs are the mainstay of the treatment.[146]

Parkinsonism

Parkinsonism in MS is mostly due to lesions of the substantia nigra, and thalamus. However, other lesions in the midbrain, frontal lobe, and globus pallidus have also been illustrated in a few studies, but the significance of these finding has not been proven yet.[136,147-150] The parkinsonism associated with MS is usually bilateral with rapid onset, much milder, and usually in the younger population.[151] In a case series of MS patients, the parkinsonian symptoms completely resolved with intravenous methylprednisolone with minimal/no response to other typical antiparkinson drugs like levodopa/carbidopa and ropinirole.[48,151-154] On the other hand, in another case series of MDs in RRMS, Nociti *et al*.,[136] illustrated two cases of mild parkinsonism who did not respond at all to corticosteroids and improved with levodopa/carbidopa. A similar illustration is given by others, hypothesizing that parkinsonism may be caused by MS lesions in basal ganglia and subside by corticosteroids like other symptoms suggesting an association between the two.[155,156] However, some studies fail to show improvement with both corticosteroids and levodopa.[157] Two cases of atypical parkinsonism (Multiple system atrophy) in MS have been reported with lesions in the midbrain, inferior olive, and cerebellum. The patients deteriorated on levodopa/carbidopa, and the autopsy proved the demyelinating pathology.[157-159] Besides antiparkinsonian drugs and corticosteroids, other modalities, including electromagnetic field, have also been tried successfully and shown good response.[159]

Eye Movement Disorder

Eye MD was illustrated to be present in MS (36–84%) from the beginning, but their diagnostic value has always been a big question mark,[160] as even after several studies, their true value was never proven till 1986.[161] Besides, it also plays a role in maintaining the quality of life, as the patient having the same found to have poorer quality of life.[161] How oculomotor disturbances are different from other MDs in MS is that unlike other MDs commonly presenting in the RRMS subtype, these are assailant to progressive subtypes (90–95% cases, throughout the course of MS).[162] Various ocular abnormal movements can appear in MS, with internuclear ophthalmoplegia (INO) being the most frequent, constructing 30% of all MS cases.[162-165] As INO progresses, saccadic latency, velocity, and range of motion are also affected progressively, leading to visual confusion, oscillopsia, reading fatigue, diplopia, and loss of stereopsis.[166,167] One case of ocular flutter has also been reported in MOG-Ab disease.[168]

Saccades

Saccadic dysmetria is the most common eye MD seen in chronic MS and clinically isolated syndrome (CIS), commonly occurring secondary to the lesion of the dorsal vermis.[169] Saccades have three important components, each of which localizes the lesion at a different level, i.e., peak saccadic velocity (PSV) denotes the function of the paramedian pontine reticular formation (PPRF), saccadic accuracy is a function of the cerebellum, and basal ganglia and latency depict the neural conduction times of the whole visual (afferent and efferent) pathway system.[170] The role of this parameter is in the early detection of MS.[170] Hypometria occurs in a lesion of the vermis alone, whereas hypermetria occurs due to the involvement of the deep nuclei.[171] There can be an increase in saccadic latency, initiation time, average inter-saccadic interval, and decreased saccadic velocity, which is studied as a marker of cognitive slowing (hypometric saccades).[171] Decreased saccadic latency seen in CIS cases is probably due to reduced inhibition.[172] To standardize the disturbance, the versional dysconjugacy index (VDI) has been used, which accounts for all the components of the saccades like velocity, acceleration, amplitude, and latency in both the abducting and adducting eye.[173] In a study of nine patients with INO, it was illustrated that VDI increased in mild cases of INO; however, in severe cases, it decreased.[173] Last is the phase-plane analysis which takes the velocity as a function of eye position and removes the variations caused by the temporal variation.[174] Besides this, nystagmography was also used in some studies for illustrating the slowing of saccades.[174,175] However, these parameters act as indicators but cannot be fully relied on.[175]

Saccades can be measured by infrared reflection oculography, infrared oculography, infrared eye-tracker, electro-oculographic technique, and the combination of infrared oculography and diffusion tensor imaging (DTI).[175] Various medications have been tried to improve the latency of saccades, including fampridine.[176]

Pursuit

Pursuit is the smooth tracking movement that helps in keeping the targeted object fixated at the fovea. It originates from cortical and subcortical areas, including the frontal eye field, dorsolateral pontine nucleus, cerebellar flocculus, vestibular nuclei, and dorsal vermis. Impaired pursuit is not uncommon in MS, and it has been illustrated as a marker of CIS in many studies. It can be seen in 30% of MS cases, leading to a low-gain pursuit in which the eye movements are inordinately slower than the moving target.[177,178] Due to the involvement of cerebellar flocculus, the vestibular-ocular reflex cancellation is impaired, which is imperative for the foveal fixation of the target during the active head and eye movement.[179]

Nystagmus

Nystagmus is an oscillatory movement of the eye and occurs in 70% of MS patients affecting tracts from the cerebellum, dorsal medullary, medial pontine, and superior colliculi, leading to

alteration of the fixation, gaze holding, vestibular-ocular reflex, and thence to nystagmus.[180] However, it is not as common in chronic MS as other oculomotor dysfunction.[180] Nystagmus is hypothesized to be due to the alteration in the neural integration system. This visual stimulus also impacts eye movement, as a greater oscillation of nystagmus has been found in the eye with optic nerve involvement.[181]

MS is the most common cause of acquired pendular nystagmus (APN) secondary to the lesions of the paramedian tract.[182-184] Optokinetic nystagmus has also been reported in MS.[185] Treatment suggested are gabapentin, memantine, 3,4-diaminopyridine, baclofen, fampridine, prisms, and surgery. Besides these, the vibratory method has also been tried. Beh *et al*.[186] used a mini muscle massager over the vertex, mastoid, and chin in patients of MS with monocular horizontal nystagmus and vexatious oscillopsia, explaining the mechanism as the excitation of the vestibular system and proprioceptive signal to eye movement for gaze holding system.

Gaze-evoked nystagmus (GEN) is counted as the most frequent nystagmus and is mostly seen in chronic MS (45%), except the upbeat nystagmus (UN), which is present in the acute phase.[187] Upbeat nystagmus is usually associated with bilateral internuclear ophthalmoplegia (INO).[176] UN in the primary position is caused by the lesion in the caudal medullary or pontine tegmentum. Characteristic of this nystagmus is that it changes with head position and diminishes in a prone or supine position. Downbeat nystagmus (DBN) is caused by the vestibular nuclei disinhibition due to the floccular nuclei lesion, but this is not as common in MS as UN.[188] Among all the nystagmus in MS, APN and DBN are most responsive to treatment.[189] Aminopyridine in DBN, baclofen in APN, and memantine in UN are the most effective medications tried.[189] Botulinum toxin has been tried in acquired nystagmus, but side effect like diplopia and ptosis make it less favorable.[190] Horizontal gaze-evoked nystagmus is more commonly associated with NMOSD as compared to MS.[191] Central positional nystagmus and opsoclonus are rarely reported in MS.[192]

See-saw nystagmus consists of supraduction and incyclotorsion of one eye and infraduction and excyclotorsion of other eyes and it is caused by the para sellar, chiasmal, or midbrain lesion.[193]

Besides these, torsional nystagmus, skew deviation, and ocular micro-tremor have been rarely reported in demyelinating lesions.[194-196]

Conclusion

MDs are not frequent in MS, but not as rare as earlier perceived. Tremor is the most common MD reported in MS, but other MDs may also occur and may even be the presenting feature. Questions are often raised regarding the causal relation between MDs and demyelinating diseases, but certain clues like abrupt onset, temporal relation with the demyelinating lesion, and response to treatment are helpful in making the correct diagnosis. With the evolution of better imaging studies and better evaluating modalities, MDs are more easily recognized and can help in the early recognition of the demyelinating disease, prognostication, and better management of the quality of life of patients with MS. So, physicians should always keenly observe these movements.

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Conflicts of interest

There are no conflicts of interest.

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