REVIEW ARTICLE

MULTIPLE SCLEROSIS: A COMPREHENSIVE REVIEW FOR THE OSTEOPATHIC PROVIDER

Ethan Charles Blocher-Smith, MS, DO[1,2]; Anthony Izokaitis, DO[1,2]

[1]Fruitport Family Medicine, Fruitport, MI
[2] Mercy Health Mercy Campus, Muskegon, MI

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Abstract:

Multiple sclerosis (MS) is an uncommon neurological pathology frequently initially discovered by primary care providers in their workup of new focal neurological deficits. Many cases go undiagnosed for years despite multiple flares, with risk of cumulative disability. Early treatment is key to slowing or preventing the accumulation of this disability and maximizing function in the long term. This literature review covers all aspects of MS, including pathophysiology, diagnostic testing and differential diagnosis, disease classification, and disease-modifying agents for acute and chronic treatment. This study also summarizes support services, including osteopathic manipulative treatment, that help to maximize patient function and independence. While better therapeutics continue to emerge, significant limitations, side effects and continued progression—despite optimal therapy—result in progressive and irreversible loss of function for many patients. Heightened awareness of current progress in MS diagnosis criteria and initial testing amongst primary care providers can shorten the time to treatment and formal diagnosis, allowing patients to live their best lives despite their MS diagnosis.

INTRODUCTION

Multiple sclerosis (MS) is a complex disease state in which autoantibodies attack the central nervous system (CNS). These attacks result in progressive damage and subsequent disability, with eventual discovery typically coming from this disability. MS has an estimated minimum prevalence of 2.88 per 1000 individuals in the United States and, like most autoimmune conditions, is more likely in women with ~3:1 predominance.[1] The exact cause of this immune attack is unknown and appears to be multifactorial. There does appear to be a genetic component, as studies have shown a correlation between risk of MS in families proportional to amount of genetic similarity.[2] A monozygotic twin carries a risk of 25% for MS if their twin has the disease, which drops to around 5% for dizygotic twins or primary relatives, 1-2 percent for secondary relatives, and above base rate but less than 1% for tertiary relatives.[2] However, the low rates of incidence even with identical DNA imply a concomitant environmental component. Cases have been reported after Epstein–Barr virus,[3] human herpesvirus [6][4] and mycoplasma pneumoniae exposures,[5] implying a possible mechanism similar to that in type 1 diabetes with Coxsackie B virus,[6] with structures similar to that of the myelin sheath presenting on these agents to the immune system. Low vitamin D levels are shown to increase risk of MS,[7] with possible mechanism via immune cell activation on B/T cells and macrophages by vitamin D receptors.[8] This does also result in significant difference in MS prevalence based on latitude of primary residence. While several studies have argued that increased Vitamin D supplementation may modify MS severity, this is not conclusively proven with substantial disagreement in the literature at this time.[7] Smoking also appears to contribute, with history of smoking associated with relative risk of 1.5 for MS diagnosis, along with worsening frequency of relapse, higher conversion to progressive MS from remitting courses, and increased rate of disability accumulation.[9] There does appear to be an association with obesity as well, with a recent pediatric study showing twice the rate of MS in obese German children (OR 2.19 females, 2.14 males, $p \leq 0.003$) and worse response to first line agents in obese children, though whether this is causative or simply a secondary association is unknown.[10]

PATHOPHYSIOLOGY

While the initial cause of autoimmune attack is multifactorial and still not fully understood, the mechanism of injury and progression of an MS flare are well characterized. Classically, it was thought that CD4+ T-cells caused the injury in MS.[11] Further characterization has shown involvement of much of the immune system, with CD8+ T-cells, B-cells, Th1 and Th17 helper cells, CD4 and CD8+ T-regulatory cells, NK cells, mast cells, dendritic and microglial

CORRESPONDENCE:
Ethan Charles Blocher-Smith, MS, DO
eblochersmith756@marian.edu

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cells, macrophages, among others.[12,13,14] These immune cells infiltrate a region within the CNS and attack nearby myelin sheaths and their supporting oligodendrocytes.[15] Depending on the severity of attack, this may only demyelinate a number of neurons resulting in temporary loss of their function until this sheath repairs itself across a period of weeks to months. In more severe episodes, however, this may progress to neuronal death, resulting in permanent loss of function.[15] As this attack increases in severity, the more temporary and permanent disability will occur with each episode. This accumulation of immune cells, damaged neurons, and surrounding inflammatory edema/cytokines results in characteristic plaques that are easily seen on MRI.[16] As the inflammation clears, glial cells proliferate to fill in any residual defect resulting in astrogliosis, leaving a permanent "scar" of the neural tissue.[16]

The exact loss of function resulting from a MS flare is dependent on the location of the immune attack. Occipital or medullary lesions may cause blindness or ophthalmoplegia, cerebellar lesions may cause poor balance, damage to the motor cortex or motor pathways in the spinal cord may cause paralysis, damage to frontal territories may affect behavior or mood, etc.[17] Due to the fact that every neurological system may be affected, initial diagnosis of MS may be very challenging. This is especially concerning, as every new attack without medication support is a roll of the dice to permanently lose CNS function.[18] Disability in MS is typically scored by the Kurtzke Expanded Disability Status Scale (EDSS) a scale that ranges from 0–10 as shown in Table 1.[19] Prior to the creation of modern therapies for treatment, mean progression of disability was estimated at 0.27 EDSS points every 2 years for patients with relapsing-remitting MS.[20] More recent studies have shown >50% of progressive MS cases will have EDSS >6 within 10 years of symptom onset.[21] Additionally, many patients may not realize the significance of early deficits, instead thinking that they are simply being clumsy or mistaking mood changes as a primarily psychological issue instead of the true neurological cause. As such, many primary care physicians (PCPs) may treat patients conservatively for an extended period before recognizing the significance of these disparate symptoms. A 2018 Swiss review of 1059 patients found only 62.7% of their patients were diagnosed within 2 years from initial symptoms, despite 90% having seen their PCP within the year prior to diagnosis.[22] Items from this study associated with a longer time to diagnoses were male sex, a general practitioner as the first provider contacted, and atypical symptoms from first episode.[22] Symptoms that are most common are those associated with the largest brain volume, since lesions may appear anywhere in the CNS. Thus, vision, balance, emotional and motor disturbances are most common, with hearing, speech, dysphagia, respiratory issues, or seizures less likely but still possible.[23] Aggressively treating to limit the level of immune destruction with intervention as soon as possible after diagnosis will reduce the rate of disability in both the short and long term.

TABLE 1:

EDSS Scale. The scale uses assessment in 8 functional systems (FS): Cognition and memory, pyramidal, sensory, visual, bowel/bladder function, cerebellar, brainstem, and other. A score of 4 or less is still fully ambulatory, with rapid loss of function at higher scores. In most studies, worsening disability is defined as a persistent increase in EDSS of 1 point or more.[19]

SCORE	DESCRIPTION
0	Normal neurological exam, no disability in any FS.
1.0	No disability, minimal signs in 1 FS.
1.5	No disability, minimal signs in >1 FS.
2.0	Minimal disability in 1 FS.
2.5	Mild disability in 1 FS or minimal disability in 2 FS.
3.0	Moderate disability in 1 FS, or mild disability in 3-4 FS. No impairment to walking.
3.5	Moderate disability in 1 FS and more than minimal disability in several others. No impairment to walking.
4.0	Significant disability but self-sufficient and mobile ≥12 hours a day. Able to walk without aid or rest for 500 m.
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300 m.
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200 m.
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100 m.
6.0	Requires a walking aid to walk about 100 m with or without resting.
6.5	Requires two walking aids to walk about 20 m without resting.
7.0	Unable to walk beyond ~5 m even with aid. Essentially restricted to wheelchair, wheeling self in standard wheelchair and transfers alone. Up and about in wheelchair ≥12 hours a day.
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot complete full day in standard and may require motorized wheelchair.
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally, has effective use of arms.
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions.
9.0	Confined to bed. Can still communicate and eat.
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow.
10.0	Death due to MS.

DIAGNOSIS

The hallmark of MS is lesions disseminated in both space and time—first identified in 1965 by the panel of multiple sclerosis[24]—with diagnosis now most commonly occurring under the McDonald Criteria. Originally developed in 2001 by Professor Ian McDonald of London University, a New Zealand neurologist and the foremost expert of his time on MS, along with a team of experts, these guidelines are the standby for rigorous clinical diagnosis.[25] The most recent revision, published in 2017, focuses on diagnosis as early as possible while still meeting guidelines to prevent misdiagnosis.[26]

The standby of diagnosis is magnetic resonance imaging (MRI) evidence of lesions characteristic of MS, with 2 clinical attacks and evidence of 2 different lesions categorically defining MS.[25] However, these recent changes now allow detection of CSF specific oligoclonal bands to substitute for dissemination in time requirement, allowing diagnosis of MS with a single attack so long as at least 2 lesions are characterized at that time.[26] As previously mentioned, some patients may not have recognized a prior flare and its sequelae, allowing earlier diagnosis and treatment. Typical studies for a high index of suspicion for MS include MRI of the brain and/or spinal cord, CSF analysis with paired serum sample for oligoclonal band analysis, and evoked potential studies.[23] Early referral to neurology for assessment is also extremely important. These will now each be reviewed in detail.

MRI studies of the brain and spinal cord are ordered, as comprehensive evaluation of the CNS is appropriate to characterize all lesions for diagnosis. Additionally, use of gadolinium enhancement contrast can allow for differentiation of acute lesions with high uptake vs chronic lesions with gliosis scarring. Lesions are classified into 4 regions: periventricular, cortical/juxtacortical, infratentorial and spinal cord.[27] CSF analysis will show high protein secondary to albuminocytological dissociation. This finding, classically associated with Guillain-Barré syndrome, is positive in any CNS demyelinating process as the excess protein without cellular content is from the fragments of myelin sheath that have been destroyed.[28] Additionally, CSF specific oligoclonal bands, seen only in the CSF and not in the paired serum sample drawn concurrently, correspond to the IgG antibodies attacking the brain. In particularly severe cases, there may also be IgM antibodies that are CSF specific. This corresponds to much worse outcomes overall.[29] Evoked potential studies look at systems that are challenging to examine precisely and have a high risk of clinically occult deficits. This includes visual testing, auditory testing, brainstem evoking potentials, and somatosensory testing. For example, testing of vision involves use of visual stimulus with measured conductivity of the optic nerve pathway. This is an extremely sensitive test with any change to the nerve pathway resulting in measurable signal variance.[30] Lastly, autoantibody testing may come into play for differentiating alternative diagnoses in an atypical presentation for MS and would exclusively be ordered by a neurologist.

Disease classification

Multiple sclerosis may present as 1 of 4 categories of disease state (see Figure 1):

1. **Clinically Isolated Syndrome (CIS)**: This person has symptoms of MS lasting at least 24 hours but has not yet been formally diagnosed with a true MS diagnosis. This gateway diagnosis is placed on any individual who does not yet clearly meet both the dissemination in space and dissemination in time requirements for MS. Many people may never show a second episode and thus never qualify as MS. Many are properly differentially diagnosed with alternative conditions, such as optic neuritis, that have similar symptoms. However, individuals considered at high risk of progression to a formal MS diagnosis may receive disease-modifying drugs with full U.S. Food and Drug Administration (FDA) approval.[31]

2. **Relapsing Remitting Multiple Sclerosis (RRMS)**: This is the most common type of MS encompassing about 85% of patients with true MS diagnosis. This patient will have periodic episodes of MS flares, with partial to full recovery to prior baseline after each episode. They do not tend to worsen outside of individual flares, though each flare carries the risk of more persistent deficits and progressive debility and disability as more damage accumulates in the CNS.[31]

3. **Secondary Progressive Multiple Sclerosis (SPMS)**: This type of MS initially presents as RRMS but then worsens, with slow progressions of disability both with and without evidence of acute flares. While singular severe flares certainly still occur, the majority of disability and loss of function occurs as a slow worsening outside of these flares.[31]

4. **Primary Progressive Multiple Sclerosis (PPMS)**: This is the worst type of MS with rapid progression of disability. There is no respite period of RRMS initially, instead demonstrating the same constant accumulation of disability seen in SPMS. As with SPMS, this accumulation may happen independently of visualized new activity/lesions on MRI.[31]

Remember that just because a new lesion appears and there is new damage, the patient may not show symptoms. Similarly, new deficits may appear without new lesions due to worsening damage in existing territories.[31]

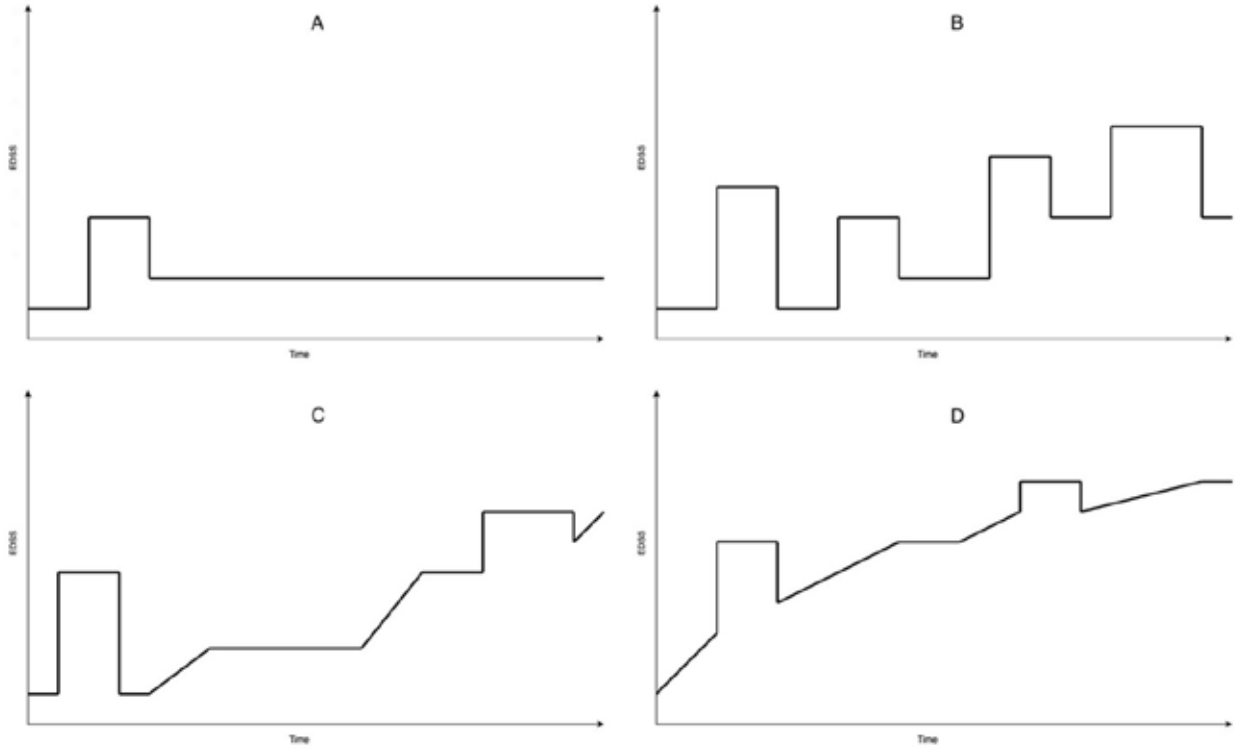
FIGURE 1:
Illustration of disease course for MS diagnoses.

FIGURE 1A:
CIS, in this case with persistent disability.

FIGURE 1B:
RRMS. Note return to baseline for flares 1 and 4, with disability progression for flares 2 and 3.

FIGURE 1C:
SPMS. Note RRMS final peak followed by start of constant disability accumulation. Once SPMS starts, in between flares is only ever worsening or flat.

FIGURE 1D:
PPMS, which starts immediately with constant progression and rapid deterioration.



Differential diagnoses

As would be expected in a condition with such a wide range of symptoms, the list of potential alternative diagnoses is extensive. Many other conditions may cause MRI enhancing lesions with acute deficits, such as tertiary syphilis, human immunodeficiency virus, human T-lymphotropic virus type 1 or Lyme disease.[32,33] Many alternative autoimmune conditions may also mimic this, such as sarcoidosis, lupus of the CNS, Sjögren's syndrome, Behçet's disease or vasculitis of the CNS.[32,34,35] Rarer inflammatory conditions—such as neuromyelitis optica spectrum disorder, acute disseminated encephalomyelitis or myelin oligodendrocyte glycoprotein-related demyelination—are also possible but outside the scope of this review. Nutritional deficits can mimic the neuropathy and myelopathy symptoms of MS, such as B12 and copper deficiency.[32,36,37] Lastly, sudden onset deficits should always raise concern for primary vascular cause, such as primary stroke, as well as rare diagnoses, including cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which causes recurrent strokes with white matter lesions or retinocochleocerebral vasculopathy (Susac syndrome), which may cause sudden onset speech and hearing deficits.[32,38,39] Well-characterized MRI early in the disease course is most essential for effective differential diagnosis of these conditions. Nearly every case of MS will start showing symptoms between the ages of 20 and 50, with a vanishingly small number of cases in patients younger than 10 years old and 3.4% first diagnosed after 50.[1,40] However, due to the quality of new treatments and improved survivability, recent evaluations have shown peak prevalence in the 55–65 age group.[1]

TREATMENT

The top goals in multiple sclerosis are reducing number of flares, reducing severity of flares when they happen, and limiting persistent disability. These will each be discussed in turn. Nearly all medications that decrease frequency of flares also reduce severity, though some medications are used only for acute treatment of a new flare rather than for general prevention.[41]

TABLE 2:

Medications for MS management. Many additional medication trials exist, but only included those currently in phase 3 trials are included here. Many new medications seek to attack the Bruton's tyrosine kinase to reduce B-cells; however, no medication with this mechanism is currently FDA approved.

CLASS	GENERIC	BRAND	ROUTE	RRMS	SPMS	PPMS	2ND LINE
Sphingosine-1 Phosphate Receptor	Fingolimod	Gilenya®	Oral	X	X		
	Ozanimod	Zeposia®	Oral	X	X		
	Ponesimod	Ponvory®	Oral	X	X		
	Siponimod	Mayzent®	Oral	X	X		
Fumarate	Dimethyl Fumarate	Tecfidera®	Oral	X	X		
	Diroximel Fumarate	Vumerity®	Oral	X	X		
	Monomethyl Fumarate	Bafiertam®	Oral	X	X		
Dihydroorotate Dehydrogenase	Teriflunomide	Aubagio®	Oral	X	X		
Adenosine Analogue	Cladribine	Mavenclad®	Oral	X	X		X
Interferon Modulators	Interferon ß-1a	Avonex®	Injection	X	X		
		Rebif®	Injection	X	X		
	Peginterferon ß-1a	Plegridy®	Injection	X	X		
	Interferon ß-1b	Betaseron®	Injection	X	X		
		Extavia®	Injection	X	X		
Myelin Protein Inducers	Glatirimer Acetate	Copaxone®	Injection	X	X		
	Glatirimer Acetate	Glatopa®	Injection	X	X		
CD20 Targeting	Ofatumumab	Kesimpta®	Injection	X	X	X	
	Ocrelizumab	Ocrevus®	Injection	X	X		
	Ublituximab (Phase 3)	TG-1101	Oral	X			
CD52 Targeting	Alemtuzumab	Lemtrada®	Infusion	X	X		X
α4 Integrin Targeting	Natalizumab	Tysabri®	Infusion	X	X		
Antineoplastic DNA Crosslinking	Mitoxantrone	Novantrone®	Infusion	X	X		
Other	Evobrutinib (Phase 3)	M-2591	Oral	X			
	Tolebrutanib (Phase 3)	PRN-2246	Oral	X			
	Fenebrutanib (Phase 3)	RG-7845	Oral	X			

Direct immune modulation takes the form of oral, injectable, and infusion medications, as illustrated in Table 2. Medications targeting the sphingosine-1 phosphate receptors (-imod) work to decrease lymphocyte entry into the CNS by sequestration in the lymph nodes, thus reducing risk of damage.[42] Fumarate compounds are poorly understood but appear to modulate severity of inflammation from immune responses via antioxidative effect and are also commonly used in treatment of other inflammatory conditions like psoriasis.[43] Teriflunomide, similar to the agent leflunomide in rheumatoid arthritis, inhibits the DHO-DH enzyme resulting in impaired B- and T-cell production and suppressing immune response.[44] Cladribine is an adenosine analogue that is cytotoxic in its triphosphorylated form, though it only achieves this active form in cell lines that have low 5′-nucleotidase activity, such as lymphocytes, resulting in differential apoptosis of these immune cells.[45] However, cladribine is not perfectly targeted and thus has high risk of side effects due to cell death in other cell lines, making it a second line agent.[45]

Next, most injectable products focus on immune modulation via interferon beta. IFNß-1a is naturally produced in the human body, while IFNß-1b is a recombinant form of IFNß produced in E. coli. While the exact mechanism is not fully understood, IFNß reduces T-cell activity with emphasis on Th17, reduces pro-inflammatory cytokines and decreases lymphocyte entry into the CNS.[46] Alternatively, glatiramer acetate induces excess production of myelin sheath proteins, reducing damage to the actual myelin sheaths, while modulating immune response.[47]

Lastly, a number of monoclonal antibody products exist, all of which focus on destruction of lymphocytes. Several agents target CD20 which is expressed on B-cells resulting in focal destruction.[48] Another attacks CD52, an antigen present on most immune cells including B-/T-/NK-cells, monocytes, and macrophages.[49] Yet another attacks the α4 subunit of integrins, binding it and thus blocking the crossing of leukocytes through the blood-brain barrier.[50] Lastly, mitoxanantrone, an analogue of doxorubicin, directly attacks the cells via DNA crosslinking with strand breakage, destroying cell replication in immune cells and thus reducing them.[51] As with cladribine, this does result in some damage to other cells lines, resulting in this classification as a second line agent. Efficacy of these treatments shows that, roughly, monoclonal antibody treatments have the highest efficacy, followed by S1P receptor and fumarate drugs, with teriflunomide and the oldest standbys of INFß therapeutics and glatiramer with lowest benefit. This may change once the new oral drugs in Phase 3 trials are approved.

As many of these products diminish immune function, significant risk with infections or reactivation of chronically suppressed diseases is present. Most notably with drugs that block immune entry across the blood-brain barrier, this includes reactivation of the JC virus, resulting in progressive multifocal leukoencephalopathy (PML), which can be devastating to function and require cessation of therapy.[52] This does also include chronic hepatitis B and C reactivation,[53,54] varicella zoster,[55] and HHV-6,[56] among others.

Acute MS flares are treated with immune suppression, typically taking one of three forms. High dose IV/PO steroids were the first treatment identified and work well, however, many patients exist that may not be able to tolerate their side effects.[57] A similar option is use of high dose purified adrenocorticotropic hormone injections that induce the body to secrete steroids directly; however, this is very expensive and many locations do not have access to this therapy.[57] The last option is plasmapheresis which exchanges the plasma in the patient's blood to remove circulating antibodies, cytokines, and inflammatory biomarkers. This does have good evidence but is typically recommended when steroids are not sufficiently treating a flare.[57] IVIG has been trialed in the past but lacks high-quality evidence to support its use.

Outside of treating the underlying cause, medical therapy mainly focuses on treating the effects of MS flares to minimize disability. Optimal treatment for MS patients should include physical therapy to maximize function and accelerate return to maximal baseline.[58] This should also include occupational therapy as progressive accommodations will become necessary as disability accumulates to allow for best function and quality of life.[59] Key disability to watch for includes spastic bladder with bladder infections, loss of bowel control or motility, vertiginous symptoms, fatigue, new chronic pain and paresthesia, sexual functioning, muscular spasticity/tremors/gait problems and concomitant depression. An excellent summary of current medications for these symptoms and their use may be found through the National Multiple Sclerosis Society.[41] Dysphagia in MS is common with prevalence of 43%, requiring use of regular screening and speech-language pathology for evaluation and therapeutic treatment.[60]

Use of OMT for MS patients should focus on restoring as much homeostatic balance as possible. Because mobility is limited in many MS patients, opening the thoracic inlet is a low complexity intervention that can improve biomechanics and respirations along with lymphatic flow. Similarly, sacral rock/sacral wobble can help with parasympathetic tone and aid with GI functioning, which is likely to be affected either primarily by MS damage or secondarily by low gut motility from decreased activity overall.[61] Several pilot studies exist that look at other OMT interventions with improvement in quality of life overall. Additionally, assessment from OMT first principles would imply that use of counterstrain, muscle energy, the Still technique and others should be of use for the muscle tension and spasticity seen from loss of innervation or changes to gait mechanics from MS progression. This is likely to be a fruitful topic of future osteopathic research.

CONCLUSION

Multiple sclerosis is a complex autoimmune disease with each flare carrying the risk of additional disability. Early detection and awareness of the disease in the differential, even for common problems like anxiety/depression, gait changes, and tremor, is key for primary care providers. Imaging early with MRI if you have suspicion of MA is the mainstay for diagnosis, with more specialized labs such as CSF specific oligoclonal bands now playing an increased role in early diagnosis. DO providers should use OMT to help their patients with MS, along with utilizing a multidisciplinary team of physical therapists, occupational therapists, speech language pathologists, and other specialists to aid in maximizing function as the disease progresses. Refer to

neurology early to get new therapeutics initiated. Most importantly as a DO, it is important to provide care to the entire patient, with emotional and spiritual support as necessary as the patient deals with a significant and debilitating diagnosis.

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