

Men With Multiple Sclerosis

Men with MS comprise an unlikely minority with distinct challenges that may also intersect with other signifiers of special populations.

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Multiple sclerosis (MS) is the most common immune-mediated inflammatory demyelinating disease of the central nervous system (CNS). In 2017, an estimated 913,925 adults were

living with MS in the US, and that number continues to grow.¹ The sex-specific incidence of MS has always favored women over men with an estimated female-to-male ratio ranging from 1.4:1 in 1955 to between 2:1 and 3:1 in 2020.^{2,3} Although the basis for this widening gender gap is not fully understood, changes in many factors may contribute, of which reproductive behavior, therapeutic hormone use, or cigarette smoking are just a few.⁴ Regardless of the etiology of this difference, it is important for providers to understand the nuances of caring for men with MS because they present with distinct concerns, offer unique management challenges, and fall within an apparent minority.

Disease Course

The clinical course of MS can vary. Whereas relapsing-remitting MS (RRMS) and primary progressive MS (PPMS) refer, respectively, to a relapsing or progressive course from onset, secondary progressive MS (SPMS) denotes a gradual decline after an initial course of RRMS. Studies show that the female-to-male ratio for RR/SPMS patients is 2.5:1. Male sex, however, is independently associated with a faster progression from RRMS to SPMS. Of note, studies demonstrate that the female-to-male ratio in PPMS is 1.2:1. The etiology of these differences in sex ratio remains unidentified; however, it has been noted that male individuals with PPMS accumulate disability more rapidly than their female counterparts even in the early stages of the disease course.⁵ Alternatively, the difference in sex ratio between relapsing and progressive forms could be a result of differences in the underlying pathophysiology. In RRMS, the main mechanism fueling the disease is thought to be inflammatory, as opposed to PP/SPMS where neurodegeneration is more apparent. Underlying hormonal changes may account for the sex-specific ratios found within each

disease course. Although there is evidence to suggest testosterone may be a protective factor for the development of experimental autoimmune encephalomyelitis (EAE) in animal models, alternative data show that treatment with exogenous testosterone may be toxic for cultured oligodendrocytes. Considering the conflicting evidence, more studies are required to further understand the effects of testosterone and other hormones on autoimmunity and how this might apply to MS.^{4,6-8}

Presenting Symptoms and Disability Progression

Not only are men more likely to have a progressive form of MS, but they are also more likely to have different presenting symptoms and disability progression throughout the course of their disease (See Case Study: Clinical Presentation). In RRMS, men more frequently present with motor symptoms, whereas women more frequently present with optic neuritis.⁴ This is important to note because there is evidence suggesting pyramidal presenting symptoms increase the risk for both disability and transition to SPMS.⁹ More importantly, incomplete recovery from a relapse, regardless of the category of presenting symptom, is a poor prognostic sign in MS and portends a greater

▶▶▶ Case Study: Clinical Presentation

Mr. K is age 37 with a past medical history of depression who presents with a second episode of left leg weakness that occurred 2 years earlier with incomplete recovery, progressive gait decline for the last 15 months, and right-hand numbness and clumsiness that began 1 week ago. Mr. K's brain and cervical spine MRI demonstrates a contrast-enhancing left frontal juxtacortical lesion and a left-sided midcervical cord T2 hyperintense lesion. He and his female partner would like to start a family, but he's worried about his inability to be physically intimate with her. Mr. K's neurologic examination is notable for moderate left leg spasticity, left hip flexor and ankle dorsiflexion weakness, and left leg circumducting gait. He also has decreased sensation and impaired proprioception in the right hand. What is the best way to address all of his concerns?

degree of disability. The Expanded Disability Status Scale (EDSS) is a standardized method to quantify disability over time in people with MS. EDSS scores range from 0, indicating normal neurologic function, to 10, indicating death caused by MS. The EDSS carries more weight for ambulation deficits, often affected by pyramidal symptoms, with a key distinction at EDSS of 6 for the use of a unilateral assistive device.¹⁰ Although a large natural history study of people with MS who did not use disease-modifying treatments (DMTs) found male sex was associated with a shorter time to conversion to SPMS, individuals with PPMS in this study reached an EDSS of 6 several years earlier than those with RRMS, despite parallel development of disability in both men and women with progressive disease.⁴

MRI Characteristics

MRI is an essential diagnostic tool in MS with clear guidelines for the diagnosis of MS in the 2017 McDonald criteria that include MRI findings, clinical symptoms, and cerebrospinal fluid (CSF) analysis results. There are also potential sex-specific aspects of the MRI findings that can be followed to monitor disease activity over time. Early studies showed fewer gadolinium contrast-enhancing (Gd⁺) lesions and more T1 hypointense lesions (also known as “black holes”) on MRIs from men suggesting more axonal loss.¹¹ Larger follow-up studies that controlled for age at onset and type of MS, however, found no sex-specific difference in the number of Gd⁺ lesions or T1 hypointense lesions, although there was significantly more regional atrophy, as measured by normalized gray matter volume, in men compared with women.¹² The most recent study, from 2020, showed significant evidence for clusters of gray matter volume loss in the putamen, precuneus, and medial frontal cortex that were more pronounced in men compared with women. Men were also noted to have more significant thalamic atrophy and cortical thinning compared with women. Although it is not currently standard practice to monitor gray matter atrophy over time as a clinical predictor, it does show promise as a sensitive biomarker for clinical disability progression. These results also support the idea that male sex may confer an increased risk for disability progression.¹³

Choosing Among DMTs

When selecting an appropriate DMT for men with MS, the considerations are largely similar to those when selecting a DMT for women with MS, with only a few notable exceptions (See Case Study: Management). Of the 22 DMTs currently available, all are approved to treat RRMS. Only ocrelizumab is Food and Drug Administration (FDA) approved for the treatment of PPMS.¹⁴ Over a dozen DMTs have been approved for the treatment of SPMS

▶▶▶ Case Study: Management

Mr. K appears to have had presenting motor symptoms, and a clinical course consistent with SPMS with activity. It is important to discuss the implications of this diagnosis and risk of disability progression highlighting the need to start a DMT as soon as possible. It would be prudent to offer a high-efficacy treatment, and ocrelizumab (considering positive trials in RRMS and PPMS) and siponimod (considering a positive trial in SPMS) may be prioritized. In light of Mr. K's intention to begin a family, he may be advised against teriflunomide or cladribine because of risk of teratogenicity potentially transmitted via semen. Another issue to address is sexual dysfunction, focusing on any medications Mr. K may be taking to treat his underlying depression and the psychologic effect of this comorbidity on his sexual function. Referral to a physical therapist or physiatrist and the consideration of a starting dose of baclofen can be recommended to alleviate his moderate left-sided spasticity and prevent contracture.

with activity, defined as having either a clinical relapse or MRI activity during a progressive course of disease. Only siponimod, however, has demonstrated a decreased risk of disability progression in a large randomized clinical trial of patients with SPMS.¹⁵ Notably, no DMTs have been approved for SPMS without activity. The observation that men who have RRMS appear to have a shorter time to conversion to SPMS than women suggests there is a narrower therapeutic window when the majority of FDA-approved DMTs will exert a clear benefit for male individuals, especially if they go on to develop SPMS without activity. Furthermore, because male sex is considered a risk factor for poor prognosis, it is reasonable to offer a high-efficacy DMT as first-line treatment.

Another facet to consider in DMT selection is family planning. There is a wealth of literature outlining the risks and benefits of selecting a DMT for female individuals with MS who are planning to conceive, but what are the implications for male people with MS who may wish to have biologic children? For men with reproductive potential, caution must be used when prescribing 2 of the available DMTs. The first is teriflunomide, which carries a risk of teratogenicity for fetuses exposed in utero, but potentially can also be transmitted via the semen of male individuals. There is evidence, however, to suggest that the risk of teratogenicity through this exposure is minimal. In a registry from Denmark, 18 pregnancies were fathered by male individuals treated with teriflunomide for MS. Of these, 18 (100%) resulted in live births, 17 (94%) were full-term, and only 1 newborn (6%) developed plagiocephaly, a congenital malformation characterized by an asymmetrical cranial distortion.¹⁶ Despite this evidence, in the US it is still recommended that clinicians counsel male patients to

use appropriate contraception and advise against fathering children during treatment with teriflunomide. Cladribine is the second DMT for which caution is warranted because it interferes with DNA synthesis and has the potential to cause fetal harm through this mechanism of action. Men with reproductive potential taking cladribine should be advised to use contraception to prevent pregnancy during the duration of cladribine dosing and for at least 6 months following the last dose in each treatment course.¹⁷

Symptom Management

People with MS may encounter various symptoms throughout their disease course that often diminish their quality of life (See Case Study: Management). Spasticity and ataxia were more often seen in men with relapsing forms of MS, whereas sexual dysfunction was more commonly seen in men with progressive forms of MS.⁴ Here, we highlight those symptoms that are particularly common in men with MS so as to emphasize the approach to treating these symptoms.

Spasticity

Spasticity is a direct result of damaged upper motor neurons in the corticospinal tract that results in increased muscle tone caused by a hyperexcitable stretch reflex, most often in the setting of underlying weakness. Considering the predisposition of men with MS to present with pyramidal symptoms, spasticity is a common symptom with which men with MS struggle. Referrals to physical therapy and rehabilitation medicine play a central role in addressing spasticity in order to expand functional abilities and prevent contracture formation.

Beyond this, several medications can be prescribed to

alleviate spasticity (Table). Baclofen improves spasticity while decreasing the frequency of spasms and clonus. Tizanidine is a short-acting muscle that decreases spasticity and improves muscle tone but has notable side effects including sedation, slowed heart rate, and hypotension. Benzodiazepines promote muscle relaxation, again with potential side effects. Gabapentin decreases spasticity but does not affect clonus or reflexes. Various cannabis-based drugs have also been used to treat spasticity. Nabiximols is an oromucosal cannabis extract shown in clinical trials to have a positive effect on spasticity but is not approved within the US. Noteworthy side effects of nabiximols include dizziness.¹⁸ Botulinum toxin A is another mainstay of treatment that improves spasticity, decreases spasm frequency, and improves muscle tone.

Spasticity refractory to any of the above treatments can be managed effectively with intrathecal baclofen. Individuals must have an intrathecal baclofen test of functional performance. If baclofen is effective, a pump can be placed for titration and continuous delivery at a therapeutic dose. Side effects include drowsiness, dizziness, blurred vision, and dysarthria, and pump maintenance should be handled by a trained provider.¹⁸

Ataxia

Men with MS are reported to experience ataxia more commonly in their MS course than women with MS. Physical therapy can offer different strategies to help individuals learn to function with ataxia. Balance-specific exercises involving somatosensory and motor strategy facilitation are often used. Additionally, exercises targeting core strength and lumbar stabilization can also improve imbal-

TABLE. TREATMENT OF SPASTICITY IN MULTIPLE SCLEROSIS

Drug	Dose	Notable side effects	Mechanism
Baclofen ^a	Starting dose 10 mg/day, can titrate up to 60 mg/day in divided doses; maximum 100 mg/day	Sedation, dizziness, weakness, blurred vision	Gamma-aminobutyric acid (GABA) analogue inhibits motoneuron and interneurons in stretch reflex pathway
Tizanidine	Starting dose 2 mg/day, can titrate up to 36 mg/day in divided doses	Sedation, reduced heart rate, hypotension, transiently elevated liver enzymes	Short-acting muscle relaxant stimulates central α_2 -adrenergic receptors, reducing excitatory neurotransmitter release at spinal and supraspinal levels
Diazepam	Starting dose 5 mg/day can titrate up to 15-30 mg/day	Sedation	Enhances GABA effects to inhibit neuronal activity and promote muscle relaxation
Gabapentin	Starting dose 300 mg/day, can titrate up to 3,600 mg/day	Drowsiness, dizziness	GABAergic agonist at neocortical GABA receptors
Nabiximols ^b	Up to 12 sprays/day, delivered oromucosally	Dizziness	Cannabis extract containing Δ^9 -tetra-hydrocannabinol (THC), cannabidiol (CBD), and other cannabinoids
Botulinum toxin A	Doses vary based on muscle group	Injection site reactions, weakness	Inhibits muscle contraction by blocking acetylcholine release at the neuromuscular junction

^aMay be used intrathecally at a titrated therapeutic dose for refractory spasticity. ^bNot approved for use in the US.

ance. Nonpharmacologic treatments are the mainstay of therapy for ataxia. On the other hand, pharmacologic treatment has largely been deemed ineffective, including isoniazid, propranolol, and levetiracetam demonstrating no significant effects on ataxia. Paroxysmal ataxia, however, may respond to pharmacologic treatment with low doses of anticonvulsants (eg, carbamazepine), which have been successful in treating other paroxysmal symptoms in people with MS. Dosing begins at 100 mg extended release every 12 hours and can be increased up to 200 mg extended release twice a day if needed. Side effects include dizziness, drowsiness, and paresthesias.¹⁹

Sexual Dysfunction

The most common presentations of sexual dysfunction in men with MS are erectile dysfunction, decreased libido, and anorgasmia, some of which may be a direct result of demyelinating lesions within the CNS. Preliminary data suggest that erectile dysfunction correlates with pontine atrophy or spinal cord lesions and anorgasmia correlates with brainstem lesions and total lesion load in men with MS.¹⁶ Although sexual dysfunction in MS is likely neurogenic in etiology, it is important to have an open dialogue to identify any possible alternative etiologies. Often, medications prescribed for other symptoms may interfere with sexual function. Among these are selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors for depression, amantadine and amphetamines for fatigue, baclofen for spasticity, and tricyclic antidepressants for pain. Reviewing a patient's medication list should be the first step in addressing sexual dysfunction. Second, underlying medical comorbidities such as diabetes mellitus or hyperlipidemia can contribute to sexual dysfunction as an early manifestation of atherosclerosis. If a neurogenic etiology seems unlikely, hormone levels should be measured to evaluate for underlying hypogonadism. Finally, the psychologic burden of an MS diagnosis can negatively affect sexual function. For treatment, phosphodiesterase-5 (PDE5) inhibitors can be prescribed to manage neurogenic erectile dysfunction. Side effects of PDE5 inhibitors include headache, flushing, nasal congestion, and rarely, blue vision. These agents are contraindicated in anyone taking nitrates for angina. Referral to a mental health provider can also be incredibly helpful in tackling sexual dysfunction from a psychosocial perspective.²⁰

Conclusions

It is unusual for men, as a group, to be considered a minority or underserved population, and men with MS present distinct challenges for both patients and the providers caring for them. For male patients, having what is typically thought of as a "female disease" may increase

challenges associated with diagnosis, acceptance, and treatment adherence. Being a man with MS may also intersect with other signifiers of special populations discussed in this issue, such as Black or Hispanic/Latinx men with MS, or men with MS who are over age 55. As such, a personalized treatment plan, tailored to the needs of each individual patient, is essential. ■

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Disclosures

NVS & SK have disclosures at www.practicalneurology.com