Sleep in Patients With Multiple Sclerosis

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Abstract Sleep disorders are highly prevalent and consequential comorbidities among patients with multiple sclerosis (MS) yet remain notably under-recognized in clinical practice. Improved understanding of the specific clinical features of MS that may influence patients' risk for sleep disturbances or response to treatment could enhance opportunities to improve functional status and quality of life in persons with MS. This review aims to discuss current prevalence estimates, disease-specific risk factors, and consequences of the most common sleep disorders experienced by patients with multiple sclerosis. Suggested methods to address MS-specific symptoms and comorbidities that may influence diagnostic and treatment strategies for these conditions are also highlighted.

Keywords Multiple sclerosis · MS · Fatigue · Sleepiness · Insomnia · Sleep-disordered breathing · Obstructive sleep apnea · OSA · Central sleep apnea · CSA · Restless legs syndrome · RLS · Willis-Ekbom Disease (WED) · Brainstem · Spinal cord · Hypnotic · Diphenhydramine · Depression · Pain · Spasticity

Introduction

Multiple sclerosis (MS) is an autoimmune disease that results in inflammation, myelin destruction, and axonal degeneration of the brain, spinal cord, and optic nerves. According to esti-

mates from the National Multiple Sclerosis Society, MS affects nearly half a million people in the USA and over 2.5 million people worldwide. Approximately 85 % of patients will initially present with a relapsing-remitting course (relapsing-remitting MS), characterized by clearly defined episodes of neurological dysfunction (relapses, exacerbations, or “flare-ups”) separated by periods of relative clinical stability (remissions). If left untreated, the majority patients with relapsing-remitting MS will eventually develop a gradual deterioration of neurologic function, usually in the form of paraparesis, hemiparesis, or dementia (secondary-progressive MS). A primary-progressive subtype occurs in a smaller percentage of patients, characterized by a slow deterioration in neurologic function from onset, without distinct relapses.

In addition to neurological morbidity, MS is associated with a disproportionately high prevalence of sleep disorders. In particular, sleep-disordered breathing, restless legs syndrome, and chronic insomnia are frequent contributors to poor functional outcomes in MS, as well as fatigue—one of the most common and debilitating symptoms experienced by MS patients [1, 2, 3–9]. Multiple sclerosis patients with suspected sleep problems are more likely than controls to emphasize problematic fatigue, tiredness, and lack of energy, as opposed to sleepiness [10]. Timely diagnosis and treatment of sleep disorders in MS patients offers a key opportunity to reduce fatigue, optimize general health, and enhance quality of life in this population, but an in-depth knowledge of MS-related symptoms and pathology that may influence this approach is necessary for optimal management.

Insomnia

The International Classification of Sleep Disorders Diagnostic Manual Third Edition (ICSD-3) defines insomnia as “a persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite the opportunity and

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circumstances for sleep, and results in some form of daytime impairment.” [11] Impairments in daytime functioning related to insomnia are similar to many of the chronic symptoms experienced by MS patients and include fatigue, impaired concentration or memory, mood disturbances, excessive daytime sleepiness, behavioral problems, reduced motivation or energy, impaired social, family, academic, or occupational performance, proneness to errors, and concerns or dissatisfaction with sleep [11]. Also relevant to MS, the ICSD allows for specific clinical and pathophysiological subtypes of insomnia—including insomnia due to a medical condition or another mental disorder. Within this framework, at least 30–40 % of patients with MS are at increased risk for insomnia [1•, 2•, 12, 13].

Common triggers for insomnia in MS include chronic pain, urinary frequency, spasticity, anxiety, and depression. In a recent survey, a study of 195 clinically definite MS patients followed in a tertiary MS center, 46 % were found to have moderate to severe clinical insomnia as defined by the Insomnia Severity Index (ISI) [1•]. Furthermore, 85 % of patients studied endorsed at least one nocturnal symptom (pain, tingling, spasticity, feelings of restlessness, urinary urgency, anxiety, an inability to shut off the mind, or muscle twitching) to interfere with their ability to get a good night’s sleep, with 54 % of patients endorsing three or more of these symptoms. In this study, the number of nocturnal symptoms emerged as a strong predictor of ISI score, adjusting for other important clinical confounds [1•]. Similarly, in an anonymous survey study of 2375 community-dwelling adults with self-identified MS [2•], 31 % of those surveyed met ISI criteria for moderate to severe insomnia, while only 10 % of these patients endorsed a formal diagnosis of insomnia by a physician, highlighting a large discrepancy between insomnia prevalence and recognition in this population.

Given these findings, it is recommended that all MS patients who endorse daytime impairment or express concerns about prolonged sleep latency, fragmented sleep, unrefreshing sleep, or early terminal awakenings be evaluated for insomnia. This can be accomplished with a systematic approach that integrates a thorough assessment of MS-specific comorbidities and symptoms with the sleep history. If not initially volunteered, a thorough review of daytime symptoms should also be conducted to characterize any associated daytime distress or impairment. As with non-MS patients, further inquiries should be directed toward external factors or habits that may interfere with sleep hygiene.

A thorough medication assessment (that includes over-the-counter medications) is also a key component of the insomnia assessment, with special focus on centrally acting agents such as selective serotonin reuptake inhibitors, stimulants and wake-promoting agents, and over-the-counter antihistamines, as these therapies are frequently used in patients with MS [13, 14]. Corticosteroids, which are typically used for short periods to treat MS exacerbations may also contribute to symptoms of insomnia in the short term (Table 1) [15]. Patients who use beta-interferon disease-modifying therapies for their MS are also at increased risk for sleep disturbances. This risk may be increased in patients who administer their medication during the evening hours [16].

Treatment of insomnia in patients with MS should start with amelioration of any precipitating causes, either prior to or in tandem with first-line therapies. Medications or substances that may contribute to insomnia should be minimized, if possible. Wake-promoting agents and stimulants should be reserved for the early hours of the day. Chronic symptoms such as nocturnal spasticity, neuropathic pain, or nocturia should be addressed. If neuropathic pain or spasticity are contributing factors, effective medications that also have sedating

Table 1 Factors that may exacerbate or influence vulnerability to common sleep disorders in MS patients

Insomnia	Sleep-disordered breathing	Restless legs syndrome
Medications	Medications	Medications/substances
- Corticosteroids	- Opioids	- 1st-generation antihistamines
- Stimulants/wake-promoting agents	- Benzodiazepines	- Dopamine antagonists
- SSRI’s	- Antispasmodics	- Lithium
- Beta-interferons	Brainstem dysfunction	- Alcohol
Depression/anxiety	Increased disability	- Tobacco
Pain	Progressive MS subtype	- Caffeine
Spasticity	General risk factors	Primary progressive MS
Nocturia	- Age >50 years	Increased disability
Other sleep disorders	- Obesity	Cervical spinal cord lesions
- Sleep-disordered breathing	- Increased neck circumference	Iron deficiency
- Restless legs syndrome	- Crowded oropharyngeal outlet	Family history
- Periodic leg movements of sleep	- Retrognathia/micrognathia	
Poor sleep hygiene		

properties (such as tricyclic antidepressants or antispasmodics, respectively) may be reasonable first options.

If comorbid symptoms are not significant contributing factors, psychological and behavioral therapies should be considered. Cognitive behavioral therapy for insomnia (CBT-I) aims to target maladaptive thoughts and behaviors that can perpetuate insomnia. The benefits of CBT-I are well studied [17–20], making it an ideal treatment approach for patients with MS, particularly in patients with comorbid depression. Depression affects approximately 50 % of MS patients at some point during the disease course and shares a bidirectional relationship with insomnia [21]. Recent data show that rates of insomnia are higher in depressed MS patients than non-depressed MS patients and suggest that insomnia management should commence beyond the treatment of the underlying comorbid psychiatric disorder [22]. Cognitive behavioral therapy may also be an effective treatment modality for MS-related fatigue [23].

For patients who are not responsive to more conservative strategies, pharmacological therapies may be necessary. In this case, as with non-MS patients, selection of an appropriate agent should be guided in part by the drug's half-life, as well as the patient's intolerances and comorbidities. Benzodiazepine receptor agonists, melatonin receptor agonists, and newer orexin receptor antagonists are all potentially useful therapies for MS patients with insomnia. Although the affordability and widespread availability of over-the-counter antihistamine-containing products make them a popular treatment for insomnia, it is recommended that these agents be avoided in patients with MS. Recent evidence suggests that nocturnal antihistamine use is independently associated with increased daytime fatigue in MS patients [13].

Sleep-Disordered Breathing

Obstructive sleep apnea (OSA) is characterized by repeated episodes of upper airway obstruction and hypoxia during sleep. According to recent reports, up to 21 % of MS patients may carry a formal diagnosis of OSA [1•]. Furthermore, a much higher proportion of MS patients (38–56 %) may be at risk for OSA, based on two recently published studies [1•, 2•] that evaluated MS patients with a validated OSA screening tool [24].

While reasons behind this relationship require further exploration, underlying neuroanatomical and immunological features of MS may be contributing factors. Central nervous system disorders that disrupt brainstem pathways responsible for the maintenance of nocturnal airway patency have the potential to impair nocturnal respiration [25–28]. In a previous study, MS subjects referred for overnight polysomnography—and particularly those patients with MRI evidence of brainstem involvement—were found to have more severe OSA than control subjects without MS [29•]. Among the MS subjects in this study, progressive subtypes of MS and MS immunomodulatory therapy use also

predicted apnea severity. Immunomodulatory therapy use in particular emerged as a strong predictor of *reduced* apnea severity.

Central nervous disorders that affect brainstem respiratory generators, including MS, may also be associated with an increased risk for central sleep apnea [28, 29•]. In addition to alterations in control of nocturnal airway patency, patients with evidence of brainstem dysfunction may be more vulnerable to impairments in autonomic nocturnal respiratory control, due to damage of key brainstem respiratory centers located in the pons and medulla [30, 31].

Multiple sclerosis patients who have a diagnosis of OSA and those at elevated risk for OSA have increased fatigue levels compared to undiagnosed or low-risk patients [1•, 2•, 3, 4]. Obstructive sleep apnea is also a predictor of diminished quality life in MS [6], and preliminary research suggests that apnea severity may correlate with cognitive impairment in MS [32].

Given the detrimental effects of OSA in this population, early identification and treatment of sleep-disordered breathing is critical. All MS patients should be asked about common symptoms of OSA, such as snoring, gasping or choking upon awakening, non-restorative sleep, excessive daytime hypersomnolence or fatigue, cognitive disturbances, or nighttime arousals. Clinical signs of brainstem dysfunction (such as dysarthria or dysphagia) or the presence of brainstem lesions on MRI should also alert clinicians to consider full-night polysomnogram (PSG) to rule out OSA or CSA.

Positive airway pressure therapy improves fatigue as well as sleepiness in non-MS patients [33] and is the gold standard treatment for MS patients with OSA. In select cases, oral appliances may also be considered. Although surgical approaches for OSA are also available, the expected neurological dysfunction as a possible exacerbating factor of OSA among MS patients usually makes surgery less attractive as a definitive treatment.

Restless Legs Syndrome

Restless legs syndrome (RLS, also known as Willis-Ekbom disease) is characterized by an urge to move the legs, often accompanied with restlessness or an uncomfortable sensation that is exacerbated by rest and inactivity, has a tendency to occur in the evening or before bedtime, and is relieved with movement [34, 35]. This condition affects approximately 10 % of the general population [36]. Restless legs syndrome is classified as idiopathic or primary if no other cause can be identified, or secondary (symptomatic) if associated with another comorbid condition such as MS.

While the exact mechanism underlying primary RLS is unknown, dysfunction of brain circuits that require the neurotransmitter dopamine have been implicated in the pathogenesis of RLS [37]. As iron is a component of the enzyme

tyrosine dehydroxylase (responsible for the rate-limiting step in dopamine synthesis), it seems intuitive that impaired iron metabolism is also thought to contribute to the pathogenesis of RLS. This hypothesis is supported clinically by lower serum and CSF ferritin levels in patients with idiopathic RLS [38] and low brain iron stores in RLS patients in MRI and autopsy studies [39, 40]. A genetic etiology for RLS is favored for younger patients who experience signs of idiopathic RLS before age 40 [41–43].

Other investigators suggest that RLS may be caused by dysfunction of downstream dopaminergic pathways, namely diencephalospinal and reticulospinal pathways [44] that project from the brain to the spinal cord. These pathways are thought to be responsible for the suppression of excessive sensory inputs and autonomic output and are susceptible to damage from a variety of pathologic processes, which may explain the increased prevalence of RLS in MS and other conditions that can affect the spinal cord [45–47]. Restless legs syndrome is approximately three times more common in MS as compared to the general population [45, 48, 49]. In a pivotal study of prospectively surveyed MS subjects, 32 % met criteria for RLS. Clinical features of MS that predicted RLS in this study included primary progressive MS subtype and higher level of neurological disability [45]. Similar prevalence estimates were identified in two recent survey studies of MS patients [1•, 2•]. In a multicenter case-control study of 861 MS subjects [50], 19 % experienced frequent RLS symptoms at least twice per week (lower frequencies were not included in this estimate). In this study, RLS was again more common in patients with increased disability. Studies of radiographic correlates of RLS in MS subjects suggest that cervical cord damage may also be an independent risk factor for RLS, highlighting a potentially important relationship between RLS and dopaminergic spinal cord projections [46, 50].

Patients with RLS most often describe an uncomfortable sensation in their legs (or less frequently, the arms) that interferes with their ability to rest [34]. Many descriptors have been used to define this sensation, including creeping, crawling, itching, burning, tightening, or tingling. Others will describe this sensation as painful [51]. While heterogeneity in descriptions is common, the diagnosis of RLS requires that the symptoms of discomfort are not better accounted for by another medical or behavioral condition. The differential diagnosis for RLS is broad and includes several other symptoms that may be particularly common in MS, such as cramping, spasticity, or neuropathic pain [52]. While distinguishing between these symptoms can be challenging, reports of a circadian predilection and relief with movement is more suggestive of RLS, while painful, involuntary muscle contractions, or symptoms not relieved by movement may be more suggestive of spasticity or neuropathic pain, respectively.

To date, there are no MS-specific treatment guidelines for the management of RLS, but in the author's experience, treatment should be individualized and tailored to the patient's symptoms and other comorbid conditions whenever possible. As in non-MS patients, the treatment of RLS in MS patients ranges from conservative to pharmacological approaches, which can be employed alone or in combination. Conservative approaches include the removal of various agents known to exacerbate RLS such as alcohol, tobacco, and caffeine. Serum ferritin levels should be assessed and iron supplementation should be implemented for ferritin levels less than 50 ng/ml. An evaluation of the patient's medication list is also recommended, with minimization of medications that can cause or worsen RLS such as dopamine antagonists, lithium, selective serotonin reuptake inhibitors, and tricyclic antidepressants. Multiple sclerosis patients should also be screened for antihistamine use, as the use of over-the-counter antihistamine hypnotic use is common in MS and is associated with a higher prevalence of RLS [13].

Dopamine agonists (rotigotine, pramipexole, and ropinirole) and the alpha-2-delta ligand gabapentin enacarbil are the only FDA-approved first-line medications for moderate to severe RLS and are reasonable pharmacologic choices for MS patients with RLS [53, 54]. Common side effects of dopaminergic agents—including nausea, hypotension, hallucinations, dyskinesias, and increased risks of impulse control behaviors—should be discussed with the patient before initiation and should be reconsidered in MS patients with concomitant autonomic dysfunction. Patients should also be followed closely for signs of augmentation, a phenomenon that involves worsening of RLS symptoms earlier in the day with geographic spread to other body regions over time [55]. If dopaminergic agents are inappropriate or poorly tolerated, other drug classes should be considered.

Several anticonvulsants, including gabapentin, carbamazepine, and most recently pregabalin [56•], are reasonable pharmacologic alternatives for patients who cannot tolerate or have failed dopaminergic agents and may be particularly ideal choices for MS patients who are more likely to suffer from concomitant conditions such as neuropathic pain or seizures.

Benzodiazepines have also demonstrated therapeutic effect in RLS, although data supporting these agents are less robust and confounded by other benzodiazepine effects on sleep [57]. Given the long half-life of some benzodiazepines (which may cause next day carry-over effects), their use is generally not recommended in MS patients who already suffer from daytime fatigue. Various opioid agents, including oxycodone and methadone, may be of benefit in selected individuals whose RLS symptoms may be refractory to first-line agents, but the addiction potential and side effect profile associated with opioids limit their use, and opioids are discouraged in MS patients.

Conclusion

Insomnia, sleep-disordered breathing, and restless legs syndrome are common and yet frequently under-recognized conditions in patients with MS. Providers caring for MS patients should maintain a low threshold to screen for sleep disorders, given their high prevalence and serious consequences. Increased efforts are needed to identify sleep disorders among MS patients who are most vulnerable, and a systematic approach is necessary to distinguish sleep disturbances from other comorbid conditions in MS. Improved recognition and treatment of sleep disturbances have the potential to significantly improve MS patients' functional outcomes and quality of life.

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Compliance With Ethics Guidelines

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