Helping MS Patients Achieve

A sleep specialist reviews the literature on the causes of and treatments for the multitude of sleep disorders that affect MS patients.

By Antonio Culebras, MD
Patients suffering from clinically active multiple sclerosis (MS) experience generalized daytime fatigue at levels far exceeding those of the general population. Typically, fatigue is among their top three complaints about living with MS. In addition to fatigue, a variety of concomitant sleep disorders are also occurring in MS patients. In fact, fatigue may be an indicator of underlying sleep dysfunction that should warrant further investigation with polysomnography and other sleep testing methods. MS patients more frequently report difficulty falling asleep, restless sleep, nonrestorative sleep and early morning awakening than controls.¹ The number of nocturnal awakenings and number of daytime naps are increased in MS. Frequent causes of awakening are bladder problems, muscle spasms, anxiety, depression and periodic limb movements. This article will review the presentation and management options available to help MS patients minimize the effects of sleep-related disorders stemming from their condition.

**History and Prevalence**

European reports published in the first half of the 20th century cite cases of MS associated with sleep attacks variously termed as narcolepsy, drowsiness and deep sleep.² In 1949 the association between MS and narcolepsy was mentioned in a review and case presentations of narcolepsy.³ Subsequently, cases of narcolepsy-cataplexy and MS⁴ and of familial MS with narcolepsy-cataplexy were reported.⁵ Based on the presence of DR2 histocompatibility antigen in two patients with narcolep-
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sy and MS, Younger and colleagues suggested a common inheritance for both conditions.6

Other authors have indicated that sleep disturbance is relatively common in MS, suggesting a multifactorial etiology that ranges from depression to lesion site.9,10 A polysomnographic study of 25 patients with definite MS showed significantly reduced sleep efficiency and more awakenings during sleep.10 Periodic leg movements were found in 36 percent of patients compared to eight percent in controls. Central sleep apnea was found in two patients. MRI of the brain showed a greater load of lesions in cerebellum and brainstem in patients with periodic leg movements.

The prevalence of nocturnal sleep difficulties assessed by the Minnesota Multiphasic Personality Inventory in patients with mild definite MS was 25.2 percent.12 In another study, the prevalence of daytime sleep attacks was 77 percent and prevalence of cataplectic attacks was 56 percent.13 In this series, no objective evidence of narcolepsy or excessive sleepiness was obtained using polygraphic evaluation, suggesting a major discordance between sleep symptoms and objective findings in patients with MS. The prevalence of sleep disorders in MS, according to a study conducted in 100 patients in Spain, was 36 percent.14 In this study, depression was the only variable independently related with the presence of sleep disorders in MS patients.

Clinical Manifestations

Excessive somnolence and inappropriate daytime sleep can occur in patients with MS. In some individuals excessive daytime sleepiness and sleep attacks occur in conjunction with cataplexy, sleep paralysis and hypnagogic hallucinations, leading to a diagnosis of narcolepsy. Excessive somnolence and other narcoleptic symptoms may appear before11 or after the onset of MS,16 and the age of presentation has varied widely. In some patients, a remitting course of the symptoms of narcolepsy has suggested MS as the cause of the sleep disorder. In older reports, laboratory confirmation of narcolepsy is lacking, or if present, has failed to confirm a diagnosis of narcolepsy.11

In a review of the symptomatic narcolepsies, Autret and colleagues indicate that nine cases of probable or certain MS associated with narcolepsy have been published.17 In one more recent case report, REM sleep behavior disorder was the heralding manifestation of MS; the patient had MRI hyperintensities in the pons and in a periventricular location.18 In another case report, a 51-year-old woman developed nocturnal manifestations suggestive of REM sleep behavior disorder following an acute attack of MS. The patient had no recall of dreams associated with bizarre nocturnal behavior. However, the polysomnogram showed REM sleep without atonia. MRI of the brain showed increased T2 signal in the dorsal pons suggestive of demyelination. The nocturnal events responded to the administration of clonazepam at bedtime.19

Chronic fatigue is common in MS and may confound the interpretation of sleep disturbances. Patients with multiple sclerosis report difficulty falling asleep, restless sleep, non-restorative sleep, and early morning awakenings more frequently than control subjects. In a study of 28 consecutive patients with multiple sclerosis, 15 patients (54 percent) reported sleep-related problems.20 These included difficulty initiating or maintaining sleep, frequent awakenings due to leg spasms, habitual snoring and nocturia. Three patients showed episodes of nocturnal desaturation, and two had sleep apnea syndrome. Magnetic resonance imaging of the brain showed abnormalities in 20 of 22 cases studied. Sleep laboratory evaluations in patients with MS have revealed that sleep disturbance is common in these patients and that its etiology involves both physical and psychological features.21

In another study of fatigue and sleep disturbances in 30 patients with MS, the authors found a significant correlation between fatigue and interrupted sleep or abnormal sleep cycles.22 Words of caution have been raised by others suggesting that patients with MS do not often distinguish between fatigue and sleepiness and, therefore, stimulant medication may not be indicated.23 A depressive mood is the main factor influencing quality of life in patients with MS.24

Sleep disorders may be suspected by patient testimony, but confirmation in a sleep laboratory is recommended. Nocturnal polysomnography identifies sleep disruption, as well as abnormal motor behaviors, and daytime multiple latency tests measure daytime sleepiness. Narcolepsy is diagnosed when REM sleep appears in two or more segments of the multiple sleep latency test with short-onset REM sleep latency and the onset of daytime sleep demonstrates a latency of eight minutes or less.25

In a prospective study of 156 patients with MS,26 the authors found that 51 subjects (32.7 percent, mean age 43.8 +/- 12.8) met the criteria for restless legs syndrome (RLS). In a small group (8.5 percent), RLS preceded clinical MS onset, whereas in the remaining cases RLS was followed by or occurred simultaneously with the clinical onset of MS. No significant differences were found in MS duration, gender, and sleep habits between both groups of patients. The primary progressive course of MS was more represented in the RLS group and had a higher disability score (Expanded Disability Status Scale score). The authors concluded that RLS is a common finding in MS patients and should be considered among the symptomatic RLS forms. Furthermore, RLS was also associated with higher disability.

Pathogenesis and Pathophysiology

Based on the remitting course of sleep attacks exhibited by some patients with MS, the hypothesis has been advanced that MS may cause symptomatic narcolepsy.6 Castaigne and
Escourrolle observed midbrain plaques in the hypothalamic periventricular region of a patient with bouts of sleep and MS. Later, Auer and colleagues reported plaques of MS in the medulla oblongata of two patients who died in their sleep. The lesions incompletely involved the medullary reticular formation controlling automatic breathing leading the authors to hypothesize that the patients died as a result of sleep apnea.

Neuropathologic lesions in patients with MS and narcolepsy are an often cited but rarely observed occurrence as estimated by literature reports. The etiology of both MS and narcolepsy remains partially unknown. The susceptibility to MS is coded by genes within or close to the human leukocyte antigen DR-DQ subregion. Patients with narcolepsy exhibit the highest known association between the human leukocyte antigen DR2 and DQw1 antigens and a disease entity, estimated at 95 percent or above. This coincidence of genetic susceptibility between MS and narcolepsy has led some authors to postulate a common immunogenetic etiology that remains to be demonstrated. Given the common genetic linkage between MS and narcolepsy, Rumbach and colleagues measured the daytime sleep latency in patients with MS and failed to observe a clear difference in sleep latencies between DR2-positive patients and controls, suggesting that by themselves the genes coding for human leukocyte antigen DR2 and DQw1 are not sufficient to cause sleep alteration. Autret and colleagues speculate that latent narcolepsy may also be triggered by a nonspecific inflammatory reaction associated with MS.

Nonetheless, the association between MS and sleep disturbance is higher than expected, and other pathogenetic mechanisms have been investigated. Clark and colleagues found a positive correlation (25.2 percent) between MS, depression, sleep disturbance, and lesions in the supplementary motor areas identified by MRI, suggesting that the motor lesions triggered periodic limb movements during sleep resulting in sleep interruptions and depression. Others have found that MS patients engage in more daytime napping than control subjects (53 percent versus 21 percent of controls), indicating bladder problems with nocturnal and early morning awakenings as common causes of sleep alteration. Two cases of intractable hiccups and sleep apnea syndrome with lesions detected by MRI in the tegmentum of the medulla suggest a pathogenetic correlation between anatomic location and clinical manifestations. The authors indicate that development of intractable hiccups should suggest the associated presence of...
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A variety of underlying physical and emotional factors (bladder problems, spasticity, muscle spasms, periodic leg movements, depression, and anxiety) that converge to disturb nocturnal sleep in patients with MS should be considered. Excessive daytime somnolence in MS may be secondary to nocturnal disruption and nonrestorative sleep, and is likely amenable to proper management.

Diagnosis and Management

Narcolepsy-cataplexy should be distinguished from other sleep disturbances in patients with MS. Fatigue is a common symptom in MS that may be confused with or contribute to disordered sleep. A variety of underlying physical and emotional factors (bladder problems, spasticity, muscle spasms, periodic leg movements, depression, and anxiety) that converge to disturb nocturnal sleep in patients with MS should be considered. Excessive daytime somnolence in MS may be secondary to nocturnal disruption and nonrestorative sleep, and is likely amenable to proper management.

Diagnostic criteria for MS serve to identify patients with this condition, whereas polysomnography and multiple sleep latency testing are required to distinguish narcolepsy from other causes of excessive daytime sleepiness. MRI of the brain can exceptionally reveal a plaque of demyelination in the hypothalamic area, as observed in a patient with MS exacerbation who developed acute hypersomnia and had undetectable hypocretin in CSF. Nocturnal polysomnography identifies sleep disruption, and daytime multiple latency tests measure daytime sleepiness in MS patients. Narcolepsy is diagnosed when REM sleep appears in two or more segments of the multiple sleep latency test with short-onset REM sleep latency, and the onset of daytime sleep demonstrates a latency of eight minutes or less. Human leukocyte antigen typing demonstrates DR2 positivity in 50 to 60 percent of MS patients.

Sleep disturbance in MS is multifactorial, involving physical and emotional features. Bladder problems, spasticity, periodic limb movements, and sleep disorders may cause or contribute to sleep disturbance in MS. The human leukocyte antigen DR2 histocompatibility antigen underlies both MS and narcolepsy, providing strong support for a common inheritance.

Antidepressant medication has been suggested for the treatment of sleep disorders in MS. Clonazepam has been advocated for the treatment of periodic limb movements in MS, and amantadine has been suggested for the alleviation of chronic fatigue in these patients. REM sleep behavior disorder in a patient with MS responded to the administration of clonazepam 0.25mg at bedtime. The safety and efficacy of
modafinil was recently assessed in a single-blind, pilot study involving 72 MS patients. The results suggested that 200mg/day of modafinil significantly improved fatigue and was well tolerated by patients.46 However, a more recent double-blind, placebo-controlled, parallel group study of modafinil, up to 400mg/day, in 115 patients with MS showed no improvement of fatigue. The primary outcome variable was the change of the Modified Fatigue Impact Scale.47

Increased evening wakefulness has been reported by patients with MS treated with selegiline.48 Some authors have reported regression of symptoms of sleep disturbance with dexamethasone49 or prednisolone therapy.50 Sleep paralysis in a 40-year-old woman with remitting-progressive MS disappeared with weak electromagnetic field treatments delivered extracerebrally one to two times per week over a period of three weeks.51 Using weak electromagnetic field treatments in patients with MS, the same author52 reported restoration of dream recall in four patients, suggesting an improvement in REM sleep generation, and attenuation of suicidal behavior in three additional patients,53 which he attributed to improved mental depression as a result of increased serotonin neurotransmission and restoration of circadian melatonin secretion. There is also a report of resolution of partial cataplexy in a 51-year-old man with chronic progressive MS three weeks after the application of picotesla electromagnetic fields.54

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