Multiple sclerosis (MS) is a chronic inflammatory disease mediated by immune cells that promote demyelination, gliosis, and neuroaxonal degeneration in the brain and spinal cord and that ultimately may lead to a neurodegenerative process. Both genetic and environmental factors may trigger the immune dysregulation characteristic of this disease, but the exact cause remains unclear. Approximately 2.5 million individuals worldwide are affected by MS. Prevalence is highest in higher latitude countries (far from the equator), such as northern Europe, southern Australia, and the middle of North America. Multiple sclerosis is a principal cause of disability in young adults. Average age at disease onset is 30 years, and it affects more women than men (2:1). Clinical presentation and progression of the disease vary according to the affected location in the central nervous system. Common initial symptoms are fatigue, paresthesia, weakness, diplopia, vertigo, unilateral painful loss of vision, and ataxia. Among other symptoms reported, sleep disorders are a big concern. Herein we describe an atypical case of a woman presenting with a rapid eye movement sleep behavior disorder (RBD) as the initial manifestation of MS. Ethics approval was not required from the institutional review board because this is a case report. Written informed consent was obtained from the patient for the publication of this article.

**Case Presentation**

A 38-year-old woman presented to the neurology service with a 1-year history of frequent episodic movements during sleep. Her husband noted that during sleep the patient presents somnolocquy and that from 2 to 4 AM she has sudden strong movements in all her extremities, which have generated bodily harm to herself or to him. The patient is not conscious of these movements, but when her husband wakes her up she remembers exactly what she was dreaming. Dream content was usually scenes that generated terror, such as those from horror movies previously seen. She had consulted many physicians but had no specific diagnosis or treatment. She additionally noted that in the past 3 months she has had occasional paresthesia in her hands and feet and...
certain difficulties performing fine movements of her fingers, with no weakness. She denies having constipation or incontinence, speech disturbances, swallowing problems, and mood alterations.

She did not present any relevant medical history. She was taking oral contraceptives and denied taking any other medications. She denied smoking and did not present any relevant family history of disease. At neurologic examination she was alert and oriented, with no speech impairment. Her cranial nerves did not show any alterations. Results of motor and sensory examinations were normal in all four extremities. Coordination and gait were normal.

An RBD was considered, and a polysomnographic recording that was performed at another institution confirmed this diagnosis by showing electromyographic activity with excessive twitching observed in the tibialis anterior muscle and the flexor muscles of the hand in rapid eye movement (REM) sleep. However, no reported movements were seen during REM sleep. Other sleep disorders, such as parasomnias and obstructive sleep apnea (her reported apnea-hypopnea index was 1.4 per hour of sleep), were ruled out. She had normal levels of thyrotropin and vitamin B₁₂; results of anti-nuclear antibody, anti–double-stranded DNA, Venereal Disease Research Laboratory, human T-lymphotropic virus type 1, and human immunodeficiency virus virus testing were negative. Brain magnetic resonance imaging was performed (Figure 1) and revealed multiple perpendicular demyelinating lesions in the corpus callosum and the periventricular and juxtacortical regions. There were also lesions in the pons, bilateral cerebellar peduncles, and hemispheres. There was contrast enhancement of punctiform lesions in the bilateral frontoparietal regions and right inferior cerebellar peduncle and some in the periventricular region.

A lumbar puncture was performed. Results of cerebral spinal fluid cytologic analysis were normal. There were positive oligoclonal bands with a type 2 pattern. The isoelectric focusing method showed more than five well-defined bands in the cerebral spinal fluid that were not present in paired serum.

An MS diagnosis was established, and, due to its active nature and the high lesion load of the disease, treatment with fingolimod, 0.5 mg/d, was initiated, with 0.5 mg of clonazepam at night for RBD.

At the 6-month follow-up visit, the patient noted that she had had a remission of her RBD symptoms. She had adhered to the fingolimod treatment but had suspended clonazepam use owing to daytime sleepiness. A follow-up brain magnetic resonance image revealed no significant change in the number of demyelinating lesions, and there were no lesions enhanced by contrast or with diffusion restriction that suggested disease activity. At 1-year clinical follow-up the patient has remained stable, with no relapses of MS or RBD.

Discussion

Sleep disturbances are far more common in patients with MS than in the general population; they greatly decrease the quality of life of these patients.⁵⁻⁸ The reported prevalence of sleep disturbances in patients with MS ranges from 24% to 61%⁵⁻¹⁵ compared with 33.1% in the general population.⁹ In addition, women

![Figure 1. Brain magnetic resonance images](http://journalserver.allenpress.com/journalsrc/ijmsc/article-pdf/20/4/180/2092897/1537-2073_2017-001.pdf)
with MS seem to be more susceptible to sleep disorders than men with MS. Interestingly, poor sleep quality has been linked to a heightened risk of other comorbidities in patients with MS, such as pain, depression, fatigue, heart disease, diabetes, obesity, and an overall increase in mortality. In people who have chronic illnesses, sleep disorders may increase disease impact and are associated with lower work productivity, worse mental health, and higher use of health care services.

Sleep disturbances comprise a wide variety of disorders, and it is essential to recognize the specific disorder because they can be treated. Sleep disorders reported in MS include insomnia (40%-54%), sleep-disordered breathing (14%-58.1%), restless legs syndrome (14%-57.5%), and RBD (0.38%-3.2%).

Rapid eye movement sleep behavior disorder is a parasomnia characterized by recurrent episodes of loss of muscle atonia during REM sleep (mainly in the second half of the night), with enacted dreams (generally violent, action-filled, or unpleasant dreams) that cause sleep disruption, abnormal motor or verbal behavior, and occasional bodily harm to oneself or to a sleeping partner in response to the specific dream content. Complex behaviors have been noted (eg, talking, laughing, shouting, swearing, gesturing, punching, and kicking during sleep). If awakened shortly after the event, the individuals usually remember what they were dreaming about and what they were trying to do. Rapid eye movement sleep behavior disorder not associated with MS is quite different: age at onset usually is older than 50 years, and men are more likely to be affected than women, constituting 80% to 90% of cases.

The etiology of RBD might be idiopathic, or RBD may develop secondary to an underlying neurologic disease. The idiopathic form (Table 1) of RBD has, however, been challenged because many authors have suggested that this may be a precursor syndrome of neurodegenerative disorders (often following a delay of decades). In well-characterized cohorts, 50% to 70% of individuals with idiopathic RBD eventually evolve toward a clearly established α-synucleinopathy (Parkinson disease, Lewy body dementia, multiple systems atrophy) during a 10- to 15-year period.

Many other neurodegenerative disorders have been associated with the secondary form of RBD, such as olivopontocerebellar degeneration and multi-infarct dementia, among others. Interestingly, sleep is implicated in brain plasticity, a process impaired in these neurodegenerative diseases.

Other causes of secondary RBD have been associated, such as genetic diseases (Machado-Joseph disease, olivopontocerebellar degeneration and multi-infarct dementia, among others. 

### Table 1. Diagnostic criteria for idiopathic REM sleep behavior disorder from the ICSD-3

<table>
<thead>
<tr>
<th>Criteria A-D must be met:</th>
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<tr>
<td>A. Repeated episodes of sleep-related vocalization and/or complex motor behaviors</td>
</tr>
<tr>
<td>B. These behaviors are documented by polysomnography to occur during REM sleep or, based on clinical history of dream enactment, are presumed to occur during REM sleep</td>
</tr>
<tr>
<td>C. Polysomnographic recording demonstrates REM sleep without atonia</td>
</tr>
<tr>
<td>D. The disturbance is not explained more clearly by another sleep disorder, a mental disorder, medications, or substance use</td>
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</table>


Moebius syndrome, etc., focal brainstem lesions (MS, tumor, stroke), nonfocal lesions (epilepsy, autism, limbic encephalitis, etc.), and substance induced (tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, mirtazapine, alcohol, caffeine). The diagnosis of RBD is usually made according to the patient’s history (via precise description of events by a reliable eyewitness and corroboration of the dream content by the patient) and is confirmed via a polysomnographic recording. When abnormal behaviors of dream enactment do not happen overnight, polysomnography can still establish the diagnosis of lack of REM sleep atonia by showing increased REM sleep motor tone and/or increased phasic motor activity.

The differential diagnosis of RBD includes nocturnal frontal lobe epilepsy, non-REM sleep parasomnias (sleepwalking and sleep terrors), and other REM parasomnias (such as sleep paralysis, nightmare disorder, and sleep-related hallucinations). Careful review of the patient’s nocturnal episodes, ideally with the help of a sleeping partner, can aid in differentiating RBD from other sleep disorders.

Physiologically, the usual suppression of motor activity during normal REM sleep results from multiple interacting nuclei and pathways that initiate in the brainstem. Important brainstem nuclei include REM-off nuclei (the ventral lateral portion of the periaqueductal gray matter and the lateral pontine tegmentum) and REM-on nuclei (precoeruleus and sublaterodorsal nucleus, locus coeruleus, laterodorsal tegmental nucleus, pedunculopontine nucleus, and raphe nucleus). The REM-on and REM-off distinction is based on higher activity during either REM sleep or non-REM sleep and waking.
Most REM-on neurons synthesize glutamate and directly recruit inhibitory γ-aminobutyric acid and glycine-containing spinal interneurons, causing active inhibition of muscle activity in REM sleep by suppressing α-motoneuron activity in the anterior horn of the spinal cord. An indirect pathway is also hypothesized, which suggests that the laterodorsal tegmental nucleus neurons project to the magnocellular reticular formation and from there to spinal interneurons via the ventrolateral reticulospinal tract. Lesions of the laterodorsal tegmental nucleus decrease activation of spinal interneurons, manifesting as a lack of muscle tone inhibition. Atonia during REM sleep is reinforced by reduced excitatory input of glutamatergic, noradrenergic, serotoninergic, dopaminergic, and hypocretinergic stimulation to the α-motoneurons. Interestingly, midbrain and forebrain structures have also been tied to this complex circuitry, including the substantia nigra, hypothalamus, thalamus, basal forebrain, and frontal cortex.

Previous case reports have described RBD symptoms in relation to acute MS attacks and, uncommonly, as the first clinical manifestation in patients with MS (Table 2). These clinical presentations have usually been attributed to lesions in the pedunculopontine nuclei, located in the dorsal pons (pontine tegmentum), that supply the locus coeruleus and reticular formation. This would explain the higher prevalence of RBD in patients with MS compared with the general population, because demyelinating lesions in the brainstem are frequent in patients MS.

The present patient had a dorsal pontine lesion that could explain the origin of RBD. The location of lesions associated with RBD in MS is, however, controversial, probably owing to the complex circuitry that controls this physiologic process. Gómez-Choco et al. reported that of three patients with confirmed RBD, only one had a pontine lesion.

Note that, generally, patients with MS do not consult a physician because of RBD and, when they do consult, RBD symptoms are frequently subtle and not disclosed to health care professionals; patients will also try to prevent sleep-related injury (eg, by sleeping on a floor in a room without furniture) years before seeking medical attention. Clinicians should, therefore, routinely ask about sleep disorders in patients with MS owing to their higher prevalence in such patients and the potential effect of sleep on overall disease impact.

It is necessary to administer the appropriate treatment to improve the sleep and quality of life of these patients. The initial goal in RBD therapy is to protect the patient and sleeping partner by adjusting the sleeping environment. Sleeping partners should sleep separately until the dream enactment behavior is under control; the bed should be distanced from a window, and all bedside objects that could cause injury (eg, night table, lamps, 

Table 2. Demographic and clinical characteristics of patients with MS reported in the literature with diagnosis of RBD

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Sex/Age, y</th>
<th>RBD as first manifestation of MS</th>
<th>PSG confirmation</th>
<th>Intake of SSRI</th>
<th>Treatment for RBD</th>
<th>Response to treatment</th>
<th>MRI (infratentorial lesions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plazzi (2002)</td>
<td>Italy</td>
<td>F/25</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>ACTH 40 U/d × 5 d</td>
<td>RBD and nightmares progressively diminished from 5-7 to 1-2 episodes/wk, and disappeared 8 mo after her first admission</td>
<td>Pons</td>
</tr>
<tr>
<td>Tippmann-Peikert (2006)</td>
<td>USA</td>
<td>F/51</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Clonazepam</td>
<td>Significant improvement in frequency and severity of RBD, but occasional dream enactment behavior persists</td>
<td>Pons</td>
</tr>
<tr>
<td>Gómez-Choco (2007)</td>
<td>Spain</td>
<td>M /49</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Clonazepam</td>
<td>Yes</td>
<td>Pons</td>
</tr>
<tr>
<td>Gómez-Choco (2007)</td>
<td>Spain</td>
<td>M/37</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Clonazepam</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Gómez-Choco (2007)</td>
<td>Spain</td>
<td>F/37</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Clonazepam</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Gómez-Choco (2007)</td>
<td>Spain</td>
<td>F/52</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Clonazepam</td>
<td>Yes</td>
<td>Pons</td>
</tr>
<tr>
<td>Samara (2015)</td>
<td>USA</td>
<td>F/27</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
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<tr>
<td>Present study</td>
<td>Colombia</td>
<td>F/38</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Clonazepam</td>
<td>Yes</td>
<td>Pons</td>
</tr>
</tbody>
</table>

Abbreviations: ACTH, adrenocorticotropic hormone; MRI, magnetic resonance imaging; MS, multiple sclerosis; PSG, polysomnogram; RBD, rapid eye movement sleep behavior disorder; SSRI, selective serotonin reuptake inhibitor.
PRACTICE POINTS

- Symptoms of rapid eye movement sleep behavior disorder are frequently subtle and not disclosed to health care professionals.
- MS should be considered among the differential diagnoses in patients who present with symptoms of rapid eye movement sleep behavior disorder, particularly if they are young and female.
- Clinicians should routinely ask about sleep disorders in patients with MS.

firearms) should be removed. In idiopathic RBD, the first-line symptomatic treatment is clonazepam and/or melatonin. The mechanism of action seems to be related to its ability to reduce phasic activity in REM sleep. A dose of 0.5 to 2 mg of clonazepam is usually effective. Melatonin should be given in doses of 6 to 15 mg nightly to reestablish normal REM atonia. Unfortunately, randomized controlled trials of pharmacologic treatments are unavailable. It is also necessary to control the inflammation cascade in RBD associated with an acute MS relapse with a course of corticosteroids or other immunomodulatory therapies to potentially expedite the patient’s recovery. It should be clear, however, that corticosteroids are suggested only for acute relapses/inflammation and not as a primary treatment for RBD symptoms in MS of longer or unclear duration. It is important to remember that antidepressant agents should be avoided/discontinued because they can either precipitate, aggravate, or unmask RBD.

In conclusion, the presenting syndrome in patients with MS may be RBD, as in the patient described herein. This constitutes a clinical challenge for the neurologist. Multiple sclerosis should be considered among the differential diagnoses in patients who present with symptoms of RBD, especially if they are young and female.

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References