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Abnormal motor behavior during sleep

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Abstract

Abnormal motor behaviors during sleep can be classified into four categories, ranging from myoclonic jerks to complex and integrated motor behaviors. There have been recent developments in several of these conditions, in particular restless legs syndrome (RLS) and rapid-eye-movement sleep behavior disorder (RBD). RLS is one of the major causes of insomnia. Familial aggregation of RLS has been demonstrated by several groups, and molecular genetics studies have suggested the presence of susceptibility genes on chromosomes 12q and 14q. Pharmacologic and brain imaging studies suggest the involvement of dopaminergic mechanisms in RLS, but recent work has focused on brain iron metabolism. Studies indicate that RBD patients may eventually develop Parkinson' s disease (PD). Conversely, RBD has been found in patients already diagnosed with PD. Single-photon emission computed tomography and positron emission tomography studies have shown a decrease in binding to presynaptic dopamine transporter in both idiopathic RBD and PD. Patients with RBD (associated or unassociated with PD) also have neuropsychological deficits. RBD may therefore represent the prodrome of a neurodegenerative disease leading to multiple system atrophy and Lewy body dementia. Understanding the underlying pathophysiology of abnormal sleep motor behaviors may prove useful in the management of insomnia.

Keywords: Insomnia; Motor behavior; Restless legs syndrome (RLS); Rapid-eye-movement sleep behavior disorder (RBD)

1. Introduction

Up to 40% of individuals worldwide experience sleep difficulties within a given year, and the prevalence of chronic insomnia has been estimated at 10–19% [1–4]. Excessive daytime sleepiness has measurable negative effects on performance and physical and mental health, and the condition imposes a significant burden upon society, as well as on individual sufferers. Abnormal motor behaviors are a common cause of sleep disturbances [5]. The sleep disturbances can range from mild to severe, but they are often the reason that people suffering from abnormal motor behaviors during sleep seek a doctor' s help.

Abnormal motor behaviors during sleep can be classified into four categories: aperiodic myoclonic contractions, periodic and stereotypic movements, complex and disorganized behaviors, and complex and organized behaviors [5]. In the past few years, there have been significant advances in understanding the epidemiology and pathophysiology of these conditions. In particular, researchers have made important progress in restless legs syndrome (RLS; a periodic and stereotypic movement) and rapid-eye-movement sleep behavior disorder (RBD; a complex and organized behavior). Here, recent developments in these common disturbances are reviewed.

2. RLS

2.1. Diagnosis of RLS

RLS is a common yet frequently undiagnosed sensorimotor disorder [6]. Subjects suffering from RLS experience an urge to move usually associated with uncomfortable creeping, crawling sensations in the legs. These symptoms increase throughout the day, and are worse when still or in bed. A high proportion of patients with RLS also complain of arm paresthesia [7]. To relieve the discomfort, subjects stretch or bend the limbs, toss or turn in bed, or get up and pace the floor. The minimal criteria for the diagnosis of RLS are shown in Table 1 [6].

The Suggested Immobilization Test (SIT) has been developed to evaluate objectively the presence of these criteria by quantifying leg movements and discomfort during a 1-hour period of immobility prior to bedtime [8]. Compared with healthy controls, SIT measurements of immobility significantly worsen both leg discomfort and periodic leg movements in patients with RLS.

2.2. Epidemiology of RLS

RLS symptoms have been reported to occur in 10–15% of Caucasian subjects [9–11] and in less than 1% of Asian subjects [12]. In Caucasians at least, the prevalence of RLS appears to increase with age [10]. A recent study of 15,391 individuals, conducted in five countries, indicated that of 926 (6%) subjects who fulfilled all criteria for RLS at least once a week and who had an impaired quality of life, 609 (65.8%) had consulted a physician about their symptoms but only 33 (5.4%) had received a correct diagnosis [13].

Familial aggregation of RLS has been demonstrated by several groups [14,15]. The genetic association appears to be limited to early-onset patients (younger than 30 years old), whereas late-onset RLS (aged over 30 years) seems to have no genetic contribution [16]. However, this apparent difference could be due to a lack of appropriate epidemiological data, and needs to be confirmed by further studies. In the search for predisposing genes for RLS, genome-wide scans have suggested the presence of major susceptibility genes on chromosome 12q in several French Canadian families [17] and, in a study in Northern Italy, on

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Table 1
Diagnostic criteria for RLS and RBD [6,33]

Diagnosis of RLS	Diagnosis of RBD
• Urge to move associated with dysesthesia • Worsening during period of rest or inactivity such as lying down or sitting • At least temporary relief by activity • Worsening of the symptoms in the evening or in the night	• Complaint of abnormal motor behaviors during sleep associated with dream mentation • Elaborate motor activity occurring in REM sleep • Loss of REM sleep muscle atonia • Increased phasic EMG activity in REM sleep

chromosome 14q [18]. These studies need to be replicated in other Caucasian and non-Caucasian gene pools, but meanwhile the data appear to suggest a genetic heterogeneity associated with RLS.

2.3. Pathophysiology of RLS

Having established that there may be a molecular genetic basis for RLS [17,18], the next step was for researchers to determine the underlying mechanisms of the condition. Pharmacologic and brain imaging studies have suggested the involvement of dopaminergic mechanisms, and recent studies suggest the possible involvement of brain iron metabolism.

The dopaminergic hypothesis in RLS stems from knowledge that the dopaminergic system is involved in movement control, and that dopamine precursor combinations such as carbidopa–levodopa [19] and dopamine agonists such as bromocriptine [20], pergolide [21], pramiprexole [22], cabergoline [23], and ropinirole [24] have been successful in the treatment of these abnormal motor behaviors during sleep.

In order to examine the genetic substrate of the dopamine hypothesis in RLS, researchers began by looking at likely suspect genes. Desautels *et al.* [25] analyzed eight genes coding for receptors and enzymes related to dopaminergic transmission, using a population of 92 patients with RLS and 182 controls matched for ethnic background. However, no significant differences between groups were found in the genotypic or allelic distributions of D1 to D5 receptors, dopamine transporter (DAT) gene, tyrosine hydroxylase (TH) or the dopamine beta hydroxylase gene (DBH). Furthermore, no effect of the loci examined was observed with stratification using clinical parameters such as age at onset or periodic leg movements during sleep index [25]. A structural polymorphism in the neurotensin gene located within the alleged susceptibility locus on chromosome 12q was another suspected contributor that has been shown unlikely to be associated with RLS [26].

A major mystery therefore seems to be why, if dopaminergic systems are involved in RLS, an allelic association with dopaminergic genes cannot be found. It is feasible that associations are not being detected due to a lack of sub-analysis for early- and late-onset subjects, but it is also possible that the responsible genes are located elsewhere. Further research is clearly needed to elucidate the genetic substrate of the dopamine hypothesis in RLS, and to explain the nature of the familial aggregation seen in early-onset RLS patients.

Data suggesting the involvement of iron metabolism in RLS come from the early work of Ekbom [27]. Recently, Earley *et al.* [28] reported that RLS patients had lower cerebrospinal fluid (CSF) ferritin levels and higher CSF transferrin levels than healthy control subjects, indicating brain iron insufficiency in patients with RLS (Fig. 1). Using magnetic resonance imaging (MRI), Allen *et al.* [29] assessed regional brain iron concentrations in 10 subjects (five with RLS, five controls). MRI measurements of iron concentrations were significantly decreased in the substantia nigra, and somewhat less significantly in the putamen, both in proportion to RLS severity. The

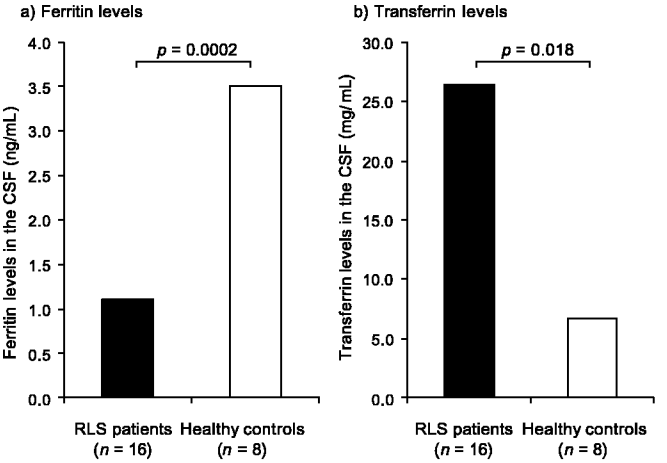

Fig. 1. Levels of a) ferritin and b) transferrin in RLS patients and healthy control subjects. Adapted with permission from Earley *et al.* [28].

results indicated that brain iron insufficiency may occur in particular brain regions in patients with RLS.

Neuropathologic studies in patients with RLS have since given novel insight into the underlying mechanisms of the condition. A standard neuropathologic evaluation was performed on seven brains from RLS patients, compared with five age-matched control brains with no neurologic history [30]. There were no histopathologic abnormalities unique to the RLS brains. However, marked decreases of H-ferritin and iron staining were seen in the RLS substantia nigra. Transferrin receptor staining on neuromelanin-containing cells was also decreased in the RLS brains, whereas transferrin staining in these cells was increased. These findings need to be replicated in other studies involving larger samples, but the authors concluded that RLS may not be rooted in pathologies associated with traditional neurodegenerative processes, but rather that it may be a functional disorder resulting from impaired iron acquisition. The underlying mechanism appears to be a defect in the regulation of transferrin receptors [30]. Impaired iron metabolism in the central nervous system may lead to a decrease of dopaminergic transmission since iron is important for the action of tyrosine hydroxylase and post-synaptic D2 receptor function.

3. RBD

3.1. Diagnosis of RBD

RBD is a parasomnia that occurs only during REM sleep. It is characterized by the loss of skeletal muscle atonia, which is the principal feature of REM sleep, and by abnormal behavior representing the attempted enactment of dreaming [31,32]. Clinically, it consists of abnormal behavior that is frequently violent and may lead to injuries. A polysomnographic (PSG) study is necessary to show the absence of REM sleep atonia and related abnormal behavior. The principal criteria for the diagnosis of RBD are shown in Table 1 [33].

3.2. RBD: association with neurodegenerative disorders

RBD is most prevalent in older men, is sometimes linked with drug use or exposure to toxic conditions, and an association with neurological disorders is frequently reported [31]. RBD is also often associated with dementia with Lewy bodies (DLB) [34] and Parkinson' s disease [35]. In many cases, RBD symptoms occur several years to decades before the onset of these diseases [34,35]. Using PSG recordings, RBD has been detected in about 33% of patients with Parkinson' s disease [36]. An additional 24% showed PSG features of RBD, namely REM sleep without atonia, but no behavioral manifestations in REM sleep.

3.3. Pathophysiology of RBD

As described above, several studies indicate that RBD may be associated with DLB or Parkinson' s disease [34–36], yet the pathophysiology of RBD associated with these diseases remains unclear.

A higher theta power during wakefulness has been demonstrated in Parkinson' s patients with RBD, compared with Parkinson' s patients without RBD or healthy controls (Fig. 2) [37]. This increase

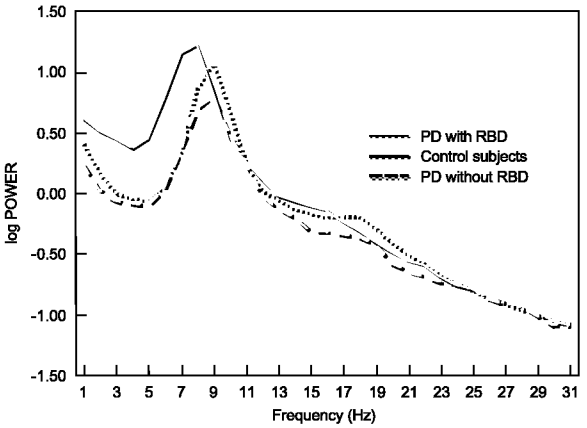

Fig. 2. EEG spectral analysis in Parkinson' s disease with and without RBD. Reprinted with permission from Gagnon *et al.* [37].

was statistically significant in occipital, temporal and frontal regions. A lower dominant occipital frequency was also observed in these patients. The topographical distribution of EEG changes in RBD patients are similar to the metabolic impairment patterns observed in DLB and in dementia associated with Parkinson' s disease [38,39]. Recent studies have shown that non-demented patients with idiopathic RBD present deficits in the same cognitive functions as patients with DLB, namely an impairment in visuospatial planning and a deficit in the recall of both visuoconstructive and verbal material [40,41].

Several subcortical structures are suspected to be implicated in the pathophysiology of RBD, such as the pedunculopontine tegmental nucleus (which provides cholinergic innervation), locus coeruleus (providing noradrenergic innervation), and the nigro-striatal system (providing dopaminergic innervation) [42–49]. These structures provide dopaminergic, noradrenergic and cholinergic innervation of the cerebral cortex, and play a role in cortical activation during wakefulness and REM sleep [50,51]. In summary, RBD may represent the prodrome of a neurodegenerative disease, possibly leading to DLB or Parkinson' s disease.

4. Discussion

Abnormal motor behaviors during sleep can range from bothersome to incapacitating. Anxiety, moodiness, depression, low concentration and excessive daytime sleepiness are associated with the impairment in both the quantity and quality of sleep in these disorders, affecting marital, family and social relations.

Pharmacologic and brain imaging studies have suggested the involvement of dopaminergic mechanisms in both RLS and RBD, and dopaminergic agents are, therefore, currently used to treat these troublesome conditions. Dopaminergic agonists were developed to treat Parkinson' s disease, but they are now considered the first-line drugs for RLS. They were also found to suppress some of the behavioral manifestations of RBD, although they do not restore REM sleep atonia [52]. Long term follow-up studies in RLS patients treated with dopaminergic agonists showed sustained efficacy in a large majority of patients. However, some patients develop what we call augmentation, i.e., an earlier onset of symptoms, an involvement of other body parts and a worsening of symptoms associated with increased dosage of medications. The clinical importance of augmentation needs to be further documented.

Perhaps the most clinically important implication of new research in RBD is that in many cases, the condition may have a predictive value, preceding other symptoms of neurodegenerative disorders with Parkinsonism. Further studies in RBD patients should include systematic neuropsychological evaluations and longitudinal neurological follow-ups.

In summary, researchers are still working to clarify the details of the mechanisms underlying abnormal motor behavior during sleep, but recent developments in understanding the pathophysiology of RLS and RBD represent an important step forward, potentially providing important diagnostic and prognostic information to clinicians managing patients with insomnia. They also offer potential for the development of new treatment strategies targeting the underlying mechanisms of these disorders. Further work on these and other abnormal motor behaviors during sleep is clearly worthwhile.

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