

Review Article

Sleep Disturbances in Parkinson's Disease

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- Sleep attack

Abstract

A common early non-motor symptom of Parkinson's disease (PD) is sleep disturbance. Indeed, rapid eye movement (REM) sleep behavior disorder (RBD) and excessive daytime sleepiness (EDS) are predictors of PD. EDS and RBD are thought to be risk factors for the cognitive disturbances observed in PD. Some researchers have suggested that RBD can be used as a predictor of the pathological progression of PD. Thus far, sleep disturbances have not been recognized as a component in the progression of the disease, and therefore have not been routinely and adequately controlled in this patient population. In this review, we present evidence that the assessment of sleep (i. e. , the presence of fragmented sleep, insomnia, RBD, EDS, and sudden onset of sleep) should be a part of the routine evaluation of patients with PD.

ABBREVIATIONS

RBD: Rapid Eye Movement (REM) sleep behavior disorder; EDS: Excessive daytime sleepiness; PSG: Polysomnography; PDSS: Parkinson's disease sleep scale; SCOPA: Scale for outcomes in Parkinson's disease; UPDRS: Unified Parkinson's disease rating scale; RLS: Restless leg syndrome; PLMS: Periodic limb movements; MSLT: Multiple sleep latency time; SOREMP: Sleep-onset REM periods

INTRODUCTION

As James Parkinson described in 1817, sleep disturbances can be extensive in Parkinson's disease (PD), including the presence constant sleepiness with slight delirium and other hallmarks of extreme exhaustion [1]. Polysomnography (PSG) studies have indicated that the latency to fall sleep, the frequency of awakenings, and the total number of hours spent sleeping increase with PD progression [2]. Fragmented sleep, disturbance of sleep initiation, and daytime sleepiness are unmet needs for patients with PD. Characterization of various sleep disturbances, understanding their degree of severity, and the appropriate strategies to treat them are important for improving the daytime symptoms of PD.

Diagnostic sleep scales and testing are described in Table 1. The Pittsburgh sleep quality index, the Epworth Sleepiness Scale (ESS), and the rapid eye movement (REM) sleep behavior disorder-screening questionnaire [3] are not specific for PD. The Parkinson's disease sleep scale (PDSS) [4], the Scale for Outcomes in Parkinson's disease (SCOPA) -Sleep scale [5], and the Movement Disorder society - Unified Parkinson's disease rating scale (MDS-UPDRS) [6] are specific for PD.

Sleep benefit

Thirty percent of patients with PD report improvements

Table 1: Sleep scale.

Test, examination		Score	Cut off
Pittsburgh sleep quality index	sleep quality, questionnaire	0~21	5/6
Epworth Sleepiness Scale	sleepiness, questionnaire	0~24	10/11
REM sleep behavior disorder screening questionnaire	RBD, questionnaire	0~13	4/5
Parkinson's disease sleep scale	sleep quality, questionnaire	15 items (0~4)	
SCOPA-Sleep scale	sleep quality, sleepiness, questionnaire	14 items	
MDS-UPDRS	sleep quality, sleepiness, questionnaire	2 items (0~4)	

in their motor symptoms in the morning, before taking any medication [7]. This phenomenon is referred to as "sleep benefit" [8]. This benefit has also been reported after short naps [9]. The clinical features of sleep benefit involve the presence of diurnal fluctuations in severity of dystonic gait disturbances that are unrelated to the effects of medication [10]. The mechanisms underlying sleep benefit were initially thought to involve the accumulation or storage of dopamine. However, sleep benefit was shown to be associated with shorter length of sleep and longer latencies before falling asleep [9]. Thus, the mechanism by which sleep produces these benefits in motor symptoms remains unknown.

Motor symptoms in sleep

Certain motor symptoms in PD are attenuated during sleep. Resting tremors persisted during stage I sleep, but disappeared with the onset of stage II sleep [11]. Tonic muscle electromyographic amplitude decreased linearly with the

progression of non-REM sleep, from stage I to IV. Moreover, un-alternating tremors persisted at a subclinical level during all stages of non-REM sleep, but disappeared during REM sleep [11]. On the other hand, nocturnal akinesia, a common motor disturbance in PD, and difficulties in making postural adjustments can result in fragmented sleep with frequent awaking [12].

REM sleep behavior disorder (RBD)

RBD is characterized by complex, vigorous, frequently violent movements during REM sleep that are often accompanied by nightmares. RBD has received increasing attention since Shneck and colleagues [13] reported that 38% of patients with RBD examined were diagnosed with PD 4 years after the onset of RBD. Histological examination revealed that 68% of patients with idiopathic RBD had developed incidental Lewy body disease (LBD) [14]. The median time interval between the diagnosis of RBD and PD was 13.0 years, and the median interval between diagnosis of idiopathic RBD and LBD was 7.0 years [15]. Of all the remaining subjects with RBD who remained free of PD symptoms, neuroimaging and olfactory tests nevertheless revealed the presence of LBD [15]. Idiopathic RBD preceded the onset of Parkinsonism by more than 15 years, and it is one of the biomarkers for early diagnosis of PD. RBD is a strong predictor of underlying synucleinopathy [16]. In 172 patients with RBD, 77 patients were diagnosed with LBD, 59 patients with LBD and Alzheimer disease, and 19 patients with multiple system atrophy.

The pathophysiology of RBD is believed to involve the nucleus reticularis magnocellularis and the peri-locus coeruleus in the pons [17,18]. Notably, patients with RBD were reported to experience improvement in at least one component of motor control during REM sleep [19]. In patients with RBD, motor improvements during REM sleep may be generated by the motor cortex followed by the pyramidal tract, bypassing the extrapyramidal system. These movements would eventually be transmitted to lower motor neurons because of brainstem lesions that interrupt the pontomedullary pathways that mediate REM sleep atonia [19].

Patients with RBD are predominantly male [17,20-22]. There are several differences between PD patients with and without RBD [20,22]. For example, constipation is more frequently observed in patients with RBD that was progress upward as the theory of Braak [23]. In a study that examined 172 subjects with RBD, 97 were diagnosed with dementia and Lewy bodies, and 32 were diagnosed with PD with or without dementia [16]. Findings from another study reported that 4 years after initial evaluation of RBD, 48% of subjects developed dementia. This is in comparison to 0% in the group of patients with PD diagnosed without RBD, suggesting that RBD is possibly associated with an increased risk of dementia. These studies suggest that RBD is a marker of a complex subtype of PD [22].

Pacchetti et al. [24] reported that the presence of RBD in patients with PD was associated with an approximate 3- fold increase in the risk of developing psychotic disorders. Arnulf et al. [25] suggested that hallucinations and delusions in non-demented patients with PD can result from abnormal REM sleep.

Restless leg syndrome (RLS) and periodic limb movements

The prevalence of RLS in patients with PD was between 0.5% and 20.8% [26-28], compared to 2.9% in controls [29]. Assessment of the prevalence of RLS in these patients is difficult, because RLS may be difficult to distinguished from other sensory dysfunctions (e. g. , akathisia), and therapies aimed at managing PD symptoms may mask RLS. The observation that the onset of motor symptoms in PD often preceded the onset of RLS supports the hypothesis that PD may be one of the risk factors for RLS [29]. However, still more than 50% patients have been reported to experience symptoms of RLS before the onset of PD [26]. RLS is common in patients with PD, though this condition does not significantly affect the quality of life or lead to an increased presence of diurnal hypersomnia [29,30].

De novo patients with idiopathic PD did not exhibit significant differences in periodic limb movements (PLMS). However, a significant increase in PLMS was observed in levodopa-treated patients compared to controls [31,32]. Thus, dopamine agonists or levodopa, which is used in the treatment of restless leg syndrome, improved PLMS in PD [33].

Excessive daytime sleepiness (EDS)

EDS is a common non-motor symptom in PD [34]. Risk of an episode of uncontrollable somnolence occurred at least once in 22% of the patients [35]. EDS was present in overall 51% of the patients with PD and in 51% of the drivers with PD [36]. EDS is more frequently observed in male patients [37]. Patients with non-tremor dominant motor phenotypes were more likely to have increased scores in the ESS [38], although this was not found consistently [37]. EDS was more frequent in patients taking dopamine agonists [37,39] or levodopa [40]. Age and disease severity were associated with EDS [37]. Patients receiving a dopamine agonist (pramipexole, ropinirole, or pergolide) were nearly three times more likely to have episodes of sudden uncontrollable somnolence as compared to patients on any other type of PD medication [35]. Severity of EDS was mild for the patients treated with clonazepam [41]. The underlying cause of EDS is not only due to medication, but the following dates are indicated the disease itself. Patients with PD and EDS showed significant atrophy of the frontal lobe, temporal lobe, occipital lobe, and limbic lobe including the nucleus basalis of Meynert, compared to patients with PD without EDS [42]. In the prospective Honolulu Asian aging study, EDS was a risk factor for PD in elderly men (odds ratio = 3.3).

A subset of patients with PD exhibited a tendency for daytime REM sleep during daytime nap testing. The Unified Parkinson's Disease Rating Scale (UPDRS) indicated that motor scores and levodopa dose were unrelated to the presence of REM sleep [43]. Multiple sleep latency time (MSLT), and sleep-onset REM periods (SOREMP) (i. e. , narcolepsy-like symptoms) were found in some patients [44].

The percentage of patients who experienced at least one episode of sudden onset of sleep while driving is of 3.8% [36]. Reports on the frequency of patients who have experienced an acute episode of irresistible sleep that occurred without warning

signs are variable (0–43%) [45]. These sudden “sleep attacks” are more common in males [46,47]. Disease duration, dopamine therapy, EDS [48], delay before the initiation of drug treatment, with the exception of levodopa [47], and RBD [20] were risk factors associated with sleep attacks.

Drugs and sleep

In mesolimbic and mesocortical dopamine systems, the increase in sleep after low doses of apomorphine, bromocriptine or, pergolide could be related to the activation of presynaptic dopamine D2 receptors [49]. The relatively selective dopamine D2 receptor agonists apomorphine, bromocriptine, and pergolide show biphasic effects on the sleep-wake cycle, with low doses increasing and high doses decreasing sleep. The risk of this adverse event was 2.8-fold higher in patients with PD who received dopaminergic drugs than in patients who received other medications, even after controlling for a wide variety of clinical and demographic variables. The data demonstrated a dose-response relationship for pramipexole, pergolide, and ropinirole [35]. A single oral dose of pramipexole induced sleepiness as assessed by MSLT in healthy young subjects. Sleepiness was not observed with levodopa or bromocriptine when compared to placebo [50]. Higher doses of dopaminergic medication taken prior to bedtime were associated with an increase in the percentage of time spent in stage II sleep and a reduction in the percentage of time spent in REM sleep [51].

The recent availability of prolonged release tablets provides continuous dopaminergic stimulation. PDSS scores were significantly improved after 24 weeks of treatment with ropinirole 24-h prolonged release tablets than with placebo [52]. The change from an immediate-release tablet formulation to an extended-release tablet formulation of pramipexole was not effective for PDSS item 2 [53]. Rotigotine transdermal patch improved mean sleep quality (PDSS item 1), and the occurrence of nocturias (PDSS item 8) [54].

Hypocretin (orexin)

Narcolepsy is caused by a loss of hypocretin (orexin) producing neurons and undetectable cerebrospinal fluid (CSF) levels [55]. Hypocretin neurons located in the lateral hypothalamus project widely to several autonomic, metabolic, neuroendocrine, and arousal systems [56]. The systems that are affected or damaged in PD include noradrenaline neurons in the locus coeruleus [57], serotonin neurons in the raphe [57], cholinergic neurons in the basal forebrain [57] and the pedunculopontine nucleus [58], and orexin neurons in the hypothalamus [59,60]. Lewy bodies have been found in the various brain regions, including the hypothalamus. The number of hypocretin neurons and the concentration of hypocretin in CSF or prefrontal cortex were reduced in the patients with PD than in controls [59,60]. The loss of hypocretin and melanin concentrating hormone neurons were significantly correlated with the clinical stage of PD, but not disease duration. Excessive daytime sleepiness was more frequent in patients with PD and dementia than in patients with PD without dementia; however, hypocretin-1 levels in the CSF were normal in these patients and were unrelated to the severity of sleepiness or cognitive status [61]. The hypocretin-1 level of

CSF in patients with SOREMP was slightly lower than in patients with PD without SOREMP [44].

Treatment of sleep disturbances

Evidence based treatment options for sleep disturbances are poor. The clinical benefits of clonazepam in RBD or RLS have been confirmed by several large case series. Clonazepam improved the symptoms of RBD and RLS within a few days. Clonazepam treatment was reported to have reduced RBD behaviors and injuries as well as appeared comparably effective [62]. However, no double-blind, placebo-controlled, randomized trials for the treatment of RBD or RLS with clonazepam are available. Open trial of melatonin was not found to be effective [63]. Antiparkinsonian drugs were effective in reducing the symptoms of RBD in some cases [20].

Dopaminergic medication is the first line of therapy in idiopathic RLS. However, patients with PD were typically already medicated or would be treated in the near future. Long-term treatment with dopaminergic compounds for RLS was complicated by the risk of augmentation (i. e. , worsening of symptoms) and low serum ferritin levels [64]. Ferrous replacement is adequate for RLS.

Two melatonin randomized double blind trial studies for insomnia revealed significant improvement [65,66]. Melatonin at a dose of 3 mg or 5 mg improved the quality of sleep in PD.

In a randomized, double-blind, placebo-controlled crossover

Table 2: Clinical trials of sleep therapy.

DRUG	Author	Study design	Efficacy	Dose
Insomnia Melatonin	Dowling GA 2005	DBPC crossover RCT	significant	5 and 50mg
	Medeiros CA 2007	DBPC	significant	3mg
EDS Modafinil	Högl B 2002	DBPC crossover RCT	significant	200mg
	Adler CH 2003	DBPC crossover RCT	significant	200mg
	Ondo WG 2005	DBPC	not significant	200mg
RBD Melatonin	Kunz D 1997	open label	not significant	3mg

DBPC: double blind placebo-controlled, RCT: randomized controlled trial

Table 3: Recommended sleep environments: from reference 69.

Maximize day time activities
Maximize daytime exposure to bright light
Minimize daytime napping
Avoid stimulants (caffeine, alcohol, tobacco) and fluids near bedtime
Avoid heavy late-night meals
Practise relaxation technique before bed
Follow a regular sleep schedule
Institute and maintain a bedtime routine
Limit time in bed (7-8 h per night)
Reserve bedroom for sleeping

study, 200 mg of modafinil improved the EDS in PD [67]; however, another study did not support these findings Table 2 [68].

Overactive bladder and obstructive sleep apnea can be treated by the established treatments. Sleep disturbance in PD is not induced by a single cause, but results from a complex convergence of multiple factors. Conducting a review of medication, daytime rehabilitation, and avoiding drinking water or caffeine before the night sleep were important. The sleep environments recommended by Ferreri were shown in Table 3 [69]. The assessment of sleep should be a part of the routine evaluation of patients with PD.

CONCLUSION

It has become clear that sleep disturbances are frequently associated with the motor symptoms observed in patients with PD. The neuronal damage associated with PD appears to cause sleep disturbances, and dopaminergic drugs may exacerbate these symptoms more than non-dopaminergic antiparkinsonian drugs do. Larger prospective studies are needed to understand and determine the appropriate treatment course for sleep disturbances in PD.

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