



Sleep Disturbances in Patients with Parkinson's Disease

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Parkinson's disease (PD) is a chronic neurodegenerative disorder having various motor and non-motor symptoms in nature. Sleep disturbance is one of major category of non-motor manifestation and exist throughout the disease course from premotor to advanced motor stages in PD. It is essential to understand pathophysiologic basis, etiologies, and clinical presentation of various sleep problems as this is important determinant of quality of life in patients with PD.

Keywords: Parkinson's disease; Sleep; Rapid eye movement sleep behavioral disorder; Restless legs syndrome

Received: March 6, 2022 **Accepted:** March 11, 2022

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INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder following dementia. The prevalence of PD is continuously increasing along with the growth of elderly population. Although PD is basically a movement disorder characterized by bradykinesia, rigidity and/or tremor, non-motor symptoms have been increasingly recognized recently [1]. Lewy body pathology of PD has been known to spread from the lower brainstem to the cortex, which indicates the natural progression of parkinsonian symptoms throughout the disease course from the prodromal phase to advanced stages [2]. Based on this study, the natural course of PD begins as non-motor symptoms such as anosmia, constipation, affective disorders, and sleep disorders before the onset of initial motor features. The premotor symptoms can be used as biomarkers of PD despite the poor specificity [1]. Sleep problems is representative non-motor features affect more than 75% of all patients with PD, and half of them have multiple sleep disorders. Further, co-morbid sleep disturbances have a great impact on safety and quality of life in patients with PD [3-5]. Sleep plays an important role in neurodegenerative disorders. Inadequate sleep is associated with neuronal injury [6] and negatively impacts the function of nervous system. Various sleep problems affect the PD patients throughout the disease course. Sleep condi-

tions have a significant impact on clinical motor symptoms and adversely affect the patients' quality of life [5,7].

VARIETY AND HETEROGENEITY OF SLEEP DISTURBANCES IN PATIENTS WITH PD

Progressive alteration of sleep architecture occurs early on in patients with PD. These changes reflect underlying degeneration of central nervous system pathology. Various sleep problems emerge in PD are associated with heterogeneous and complicated etiologies [8]. Although polysomnography (PSG) is a diagnostic gold standard for accurate evaluation of sleep status in PD, it cannot be widely used due to its limited feasibility in practice [5]. Overall sleep condition in PD is comparable to that of control [9], which is affected by numerous conditions during the degenerative course. Consistent changes in general sleep architecture associated with PD include reduction of total sleep time, sleep efficiency, sleep fragmentation, and increased wakefulness after sleep onset. Changes in REM sleep stage may differ according to the disease stage of PD. Medication use also affects sleep stages and overall sleep quality [10]. The number of concomitant sleep disorders accordingly increase with disease progression (Hoehn and Yahr stage), disease severity (Unified Parkinson's Disease Rating

Scale [UPDRS] score), total levodopa daily dose, and disease duration [5]. Sleep disruption in PD might present as common syndromes like insomnia, restless legs syndrome (RLS), rapid eye movement sleep behavioral disorder (RBD), excessive daytime sleepiness (EDS), and sleep-disordered breathing. PD-related motor symptoms, such as nocturnal akinesia and pain during the off period can also affect sleep condition in PD. Adequate sleep control is effective against motor symptoms of PD and vice versa [11]. In a 5-year longitudinal follow-up study known as Parkinson's Progression Markers Initiative (PPMI), 31.7% of subjects with PD reported at least one of the three types of sleep disturbance including insomnia, EDS, and RBD; 11.5% reported two types; and 1.4% reported all three types at baseline, progressing to 39.0%, 23.4%, and 7.3%, respectively, at 5 years. The control group remained stable during the follow-up period. The rate of increase was also the greatest in insomnia (44.5%), followed by EDS (32.1%) and RBD (31.2%) in PD [12]. Concomitant use of the medication should always be considered, especially in elderly patients with chronic diseases undergoing polypharmacy. While dopaminergic medication improves the efficiency and quality of sleep, treatment-related motor complications such as nighttime 'off' or dyskinesia interfere sleep maintenance in advanced PD. Some of dopaminergic medications, especially dopamine agonists, are associated with EDS and sleep attack. In the PPMI study, PD subjects who reported multiple sleep disturbances (insomnia, EDS and RBD) had higher levodopa equivalent daily doses compared with PD without sleep complaints [12]. Frequently, co-existing affective disorders in PD are well-known factors that contribute to the initiation and maintenance of sleep problems, early awakening, and EDS. Using sleep-related questionnaires, another Japanese cohort study of 436 PD patients reported a higher prevalence of multiple co-morbid sleep disorders than in controls. In this study, sleep problems varied according to the PD motor subtype with higher PD sleep scale-2 (PDSS-2) and Epworth Sleepiness Scale (ESS) scores in the postural instability and gait disorders (PIGD) group than in tremor-dominant group, while RBD screening questionnaire and RLS did not differ between motor subtypes. This implies the possibility that sleep problems in PD are closely related to disease-related disability [7].

In this review, the anatomical substrates of sleep problems in PD progression and the importance of sleep in neurodegenerative diseases are discussed. The diagnosis and management of several representative sleep disorders in PD are also reviewed.

SLEEP AND THE RISK OF NEURODEGENERATION

The association of sleep disturbances and cognitive decline in degenerative synucleinopathy has been recently investigated. According to previous studies, a lower baseline portion of N3/slow wave sleep in electroencephalography predicted rapid cognitive scores during the 4-year follow-up period [13]. Sleep accelerates the rate of β -amyloid clearance in the brain. Thus, inadequate sleep

may affect cognitive impairment in many aspects [14,15]. Proper sleep integrity is mandatory for memory consolidation; attention/executive functions are closely connected with sleep quality [16]. The relationship between sleep and the risk of parkinsonism remains to be elucidated [6,17], though previous reports have hypothesized the presence of similar mechanisms associated with β -amyloid in brain α -synuclein accumulation in the development of parkinsonism [18]. Degeneration of serotonergic system in PD has been documented in both neuroimaging and pathological studies. Sleep disturbances and fatigue are critically linked to serotonergic degeneration in non-motor symptoms of PD [19]. Various sleep conditions affect patients with PD differently. Of these, affective disorders have a great impact on sleep in PD. An inter-group analysis based on the general quality of sleep showed significant differences in anxiety and depression. Bad nighttime sleepers reported higher scores of depression and anxiety, whereas lower daytime sleepiness showed higher levels of anxiety suggesting multidirectional relationship between various factors [20]. Total sleep time is associated with depression scores and even predicts and reflects disease severity in PD [21]. Yang et al. [22] classified sleep disturbances in PD into three latent groups: less-troubled sleepers, PD-related nocturnal difficulties, and disturbed sleepers based on K-PDSS-2. The results showed that mood status based on Korean-non-motor symptoms scale [23], depression score (Korean version of the Montgomery-Asberg Depression Rating Scale), and health-related quality of life score (Korean version of the Parkinson's Disease Questionnaire-39 summary index) [24] show the strongest correlation respectively with sleep-related latency in PD.

SPECTRUM OF SLEEP DISTURBANCES IN PD

Sleep problems occur before the development of parkinsonian motor symptoms as the non-motor symptoms (prodromal phase) and sleep dysfunctions evolve throughout the disease course. Many of these problems are also affected by PD treatment. Sleep in PD can be classified in many ways but can be summarized as follows: daytime vs. night-time sleep disorders, disease-specific vs. treatment-related sleep abnormality, and prodromal signs vs. disease progression (Figure 1). Contributors to sleep disturbances in PD include loss of sleep-regulating neurons due to neurodegeneration, and PD-related symptoms such as nocturnal hypokinesia and stiffness. PD medications are the other important contributors to sleep problems such as insomnia and EDS. For example, RBD is a highly specific premotor biomarker of PD, while the presence of RBD in PD reflects widespread neurodegeneration that predicts rapid aggravation of other symptoms during the course [25].

SCALES TO EVALUATE SLEEP PROBLEMS IN PD

Given the broad spectrum of sleep disorders in PD, disease-

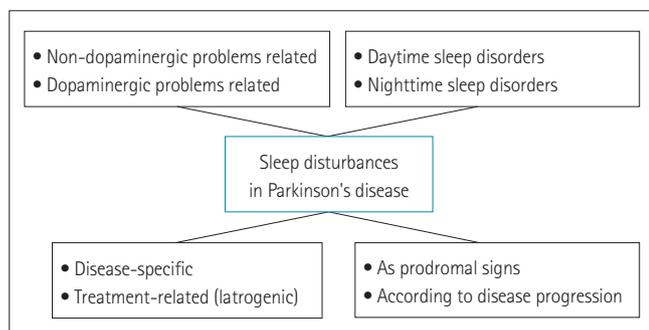


Figure 1. Various spectrum of sleep disturbances in Parkinson's disease.

specific scales are needed to assess sleep state and wakefulness in PD. Among the various sleep questionnaires developed and validated, the Movement Disorder Society (MDS) Task Force identified six scales to meet the recommended criteria for sleep evaluation in PD. The PDSS and the Pittsburgh Sleep Quality index (PSQI) are recommended for rating the overall sleep problems by screening and measuring disease severity. The Scales for Outcomes in PD-sleep (SCOPA-sleep) is recommended for rating overall sleep problems by screening and measuring the severity as well as rating daytime sleepiness. The ESS is recommended for rating daytime sleepiness to screen and measure severity. The Inappropriate Sleep Composite Score is suggested for rating severe daytime sleepiness or sleep attacks to screen and measure severity. The Stanford Sleepiness Scale is suggested for rating sleepiness and to measure severity at a specific moment [26]. Among those scales, PDSS and SCOPA-sleep are PD-specific evaluation tools. PDSS can identify potential causes of night-time sleep problems, but is not useful in assessing daytime sleepiness. SCOPA-sleep can be used to assess both night-time and daytime sleep problems, without identifying the causes [27]. A PDSS-2 was introduced to improve the scale accuracy by including additional nocturnal symptoms such as RLS, sleep apnea, nocturnal akinesia and pain [28]. PD-specific sleep scales were translated and validated for use by Korean-speaking patients: Korean version of PDSS (K-PDSS-2) and SCOPA-Sleep (K-SCOPA-Sleep) [22,29].

COMMON SLEEP DISTURBANCES IN PD

Insomnia

Insomnia is the most common sleep problem in PD reported in 54%–60% of the patients. In the PPMI study, insomnia was the most common sleep issue throughout the 5-year follow-up period [12]. Overall characteristic features of insomnia in PD include sleep fragmentation, short total sleep time, and long sleep onset latency. Destruction of nocturnal sleep structure is linked to disease duration that is related to short total sleep time, long sleep latency, less deep sleep and REM time as disease progressed [30]. Direct evidence of blunted circadian regulation has been reported in PD suggesting that plasma melatonin concentration is significantly lower than in healthy controls [31]. Further, the melato-

nin concentrations differed according to the presence of EDS in the PD population. Suprachiasmatic nucleus (SCN) is known to play a role in the generation of circadian rhythms and pathologic changes in the SCN have been reported in various patients diagnosed with parkinsonism [32]. While, blunted circadian regulation in elderly people is associated with an increased risk of developing PD. In one follow-up cohort study, participants who developed PD showed blunted circadian activity with an odds ratio (OR) more than 3.0 [33]. Nocturnal hypokinesia, which is characterized by decreased ability to perform adequate axial rotation and/or truncal flexion to turn in bed, is a significant sleep problem with a prevalence up to 50% in patients with advanced PD [34]. Further, fewer changes in body position during sleep correlate with higher apnea-hypopnea index and EDS. Treatment of insomnia in PD usually starts with proper control of motor symptoms, such as tremors and management of underlying causes. Initiation of dopaminergic medications improves general sleep quality [11]. Pharmacological treatment includes eszopiclone and/or melatonin in selected cases [35].

Excessive daytime sleepiness

The prevalence of EDS varies with the study and ranges from 15% to 75% in patients with PD. Subjective reports of EDS by patients with PD revealed severe motor impairment, rapid progression of motor symptoms, and cognitive decline. Hypothalamic wake-promoting hypocretin cell loss is suggested as the pathophysiological basis of EDS in PD [36]. Further, EDS is associated with expanding Lewy body pathology in PD [37]. EDS is reported throughout the disease course of PD. The Honolulu-Asia Aging cohort Study reported that subjects having EDS showed a significantly increased risk of subsequent PD development [38]. The highest risk of developing 11-year PD in the general population was an EDS involving more than 1-hour nap [39]. During the disease course of PD, predictors of EDS over time include male sex, cognitive and autonomic dysfunction, co-morbid hallucination, PIGD PD subtype, high dosage of dopamine agonists, and use of antihypertensive medications [40]. Treatment of underlying causes is important for the management of EDS in PD due to the diverse etiology. Counselling for patient safety during daily activity and review of medications is a priority. Nonpharmacological timed light therapy improves alertness during daytime. Modafinil, which is a novel psychostimulant, can be possibly considered followed by caffeine, methylphenidate, and sodium oxybate based on investigational evidence [35,41,42].

REM SLEEP BEHAVIOR DISORDER

RBD is a unique parasomnia in PD population. Its importance in clinical practice is based on its strong prodromal diagnostic value indicating underlying synucleinopathy in the brain preceding the onset of clinical symptoms of neurodegenerative diseases. The presence of RBD in PD suggests poor prognosis and cognitive decline, increasing visual hallucination and cardiovascular

autonomic dysfunction. Approximately 6%–7% of patients with idiopathic RBD (iRBD) manifest newly developed neurodegenerative diseases each year [43,44]. RBD is a male-predominant parasomnia [45]. RBD in premotor stage of PD can be easily unrecognized as RBD symptoms are mostly not intractable and less troublesome than other sleep disorders in PD. In the year 2012, a single-question screening tool (RBD1Q: Have you ever been told, or suspected yourself, that you seem to ‘act out your dreams’ while asleep) was validated compared with previous longer questionnaires with high sensitivity (93.8%) and specificity (87.2%) [46]. Recently however, Yao et al. [47] reported in the Canadian Longitudinal Study on Aging (CLSA) that low positive predictive value of annual phenoconversion rate of RBD screen question (RBD1Q) (0.16%) compared with PSG-confirmed iRBD cohort cases (6.25%) for the future risk of parkinsonism [43]. GBA variants of PD gene carriers also increase RBD risk (9.5%) compared with controls (4.1%) with an OR of 2.45 [1.87–3.22] [48]. RBD in PD was associated with the risk of dementia in a prospective study suggesting widespread underlying neuropathology in the brain [49,50]. This finding demonstrated in the study that levels of α -synuclein oligomer and neuroinflammatory markers related to iron metabolism in cerebrospinal fluid and serum were significantly elevated in PD with probable RBD [51]. Prediction of disease progression using RBD as a prognostic biomarker was reported in an early PD cohort of PPMI study indicating that the presence of RBD at baseline was related to rapid progression of axial motor subscore, Hoehn and Yahr stage in patients with extensive synuclein and dopaminergic pathology, and cognitive decline based on MDS-UPDRS parts I and II in patients with severe synuclein and amyloid pathology. RBD in PD was also associated with worsening of depression and anxiety [52]. A review of current medications that might attribute to RBD is important. It is mandatory to ensure a safe sleep environment both for the patient and caregiver. As sleep apnea easily mimics RBD manifestations in general, a precise diagnosis to exclude such conditions is critical for the management of RBD [53]. In such a case, treatment of sleep apnea improves the symptoms. Melatonin is the first-line therapy due to its better safety profile. Clonazepam is effective in reducing RBD symptoms, but caution is needed due to its side effects [35,42,54].

RESTLESS LEGS SYNDROME

RLS is associated with dopaminergic treatment in PD; however, the precise relationship between RLS and PD needs to be further elucidated. It is widely known that RLS is more frequent in PD [55]. However, whether the prevalence of RLS is higher in PD than in age-matched healthy controls, and whether the risk of PD increases with baseline RLS is unknown. Although restlessness of leg movement, and not true RLS, is 3-fold higher in PD than in controls [56], the majority of patients with RLS in PD reported the onset of RLS after or together with the onset of PD motor symptoms [57], which suggests the possibility of disease-specific

nature of RLS in PD. Further, there is no correlation between dominant parkinsonism and RLS symptoms. However, RLS severity in PD is positively correlated with PD disease duration, longer dopaminergic treatment, and total daily dosage of levodopa treatment [58]. The findings that RLS severity are correlated with the degree of depression in PD and the use of antidepressants are known to promote RLS symptoms linked to serotonergic dysfunction of RLS in PD [59,60]. Periodic limb movements in sleep occur in up to 80% of patients with RLS, which may trigger microarousal during sleep [61].

Co-morbid RLS is associated with EDS, co-morbid depression, anxiety, and poor quality of life in PD [62]. Symptoms of RLS respond well to low dosage of dopaminergic drugs. Long-acting dopamine agonists or calcium channel α -2-delta ligands can be used as monotherapy or combination therapy. Another option for refractory RLS includes benzodiazepines and opiates [42,63].

CONCLUSION

Sleep disturbance is highly prevalent and the most common non-motor symptom in PD. Some of them occur in the premotor phase, which reflects underlying neurodegeneration in advance. Both neurodegeneration and disease-related medications contribute to further worsening of sleep problems and impaired quality of life in patients. Prompt recognition, diagnosis, and treatment of sleep disorders can yield meaningful prognosis. Although understanding of sleep problems in PD is challenging, prompt recognition and accurate clinical assessment of sleep problems is mandatory for proper PD management. Appropriate management of non-motor symptoms can improve the functional status and quality of life in patients diagnosed with PD and may potentially alter the course of disease progression.

Funding Statement

None

Conflicts of Interest

The author has no potential conflicts of interest to disclose.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

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