Sleep Disorders in Parkinson’s Disease

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ABSTRACT

Parkinson’s disease (PD) is a neurodegenerative disease that is associated with degeneration of dopaminergic neurons in the substantia nigra. Therefore, patients who are diagnosed with PD will exhibit clinical symptoms of dopaminergic depletion including motor and non-motor symptoms. Previously, physicians (please see comment on page 4) and researchers have been most interested in the aspect of motor problems. However, more recently, non-motor symptoms (NMS) have received similar recognition to motor symptoms. Some of the most common NMS are sleep disorders. The prevalence of sleep disorders ranges from 40 to 90 percent and the common sleep problems in patients with PD are insomnia, excessive daytime sleepiness, rapid eye movement, sleep behavior disorders, sleep related breathing disorders, restless leg syndrome and nocturia. This article includes the epidemiology, etiologies, common patterns and managements of sleep disorders in patients with PD.

Keywords: Sleep disorders in Parkinson disease, insomnia, rapid eye movement behavior disorders, restless leg syndrome, obstructive sleep apnea, nocturia

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INTRODUCTION

Parkinson’s disease (PD) is a neurodegenerative disease relating to progressive degeneration of dopaminergic neurons in the substantia nigra. The diagnostic criteria of PD were defined in a clinico-pathological study proposed by United Kingdom Parkinson’s Disease Society (UKPDS) in 1988. The consequence of degeneration of these neurons is depletion of dopamine in the central nervous system. Therefore, patients diagnosed with PD will exhibit clinical symptoms of dopaminergic depletion such as motor and non-motor symptoms (NMS). Motor symptoms in PD have been recognized in terms of four cardinal characterizing features; resting tremors, bradykinesia, rigidity and postural instability. Recently, NMS, such as autonomic dysfunctions, fatigue, pain, sleep disorders, hyposmia, abnormal behaviors and neuropsychiatric manifestations have become increasingly recognized. NMS occur in up to 60 percent of patients with PD. Some of the most common NMS are sleep disorders. The significant impact of sleep disorders on patients with PD is in poor quality of life when compared with the normal population. This article will focus on the epidemiology, possible causes of sleep disorders, scale systems to assess sleep impairment in PD, common sleep problems of patients with PD and current managements.

Epidemiology

The prevalence of sleep disorders in patients with PD ranges from 40 to 90 percent. This figure was supported by a recent study conducted by Goetz et al. The study showed a high prevalence of sleep disorders that approached to 98 percent at 10-years of follow-up. According to Braak’s postulation, sleep disorders can develop in any state of PD such as the pre-motor state, the motor state or the advanced state. The evidences of sleep disorders which develop in the pre-motor state have been confirmed by many studies. Abbott and colleagues demonstrated that elderly who had excessive daytime sleepiness (EDS) were at a higher risk of developing PD when compared to subjects who did not present EDS (odds ratio = 3.3, 95% CI = 1.4 to 7.0, p-value = 0.004). Another study conducted by Claassen et al found that 4.9 percent of patients with rapid eye movement sleep behavior disorder (RBD) subsequently developed parkinsonism and / or dementia (PD, diffused Lewy body dementia (DLB), or multiple system atrophy (MSA) and that the latency between the onset of RBD and other clinical features...
was at least 15 years. A study of the overall prevalence of sleep disorders in Thai patients with PD has not been conducted yet.

Common sleep problems of patients with PD are insomnia, EDS, RBD, sleep related breathing disorders (SRBD), restless legs syndrome (RLS) and nocturia.

**Etiologies of sleep disorders in patients with PD**

Appropriation of sleep activity is usually based upon the interaction between the individuals and the environmental circumstances such as either light or dark environments and either noisy or silent environments. Despite the control of environmental factors, patients with PD also have various causes that disturb their sleep activity. The etiologies can be grouped into three categories; 1) PD related to sleep disorders, 2) specific causes of sleep disorders and 3) treatments related to sleep disorders. The possible causes of sleep disorders related to patients with PD have been summarized in Table 1.

**Scale systems to assess sleep impairment in PD**

Because of the high prevalence and various types of sleep disorders in PD, researchers have developed many tools for detecting these sleep problems such as sleep scales or neurophysiologic methods. Unfortunately, the neurophysiologic studies are expensive, are time consuming and require a sleep medicine subspecialist to interpret the results. Thus, the sleep scales have become more popular. The benefits of sleep scales are that they are easy to use in out patient or community-based settings, inexpensive and mostly self-assessed. However, using the scales has some limitations in determining problems. First of all, assessment by sleep scale is subjective evidence. If the patient or caregiver lacks awareness of sleep problems, the result will not be accurate. Another limitation is the patient with PD may develop multiple types of sleep disorders. Due to this reason, a physician may need many sets of scales for detecting sleep problems in one patient. Finally, if a patient develops cognitive impairment, the data gathering and data interpretation will be of diminished accuracy.

The PD Sleep Scales (PDSS) is the most popular scale for screening sleep disturbances and the severity of sleep problems over the previous week including both nighttime and daytime symptoms. This scale is composed of 15 items. Each item is rated by a visual analog scale from 0 (most severe) to 10 (no disturbance) with a higher score reflecting a better sleep quality. This scale is a screening test. It has no power to diagnose the specific sleep problems such as RBD, SRBD and RLS. Another scale is the Pittsburgh Sleep Quality Index (PSQI), a self-assessment scale that was proposed to assess sleep quality over the previous month. This scale is composed of 19 items. Each item is categorized into 4 sub-scores with, 0, 1, 2 or 3 points, respectively. Then each item is combined to create 7 components following the instructions of a protocol. The maximum score is 21 points with a higher point reflecting a lower sleep quality. The cut-off point indicating a poorer sleep quality is more than 5 points. Similar to the PDSS, this scale is only a screening test. The Scales for Outcome in PD (SCOPA-SLEEP) was developed for evaluating daytime sleepiness and sleep quality in PD over the past month. This scale is composed of 3 sub-scales; a nighttime scale, a sleep quality scale and a daytime scale. The nighttime scale is composed of 5 items (rated from 0 to 3 points for each item). Thus, the maximum score is 15 points with a higher point reflecting greater nighttime sleep problems. The sleep quality scale is a single item referring to a global measurement of sleep quality. The daytime scale is composed of 6 items (rated from 0 to 3 points for each item). Thus, the maximum score is 18 points with a higher point reflecting greater

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**TABLE 1.** The possible causes of sleep disorders in patients with PD

<table>
<thead>
<tr>
<th>1) PD related sleep disturbances</th>
<th>1.1) Nocturnal motor symptoms</th>
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<tr>
<td>1.1.1) Tremors</td>
<td>1.1.2) Dystonia</td>
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<td>1.1.3) Dyskinesia</td>
<td>1.1.4) Rigidity, akinesia</td>
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<td>1.1.5) Limbs jerking</td>
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<td>1.2.1) Autonomic dysfunction e.g. urinary incontinence</td>
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<td>1.2.2) Neuropsychiatric manifestations e.g. dementia, delusion, hallucination, depression and anxiety</td>
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<td>1.2.3) Sensory disturbances e.g. muscle cramp and pain</td>
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<tr>
<td>2) Specific sleep disorders</td>
<td>2.1) Dyssomnias e.g. insomnia, excessive daytime sleepiness (EDS)</td>
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<td>2.2) Parasomnia e.g. rapid eye movement sleep behavior disorder (RBD)</td>
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<td>2.3) Sleep related breathing disorders (SRBDs) e.g. obstructive sleep apnea (OSA)</td>
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<td>2.4) Restless leg syndrome (RLS)/Periodic limb movement during sleep</td>
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<td>2.5) Circadian rhythm disruption</td>
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<td>3) Treatments related sleep disturbances</td>
<td>3.1) Medication e.g. levodopa, dopamine agonist, MAOB inhibitor,anticholinergics and antipsychotics</td>
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<td>3.2) Deep brain stimulation (DBS)</td>
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MAOB – Monoamine oxidase B, COMT – Catechol-o-methyl transferase
Common sleep problems of patients with PD and managements

Insomnia

The clinical characteristics of insomnia are defined as at least one symptom of difficulty in falling asleep, difficulty to maintain sleep, early awakening, or inability to get refreshing sleep occurring despite adequate opportunities for sleep. Among the characteristics of insomnia, the category of difficult sleep maintenance, which causes greater sleep fragmentation and frequent night awakening, is the most common pattern of insomnia in patients with PD. The consequences of disruption of sleep maintenance are reduction of total sleep times and increasing daytime somnolence from circadian rhythm disruption. The various causes of disturbance of sleep maintenance are identified as; abnormal movements associated with primary PD pathology or associated with anti-parkinsonian medication, and frequent nocturia or neuropsychiatric manifestations such as delusion, hallucination or depression. Previously, Lee and colleagues showed factors disturbing sleep maintenance overnight in patients with PD including; nocturia (79%), difficulty of turning over in bed (65%), painful muscle cramps (55%), nightmares (48%), limb or facial dystonia (34%), jerking of legs (33%), and visual hallucinations (16%).

Another cause of insomnia in patients with PD is anti-parkinsonian medications such as Monoamine oxidase B (MAOB) inhibitors, particular in selegiline because a metabolite of selegiline is a derivative of amphetamine. Therefore, patients with PD prescribed selegiline in the evening or before bedtime may develop insomnia. Insomnia is associated with the duration of PD, the severity of motor symptoms, complications of dopaminergic treatments and depression.

Managements include demonstrating and correcting the factors that disturb the sleep-wake cycle such as inappropriate environment, abnormal movements during nighttime (dyskinesia, akinesia, tremor, RLS), and neuropsychiatric symptoms (hallucination, delirium, depression, anxiety). If those factors are corrected and patients still have sleeping difficulties, the physician can consider prescribing medications. Zolpidem, a non-benzodiazepine, that has been approved by United States Food and Drug Administration (U.S. FDA) for treating insomnia should be considered. Other medications such as eszopiclone, melatonin and low dose quetiapine may have some potential for improving insomnia.

Excessive Daytime Sleepiness (EDS)

Another entity of diurnal alterations of sleep pattern is EDS. EDS is defined by the Epworth Sleepiness Scale (ESS) as being more than 10 points or a mean sleep latency less than 5 minutes on the Multiple Sleep Latency Test. Previous epidemiologic studies showed the prevalence of EDS in patients with PD ranged from 15 to 50 percent. EDS creates negative impacts to quality of life such as automobile accidents. The manifestations of EDS are divided into two types. First, patients know that they feel sleepy in the daytime and they try to resist it, but they cannot avoid falling asleep. Second, the sudden onset of sleep was described by Frucht et al., who coined the term “sleep attack”. In sleep attack, patients do not have self-awareness which is similar to narcolepsy. The differential symptom between PD and classic narcolepsy is that patients with PD have a lack of clinical cataplexy. The role of low orexin levels in the cerebrospinal fluid is that patients with PD have self-awareness which is similar to narcolepsy. The International RLS Study Group (IRLSSG) composed of 8 items (rating from 0 to 3 points) for detecting nocturia includes 7 items. Question number 7 is for screening the symptom of nocturia and is used for detecting nocturia on sleep quality. This scale is composed of; an urge to move the legs, usually accompanied by uncomfortable and unpleasant sensations, onset or aggravation during periods of inactivity, and relief by movement and worsening in the evening or at night. RBD is diagnosed by history from their sleep partner of shouting, walking or kicking with definite diagnosis requiring polysomnography. The RBD screening questionnaire (RBDSQ) is a promising tool for screening RBD, but validation in different populations is required. Finally, detection of nocturia is a clinical observation. The International Prostate Symptom Score (IPSS) includes 7 items. Question number 7 is for screening the symptom of nocturia and is used for detecting nocturia and other urinary symptoms in both men and women in a variety of population groups. A higher score reflects greater urinary problems which produce a negative impact on sleep quality.
correct factors that disrupt the sleep-wake cycle. Physicians should stop the medications that cause nighttime awakening such as selegiline. All anti-parkinsonian medications can cause EDS in particular dopamine agonists. Reducing dosage or discontinuation of dopamine agonists should be considered in patients with sleep attack. If the patients cannot tolerate to reduce their anti-parkinsonian medications because of worsening motor symptoms, administration of psycho-stimulants such as modafinil, 38,39,40 armodafinil, 41,42 sodium oxybate 43 and tiprolisant 44 should be considered.

**Rapid Eye Movement (REM) Sleep Behavior Disorder (RBD)**

RBD is categorized in the subgroup of parasomnias. Characteristic of RBD are defined as loss of muscle atonia during REM sleep period, proven by electromyography, which results in dream-enacting behavior associated with nightmares or vivid dream. In REM sleep periods, patients may shout, kick, or jump out of their bed which often leads to injury of the individual or their bed partner. The brain areas that may play a role in the pathophysiology of RBD were described to be the locus coeruleus, the pedunculopontine nuclei, the cholinergic nuclei, the laterodorsal tegmental nuclei and the limbic area. 2,45 According to the data from Scheck et al, many recent studies have shown a relationship between RBD and the risk of developing PD and other synucleinopathies associated neurodegenerative disorders such as MSA and DLB. 46 One study reported a cumulative risk of developing neurodegenerative disorders in patients with RBD as 17.7, 40.6 and 52.4 percent at 5,10 and 12-years of follow-up, respectively. 47 RBD can occur in all states of PD. The latency between RBD and the onset of motor symptoms ranges from 15 to 50 years (mean = 28.4 years). 48 Idiopathic RBD patients present with some non-motor manifestations that can found in PD, and other synucleinopathies associated neurodegenerative disorders, such as olfactory deficits, 48,49 color vision impairment, 48 cognitive impairment on neuropsychological testing, 50 slowing of electroencephalography, 51 abnormalities of cardiogenic autonomic nervous systems, 52,53 and reduced cardiac 123I-MIBG scintigraphy. 54 These finding suggest that idiopathic RBD may share some pathophysiology with PD. Almost all patients with PD who develop clinical signs of RBD are of the non-tremor phenotype, exhibiting; frequent falling, poor response to dopaminergic medications, orthostatic hypotension and impaired color vision. On the other hand, disease severity and motor complications did not differ between patients with PD together with RBD and those without RBD. 55,56 Some medications potentially induce RBD such as antidepressants; for example, selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants and serotonin norepinephrine reuptake inhibitors (SNRI), beta-blockers and barbiturates. 57

Medications that can relieve symptoms of RBD in idiopathic RBD and RBD associated with PD are similar. Clonazepam, a long acting benzodiazepine, is the most effective medication for controlling symptoms of RBD. 58 Other medications such as melatonin, 59,60 pramipexole, 61,62 zopiclone, levodopa, sodium oxybate 63 and donepezil 64 have been reported for efficacy in controlling symptoms of RBD.

**Sleep Related Breathing Disorders (SRBD)**

SRBD or sleep apnea syndromes have been observed in patients with PD. Previous studies have shown the prevalence of SRBD ranges from 20 to 66 percent in patients with PD. 65,66 The most common clinical syndrome observed in PD is OSA. OSA is defined as; heavy snoring, an apnea-hypopnea index of more than 5 and oxygen desaturation. The severity of OSA in PD usually presents in a mild to moderate degree when compared with primary OSA. 67 A recent study has shown that the rate of OSA in patients with PD does not significantly differ from the general population. 68 In contrast, one study showed the rate of sleep apnea was less observed in PD than in an in-hospital control group who exhibited daytime sleepiness that was caused by non-apneic mechanisms (27 percent versus 40 percent). 69 In summary, the relationship between SRBD and PD is inconclusive. Two possibilities that could explain clinical symptoms of upper airway obstruction in patients with PD have been proposed: 1) dysfunction of upper airway muscles due to akinesia or dyskinesia 70,71 and 2) vocal cord abductor dysfunction that can cause sudden death during the nighttime. 70

The important issues of OSA are increasing cardiovascular events and upper airway obstruction at nighttime. Both conditions are life threatening. Therefore, physicians must ask the patient’s partner for the frequency and the duration of apnea intervals and the frequency of nighttime awakening. If the patient’s partner notices this condition, the patients must be scheduled to have polysomnography performed. Additionally, the physician should make a decision to treat the patient with a continuous positive airway pressure ventilation method.

**Restless Leg Syndrome (RLS)**

RLS is a clinical diagnosis that is diagnosed by criteria from the IRLSSG (mentioned earlier). 19 Therefore, RLS can disturb the sleep-wake cycle and produce insomnia. Previous epidemiologic studies have reported the prevalence of RLS in PD ranges from 0 to 49 percent. 19,72 A recent study that was conducted by Bhalsing and colleagues from India showed the prevalence of RLS in neurodegenerative diseases compared with healthy controls. According to the results of this study, the prevalence of RLS in the neurodegenerative disease group was higher than in the control group (9.6 vs. 2.9 percent; p=0.009) and the prevalence of RLS in PD (11.9 percent) was higher than in MSA, PSP and DLB. 72 The explanations for this variety of prevalences of RLS in PD are: dopaminergic agents diminishing motor symptoms, which include RLS symptom and some patients recognizing RLS symptoms as part of PD. At present, the pathogenesis of RLS is still unknown and the relationship between the pathogenesis and neuropathology of RLS and PD is inconclusive. Most researchers suggest that RLS might share the same pathogenesis as PD. The supportive evidence is clinical response to dopaminergic agents such as dopamine agonists similar
to PD. However, autopsy study showed a low level of iron deposit in the substantia nigra\textsuperscript{73} in contrast with PD, which showed a high level of iron deposit in the substantia nigra.\textsuperscript{74} Another possible pathogenesis is iron or ferritin deficiency. Low serum ferritin level, less than 50 ng/mL was observed in RLS. Furthermore, some studies have shown that low iron and ferritin levels in the CSF were also detected in patients with RLS.\textsuperscript{75,76} The interaction between iron depletion and dopaminergic dysfunction is unclear. However, a previous study in an animal model conducted by Zhao et al., showed that the synergistic effect of iron deficiency and dopamine depletion could significantly worsen the symptoms of RLS compared with only the dopamine depletion group. In addition, this study also found that iron deficiency and dopaminergic depletion produced a high degree of reduction of the binding capacity of dopamine receptor subtype 2 (D2)\textsuperscript{77}. Symptoms of RLS are aggravated by caffeine, alcohol, and several medications such as antihistamines, dopamine antagonists, tricyclic antidepressants and SSRIs.\textsuperscript{78} Another possible pathogenesis of RLS is genetic transmission. A previous epidemiologic study showed that the patients diagnosed with idiopathic RLS had a positive family history of idiopathic RLS at a rate of approximately 63 to 90 percent. The mode of inheritance is usually autosomal dominant.\textsuperscript{79} Mappings of the RLS locus on the chromosome were varied depending on the ethnic group. For example, the RLS locus was located on the long arm of chromosome 14 in Italian populations,\textsuperscript{80} the short arm of chromosome 20 in Dutch populations\textsuperscript{81} and the long arm of chromosome 13 in Turkish populations.\textsuperscript{82} However, the gene most reported in various populations was BTBD9 on the short arm of chromosome 6.\textsuperscript{83}

Treatment response is individualized. It depends upon the severity of symptoms. Various medications can relieve symptoms. The first line pharmacologic treatment is dopamine agonists in particular pramipexole and ropinirole.\textsuperscript{84,85} Both agents have been approved by the U.S. FDA for moderate to severe RLS. Another medication is levodopa. A levodopa study, involving 28 patients, showed improvement of sleep quality, increasing sleep time, and reduction of symptom of RLS.\textsuperscript{86} In the case of non-responsiveness to dopaminergic agents, if a low serum ferritin level of less than 50 ng/mL is detected, the patients should be treated by oral ferrous sulfate. The second-line medications such as opioids\textsuperscript{87} (methadone, oxycodone and codeine), clonazepam,\textsuperscript{88} gabapentin\textsuperscript{89} and pregabalin\textsuperscript{90} should be considered in patients who do not respond to first line agents.

**Nocturia**

The lower urinary tract symptoms in PD such as nocturia, urgency, frequency and urge incontinence are not uncommon. A recent multicenter study, the PRIAMO study, showed that the overall prevalence of lower urinary tract symptoms in any stage of PD was approximately 57 percent and nocturia showed a high prevalence in this group (35 percent).\textsuperscript{91} This result is concordant with a previous study that was conducted by Campos-Sousa et al. The study reported a high prevalence of nocturia in patients with PD (greater than 60 percent).\textsuperscript{92} The possible mechanisms of nocturia in patients with PD are divided in to 2 possibilities; 1) lower urinary tract dysfunction associated with the disease process and 2) pharmacological effects of anti-parkinsonian medications. The most possible explanation of the symptom of nocturia in PD is due to the process of detrusor overactivity. A previous study in patients with PD showed an involuntary rise in detrusor pressure in the period of filling of the bladder.\textsuperscript{93} The explanation of detrusor overactivity is disinhibition of dopaminergic action via dopaminergic subtype 1 (D1) receptors. Normally, the micturition reflex is inhibited by the basal ganglia due to the stimulation of D1 receptors. In PD, the dopaminergic circulation in the basal ganglia circuit is reduced due to the neuronal degeneration. Because of dopaminergic depletion, the activation of D1 receptors is reduced. Therefore, the inhibition of the micturition reflex by the basal ganglia is decreased causing detrusor overactivity.\textsuperscript{94} Another possible mechanism that causes nocturia is the pharmacological effects of anti-parkinsonian medications. The level of levodopa on urinary dysfunction has been studied and the results were inconclusive. One study conducted by Brusa et al., showed levodopa aggravated the symptoms of detrusor overactivity in the early stage of PD.\textsuperscript{95} The other study, conducted by Winge et al., showed levodopa increased bladder capacity in patients with PD who had more troublesome bladder symptoms than at the off treatment stage.\textsuperscript{96} More evidence that supports the inhibition of the micturition reflex via the action of the D1 receptors comes from the studies of dopamine agonists that produce a high affinity to D1 receptors. Apomorphine\textsuperscript{97} and pergolide\textsuperscript{98} showed improvement of detrusor overactivity in PD. The negative impact of nocturia to sleep quality in patients with PD has recently been reported.\textsuperscript{99} The study used an objective sleep measurement by in-laboratory 48 hours polysomnography evaluation. The result showed high bother to urinary dysfunction, defined by the global bother question on the International Prostate Symptom Score (IPSS),\textsuperscript{21,22} whose subjects had a significantly poor sleep efficiency and total sleep time.

The medication of choice for treatment detrusor overactivity and also nocturia is anticholinergic agents. The efficacy of anticholinergic agents for reducing the symptoms of detrusor overactivity has been reported from other conditions than PD. The agents such as oxybutynin\textsuperscript{100}, tolterodine XL\textsuperscript{101} and trospium chloride\textsuperscript{102} were studied for reducing the symptoms of detrusor overactivity from any causes. The important adverse effect of anticholinergic agents is cognitive. Therefore, the physician should be aware of these conditions when prescribing the anticholinergic agents especially in the agents that are designed to act on the central nervous system such as benzhexol.\textsuperscript{103} Another adverse effect is urinary retention. The physician should perform the measurement of residual urine volume if the patients complain difficulty to void and empty their bladder.

**CONCLUSION**

Recently, NMS in patients with PD have been recognized. Some of the most common NMS are sleep
disorders that impair the quality of life in PD. This article has reviewed the common patterns of sleep disorders that can occur in PD. Recently, sleep disturbances have been extensively studied in term of mechanism of diseases, impact on quality of life and treatment modalities. Moreover, sleep disorders do not only occur in PD, but also in other neurodegenerative diseases such as DBL, MSA and Alzheimer’s disease. Areas of uncertainty in sleep disorders in other neurodegenerative diseases are still fascinating. Therefore, the field of sleep medicine must be extensively explored to solve many mysterious questions for the benefit of the neurodegenerative patients.

REFERENCES


