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Review Article

The sleeping brain in Parkinson's disease: A focus on REM sleep behaviour disorder and related parasomnias for practicing neurologists

Roongroj Bhidayasiri [a,b,*], Jirada Sringean [a], Watchara Rattanachaisit [a], Daniel D. Truong [c]

[a] Chulalongkorn Centre of Excellence for Parkinson's Disease & Related Disorders, Department of Medicine, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital and Thai Red Cross Society, Bangkok, Thailand
[b] Department of Rehabilitation Medicine, Juntendo University, Tokyo, Japan
[c] Parkinson's and Movement Disorders Institute, Fountain Valley, CA, USA

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ABSTRACT

Sleep disorders are identified as common non-motor symptoms of Parkinson's disease (PD) and recently this recognition has been expanded to include parasomnias, encompassing not only REM sleep behaviour disorder (RBD), but also other non-REM forms. RBD, a prototypical parasomnia in PD, exists even in the prodromal stage of the disease, and is characterized by the presence of dream enactment behaviours occurring alongside a loss of normal skeletal muscle atonia during REM sleep. In contrast, non-REM parasomnias are more frequently observed in the late stage PD. However, the development of these disorders often overlaps and it is not uncommon for PD patients to meet the criteria for more than one type of parasomnias, thus making a clinical distinction challenging for practicing neurologists who are not sleep specialists. Indeed, clinical recognition of the predominant form of parasomnia does not just depend on video-polysomnography, but also on an individual physician's clinical acumen in delineating pertinent clinical history to determine the most likely diagnosis and proceed accordingly. In this review article, we highlight the various forms of parasomnias that have been reported in PD, including, but not limited to, RBD, with a focus on clinical symptomatology and implications for clinical practice. In addition, we review the differences in PD-related parasomnias compared to those seen in general populations. With advances in sleep research and better technology for ambulatory home monitoring, it is likely that many unanswered questions on PD-related parasomnias will soon be resolved resulting in better management of this nocturnal challenge in PD.

Contents

* Corresponding author at: Chulalongkorn Center of Excellence for Parkinson's Disease & Related Disorders, Chulalongkorn University Hospital, 1873 Rama 4 Road, Bangkok 10330, Thailand.
E-mail address: rbh@chulapd.org (R. Bhidayasiri).

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1. Introduction

While normal individuals sleep comfortably throughout the night, patients with Parkinson's disease (PD) may experience night-time problems that can affect their, and their caregivers, quality of life (QOL) [1–3]. A number of well-controlled studies have demonstrated a high prevalence (up to 98%) of a wide variety of sleep disorders amongst PD patients [4,5]. By concentrating their evaluation only on sleep duration and maintenance, physicians may underestimate the extent of sleep problems experienced by PD patients as patients are likely to experience more than one symptom complex during the night with common symptoms including akinesia, insomnia, nocturia, psychosis, and parasomnias [4,6,7]. This review focuses on parasomnias only.

Parasomnias are defined as undesirable physical phenomena or sensory experiences that occur with entry into, during, or arousing from sleep, and consist of clinical disorders that are related to rapid eye movement (REM) sleep, non-rapid eye movement (NREM) sleep, or sleep-wake transitions (Table 1) [8]. Parasomniac experiences may be cognitive-emotional (e.g. sleep terrors) or sensory (e.g. sleep-related hallucinations) and can be either common and normal behaviours or bizarre and unusual, described by bed partners as either frightening or entertaining stories. As the initial pathology of prodromal and early stage PD is focused in the brainstem, but then gradually progresses to various cortical regions as the disease advances, it is not a surprise that the disorders relating to states of REM, NREM, and wakefulness are not distinct "flick of a switch" phenomenon. Progressive neurodegenerative changes that occur in PD can affect the 'ascending' control of sleep state transition, leading to dissociated arousals from NREM and REM sleep, as well as the 'descending' control of locomotion and muscle tone, thus creating a variety of parasomnias [9]. Of these, REM sleep behaviour disorder (RBD) is by far the best-characterized and most common parasomnia in PD patients with an estimated prevalence between 30 and 59% [7,10]. However, other forms of parasomnia have been described in patients with PD, but the knowledge of, and therefore the recognition of these non-RBD parasomnias may be low amongst non-sleep specialist neurologists who are involved in the care of PD patients [7]. In this article, we will review the available literature for the various forms of parasomnia highlighting the wide spectrum of these disorders in PD patients. While many forms of parasomnia are described in the recent 3rd edition of the International Classification of Sleep Disorders (ICSD), the selection of the disorders chosen for this review article is based on their relevance to PD in order not to duplicate the discussion of the same disorders included in other articles in this supplement (Table 1) [8]. Certain characteristics of each of the selected disorders in relation to PD will also be reviewed. Although this article is not an exhaustive systematic review of the literature on parasomnias in PD, it focuses on the clinical implications of each disorder derived from the key literature review and the authors' clinical experience pertinent to the practice of physicians who frequently take care of PD patients.

Table 1
Parasomnias with reported prevelance in patients with Parkinson's disease.

Parasomnias	Reported prevalence
REM-related parasomnias	
- REM sleep behaviour disorder	- 22.7–85% [7,10,25,64] - Association of RBD with NREM sleep parasomnias (overlapping syndrome) [7]
NREM-related parasomnias	
- Confusional arousals	- Observed in PD patients with dementia but exact prevalence is not known [25]
- Sleepwalking	- 1.7–9% [7,9,52,54] - 1.7% (RBD with sleepwalking) [7]
- Sleep terrors	- 3.9–8.3% [7,59] - 6.8% (with nocturnal vocalisation) [59]
- Sleep-related eating disorder	- 2 documented case reports [63]

2. Clinical differentiation between REM and NREM parasomnias in patients with Parkinson's disease

In PD patients with suspected parasomnias, physicians are confronted with several different diagnostic possibilities, not limited to RBD, although RBD is generally the first thought by many physicians due to its recognition in the PD literature. While it is true that RBD is the most frequent parasomnia in PD, evidence is mounting that PD patients may also suffer from NREM parasomnias, disorders of sleep-wake transitions, movement disorders in sleep (e.g. periodic limb movements, sleep apnea), or even seizures. In general, parasomniac episodes are not usually stereotypical, therefore they are easily distinguished from nocturnal seizures in which stereotypic behaviours are usually observed, at least at the beginning [11]. In a recent questionnaire survey of parasomnia in PD patients, probable RBD was identified in 39% of patients and the prevalence of other forms of parasomnias was not rare, including enuresis (21%), nightmares (17.2%), hallucinations (15.3%), and night terrors (3.9%) [7]. Indeed, over 80% of PD patients with RBD symptoms were found to have symptoms of at least one another parasomnia or some other isolated sleep symptom [7]. Therefore, it is essential that physicians be aware of all forms of parasomnia and glean pertinent clinical history from both patients and their bed partners to aid the differential diagnosis, and identify those who may need video polysomnography (v-PSG) as a diagnostic confirmation when presentations are atypical, associated with other sleep comorbidities, or a risk for self-harm or harming others [12].

In our view, when confronted with a PD patient with parasomnia, the first step is to determine when these episodes occur in relation to sleep stages. Certain clinical clues can assist physicians in the differentiation between REM and NREM parasomnias (Table 2). Unlike NREM parasomnias, RBD patients do not walk, do not interact with the environment with restricted behaviours in the bedrooms and do not make conversations with bed partners during the episode [13]. The eyes of RBD patients are usually closed in contrast to patients with disorders of arousal whose eyes are usually open. Once woken from an episode, RBD patients usually have a normal level of consciousness, whereas patients with NREM parasomnias may appear half-awake. Moreover, most patients with RBD are able to recall their dreams while recalling abilities are limited in patients with NREM parasomnias. However, it is also important to differentiate vivid dreams, night terrors, and nightmares from parasomnias, which can be mistaken for hallucinations or confusion episodes by the family [14,15]. Patients with arousal disorders usually wake up with confusion and retrograde amnesia, which is not seen amongst RBD patients. It is also important to realise that several parasomnias can occur in one patient (e.g. RBD and sleepwalking), and this is probably not uncommon in PD patients [9]. In addition, a review of the patient's medications is crucial since certain medications, particularly antidepressants, benzodiazepines and zolpidem, can potentially precipitate RBD or confusion in PD patients [16–18]. Even antiparkinsonian medications themselves have been reported to precipitate vivid dreams, night terrors, nightmares, and hallucinations [14].

3. REM sleep-related parasomnias in Parkinson's disease

3.1. REM behaviour disorder (RBD)

RBD represents a dramatic manifestation of night-time events in patients with PD, and are frequently recalled by bed partners as occurring years before the presentation of classic motor symptoms. This observation reflects the neuronal loss and Lewy-type, α-synuclein degeneration of the brainstem nuclei that modulate REM sleep (REM-on and REM-off pontine nuclei) and their anatomical inputs from other regions that occurs in PD. According to Braak's theory, this degeneration occurs in the second stage (Braak's stage 2: sublaterodorsal nucleus, magnocellular reticular formation, peri-locus coeruleus) and emerges before the propagation of similar degeneration affecting the dopaminergic-producing