Sleep disturbances in progressive supranuclear palsy syndrome (PSP) and corticobasal syndrome (CBS)

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Abstract

Introduction. Progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) are clinical manifestations of tauopathies. They are commonly associated with rapid motor and cognitive deterioration. Sleep disturbances are less frequently described as a feature of these diseases, though they are reported among 50–75% of PSP patients.

State of the art. Apart from various clinical manifestations, sleep abnormalities in PSP and CBS seem to be a factor enhancing pathogenesis as well its consequences. Multiple researchers have looked into the issue of whether the complexity of sleep disturbances in PSP and CBS could be linked to atrophic changes within structures crucial for daytime regulation, coexisting pathologies, or other less explored mechanisms.

Clinical significance. Among sleep abnormalities in PSP and CBS have been reported excessive daytime sleepiness, night-time insomnia, reduction of total sleep time, more pronounced sleep fragmentation, restless leg syndrome (RLS), agrypnia excitata, periodic limb movements, sleep respiratory disturbances, rapid-eye movement behaviour disorder, and others.

Future directions. The aim of this review was to elaborate upon the significance of sleep abnormalities in tauopathic parkinsonian syndromes, and to determine their usefulness in differential diagnosis with synucleinopathic parkinsonian syndromes. Extended analyses of sleep disturbances may provide a different perspective on atypical parkinsonisms.

Key words: progressive supranuclear palsy, corticobasal syndrome, CBS, PSP, sleep disturbances

Introduction

Progressive supranuclear palsy syndrome (PSP) and corticobasal syndrome (CBS) are clinical manifestations of tauopathies. They are classified as atypical parkinsonisms. While PSP is most commonly associated with PSP pathology, CBS is observed among patients with various pathologies, among which could be mentioned what used to be known as corticobasal degeneration (CBD), PSP, frontotemporal degeneration (FTD), Alzheimer’s disease (AD) and others.

The pathogenesis of these diseases is not fully understood [1]. There has been growing interest in the non-motor symptoms of tauopathic parkinsonian syndromes [2], and more attention has recently been paid in the context of sleep disturbances in this group, a feature often omitted in clinical examination.

Clinical significance

The frequency of sleep disorders among patients diagnosed with parkinsonisms varies widely. An observational study...
released in 2010 evaluated 1,307 patients with parkinsonisms, among whom 34 patients had multiple system atrophy (MSA), 30 had PSP, 14 had dementia with Lewy bodies (DLB), and 11 had CBD. Sleep disturbances were observed in more than 75% of patients with PSP and DLB, in c.65% of those with MSA and PD, and only in 36.4% of CBS patients [3].

This discrepancy between PSP and CBD may suggest that the sleep disturbance in parkinsonian syndromes may not be directly associated with underlying pathology, as both entities are tauopathies.

Though sleep disorders are interpreted as a common feature of PSP, they are not indicated in the criteria of diagnosis [4]. The incidence of sleep abnormalities in CBS is less specified. The aim of this review was to present an overview of findings concerning sleep abnormalities in PSP and CBS.

Material and methods

Our search for articles related to sleep abnormalities in PSP and CBS was based on the use of the PubMed database. We used the phrases “Corticobasal Syndrome Sleep”, “Corticobasal Syndrome Sleep Abnormalities”, “Progressive Supranuclear Palsy Sleep”, and “Progressive Supranuclear Palsy Sleep Abnormalities”. Due to the rarity of the syndromes, we also acknowledged case reports and research studies based on groups of fewer than 10 patients examined. Additionally, due to the evolution of terminology, certain older works referring to “Corticobasal Syndrome” used to describe it as “Corticobasal Degeneration”. The goal of our search was to obtain a perspective dedicated to these clinical entities.

Sleep disturbances

Sleep disturbances in development of neurodegeneration

Sleep disturbances have been evaluated as a factor in neurodegeneration. They may be a condition preceding the initiation of other symptoms of neurodegenerative disease. The exact relation between these processes is not verified. Growing interest is associated with dysfunction of the glymphatic system, which on the one hand is linked with slow-wave sleep, while on the other hand its abnormalities have been found to contribute to neurodegeneration [5]. The role of the glymphatic system has been evaluated in PD, where the extracellular accumulation of alpha-synuclein is a feature impacting upon the neuroinflammatory and glymphatic response [6]. Deficits of the glymphatic system, a deterioration in eliminating waste proteins, and the correlation between this and an increase of tau accumulation have also been studied in AD [7]. Abnormalities of the system have been interpreted as possibly modifiable points in the pathogenesis of dementia [7]. Sleep abnormalities have been indicated as parallel features correlated with this process, as the accumulation of tau may disrupt the wake-sleep cycle. To the best of our knowledge, no study presenting this issue in PSP and CBS has previously been published.

Sleep disturbances in progressive supranuclear palsy

The first report presenting PSP indicated that fatigue was a feature of the disease [8]. With the evolution of knowledge concerning this disease, sleep abnormalities and night-time behavioural deviations became associated with approximately half of PSP patients [9]. Interestingly, the abnormalities have been interpreted as moderate to severe among almost one out of four [9]. Among sleep disturbances associated with PSP can be mentioned excessive daytime sleepiness, night-time insomnia, reduction of total sleep time, more pronounced sleep fragmentation, rapid-eye movement behaviour disorder, restless leg syndrome (RLS), and sleep respiratory disturbances [10–13]. Insomnia and deviated sleep architecture are the most common sleep abnormalities in PSP [14]. Sleep disturbances are rarely observed at the time of diagnosis. However, they are reported by 50% of patients who have experienced three years or more of disease duration [15].

Sleep disturbance has been interpreted as a factor inducing up to a quadrupling in mortality in PSP [16]. Additionally, the pathogenesis of sleep abnormalities seems multifactorial, being on the one hand linked with neurodegenerative changes within the brainstem, and on the other hand being associated with cognitive, pseudobulbar and extrapyramidal disturbances [17]. The sleep disturbances in PSP may be also related to degeneration of the thalamus, as this has been interpreted as a milestone in the gating of sensory information, which induces different patterns of activity during sleep and wakefulness [18]. Abnormalities related to the thalamus have been reported in various works, although the issue of sleep disturbances associated with these deviations was not explored [19–21]. Hypothalamus, another structure impacted upon by PSP degeneration, is associated with decreased pre- or postsynaptic orexin neurotransmission [22]. In a work evaluating orexin levels in the cerebrospinal fluid in PD, DLB, PSP and CBD, it was revealed that its levels were significantly lower in tauopathic parkinsonian syndromes [23].

The disturbance of orexin regulation may cause abnormalities in the sleep–wake cycle [24]. Interestingly, disturbances of this cycle may be both a manifestation and a cause of neurodegenerative disorders [25]. PSP and CBS have also been examined in the context of wake-promoting neurons. It was found that the structure, though highly impacted upon by AD, is spared in both PSP and CBS [26].

Sleep abnormalities in PSP refer to different entities. The quality of sleep in PSP is interpreted as being more deteriorated partly due to its fragmentation, which can be observed in polysomnographic examination (PSG) [27]. Patients with PSP are considered as experiencing a longer duration of falling asleep [28]. The neurodegeneration and subsequent atrophic changes within the brainstem result in deviations affecting sleep regulating structure [16]. Due to the degeneration of the brainstem, insomnia in patients with PSP is more severe than the insomnia observed in Parkinson’s Disease (PD) and AD. [29]. This deterioration within the brainstem has been
found to be correlated also with excessive daytime sleepiness and obstructive sleep apnoea [30]. The atrophies within the pedunculopontine tegmentum significantly decrease the percentage of REM sleep in PSP [31, 32]. Additionally, the durations of N2 and N3 sleep have been shown to be significantly decreased [28]. Vertical saccadic restriction was also found to decrease both sleep time and its efficiency [33]. In a work presenting two phenotypes of PSP-PSP Richardson Syndrome (PSP-SR) and PSP-speech and language subtype (PSP-SL) it was pointed out that sleep deviations are more frequent in probable PSP-RS than in PSP-SL. The work was based on a screening questionnaire evaluation of 90 patients with PSP-SL and 71 with PSP-RS. Interestingly, the threshold of at least one sleep disturbance has been observed in almost twice the number of patients with PSP-RS compared to PSP-SL. Features such as using one’s voice during sleep or acting out dreams, commonly associated with having an aspect of synucleinopathies, have been found to be often present in probable PSP-RS [34]. Excessive daytime sleepiness was not considered a differentiating feature of the examined entities. Fatigue in PSP patients has not been fully explored [35]. Its increased level correlates not only with severely disturbed sleep hygiene, but also a more pronounced tendency towards depression [36]. The EEG patterns of sleep in PSP have been considered to resemble those reported in presenile dementia [37].

Rapid Eye Movement Behaviour Disorder (RBD), a feature commonly associated with synucleinopathies, is one of the sleep abnormalities found in tauopathic parkinsonian syndromes [38–43]. Extended research has revealed that abnormalities such as RBD, which have been primarily described in synucleinopathies, have also been found to be present in PSP and CBS. In PSP, RBD is linked with recurrent dream enactment behaviour [11]. RBD is associated with 14–33% of patients with PSP compared to c.60% in PD [10, 11, 44]. A different study investigating the incidence of RBD showed significantly lower rates of RBD among patients afflicted by PSP — 36.7% and especially CBS — 5.5%, when compared to those afflicted by PD, DBL and MSA (58–81.9%) [45]. The authors, Smilowska et al., revealed that although RBD is not a common feature of PSP, it should be interpreted as a possible aspect of the disease, unlike CBS [40]. A different work presenting similar rates (11–14%) of RBD among PSP and CBS patients was affected by smaller groups — 35 with PSP and only seven with CBD [46].

The frequency of REM without atonia (RWA) in PSP has been evaluated in various works. In the study by Arnulf et al., evaluating 15 patients with PD, 15 with PSP and 15 controls, the incidence of RWA in both diseases was similar, ranging from 28% to 36% [47]. This study was based on sleep interviews, overnight polysomnography (PSG), and Multiple Sleep Latency Tests. In the work by Nomura et al. examining 20 patients with PSP and 93 with PD, RWA was more common in PD [48]. The authors verified interviews with patients and their caregivers, and subsequently assessed the clinical backgrounds and PSG parameters. None of the abovementioned works acknowledged any differentiation between phenotypes of PSP. The study highlighting the higher prevalence of RWA among PD patients was based on older PD and PSP patients than the work by Arnulf et al. (75 ± 7 years in PSP and 73.4 ± 7.9 in PD compared to 68 ± 8 in PSP and 67 ± 7 in PD) [47]. The percentage of males in the study indicating lower RWA incidence in PSP was three times higher than females. The disease duration of the PD group with similar to PSP. RWA incidence was more diverse. Comparing these works may suggest an additional impact of sex, age at onset, and disease duration on the prevalence of RBD in both diseases. Restless leg syndrome, RLS, though commonly linked with PD, is also frequently present in PSP, and has been correlated with deviated sleep efficiency and duration [30]. PSP rating scale (PSPRS), a common test evaluating PSP, is interpreted as feasible in the evaluation of sleep disturbances. In the section covering daily activities can be found a query regarding sleep difficulties. This part of the test is dedicated to insomnia in PSP and may be insufficient in other sleep abnormalities [49].

**Sleep disturbances in corticobasal syndrome**

The interpretation of sleep abnormalities in CBS is more difficult than in PSP, due to the more diverse underlying pathologies and the lower incidence of the disease. Recent advances have revealed that CBS should be interpreted as a group of diseases among which could be mentioned most commonly tauopathies, however the group also includes vascular changes, TDP-43 pathology and others [50–52]. The presence of TDP-43 pathology has been reported in up to 17%, while the incidence of vascular CBS is not yet fully evaluated [53]. Among sleep disturbances in CBS one can mention insomnia, RLS, agrypnia excitata, sleep respiratory disorders, inversion of sleep and vigilance pattern, periodic limb movements, and less commonly RBD [45, 46, 54–61]. Periodic limb movements in CBS may be unilateral. Their presence is linked with disrupted inhibitory pathways initiated in the cortex or basal ganglia [62].

A work highlighting Lewy body disease with clinical manifestation of CBS showed a lower incidence of RBD and a younger age at disease onset among these patients when compared to LBD [63]. The incidences of RBD in CBS are commonly based on a small number of patients or case reports [45, 46, 54, 55, 57]. Patients with CBS and RBD may experience symptoms of overlapping synucleinopathic and tauopathic parkinsonian syndromes. One of the patients with clinical manifestation of apraxia, rigidity, bradykinesia and right arm myoclonus, suffered due to hallucinations and RBD. Neuropathological evaluation revealed astrocytic plaques, and thorny astrocytes were disseminated within cortical, subcortical and limbic structures [51, 53]. Lewy bodies were found in the substantia nigra, locus ceruleus and nucleus of the solitary tract. The appearance of subclinical RBD in CBS is associated
Table 1. General overview on sleep disturbances in PSP and CBS

<table>
<thead>
<tr>
<th>Sleep disturbances — clinical features</th>
<th>Progressive supranuclear palsy syndrome</th>
<th>Corticobasal syndrome</th>
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<tr>
<td>Frequency*</td>
<td>75%</td>
<td>36.4%</td>
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<td>Most common:</td>
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<tr>
<td>— excessive sleepiness</td>
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<td>— insomnia</td>
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<td>— insomnia</td>
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<td>— restless leg syndrome</td>
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<td>— sleep fragmentation</td>
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<td>— agrypnia excitata</td>
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<td>— night-time insomnia</td>
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<td>— sleep respiratory disorders</td>
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<td>— reduction of total sleep time</td>
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<td>— inversion of sleep vigilance pattern</td>
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<tr>
<td>Less common:</td>
<td></td>
<td>— periodic limb movements</td>
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<tr>
<td>— rapid-eye movement behaviour disorder</td>
<td></td>
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<td>— restless leg syndrome</td>
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<tr>
<td>— sleep respiratory disturbances</td>
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| Sleep disturbances — related features  | Decreased level of orexin | Decreased level of orexin |

CBS — corticobasal syndrome; PSP — progressive supranuclear palsy syndrome

with simultaneous atrophic changes in the cortex, thalamus and brainstem [59]. Brainstem nuclei and pontomedullary pathways being affected is considered to be a possible cause of RBD in CBS [64].

Conclusions

Our review of sleep disturbances shows them to be an insufficiently explored aspect of PSP and CBS (Tab. 1). Undoubtedly, PSP and CBS show a significantly lower rate of RBD incidence than synucleinopathic parkinsonian syndromes. However, the presence of RBD should not be a factor leading to the exclusion of tauopathic parkinsonian syndromes in a differential diagnosis. On the other hand, the presence of factors such as insomnia, excessive daytime sleepiness and sleep fragmentation combined with parkinsonian syndrome may not necessarily be observed in PD or other synucleinopathies, however they can be also associated with possible tauopathic atypical parkinsonisms. There are several limitations which make interpretation of the studies more difficult. Chief among these is the lack of neuropathological verification in the majority of the presented works; also, the diverse pathology of CBS, the small groups rarely exceeding 20 patients in the research studies in the context of CBS, and the lack of indication regarding subtypes of PSP. Any of these could additionally impact upon the obtained results.

In the context of PSP and CBS, the features regarding the course of sleep disturbances are multifactorial. The evolution of the abnormalities is likely to be correlated with the stage of atrophic changes, and the dissemination of pathological proteins and other coexistent mechanisms. The presence of RBD may be additionally impacted upon by the coexistence of Lewy bodies in neuropathological examination.

Analysis of the combination of sleep deviations may be interpreted as an interesting feature of disease progress and may provide additional hints on the possible underlying pathology. Our review shows that patients with diagnoses of probable or possible PSP and CBS, or their caregivers, should undergo a detailed interview concerning sleep disturbances. The course of these abnormalities may be both a manifestation and a cause of the progress of the disease. Further research in this field is required.

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References


