Sleep Architecture in Progressive Supranuclear Palsy: A Video-Polysomnography Study

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Abstract

Background: Sleep disturbances have been reported to occur in progressive supranuclear palsy (PSP). The anatomical regions affected in PSP and those regulating sleep and wake cycle like dorsal raphe nucleus, locus coeruleus (LC), and pedunculopontine nucleus (PPN) overlap. There is a paucity of polysomnographic studies in PSP and they have shown altered sleep architecture. Objective: To study the sleep architecture in patients with PSP using video-polysomnography (vPSG) and correlate it with the disease severity and duration. Methods: This was a prospective, cross-sectional, case-control, single-center study. A total of 22 patients with PSP and 15 age and gender-matched controls were recruited. The cases and controls underwent clinical assessment, face-to-face interviews with sleep questionnaires, anxiety and depression scales, and one overnight vPSG. The sleep architecture was analyzed in detail. Results: The sleep architecture was altered as compared to the controls. The total sleep time, stage N2 duration, stage N3 duration, rapid-eye-movement (REM) sleep duration, sleep efficiency %, and N2%, N3%, and REM% were significantly lesser in PSP patients. The wake duration, wake after sleep onset (WASO) duration, wake%, WASO%, stage N1 duration was significantly greater in PSP patients. The stage N2 and N3 latencies were significantly prolonged in patients. REM sleep without atonia was noted in four patients and no patients had vPSG proven REM sleep behavior disorder. Conclusions: Sleep architecture is altered in PSP even during the early stages of the disease. There is reduced total sleep including both non-REM and REM sleep, sleep efficiency, prolonged sleep latencies, and increased wake duration. This correlates with the neurodegenerative processes affecting the anatomical region regulating the sleep/wake cycle like dorsal raphe nucleus, locus coeruleus (LC), pedunculopontine nucleus (PPN).

Keywords: Non-rapid eye movement sleep, progressive supranuclear palsy, rapid-eye movement sleep, sleep duration, sleep efficiency

INTRODUCTION

Sleep-wake disturbances have been commonly encountered symptoms in neurodegenerative diseases, especially movement disorders. Sleep quality is associated with the quality of life. The presence of sleep disturbances further increases the morbidity of the disease.1 Progressive supranuclear palsy (PSP) is a tauopathy characterized by the hyperphosphorylation and subsequent aggregation of the microtubule-associated protein, tau, causing degeneration of cortical and subcortical brain structures, particularly the midbrain.2,3 Clinically, patients present with supranuclear ophthamoplegia, postural instability, parkinsonism, and pseudobulbar palsy.4 Sleep disturbances have been reported to occur in PSP.5 The anatomical regions affected in PSP and those regulating sleep and wake cycle overlap. In PSP, neuronal loss is seen in the basal nucleus of Meynert, globus pallidus, subthalamic nucleus, thalamic intralaminar nuclei, superior colliculus, periaqueductal gray matter, oculomotor nuclei, substantia nigra, dorsal raphe nucleus, locus coeruleus (LC), pedunculopontine nucleus (PPN), pontine nuclei, vestibular nuclei, medial tegmentum, and inferior olives.6,7 Wake promoting areas include noradrenergic neurons of the LC located in the pons, serotonergic neurons of the dorsal and median raphe nuclei located in the midbrain, dopaminergic neurons of the ventral tegmental area of the midbrain, and histaminergic neurons of the tuberomammillary nucleus, glutaminergic neurons of the parabrachial nucleus and orexinergic neurons of the lateral hypothalamus. Areas involved in non-rapid eye movement (NREM) sleep activation include ventrolateral preoptic area (VLPO) and median preoptic nucleus (MnPO) located in the anterior hypothalamus, basal forebrain, neurons of the parafacial zone (PZ), and cerebral cortex. Rapid eye movement (REM) sleep-promoting regions include glutaminergic neurons in the sub-laterodorsal nucleus (SLD), located in the pons, cholinergic neurons of the pedunculopontine and laterodorsal tegmental nuclei (PPT/ LDT),6,9 REM sleep behavior disorder (RBD), restless leg syndrome (RLS), periodic leg movement in sleep (PLMS), obstructive sleep apnoea (OSA)/central sleep apnoea (CSA), insomnia, and excessive daytime sleepiness (EDS) are the reported sleep abnormalities in PSP.10 There is a paucity of

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polysomnographic studies in PSP and they have shown altered sleep architecture. This study was aimed to study the sleep architecture in PSP by using video polysomnography (vPSG).

**Materials and Methods**

**Study design**
This was a prospective, cross-sectional, case-control study conducted in the department of neurology at the National Institute of Mental Health and Neurosciences, India.

**Study subjects**
We recruited 22 PSP patients who met the movement disorder society (MDS) PSP criteria (2017).\(^{[12]}\) Fifteen age and gender-matched subjects without any neurodegenerative disorders affecting the cerebellar system, pyramidal system, or extrapyramidal system were included as healthy controls. Patients with significant medical comorbidities, other neurodegenerative diseases which can affect sleep were excluded from the study. Written informed consent was taken from all the patients and controls. Institutional ethics committee (NO. NIMH/DO/IEC-BS& NS DIV/2018-2019/29-11-2018) approval was taken. The study period was from December 2018 to December 2020 with a total duration of 24 months.

**Data collection**

**Neurological assessment**
The sociodemographic details of patients and controls which included age at presentation, age of onset, gender, duration of illness, educational qualification, socio-economic status, and comorbid illness; clinical data – details about tremors, bradykinesia, rigidity, postural instability, falls, dysarthria, dysphagia, levodopa responsiveness, and neurological examination findings were recorded. The severity of PSP was assessed by progressive supranuclear palsy rating scale (PSPRS).\(^{[13]}\) Unified Parkinson’s Disease Rating Scale (UPDRS) part III was used to assess the severity of motor symptoms of parkinsonism.\(^{[14]}\) The assessment of sleep was done using well-validated questionnaires that include the Pittsburgh sleep quality index (PSQI) which assesses the overall sleep quality and presence of insomnia, Epworth Sleepiness Scale (ESS) which assess the presence of EDS, Mayo sleep questionnaire which assesses the RBD, Berlin sleep questionnaire that assesses the risk of OSA and the restless leg syndrome rating scale (RLS- RS) to assess RLS symptoms.\(^{[15-19]}\) The presence and severity of depression and anxiety were done using Hamilton’s anxiety and depression scales (HAM-A and HAM-D).\(^{[20,21]}\) Both depression and anxiety can cause sleep disturbance and the disease itself could be the cause of depression or anxiety.

**Video polysomnographic assessment**
Cases and controls underwent one overnight vPSG in the sleep lab. vPSG was performed as per the guidelines laid down by the American Academy of Sleep Medicine (2017) using SOMNO medics, Germany.\(^{[22]}\) The vPSG included eight-channel electroencephalography electrodes according to the 10-20 international system, right and left electrooculogram, chin/tibialis anterior electromyogram activity, electrocardiogram, microphone, respiratory effort, and airflow sensor. A sleep lab technician monitored each vPSG recording. The sleep parameters which were analyzed were known as total sleep time (TST), wake duration, wake after sleep onset (WASO), N1, N2, N3, REM sleep duration and latencies, latency to sleep onset, arousal index and number of awakenings, sleep efficiency, sleep maintenance, number of REM sleep episodes and percent time in N1 sleep, N2 sleep, N3 sleep, and REM sleep. Time in bed (TIB) refers to time from the start of the recording to the end of the recording, TST was the total time spent in NREM or REM sleep after the start of the N2 stage, sleep efficiency was defined as TST/TIB, sleep onset latency was the time from the start of the recording and beginning of the first N2 stage, REM latency was the time from the sleep onset to the first epoch of REM sleep, wake duration was the time spent during wake episode during sleep and WASO was the difference between the total recording time and the start of the record to the first epoch of sleep minus the actual sleep time. Apnoea was defined as the drop of peak amplitude by >90% in nasal thermistor lasting for a duration of >10 seconds, hypopnea was defined as the drop in the peak signal by >50% along with an oxygen saturation drop of >4% from baseline, lasting for a period of 10 seconds. REM sleep without atonia (RSWA) was defined as the number of epochs of REM sleep without atonia per hour of REM sleep.

**Sleep data scoring and analysis**
The acquired sleep data was converted into European Data Format and was analyzed in Polyman software version 1.15. The sleep data were analyzed based on scoring guidelines AASM 2017. The rest of the parameters like apnoea, hypopnea index, arousal index, and periodic leg movement index were calculated using the SOMNO medics, Germany system.

**Statistical analysis**
Categorical and continuous variables were expressed using frequency, percentage and mean, and standard deviation, respectively. The normality of data was assessed using the Shapiro-Wilks test. Student’s t-test and Mann-Whitney U test were used for comparison of continuous variables following normal and not following normal distribution, respectively. Kruskal-Wallis test or One-way analysis of variance were used for comparison of continuous variables among three groups depending on the normality of the data. Categorical variables were analyzed by Pearson’s Chi-Square test. A P-value of < 0.05 was considered significant. Data were analyzed with Statistical Package for Social Sciences V20.0 (SPSS Inc, Chicago, IL, USA) and Microsoft Excel sheet.

**Results**
A total of 22 cases and 15 controls were recruited. vPSG was done in 21 cases, and one case did not give consent for vPSG. The mean age of patients with PSP was 61.2 ± 7.1 years (range-47-70 years) and controls were
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53.9 ± 4.2 years. Nineteen were male patients and three were female patients. The mean duration of illness was 19.6 ± 4.8 months (range- 12-24 months). The mean PSPRS score was 30.0 ± 10.7. The mean UPDRS part III score was 29.4 ± 11.1. Nineteen patients belonged to probable PSP- Richardson syndrome and three patients to possible PSP-oculomotor subtype. The frequency of symptoms and signs in PSP patients are summarized in Table 1.

Sleep, anxiety, and depression scales
Poor sleep quality (PSQI score >5) was seen in 6 out of 22 (27.2%) PSP patients. The mean PSQI score in patients was 4.4 ± 4.7. EDS (ESS score of >10) was present in 2 out of 22 (9%) PSP patients. The mean ESS score was 4.5 ± 4.1. Two patients (9%) had RBD as per the Mayo sleep questionnaire. Two patients (9%) had OSA as per the Berlin sleep questionnaire. One patient had RLS (4.5%). HAM-A score of > 14 is a cut off score for anxiety. Two patients had anxiety (9%). The mean HAM-A score was 2.9 ± 3.7. HAM-D score > 7 is a cut off score for depression. Six patients (27.2%) had depression. The mean HAM-D score was 5.4 ± 4.2.

Comparison of vPSG parameters [Table 2]
The total sleep recording duration was comparable between the two groups with no statistically significant difference. The TST, N2 duration, N3 duration, REM duration, sleep efficiency%, N2%, N3%, and REM% were significantly lesser in PSP patients. The wake duration, WASO duration, wake%, WASO%, and N1 duration were significantly greater in PSP patients. A high percentage of WASO indicates difficulty maintaining sleep after sleep onset. The sleep, N1, and REM latencies were similar in both groups. The N2 and N3 latencies were significantly prolonged in patients. The N1% was not significantly different between the groups. REM sleep was absent in seven PSP patients (33%), but none in controls had absent REM sleep. RSWA was noted in four PSP patients [Figure1 and 2]. The mean apnoea-hypopnoea index (AHI) was 10.3 ± 18.1. AHI >5 was noted in seven PSP cases, and AHI >15 was noted in three PSP cases. The mean percentage of sleep in the supine position in cases was 74 ± 22.4% and controls were 39.8 ± 7.7% suggesting that the PSP patients spent more time of their sleep in the supine posture.

Correlation of vPSG parameters with disease duration and severity [Table 3]
PSPRS had a positive correlation with wake percentage suggesting increasing severity of disease resulted in more wakefulness. PSPRS had a negative correlation with total sleep time, N1, N3, and REM percentage and duration suggesting increasing disease severity resulted in reduced total sleep including NREM and REM sleep. The duration of illness had a significant negative correlation with N3 latency only.

DISCUSSION
The present study was aimed at deciphering the sleep architecture in patients with PSP. Patients with PSP had altered sleep architecture in the form of reduced TST, more time in the wake, reduced NREM sleep duration (except N1 stage duration which was more as compared to controls), prolonged N2, N3 latencies, reduced sleep efficiency, and absent REM sleep in 33% of patients. Patients with PSP had poor sleep quality but the frequency of RBD, RLS, CSA/OSA, and EDS was less. We found a high wake percentage with a positive correlation with disease severity that could be due to motor disability (nocturnal akinesia) as evidenced by the high amount of sleep in the supine posture, due to lack of adaptation to PSG

| Clinical features | n (%) |
|------------------|------|
| Tremors          | 3 (13.6) |
| Bradykinesia     | 16 (72.7) |
| Falls            | 18 (81.8) |
| Dysarthria       | 13 (59.0) |
| Dysphagia        | 7 (31.8) |
| Apathy           | 8 (36.3) |
| Urinary incontinence | 1 (4.5) |
| Axial rigidity   | 18 (81.8) |
| Limb dystonia    | 3 (13.6) |
| Postural instability | 14 (63.6) |
| Oculomotor dysfunction | 22 (100) |
| Insomnia         | 6 (27.2) |
| Excessive daytime sleepiness | 2 (9) |
| Dream enactment  | 2 (9) |
| Restless legs syndrome | 1 (4.5) |

| vPSG parameter | Cases (n=21) | Controls (n=15) | P |
|----------------|-------------|----------------|---|
| Total Recording duration (Minutes) | 430.6±89.7 | 430±62.3 | 0.83 |
| Total Sleep Time (Minutes) | 188.7±118.8 | 324.8±71.6 | <0.001* |
| Wake Duration (Minutes) | 224.8±104.8 | 103.5±50.5 | <0.001* |
| WASO Duration (Minutes) | 176.4±76.9 | 90.7±47.4 | 0.001* |
| N1 duration (Minutes) | 105.0±83.5 | 121.0±12.4 | 0.009* |
| N2 duration (Minutes) | 64.2±31.1 | 171.3±31.1 | <0.001* |
| N3 duration (Minutes) | 25.2±23.9 | 55.6±23.3 | <0.001* |
| REM duration (Minutes) | 45.9±31.4 | 57.4±30.1 | 0.002* |
| Sleep latency (Minutes) | 48.4±68.6 | 15.0±12.8 | 0.25 |
| N1 latency (Minutes) | 27.0±32.3 | 14.7±11.8 | 0.11 |
| N2 latency (Minutes) | 60.1±55.4 | 17.1±12.5 | 0.001* |
| N3 latency (Minutes) | 118.5±105.9 | 75.9±111.7 | 0.04* |
| REM latency (Minutes) | 144.8±139.6 | 99.9±62.1 | 0.69 |
| Sleep efficiency % | 56.4±17.6 | 72.8±10.0 | <0.001* |
| Wake % | 60.2±25.8 | 23.3±11.5 | <0.001* |
| WASO % | 42.12±10.8 | 21.9±11.2 | <0.001* |
| N1% | 14.7±14.1 | 6.8±3.9 | 0.12 |
| N2% | 15.5±13.9 | 56.7±8.4 | <0.001* |
| N3% | 2.6±4.6 | 16.9±7.3 | <0.001* |
| REM% | 5.8±6.3 | 18.1±7.4 | <0.001* |

Values are expressed as mean±standard deviation, *P<0.05- statistical significance, WASO- wake after sleep onset, REM- rapid-eye movement
study (or) due to disease process involving the anatomical region regulating the sleep-wake cycle are involved due to disease process. The decrease in the percentage of N2 and N3 stages can be explained by the involvement of the cortex, parafacial zone, and basal forebrain by the disease process, and the decrease in the REM sleep percentage may be due to the involvement of REM sleep-promoting areas in pons and midbrain (PPT and SLD nucleus). Insomnia in PSP is due to hyper-arousal state secondary to diminished homeostatic sleep drive due to cholinergic loss in the basal forebrain as well as the motor (significant axial rigidity and nocturnal akinesia) and non-motor symptoms disrupting sleep.\(^\text{[23]}\)

Gross et al.\(^\text{[24]}\) was the first case series to evaluate sleep architecture in PSP using PSG. They found decreased TST and REM sleep, along with a significant increase in the number and duration of nocturnal awakenings. Aldrich et al.\(^\text{[25]}\) showed decreased sleep efficiency, increased percentage of wakefulness, reduced percentage of REM sleep and stage 2, decreased rapid eye movements during REM sleep, increased number of awakenings, and poorly formed or absent sleep spindles in PSP. Montplaisir et al.\(^\text{[26]}\) (1997) reported a high percentage of time spent awake, shorter total sleep time, a lower sleep efficiency, increased stage one sleep duration, reduced k complex, and spindle density in stage 2, reduced percentage of stage 2 sleep, and a lower percentage of REM sleep. The lower percentage of REM sleep was the result of both a reduction in the number of REM periods and a reduction in the mean period of duration. Arnulf et al.\(^\text{[27]}\) reported decreased total sleep time, decreased sleep efficiency, longer duration of WASO. Sleep onset latency, stage 2, stage 3, and stage 4 sleep were comparable to the controls, but they noted an increase in the percentage of stage one sleep. REM sleep duration was decreased and REM latency was prolonged in their cohort. Sixel-Döring et al.\(^\text{[28]}\) reported decreased sleep efficiency, prolonged sleep latency, decreased stage 2 slow-wave sleep in PSP patients. Walsh et al.\(^\text{[23]}\) reported prolonged sleep latency, reduced total sleep time, more WASO, less N2, N3, and REM sleep in PSP. The neuropathologic underpinnings for the decreased slow-wave activity in PSP may be due to the monoaminergic loss in the locus coeruleus, dorsal raphe, and tuberomammillary nucleus, and cholinergic loss in the magnocellular nucleus. The increased WASO may be due to the neuronal loss within the intermediate nucleus (human VLPO homologue) and para-facial zone, which is galaninergic and GABAergic/Glycinergic, respectively, and the decreased sleep spindles could be due to the involvement of connections between the PPT and the reticular nuclei of the thalamus.

Arnulf et al.\(^\text{[27]}\) reported RSWA in four (27%) and RBD in two (13%) patients out of 15 patients who underwent PSG. Sixel-Döring et al.\(^\text{[28]}\) (2009) studied PSG in 20 patients with PSP and found RSWA in 17 (85%) and RBD in 7 (35%) patients. Nomura et al.\(^\text{[29]}\) reported no RBD and RSWA in 5 (25%) patients in their cohort of 20 patients with PSP. We found RSWA in four (19%) patients and no PSG-proven RBD in our cohort. Munhoz et al.\(^\text{[30]}\) reported RBD in 37% (32 out of 87) patients wherein the RBD was diagnosed based on the questionnaire. RBD is more commonly seen in synucleopathies. However, these studies have proven the occurrence of RBD in PSP. The presence of RBD will not rule out tauopathy. The possibility of earlier and consistent affliction of areas controlling REM sleep in synucleopathies may be the reason for the higher prevalence of RBD. The reason for the higher prevalence of RBD among Parkinson’s disease (PD) compared to PSP is postulated to be due to the severe involvement of LC in PD as compared to PSP. The degeneration of both PPN and LC is essential for the occurrence of RSWA.\(^\text{[24]}\)

Subjective sleep quality has been reported to be poor in PSP. Gama et al.\(^\text{[31]}\) reported poor sleep quality in 43% of PSP patients (6 out of 14 PSP). Bhalsing et al.\(^\text{[32]}\) reported higher PSQI scores in patients with PSP as compared to controls suggesting poor subjective sleep quality. We found poor sleep quality in 27% of patients. EDS has been reported in PSP and the frequency increases with an increase in the disease duration. It can occur due to sleep-disordered breathing (SDB), RLS, motor impairment due to axial rigidity and nocturnal akinesia, low orexin-A/hypocretin -1 levels due to loss of orexin neurons. Gama et al.\(^\text{[31]}\) reported EDS (ESS > 10) in 6 (43%) patients. Arnulf et al.\(^\text{[27]}\) reported EDS in 2 (13%) patients. In our cohort, EDS occurred in two (9%) patients. The low frequency of EDS in our cohort may be the shorter duration of illness (around 2 years). We had one patient with RLS. Gama et al.\(^\text{[31]}\) reported eight patients (57.1%) with RLS. Bhalsing et al.\(^\text{[32]}\) reported one patient with RLS (27 patients). The prevalence of RLS increases with age and disease duration. The low frequency of RLS in our cohort may be the shorter duration of illness (around 2 years).

### Table 3: Correlation of vPSG parameters with disease severity and duration

|                      | PSPRS  |     | Disease duration |
|----------------------|--------|-----|------------------|
|                      | r      | P   |                  |
| Wake %               | 0.482  | 0.02*| 0.153            |
| Wake duration        | 0.09   | 0.68 | -0.124           |
| WASO duration        | -0.21  | 0.37 | -0.194           |
| N1%                  | -0.591 | 0.005*| -0.384          |
| N2%                  | -0.15  | 0.95 | 0.036            |
| N3%                  | -0.475 | 0.02*| -0.130           |
| REM%                 | -0.526 | 0.01*| -0.350           |
| Total sleep time     | -0.473 | 0.03*| -0.247           |
| Sleep onset latency  | 0.106  | 0.64 | 0.196            |
| Sleep efficiency     | -0.370 | 0.09 | -0.119           |
| N1 latency           | 0.157  | 0.50 | 0.092            |
| N2 latency           | -0.213 | 0.38 | -0.299           |
| N3 latency           | -0.450 | 0.19 | -0.782           |
| REM latency          | 0.093  | 0.74 | -0.112           |
| N1 duration          | -0.601 | 0.004*| -0.384          |
| N2 duration          | -0.319 | 0.15 | -0.153           |
| N1 duration          | -0.503 | 0.02*| -0.162           |
| REM duration         | -0.591 | 0.005*| -0.344          |

WASO- wake after sleep onset; REM- rapid-eye movement; *P<0.05- statistical significance.
The strength of the study was that it was one of few studies in PSP where vPSG was used to decipher the sleep architecture alteration in PSP patients and the inclusion of patients with shorter disease duration. The limitations of the study were relatively small sample size of cases and controls, controls were not exactly matched for age and gender, lack of adaptation to new sleep environment termed as the first night effect might have impacted the sleep architecture and results as it was a single night vPSG.

**Conclusion**

Sleep architecture is altered in PSP even during the early stage of the disease. There is reduced total sleep including both NREM and REM sleep, sleep efficiency, prolonged sleep latencies, and increased wake duration. Patients with PSP had poor subjective sleep quality but the frequency of RBD, RLS, CSA/OSA, EDS was less. Future studies should include a larger cohort of patients and the correlation of sleep architecture with the anatomical region involvement using neuroimaging. The identification of the sleep disturbances and appropriate therapeutic intervention will help in improving the quality of life of the patients.

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**Conflicts of interest**

There are no conflicts of interest.

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