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Sleep Disturbances in the Speech-Language Variant of Progressive Supranuclear Palsy

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Abstract

Introduction: Progressive supranuclear palsy (PSP) variants other than PSP-Richardson Syndrome (PSP-RS) have been recognized, including PSP with speech and language problems (PSP-SL). Given the reported sleep disruptions in PSP-RS, we investigated sleep abnormalities in PSP-SL.

Methods: Four sleep-related screening questions were given to the caregivers of 90 patients with PSP-SL (59 suggestive of PSP-SL and 31 possible PSP-SL) and 71 probable PSP-RS (prob. PSP-RS) patients.

Results: At least one sleep-related disturbance was observed in 35.6% of suggestive of PSP-SL, 38.7% of possible PSP-SL, and 67.6% of prob. PSP-RS, the most common being “unable to fall

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or stay asleep". Prob. PSP-RS showed higher frequency of "screaming or talking in sleep", "acting out dreams", and "unable to fall or stay asleep" compared to both PSP-SL groups, but did not differ from possible PSP-SL in "excessive daytime sleepiness".

Conclusion: Sleep abnormalities are common in PSP-SL, but less frequent than prob.PSP-RS.

Introduction

Progressive supranuclear palsy (PSP) is a neurodegenerative disorder typically characterized by falls, imbalance and vertical supranuclear gaze palsy. PSP has been associated with sleep abnormalities such as insomnia and impaired sleep architecture and rapid eye movement (REM) sleep behavior disorder[1–3]. In 2017, the Movement Disorders Society (MDS) published criteria recognizing many clinical variants of PSP in addition to the most frequently studied form of PSP-Richardson Syndrome (PSP-RS)[4]. One such variant is characterized by progressive speech and language problems (PSP-SL). Patients with progressive apraxia of speech or the non-fluent/agrammatic variant of primary progressive aphasia meet criteria for suggestive of PSP-SL (s.o. PSP-SL). Once they develop ocular motor impairment they meet criteria for possible PSP-SL (poss. PSP-SL). Many patients with poss. PSP-SL eventually go on to develop postural instability, falls and akinesia5. It is unknown whether sleep abnormalities occur in PSP-SL. We assessed the utility of sleep questions for clinical detection of sleep disorders in PSP-SL and compare the sleep disturbances in PSP-SL to PSP-RS.

Methods

The Neurodegenerative Research Group at the Mayo Clinic Rochester prospectively recruited 161 patients with a clinical diagnosis of either PSP-RS (n=71) or PSP-SL (n=90) between 14 September 2009 and 5 October 2020. The Mayo Clinic Institutional Review Board approved this study and all patients gave consent to participate. According to the MDS PSP criteria[4], of our 90 PSP-SL patients, 59 met criteria for s.o. PSP-SL and 31 met criteria for at least poss. PSP-SL. All PSP-RS patients met criteria for prob. PSP-RS.

All patients underwent a neurological and neuropsychological evaluation. The PSP-SL patients also underwent a speech-language battery. The presence of apraxia of speech and agrammatic aphasia were determined by consensus between at least two speech-language pathologists. We utilized the Montreal Cognitive Assessment battery (MoCA) for assessment of general cognitive function; the Frontal Assessment Battery (FAB) for executive function, the Frontal Behavior Inventory (FBI) for behavioral disturbance, the Boston Naming Test (BNT) for confrontation naming, the Apraxia of Speech Rating Scale (ASRS) for the presence and prominence of a number of clinical features associated with apraxia of speech, the Movement Disorders Society Sponsored revision of the Unified Parkinson's Disorder Rating Scale I, II and III (MDS-UPDRS III) for Parkinsonism, the PSP Rating Scale for PSP disease severity, and the PSP Saccadic Impairment Scale (PSIS) to assess ocular motor impairment. We also abstracted data on sleep medication (Zolpidem, Zaleplon, Eszopiclone) for all patients.

For sleep assessment, four sleep-related screening questions were scored as present/absent by the caregiver: “screaming or talking during sleep”, “acting out dreams during sleep”, “unable to fall or stay asleep”, and “excessive daytime sleepiness”. They were summed to create a sleep composite score. Each item and sleep composite were compared across groups using Fisher`s exact test or Kruskal Wallis test in SPSS 27.0. Relationships were assessed between all four sleep questions plus the composite score and sleep-related questions from the PSP Rating Scale (item 7) and MDS-UPDRS (item 1.7 on sleep problems and 1.8 on daytime sleepiness), as well as total PSP Rating Scale, using Kruskal-Wallis tests for present/absent variables and Spearman correlations for the sleep composite. The raw data used for this study is available upon request to the corresponding author.

Results

The three groups did not differ in demographics, except poss. PSP-SL had a longer disease duration from onset to evaluation than s.o. PSP-SL and prob. PSP-RS ($p < 0.001$) (Table 1). The s.o. PSP-SL group performed better on the MoCA and FAB than poss. PSP-SL and prob. PSP-RS ($p=0.018$ and <0.001, respectively). All groups were similar on the FBI and BNT. As expected by their speech disturbance, s.o. PSP-SL and poss. PSP-SL performed worse on the ASRS than prob. PSP-RS ($p < 0.001$). On all measures of Parkinsonism (MDS-UPDRS I, II and III) and the PSP Rating Scale, s.o. PSP-SL performed better than poss. PSP-SL and prob. PSP-RS ($p < 0.001$ for each) (Table 1). Only five patients were on a sleep medication at the time of the study (one PSP-RS and four s.o. PSP-SL).

On sleep assessment (Table 2), 35.6% of s.o. PSP-SL, 38.7% of poss. PSP-SL and 67.6% of prob. PSP-RS group endorsed at least one sleep symptom, with prob. PSP-RS showing a higher frequency than the other two ($p < 0.001$). The most common sleep disturbance was “unable to fall or stay asleep”, reported by 32.9% patients in total whereas the least common was “acting out dreams”, reported by 3.7% of patients. The frequency of individual sleep problems was similar in s.o. PSP-SL and poss. PSP-SL groups, including “screaming or talking in sleep” (1.7% vs 0.0%), “acting out dreams” (0.0% vs 0.0%), and “unable to fall or stay asleep” (20.3% vs 19.4%), but these sleep problems were more common in prob. PSP-RS (11.3%, 8.5% and 49.3%, respectively). “Excessive daytime sleepiness” was more common in prob. PSP-RS (39.4%) than s.o. PSP-SL (15.3%) and was similar to poss. PSP-SL (29.0%). The sleep composite score was similar in s.o. PSP-SL and poss. PSP-SL groups (0.37 ± 0.52 vs 0.48 ± 0.68) while being lower than that of prob. PSP-RS (1.06 ± 0.94) ($p < 0.001$).

The “unable to fall or stay asleep” question and the sleep composite were related to item 7 on the PSP Rating Scale ($p<0.001$ and $p=0.002$, respectively) and item 1.7 on the MDS-UPDRS ($p<0.001$ for both). The “excessive daytime sleepiness” question and the sleep composite were related to item 1.8 on the MDS-UPDRS ($p<0.001$ for both). None of the sleep questions or composite corelated with total PSP Rating Scale.

Discussion

In this study we show that patients with PSP-SL show similar sleep abnormalities to patients with prob. PSP-RS, most commonly trouble falling or staying asleep and excessive daytime sleepiness, although they occur in a lower proportion of patients.

While investigating the sleep disturbances we chose to use a caregiver-report and the caregiver was often the spouse. This approach allowed us to detect problems of which the patient may not be aware, such as screaming or talking in sleep and acting out dreams, or of which the patient may lack insight, as proposed by prior research showing that subjective sleep reports were an underrepresentation of sleep disturbances in PSP[3]. Our battery with 4 simple questions that can be completed within a minute was adequate to demonstrate the high frequency of sleep disturbances across PSP variants. In total, half of the patients in this study had at least one sleep related symptom; specifically, two thirds of prob. PSP-RS patients and more than one third of s.o. PSP-SL and poss. PSP-SL patients. Overall, the severity of sleep problems were mild which is in keeping with the fact that less than 5% of the cohort was taking a prescription sleep medication at the time of the study; it is possible that other none FDA approved prescriptions or none prescription over the counter or holistic medications were being utilized.

In our study, “unable to fall or stay asleep” was the most common sleep impairment across all patients, being particularly common in prob. PSP-RS. This finding, coming from the largest PSP-RS cohort reported to date in a sleep study, is in line with the studies showing decreased total night sleep time in PSP-RS, both pre-dating the MDS criteria[6,7] and also using the MDS PSP criteria[2]. The second most common sleep symptom was “excessive daytime sleepiness”, again seen most frequently in prob. PSP-RS, exceeding one-third of this group. Greater subjective daytime sleepiness in our cohort parallels the work of Walsh et.al, who reported subjective increased daytime sleepiness in a cohort of 19 PSP patients, in whom 15 had PSP-RS and none had PSP-SL. Notably, despite having subjective daytime sleepiness, Walsh et al’s PSP cohort showed features of excessive daytime and night time hyperarousal, indexed by greater waking EEG gamma power, reduced objective daytime sleepiness on multiple sleep latency testing, and decreased nocturnal sleep time and N3 sleep, implying dysfunctional homeostatic sleep drive in PSP relative to controls. Conversely, other possible mechanisms for daytime sleepiness in PSP could involve degeneration of brain stem, thalamic, and hypothalamic structures which govern sleep-wake regulation[2].

In this study, “acting out dreams” and “screaming or talking in sleep” were rare across all groups, although most frequent in prob. PSP-RS, being present in 8.5% and 11.3% of the group, respectively. These symptoms may indicate probable REM sleep behavior disorder. This finding may support the notion that REM sleep behavior disorder is not restricted to synucleinopathies but can also be seen in PSP-RS, a tauopathy, as has been documented by polysomnography[3] although another systematic study of polysomnographic REM sleep without atonia (RSWA) instead suggested that RSWA is a relatively specific biomarker for synucleinopathies, and found no evidence for greater RSWA in PSP patients than controls[8]. We cannot exclude the possibility that some of our patients or those in prior

studies associating PSP with RBD may have had mixed tau and synuclein pathologies, with covert alpha-synuclein pathology causing RBD. Regardless, our study, suggests that probable RBD is a relatively uncommon finding in PSP (i.e., 8.5–11.3%) that is comparable in frequency to similarly aged community controls (i.e.,7.2–13%)[9,10].

Here we showed that the PSP-SL patients less commonly reported sleep abnormalities than prob. PSP-RS, as evidenced by the items of “any sleep symptom”, “unable to fall or stay asleep” and the sleep composite score. Sleep abnormalities in PSP have been attributed to degeneration of REM promoting structures such as the pedunculopontine nucleus and pontine tegmentum[11]; and midbrain and brainstem structures are typically less Journal affected in poss. PSP-SL compared to prob. PSP-RS[5]. Little is in fact known about sleep abnormalities in these speech-language syndromes. Further longitudinal follow-up will be helpful to determine how commonly sleep abnormalities develop over time in PSP-SL.

This study used recently published MDS PSP criteria for PSP variant classification and reports sleep data from the largest cohort of PSP-RS and PSP-SL patients. While replicating the sleep problems in PSP-RS, using a 4-item questionnaire, it also adds the first sleep findings about PSP-SL to the literature. A limitation of the study, however, is the lack of objective polysomnography assessments of sleep. In addition, our sleep questions were not previously validated but the results were strongly associated, as expected, with sleep-related questions on the PSP Rating Scale and the MDS-UPDRS. Medical comorbidities that may account for sleep disturbances cannot be fully ruled out. Future studies of PSP variants involving larger patient cohorts and using both subjective and objective sleep evaluations and neuroimaging correlation are needed to further understand mechanisms underlying sleep disturbances and to inform rational treatment strategies for these common non-motor PSP features.

In this study we show the frequent nature of sleep disturbances in PSP-SL and PSP-RS. A previous study showed that presence of sleep symptoms was associated with increased mortality in PSP[12] which stresses the importance of assessing sleep in these patients to aid in prognostic planning and to guide interventions that could help improve sleep and potentially clinical outcomes.

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Highlights

- PSP-SL is progressive supranuclear palsy variant with speech and language problems
- At least one third of PSP-SL patients endorse sleep disturbance
- The most common problem is inability to fall or stay asleep
- Sleep problems in PSP-SL are less frequent than those of PSP-RS (Richardson Syndrome)

Table 1.

Demographic and clinical features.

Variable	s.o. PSP-SL (n=59)	poss. PSP-SL (n=31)	prob. PSP-RS (n=71)	p-Value	Post-hoc
Demographic and clinical features					
Gender (% male)	28 (47.5)	15 (48.4)	40 (56.3)	0.557	n.s.
Education (years)	16.00 (13.00, 17.00)	15.00 (12.00, 16.00)	16.00 (12.50, 16.00)	0.729	n.s.
Age at onset (years)	66.81 (60.25, 72.19)	68.75 (59.97, 72.83)	65.41 (60.79, 69.90)	0.671	n.s.
Age at visit (years)	70.13 (62.52, 76.49)	74.21 (66.77, 80.18)	69.80 (64.86, 73.26)	0.055	n.s.
Disease duration (years)	3.56 (2.45, 5.12)	5.45 (3.99, 8.50)	3.09 (2.19, 3.97)	**<0.001**	poss. PSP-SL > s.o. PSP-SL, prob. PSP-RS
Clinical testing					
MoCA	25.00 (22.00, 28.00)	24.00 (18.00, 26.00)	24.00 (22.00, 27.00)	**0.018**	s.o. PSP-SL> poss. PSP-SL, prob. PSP-RS
FAB	15.00 (14.00, 17.00)	13.00 (8.75, 15.00)	14.00 (12.00, 15.00)	**<0.001**	s.o. PSP-SL> poss. PSP-SL, prob. PSP-RS
FBI	11.50 (6.00, 18.00)	14.00 (8.50, 24.00)	13.00 (3.50, 25.50)	0.187	n.s.
BNT	13.00 (12.00, 15.00)	13.00 (11.75, 14.00)	14.00 (12.00, 14.00)	0.468	n.s.
ASRS	16.00 (12.00, 27.00)	21.50 (12.00, 29.25)	4.00 (2.00, 6.00)	**<0.001**	s.o. PSP-SL, poss. PSP-SL> prob. PSP-RS
PSP Rating Scale	11.00 (5.00, 17.50)	38.00 (27.00, 56.00)	37.00 (29.00, 46.00)	**<0.001**	s.o. PSP-SL < poss. PSP-SL, prob. PSP-RS
PSIS	0.00 (0.00, 1.00)	2.00 (2.00, 3.00)	3.00 (2.00, 4.00)	**<0.001**	s.o. PSP-SL < poss. PSP-SL, prob. PSP-RS
MDS-UPDRS I	6.00 (2.00, 10.00)	9.50 (8.00, 15.75)	10.00 (7.00, 15.50)	**<0.001**	s.o. PSP-SL < poss. PSP-SL < prob. PSP-RS
MDS-UPDRS II	5.00 (3.00, 8.00)	17.00 (6.00, 27.00)	21.00 (11.00, 27.00)	**<0.001**	s.o. PSP-SL < poss. PSP-SL, prob. PSP-RS
MDS-UPDRS III	10.50 (5.00, 20.25)	41.50 (20.50, 63.75)	39.00 (31.00, 52.00)	**<0.001**	s.o. PSP-SL < poss. PSP-SL, prob. PSP-RS

Values are shown as median (q1, q3). Significant comparisons are bolded. s.o. PSP-SL = suggestive Progressive supranuclear palsy with predominant speech/language disorder; poss. PSP-SL = possible progressive supranuclear palsy with predominant speech/language disorder; prob. PSP-RS = probable progressive supranuclear palsy with Richardson's Syndrome; ASRS = Apraxia of Speech Rating Scale; BNT = Boston Naming Test; FAB = Frontal Assessment Battery; FBI = Frontal Behavior Inventory; MDS-UPDRS (I, II and III) = Movement Disorders Society Unified Parkinson's Disorder Rating Scale (I, II and III); MoCA = Montreal Cognitive Assessment; n.s.= not significant; PSIS = PSP saccadic impairment scale.

Table 2.

Sleep assessment.

Variable	s.o. PSP-SL (n=59)	poss. PSP-SL (n=31)	prob. PSP-RS (n=71)	Total (n=161)	p Value	Post-hoc
Any sleep symptom, N (%)	21 (35.6)	12 (38.7)	48 (67.6)	81 (50.3)	**<0.001**	s.o. PSP-SL, poss. PSP-SL < prob. PSP-RS
Unable to Fall or Stay Asleep, N (%)	12 (20.3)	6 (19.4)	35 (49.3)	53 (32.9)	**0.001**	s.o. PSP-SL, poss. PSP-SL < prob. PSP-RS
Excessive Daytime Sleepiness, N (%)	9(15.3)	9 (29.0)	28 (39.4)	46 (28.6)	**0.009**	s.o. PSP-SL < prob. PSP-RS
Screaming or Talking in Sleep, N (%)	1 (1.7)	0 (0.0)	8 (11.3)	9 (5.6)	**0.027**	s.o. PSP-SL < prob. PSP-RS
Acting Out Dreams, N (%)	0 (0.0)	0 (0.0)	6 (8.5)	6 (3.7)	**0.022**	s.o. PSP-SL < prob. PSP-RS
Sleep Composite-mean (SD)	0.37 (0.52)	0.48 (0.68)	1.06 (0.94)	0.70 (0.82)	**<0.001**	s.o. PSP-SL, poss. PSP-SL < prob. PSP-RS

% = percentage of patients exhibiting the item, SD = standard deviation. Sleep items were compared using Fisher's exact test. Sleep composite score was compared using Kruskal Wallis test. Significant comparisons are bolded. s.o. PSP-SL = suggestive progressive supranuclear palsy with predominant speech/language disorder; poss. PSP-SL = possible progressive supranuclear palsy with predominant speech/language disorder; prob. PSP-RS = probable progressive supranuclear palsy with Richardson's Syndrome.