Sleep Abnormalities in Progressive Supranuclear Palsy

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We studied sleep patterns for three nights in 10 subjects with moderate to severe progressive supranuclear palsy and correlated the findings with disease severity using quantitative measures of motor, cognitive, and eye movement impairment. All subjects had severe insomnia, spending 2 to 6 hours awake per night; the mean time awake per night for the group was more than 4 hours. Sleep latency became shorter and the number of awakenings increased with greater motor impairment, and total sleep time declined as dementia worsened. These findings indicate that in progressive supranuclear palsy insomnia is related to disease severity. Insomnia associated with progressive supranuclear palsy appears to be worse than the insomnia of Parkinson's disease or Alzheimer's disease and may be due to degenerative changes in brain structures responsible for sleep maintenance.

Aldrich MS, Foster NL, White RF, Bluemlein L, Prokopowicz G. Sleep abnormalities in progressive supranuclear palsy. Ann Neurol 1989;25:577–581

Progressive supranuclear palsy (PSP) is a degenerative neurological disorder characterized by impaired voluntary gaze, axial rigidity, and dementia. Sleep complaints are common, and sleep studies have shown prolonged sleep latency, impaired sleep continuity, decreased or absent sleep spindles [1, 2], and reduced amounts of rapid eye movement (REM) sleep [3].

Sleep disturbance in PSP could be due to degenerative neurochemical or neuropathological changes affecting areas of the brain involved with sleep regulation. If so, sleep disturbances should increase as the disease worsens. In support of this hypothesis, Perret and Jouvet [3] found that 2 patients with severe clinical impairment had greater sleep disturbance than did 7 patients with milder disease. In this study we sought to test this hypothesis further and, if we found confirmatory evidence that sleep disturbance correlated with clinical disease severity, to determine which specific aspects of clinical impairment correlated with sleep abnormalities.

Methods

Ten patients (6 women and 4 men whose mean age was 67 years; range 60–74) with clinically diagnosed PSP were included in the study. The patients, who were studied during the placebo phase of a drug trial for treatment of PSP [4], were rigorously evaluated to exclude other possible causes of dementia and rigidity. Their motor impairment ranged from mild (some difficulty with ambulation) to profound (bedridden and immobile). All subjects had dementia by criteria outlined in the *Diagnostic and Statistical Manual of Mental Disorders* [5], with mild to moderate cognitive impairment (mean full-scale intelligence quotient 86 [range 75–101] by the Wechsler Adult Intelligence Scale–Revised). None were clinically depressed.

Other than having PSP, the subjects were generally healthy at the time of the study. With the exception of glycopyrrolate (an anticholinergic agent that does not penetrate to the central nervous system), all medications, including sedatives and dopaminergic medications, had been discontinued 3 weeks prior to the study.

Subjects were admitted to the University of Michigan Clinical Research Center and underwent three sleep recordings. The recordings were scheduled from 10:30 PM to 6:30 AM on consecutive nights, but they were started up to 1 hour earlier or later, depending on the sleep habits of the subjects. For each sleep study, surface electrodes were applied to record the electroencephalogram, electrooculogram, submental electromyogram, and electrocardiogram. During the first night, 8 of the 10 subjects were also monitored for nasal-oral airflow, respiratory effort, blood oxygen saturation, and leg movements.

The first night was viewed as an adaptation night, and the presence of periodic leg movements and sleep apnea were assessed. Sleep studies from the second and third nights were scored for sleep stages using conventional scoring criteria applied to each 30-second epoch of recording [6]. All scoring was done by registered polysomnographic technologists and reviewed by an accredited clinical polysomnographer (M.S.A.).

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Received Sep 2, 1988, and in revised form Nov 4. Accepted for publication Dec 3, 1988.

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We defined sleep latency as the time from lights out to the first epoch of any stage of sleep. Persistent sleep was defined as 5 minutes or more of continuous sleep. REM sleep latency was defined as the length of time from sleep onset to the first epoch of REM sleep. Sleep efficiency was defined as the proportion of time spent asleep from sleep onset to the final awakening.

Motor function and voluntary eye movements were assessed independently by two observers (M.S.A., L.B.). A Motor Rating Scale was used to assess facial expression, speech, handwriting, postural stability, gait, balance, fine movements of the hands, and axial and limb rigidity [4]. Each feature was rated from 0 (no abnormality) to 4 (severe impairment). Voluntary eye movements were assessed by visual estimation of the degrees of ocular rotation in each of four directions (up, down, left, right). To control for day-to-day variability, the Motor Rating Scale and eye movement scores were determined serially for each subject three times during the week of the sleep studies and once weekly for the next 4 weeks.

Neuropsychological function was assessed using the following tests: Wechsler Adult Intelligence Scale–Revised, Mini-Mental State [7], Buschke Selective Reminding Task [8], Boston Diagnostic Aphasia Examination [9], Profile of Moods States [10], and Verbal Fluency examination [11]. Since some subjects were unable to complete all parts of the Mini-Mental State examination because of motor or speech impairment, the Mini-Mental State score was expressed as a fraction of the best possible score.

The results of polysomnographic analysis were compared to published values for normal men aged 60 to 69 [12] using Student's t test. We correlated polysomnographic results with clinical variables and performed regression analysis on significant correlations (Statgraphics Statistical Graphics System, Statistical Graphics Corporation, 1985).

Results

The results of the sleep studies are summarized in Table 1, and clinical and neuropsychometric assessments are shown in Table 2. Two representative sleep studies are illustrated in Figure 1. No subject spent less than 2 hours awake per night. Latencies to sleep and to REM sleep were highly variable; 4 of the subjects had REM latencies of less than 10 minutes on one or both of the recording nights.

Two subjects had sleep apnea and periodic leg movements. In 1 apnea was mainly central, and in the other it was predominantly obstructive (apneas plus hypopneas per hour of sleep were 34 and 60, respectively, for the 2 subjects). Periodic leg movements per hour of sleep were 21 and 28, respectively. We calculated mean values for polysomnographic variables in

Table 1. Polysomnographic Results

	PSP Subjects			Published Norms [12]		
Characteristic	Mean	SD	Range	Mean	SD	p^a
Time awake (min)	245.0	60.9	127–352	44.3	43.2	<0.02
Time asleep (min)	233.8	52.2	163–348	407.3	44.6	<0.05
Sleep efficiency (%)	58.1	10.9	44–80	90.0	7.0	<0.05
Percent wakefulness	50.8	11.6	27–68	9.8	6.0	<0.01
Percent stage 1 sleep	15.9	5.9	9–27	9.5	4.0	
Percent stage 2 sleep	22.1	8.3	8–35	55.5	8.8	<0.05
Percent stage 3–4 sleep	4.1	2.8	0–10	2.6	5.0	
Percent REM sleep	6.8	2.8	2–13	22.6	3.6	<0.01
Latency to sleep (min)	28.1	15.6	8–58	8.3	10.5	
Latency to persistent sleep (min)	66.4	61.8	19–239			
Latency to stage 2 sleep (min)	49.4	25.9	7–100	16.7	12.4	
REM latency (min)	80.3	57.7	9–188	83.9	38.1	
No. of REM periods	3.5	1.2	1–6	4.5	0.7	
Average REM period duration (min)	9.5	3.1	6–15	23.2	5.0	<0.05
Wake after sleep (min)	9.6	12.1	0–38			
Wake during sleep (min)	172.7	49.0	88–247	34.0		<0.02
No. of awakenings	33.3	16.7	10–69	7.5	3.7	
No. of awakenings > 2 min	13.8	5.4	4–23			

[a]Significant differences from published norms all remained statistically significant when the 2 patients with sleep apnea and periodic leg movements were excluded.

SD = standard deviation; REM = rapid eye movement; PSP = progressive supranuclear palsy.

Table 2. Clinical and Neuropsychometric Assessments[a]

Studies	No.	Mean	SD	Range
Motor Rating Scale score	10	37.4	11.1	25–56
Voluntary eye movements				
Vertical degrees: up + down	10	15.5	7.5	0–31
Horizontal degrees: left + right	10	85.3	33.3	1–117
Neuropsychometric studies				
Full-scale IQ	8	85.6	7.5	75–101
Memory quotient	8	96.6	12.6	79–117
Mini-Mental State	8	0.81	0.11	0.7–1.0
Profile of Moods States	7	43.8	12.9	32–69
Verbal Fluency	9	6.6	5.9	1–17
Boston Diagnostic Aphasia Examination Subtest: Complex Ideational Material	10	9.4	1.6	7–12
Buschke Selective Reminding Task	9	16.8	16.0	0–46
Subtest: Intrusions	9	0.4	0.4	0–1.3
Subtest: Hits	10	8.9	1.1	6–10
Subtest: False Alarms	10	0.6	0.8	0–3

[a]Some subjects were unable to complete all of the tests because of motor or speech disturbance.

IQ = intelligence quotient; SD = standard deviation.

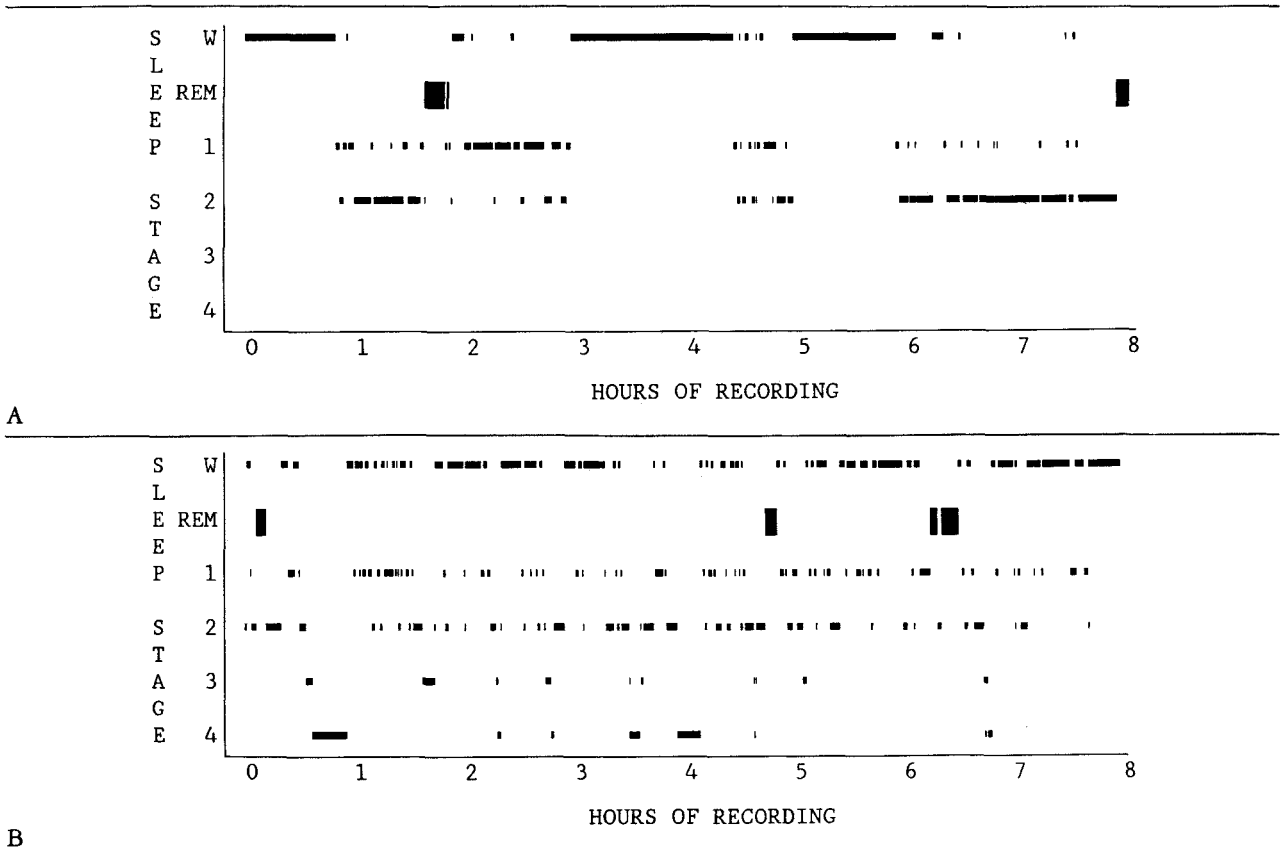

Fig 1. Two representative polysomnograms. (A) The top panel is a recording from a 72-year-old man with progressive supranuclear palsy of moderate severity (Motor Rating Scale = 26). Long sleep latency and two long awakenings account for most of the time awake. (B) The lower panel is a recording from a 67-year-old woman with severe progressive supranuclear palsy (Motor Rating Scale = 56). There is severe sleep fragmentation, with more than 62 awakenings.

Table 3. Correlation of Sleep Variables with Selected Clinical Scales[a]

Characteristic	Total Motor Rating Scale	Motor Subscales					Neuropsychometrics				
		Facial Movement	Posture	Gait	Finger Dexterity	Rigidity	Complex Ideational Material	Profile of Moods	Full-Scale IQ	Memory Quotient	Mini-Mental Status
Total time awake								.57			−.77*
Total time asleep								−.63			.82*
Minutes of stage 3–4 sleep	.85**	.77**	.88***	.95***	.87***	.79**					
Latency to sleep	−.78**	−.67*	−.58	−.66*	−.82**	−.90***	.59				
Latency to REM sleep								−.59			
Number of REM periods								.80*	−.51	−.66	−.67
Number of awakenings > 2 min	.82**	.73*	.62	.77**	.87***	.85**	−.73*	.50		−.50	

[a]Correlations less than .50 are not shown.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

IQ = intelligence quotient; REM = rapid eye movement.

the 8 subjects without sleep apnea or periodic leg movements and found that only number of awakenings and REM latency were more than 6% different from the group as a whole. The 2 apneic subjects had a mean REM latency of 33 minutes compared with a mean of 92 minutes in the other 8 subjects, and they had 62 awakenings per night compared with 26 for the other 8.

Sleep spindles were poorly formed or absent in 5 subjects. Rapid eye movements during REM sleep were also reduced in 5 and appeared to be of low amplitude by subjective assessment. In the most impaired patients, scoring of sleep stages was difficult because of one or more of the following factors: reduced or absent eye movements during sleep that showed all other characteristics of REM sleep, poorly formed or absent sleep spindles and K-complexes, persistent electroencephalographic alpha activity during stage 1–2 sleep, and increased slow activity in the waking electroencephalogram.

Significant correlations of sleep variables with clinical scales are shown in Table 3. We performed the same correlational analysis excluding the 2 patients with sleep apnea and found that all correlations were similar and remained significant. Although sleep latency was longer than published norms for this age group, latency to sleep was inversely correlated with motor impairment. Overall motor impairment correlated with sleep fragmentation as measured by the number of awakenings (Fig 2), but it did not correlate with amount of time spent awake. Cognitive and eye movement abnormalities correlated positively with sleep disturbance, but the correlations were weaker than those between motor impairment and sleep disturbance.

While the mean amount of stage 3–4 sleep was reduced in the PSP subjects as compared with published norms, the amount of stage 3–4 sleep increased with

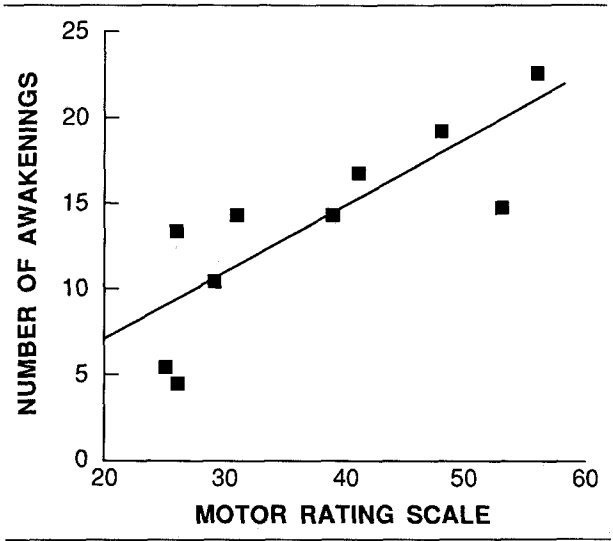

Fig 2. Number of awakenings of duration of 2 minutes or longer per night plotted against Motor Rating Scale (r = .82; p = 0.004).

increasing motor abnormalities. This increase was most likely due to increased amounts of slow electroencephalographic activity in severely affected patients. Although none of the patients were clinically depressed, Profile of Moods score correlated positively with the number of REM periods.

Discussion

Our findings suggest that insomnia in PSP is of moderate severity early in the disease course and is often associated with delayed sleep onset. As the disease progresses, sleep latency shortens, while insomnia becomes more severe and is associated more with sleep fragmentation than with delayed sleep onset or with early morning awakening. The insomnia associated with PSP therefore differs from psychophysiological insomnia, in which difficulty falling asleep is a promi-

nent complaint, and from depressive insomnia, which is characterized by early morning awakening. The findings of reduced amounts of REM sleep and decreased numbers of spindles were similar to those in previous reports [1–3].

Our data are consistent with the hypothesis that PSP insomnia is due to altered brain function from neuronal loss in brain regions involved in sleep regulation. Pathological examinations of patients with PSP have shown degenerative changes in several brainstem structures presumed to be involved in sleep regulation, including the locus ceruleus, periaqueductal gray matter, and pontine tegmentum [13]. Although the specific mechanisms that are responsible for sleep maintenance are not understood, the pons, midbrain, and basal forebrain are probably involved, and degenerative changes in these brain regions could cause sleep fragmentation. Pons and midbrain atrophy on computed tomography has been found to correlate with clinical impairment [14]. Furthermore, dopaminergic and cholinergic systems, both of which play a role in the regulation of sleep and REM sleep, are impaired in this disease [15, 16]. Cholinergic neurons of the pedunculopontine nucleus, which may be involved in the activation of REM sleep [17], are markedly reduced in number in PSP [18].

It is possible that insomnia in our subjects was due to factors associated with disease severity such as discomfort, impaired mobility, or nocturnal disorientation, rather than to neuropathological changes. We did not monitor naps in the subjects, and it is possible that frequent or prolonged daytime naps contributed to nocturnal sleep disturbance. Although these factors may have contributed to insomnia and sleep disruption, the severity of sleep disturbance we observed was greater than that observed in other neurological diseases associated with dementia and impaired mobility. Increased nocturnal wakefulness and frequent awakenings occur in Parkinson's disease [19, 20], Alzheimer's disease [21, 22], and ischemic stroke [23]. However, in these conditions, nocturnal wakefulness typically constitutes 20 to 40% of time in bed, rather than the 50% we observed with PSP. We did not find evidence that sleep apnea, periodic leg movements, or depression—three common causes of sleep fragmentation—were major contributors to the sleep disturbance in most of our subjects.

If PSP insomnia is caused by degenerative neuropathological changes, additional studies that correlate sleep disturbance with specific areas of brain dysfunction, as defined by imaging or neuropathological studies, may help to determine the areas of the brain that are involved in sleep maintenance.

Presented in part at the American Sleep Disorders Association Annual Meeting, June 1988, San Diego, CA.

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