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Daytime REM Sleep in Parkinson's Disease

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Abstract

Background—Previous studies have demonstrated both clinical and neurochemical similarities between Parkinson's disease (PD) and narcolepsy. The intrusion of REM sleep into the daytime remains a cardinal feature of narcolepsy, but the importance of these intrusions in PD remains unclear. In this study we examined REM sleep during daytime Maintenance of Wakefulness Testing (MWT) in PD patients.

Methods—Patients spent 2 consecutive nights and days in the sleep laboratory. During the daytime, we employed a modified MWT procedure in which each daytime nap opportunity (4 per day) was extended to 40 minutes, regardless of whether the patient was able to sleep or how much the patient slept. We examined each nap opportunity for the presence of REM sleep and time to fall asleep.

Results—Eleven of 63 PD patients studied showed 2 or more REM episodes and 10 showed 1 REM episode on their daytime MWTs. Nocturnal sleep characteristics and sleep disorders were unrelated to the presence of daytime REM sleep, however, patients with daytime REM were significantly sleepier during the daytime than those patients without REM. Demographic and clinical variables, including Unified Parkinson's Disease Rating Scale motor scores and levodopa dose equivalents, were unrelated to the presence of REM sleep.

Conclusions—A sizeable proportion of PD patients demonstrated REM sleep and daytime sleep tendency during daytime nap testing. These data confirm similarities in REM intrusions between narcolepsy and PD, perhaps suggesting parallel neurodegenerative conditions of hypocretin deficiency.

Keywords

Parkinson's Disease; Narcolepsy; REM Sleep

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INTRODUCTION

Parallels between Parkinson's disease (PD) and narcolepsy have been reported for a number of years. In addition to daytime sleepiness, noted to be a manifestation of PD itself and demonstrated to be independent from its drug therapy [1, 2], PD patients may show rapid eye movement (REM) on daytime naps [3–5], although not all studies have established this [6–15]. In some cases, the phenotypes can be virtually identical [16]. Neurochemically, narcolepsy with cataplexy is recognized to be characterized by widespread depletion of the neuropeptide hypocretin [17]. Findings from PD patients remain controversial with evidence both in support of [18, 19] and against [17] such an association. In this study we performed polysomnography (PSG) in a relatively large group of PD patients with a special focus on the presence of REM sleep during the day. Because nearly all PD patients in previous studies received dopaminergic medications, we had particular interest in examining whether usage of such medications was associated with the occurrence of REM during the daytime.

METHODS

Patients

The sample consisted of 63 PD patients who participated in a 48-hour laboratory in-patient protocol. The motor component of the Unified Parkinson's Disease Rating Scale (UDPRS) [20] was administered by an experienced neurologist who made the ratings under the medicated condition for those taking dopaminergic medications (N = 49). The remaining patients (N = 14) received no dopaminergic medications. Modified Hoehn-Yahr staging was also completed [21]; all patients were 3 or below. Patients were administered the Mini-Mental State Exam (MMSE) [22], which is a 30-point scale for which higher scores indicate less likelihood of impaired cognition, and the Epworth Sleepiness Scale (ESS) [23], which is a 24-point scale for which higher scores indicate greater daytime sleepiness. All dopaminomimetics (levo-dopa and dopamine agonists) were converted to a total levodopa dose equivalent using a standard conversion formula [24]. Patients also completed two questions dealing with restless legs symptoms based on an epidemiologic study of prevalence of this disorder [25].

Procedures

This was an IRB-approved protocol and all patients provided Informed Consent. Nocturnal sleep studies and daytime nap opportunities over a 48-hour period (usually Thursday night through late Saturday afternoon) were examined in an in-patient setting in a relatively sequestered laboratory environment. Patients were observed continuously on video, and note was made regarding any episodes of dream enactment during sleep. Of the 63 patients, 9 completed fewer than 8 naps, most of these opting out of participating on the second day for various reasons. The nighttime protocol consisted of conventional PSG. We analyzed both Periodic Leg Movements in sleep (PLMS), as well as the Apnea/Hypopnea Index (AHI). In the daytime, we conducted a modified Maintenance of Wakefulness Test (MWT) [26, 27]. Complete details of the protocol can be found elsewhere [28]. In brief, we recorded patients during the entire 40-minutes for each nap opportunity, regardless of whether sleep occurred. Each patient thus had 160 total minutes each day in which they could have demonstrated REM sleep. We generated three measures from the MWT: 1) the presence or absence of at least one epoch of REM sleep; 2) the Latency to the first epoch of any stage of sleep, regardless of stage (SLAT); and 3) the Sleep Efficiency (SE) of the 40-minute nap opportunity, which was calculated as the proportion of the 40 minutes in which the patient was asleep. All recordings were scored for sleep architecture following the modifications suggested for characterizing the sleep of PD patients [29].

Statistical Analyses

For overnight sleep measures we averaged Nights 1 and 2. For SLAT and SE based on MWT, we computed each patient's median value and then averaged these to obtain means across patients. Because narcolepsy is typically defined by at least 2 daytime naps with REM sleep, we classified patients into those having 2 or more REM episodes on their MWTs ($n = 11$) and compared these patients to patients having only a single REM episode on the MWT ($n = 10$) and those having no REM episodes ($n = 42$) using oneway Analyses of Variance (ANOVA) followed by pairwise Scheffe contrasts. Categorical comparisons (% male, % with observed dream enactment) were made with chi-square tests. For the analyses of the modified Hoehn-Yahr scale, we used the Kruskal-Wallis non-parametric ANOVA. Statistical significance was set at a p value of .05.

RESULTS

Across all patients, the mean (SD) MWT SLAT was 18.4 (14.8) minutes and SE was 27.3 (26.8) %. A total of 21/63 patients showed at least 1 REM period on daytime nap testing and 11 showed 2 or more REM periods. In the majority of daytime nap opportunities (34 of 46; 74%), the REM period occurred within 15 minutes of the first 30 second epoch of sleep. Table 1 shows comparisons between those patients showing one or more REM periods on daytime nap opportunities versus the remaining patients. There were no differences in demographics and most clinical variables, including years with diagnosis, Hoehn-Yahr staging, UPDRS sum motor score, total levodopa dose equivalence, restless legs symptoms, MMSE or ESS scores. None of the nocturnal sleep measures, including REM%, PLMS Index, Apnea/Hypopnea Index and observed dream enactment, differentiated these groups, however, daytime REM was associated with shorter SLAT and higher SE on daytime naps. Post-hoc contrasts indicated that groups with 1 REM episode and 2 or more REM episodes were more likely to have higher sleep efficiencies and/or shorter sleep latencies during the daytime. When using a definition of 1 or more REM episodes, there was a trend for the 8 patients receiving only a dopamine agonist to be more likely to show REM when compared to those 14 individuals receiving no dopaminergics (62.5% vs. 21.4%, Fisher's exact $p = .08$), but such a trend was not seen when comparing patients receiving only levodopa to the 14 unmedicated patients (35.7% vs 21.4%, Fisher's exact test $p = .68$).

DISCUSSION

REM sleep episodes on the daytime MWT or Multiple Sleep Latency Test (MSLT) are a feature previously reported in some [3–5], but not all [6–15], studies of PD, but their significance remains uncertain. We have described a juvenile PD case for which the phenotype was virtually identical to narcolepsy without cataplexy [16]. Given the fact that some, but not all, studies have noted hypocretin deficiency in PD [15, 17–19], it is tempting to suggest that the subgroup of PD patients with daytime REM and who were also less alert during the daytime might be those with hypocretin deficiency. This diffusely projecting hypothalamic system throughout midbrain and brainstem structures, long recognized to be crucial for sleep/wake regulation [30], may underlay the deficits in daytime alertness seen in PD

These data must be viewed with some cautions. Our modification of the MWT protocol is somewhat different than the conventional procedure in that we allowed each nap opportunity to run for a full 40 minutes regardless of whether sleep did or did not occur. This modification was made largely for practical considerations, since the determination of REM sleep in PD patients can be a complex determination [29] and insisting that lab personnel to make such determinations "on the spot" (i.e., in order to determine whether a particular MWT trial should be terminated after 15 minutes of sleep had accrued) might result in

premature termination of any particular trial. Because REM is more likely to occur as sleep accrues, the invariant 40-minute duration may have biased the findings towards a greater likelihood of REM sleep. In the clinical use of the MSLT [27], no more than 15 minutes is allowed to occur before the nap test is terminated. Because some of our patients were quite sleepy during the day, they could have obtained more sleep and may have been more likely to demonstrate REM. Although we cannot eliminate this possibility, the fact that nearly 75% of all naps containing REM showed this stage within 15 minutes of the first epoch of sleep argues against this modified procedure as being the sole cause of the observed REM during the daytime.

It was surprising that dopaminergic medications did not have bearing upon the presence of REM, although there is some suggestion that these medications affect daytime alertness, perhaps even in a dose-dependent, class-divergent manner [28] with dopamine agonists appearing to confer the greatest risk for decreased daytime alertness. In these data, there was indeed a hint of such an effect with REM sleep (on 1 or more naps) being slightly more frequent only among patients on dopamine agonists when (but not levodopa) compared to unmedicated patients. Our inclusion of 14 PD patients not receiving any dopaminergic medications is somewhat unusual, as most prior studies [3–16] have been limited to patients receiving dopaminergics, and suggests that more emphasis should be placed on evaluating how daytime REM per se may or may not be related to usage of such medications. Additionally, the importance of chronically impaired daytime alertness as possible risk factor for the development of PD [31] and as a key non-motor symptom or sign impacting quality of life [32] suggest that future efforts to understand these phenomena are warranted.

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Table 1

Characteristics of Patients with and without Daytime REM Sleep

Demographics/ Clinical	(A) Patients having No Naps with REM (n = 42)		(B) Patients having 1 Nap with REM (n = 10)		(C) Patients having 2 Naps with REM (n = 11)		Comparison F or χ^2 (p)	Contrasts
Age (years)	62.4 (9.6)	65.7 (7.8)	63.3 (12.0)	.46 (.63)				
Sex (% male)	66.7%	40.0%	81.8%	4.17 (.12)				
Modified Hoehn- Yahr (median, IQR ^a)	2.0 (0.5)	2.0 (1.0)	2.5 (1.0)	3.08 (.21)				
Disease Duration (years)	5.6 (4.4)	6.9 (3.5)	4.4 (2.6)	1.07 (.35)				
UPDRS (Total Motor)	16.6 (8.1)	14.0 (9.7)	20.7 (8.6)	1.51 (.23)				
Levodopa equivalent (mg)	483.0 (419.5)	449.9 (282.6)	397.2 (324.3)	.22 (.80)				
MMSE	28.5 (1.9)	28.9 (0.4)	28.7 (1.6)	.21 (.81)				
ESS	9.7 (4.1)	11.7 (3.6)	11.5 (6.1)	1.37 (.26)				
Bedtime Restless Legs ^b	1.7 (0.8)	1.7 (0.9)	1.9 (0.3)	.22 (.80)				
Nighttime Restless Legs ^c	2.0 (0.9)	1.8 (0.8)	1.6 (0.5)	1.11 (.34)				
Observed dream enactment in lab (%)	28.6%	60.0%	36.4%	3.52 (.17)				
Daytime Alertness (MWT)								
Median SE (%)	19.1 (23.2)	40.6 (27.4)	46.8 (26.1)	7.37 (.001)				A < C
Median SLAT (mins)	23.0 (14.7)	10.6 (12.1)	8.0 (8.5)	7.47 (.001)				A > B, C
Nocturnal Sleep								
Total Sleep Time (mins)	317.5 (107.4)	323.5 (47.7)	370.8 (74.1)	1.37 (.26)				
SE (%)	66.2 (21.1)	68.6 (13.5)	78.5 (13.7)	1.82 (.17)				
REM (%)	12.2 (9.2)	13.1 (7.7)	13.1 (7.9)	.08 (.92)				
PLMSI ^d	18.5 (34.0)	10.6 (8.1)	22.6 (45.2)	.34 (.71)				
AHI ^e	7.0 (9.2)	4.3 (5.1)	5.6 (5.9)	.50 (.61)				

Notes:^aIQR = Inter-quartile range; chi-square value obtained from Kruskal-Wallis non-parametric Analysis of Variance.^bResponses to the question: "At bedtime, does restlessness in your legs delay your falling asleep?" Categorized as: 1 = Never; 2 = Occasionally; 3 = Often; 4 = Very Often (from ref. 25)^cResponses to the question: "When you wake up during the night, how often do you feel unpleasant sensations in your leg muscles that require you to move your legs or walk in order to be more comfortable?" Categorized as: 1 = Never; 2 = Occasionally; 3 = Often; 4 = Very Often (from ref. 25)

$P_{PLMSI} = \text{Periodic Leg Movements in Sleep Index (calculated as movements per hour)}$

$e_{AHI} = \text{Apnea/Hypopnea Index (calculated as number of apneas + hypopenas per hour)}$