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Dopamine agonists and sleepiness in PD: review of the literature and personal findings

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Abstract

Background and purpose: This study is aimed at evaluating daytime sleepiness in a series of Parkinson's disease (PD) patients chronically treated with dopamine agonists (DAs) alone or in combination with L-Dopa.

Patients and methods: A preliminary series of 22 non-demented, adult PD patients (mean age 68.9, 13 men and 9 women) were evaluated by means of structured sleep interview, Epworth sleepiness scale (ESS) and 24-h ambulatory polysomnography (A-PSG).

Results: Sleep attacks (SAs) were reported by 32% of the patients, in three of them (43%) after DA treatment was initiated (alone or in addition to L-Dopa). In two patients, both with chronic use of ropinirole, we documented NREM SAs during a continuous ambulatory polysomnography (A-PSG) performed in the patients' real-life settings. The subjects experiencing SAs showed a higher degree of daytime sleep propensity than those without SA, having higher ESS scores and a higher proportion of microsleeps and intentional naps on A-PSG. Interestingly, we found that nocturnal total sleep time is higher in PD patients with SAs than in the others.

Conclusions: All in all, our data indicate that SAs are an extreme manifestation of increased daytime sleepiness. The occurrence of SAs in our series of PD patients is unlikely to depend simply on the demands of homeostatic mechanisms.

Keywords: Parkinson's disease; Daytime sleepiness; Sleep attacks; Dopamine agonists

1. Introduction

In 1999, the scientific community was alerted to the sedating effect of non-ergot dopamine agonists (DAs) in Parkinson's disease (PD) patients [1].

Several studies [2–6] indicate that DAs play a role in the genesis of excessive daytime sleepiness (EDS) in PD, most indicating that the sedating effect of DAs is related to the stimulation of the inhibitory D_2-like autoreceptors at the level of the ventral tegmental area (VTA). The sedating effect is not unique to a subgroup of DAs and seems to depend on the dose administered and on the functional state of the central dopaminergic pathways.

The mechanisms by which DAs cause daytime sleepiness in PD and the clinical phenomenology of the somnolence they induce are still a matter of debate [7]. Sleep attacks (SAs) have been reported in PD patients under treatment with DAs [8–14]. However, to date SAs had been documented during polysomnographic (PSG) recording in only two patients, in one of which sleep onset REM (SOREM) was detected [15,16].

2. Dopamine agonists and excessive sleepiness in PD: pathophysiological basis

In spite of several methodological research limitations met in exploring the mechanisms by which DAs influence vigilance in animals and humans, some facts have become established and further evidences are emerging [2].

Studies in animals indicate that the effect of DAs on vigilance and on the sleep–wake cycle depends strictly on whether D_1 or D_2 receptor is stimulated, on the site of action of the DA (pre-synaptic or post-synaptic), and on the DA

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dose administered. A sedating effect, monitored by behavioural and EEG indexes, appears to be related to the stimulation of D_2-like inhibitory central autoreceptors, while an arousing effect seems to occur via the stimulation of D_1-like post-synaptic receptors [3–5]. The VTA and mesolimbic, mesocortical dopaminergic circuits are considered to be crucial site for the action of the DAs on sleep–wake cycle. An increased daytime sleep propensity, measured by the Multiple Sleep Latency Test (MSLT), has been documented in young healthy humans taking 1.5 mg ropinirole orally. The observed effect was ascribed to the stimulation of D_2-like receptors [6].

It has been hypothesized that DAs may influence hypocretin-1 production; however, preliminary findings in three PD patients taking DAs argue against this hypothesis [7], which should be explored through further studies.

A sedating effect of DAs in PD patients has been documented in several studies. The Epworth sleepiness scale (ESS) has been widely used for the measurement of sleepiness in PD, while the MSLT alone or in combination with the ESS has been used in a few investigations. The ESS score has been reported to be higher in PD patients under treatment with DAs than in both age- and sex-matched healthy controls [8,9] and patients affected by other neurological disorders [10]. In placebo-controlled studies using the MSLT as a measure of sleepiness, the sedating effect of DAs in PD patients has been shown to depend on the DA dose and the disease severity [11]. Several studies report no difference in sleepiness between PD patients treated with ergot and those treated with non-ergot DAs [12–14]. Furthermore, EDS is also known to occur in PD patients on L-Dopa [17]. Thus, the sedating effect of DAs is neither unique to a subgroup of DAs nor to this class of anti-Parkinsonian agents.

It has been stressed that sleepiness in PD depends mainly on the PD pathology. Animal models of PD [18] confirm this hypothesis.

EDS with sleep onset REM periods (SOREMPs) has been reported to occur in untreated PD patients [19,20] and has been ascribed to a dopamine deficit at the level of mesocortical circuits.

The role both of PD severity and duration, and of the presence of comorbid conditions such as sleep-apnea, restless legs and depression, in the genesis of somnolence in PD has been stressed [10,14,19,21].

Some authors have recently signalled that, depending on the degree of integrity of the dopaminergic circuits, the DA intake in PD patients can result in either a sedating or an arousing effect [21].

All in all these data indicate that the effect of DAs on vigilance in PD derive from a complex interaction between DAs and disease-related factors.

3. Dopamine agonists and sleepiness in PD: clinical and electrophysiological features

Both continuous sleepiness and 'SAs' have been reported in PD patients. Even though some authors have questioned the very concept of SAs [22], others have reported that SAs do occur in PD patients on DAs [1,6,11,23]. Some studies indicate that the rate of occurrence of SAs is significantly higher in PD patients than in age- and sex-matched healthy controls [9]. Different SA rates have been reported in Asian [9] and Caucasian [23] PD patients.

It has been stressed that SAs in PD are narcoleptic like. In fact, SOREMPs have frequently been documented in sleepy PD patients undergoing the MSLT [19,21]. To date, PSG documentation of SAs in PD has been obtained in only two patients, in one of which [22] SAs were characterized by REM sleep onset. However, cataplexy has not been observed in these patients. It is unlikely that a comorbid PD-narcolepsy condition underlies narcoleptic-like SAs in PD. In fact, a random association between PD and narcolepsy is unlikely on an epidemiological basis, and Class II histocompatibility leukocyte antigen (HLA) patterns in PD patients with narcoleptic-like SAs did not include those typically seen in narcolepsy patients. Rather, most studies hypothesize that narcoleptic-like phenomena in PD depend on PD pathology itself. However, NREM SAs have been reported during 48-h A-PSG [23] and during MSLT [11].Thus, the phenotype of SAs is not invariably narcoleptic-like in PD patients. Similarly, the neuropathological substrate has been thought to underlie both narcoleptic-like and non-narcoleptic-like EDS in other neurological disorders [24,25].

4. Personal findings

We set out to evaluate daytime sleepiness in a series of PD patients chronically treated with DAs alone or in combination with L-Dopa. We report here preliminary findings in 22 patients.

4.1. Patients

Twenty-two adult, non-demented PD patients diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) criteria, not previously investigated for sleep disorders and not taking sedative–hypnotic drugs, entered the study. Details of the patients are presented in Table 1. Most of the patients led quiet, domestic lives and, even when driving licence holders, were not active drivers.

4.2. Methods

Patients and respective caregivers were questioned about the patient's nocturnal sleep and daytime sleepiness by

Table 1
Main clinical data of 22 selected patients

	Tot	Group A	Group B
Age (mean ± SD)	69.3 ± 5.5	71 ± 6.9	68.5 ± 4.8
Sex M (% of patients)	59	71	53
BMI, kg/m^2 (mean ± SD)	24.4 ± 3.8	24.6 ± 3	24.2 ± 4.2
Illness duration, years (mean ± SD)	9.4 ± 3.9	11 ± 3.7	8.7 ± 3.9
Motor complications duration, years (mean ± SD)	3.9 ± 2.8	5.3 ± 4.0	3.1 ± 1.6
UPDRS off (mean ± SD)	42.9 ± 14.9	45.2 ± 9.3	41.8 ± 17.1
Hoehn and Yahr stage off (median)	3	4	3
Daily equivalent L-Dopa dose, mg (mean ± SD)	1030 ± 433	1214 ± 428	944 ± 421
Dopamine agonists therapy (% of patients)	86	85	86
Daily equivalent agonists dose, mg (mean ± SD)	361 ± 180	483 ± 196	305 ± 146
L-Dopa daily dose, mg (mean ± SD)	686 ± 289	728 ± 228	666 ± 319
Beck depression inventory	16.4 ± 7.5	19.1 ± 8.4	15.2 ± 7.0

means of a structured interview. Some of the questions were designed in particular to ascertain whether the patient had, during the previous 4 weeks, experienced at least one episode of sudden falling asleep in daytime hours without a prior feeling of sleepiness or other heralding symptoms. Subsequently, the patients were administered an Italian version of the ESS [26].

Having been shown how to keep an accurate sleep log and use an event marker to signal any subjective or objective symptom of sleepiness, intentional napping or sudden involuntary falling asleep in daytime hours, the patients underwent 24-h A-PSG monitoring, which took place at home. Drug regimens and daily routines had been maintained for at least 2 weeks prior to the study and were kept unchanged throughout the 24-h A-PSG. Sleep–wake schedule and habits were also regular during the weeks prior to the monitoring.

The recordings were made on flash card by means of an 11-channel PSG (Micromed MS 40) with acquisition of EEG (referential technique with nine electrodes positioned according to international 10–20 system), Electro-oculogram (bipolar montage) and submental EMG. PSG recordings were scored visually page by page from the screen in accordance with standard sleep scoring criteria [27] by a physician who was blind to the patient's clinical interview and ESS score.

4.3. Statistical analysis

Statistical comparisons were performed using the χ^2, with the exact Fischer's test correction to compare prevalence data between groups of patients and the Kruskal–Wallis test to compare mean values. The level of statistical significance was set at $P < 0.05$.

5. Results

5.1. Daytime sleepiness: subjective and objective A-PSG findings

Seven patients (group A) reported daytime episodes of falling asleep, which appeared to have the features of so-called SAs as they occurred suddenly against a background of wakefulness and were not preceded by a feeling of sleepiness or by any other heralding symptoms. None of these patients reported either episodes of sudden loss of muscle tone in relation to pleasant emotions or other narcoleptic-like phenomena. The SAs occurred when the patients were relaxed or in conditions of moderate interactivity, the rate ranging from 1 to 4 episodes during the previous 4 weeks.

SAs occurred in three (43%) patients after they were put on DA treatment (alone or in addition to L-Dopa, in all instances non-ergot derivatives). The remaining 15 patients (group B) did not report daytime SAs.

The mean global ESS score was significantly higher in group A than in group B (14.3 SD 3.7 vs 8.3 SD 4.5, $P < 0.05$). The objective A-PSG findings concerning daytime sleepiness and sleep (prevalence, timing and duration of the specific patterns) are detailed in Table 2.

The napping pattern in groups A and B consisted of voluntary naps, generally in the early afternoon, taken while the patients were sitting in a chair or lying down. The sleep pattern on A-PSG was one of alternating quiet wakefulness and drowsiness followed by the gradual occurrence of stage 2 NREM sleep, eventually followed by stage 3 NREM, and REM sleep in only one subject (in group B). In two patients from group A, polygraphic patterns of sudden NREM sleep onset were recorded against background activity denoting wakefulness. The polygraphic pattern was one of a rapid shift from wakefulness to sleep indicated by sudden θ/δ slowing of background EEG activity, followed by a K-complex and diffuse δ activity. The sudden sleep onset occurred during the early afternoon in one patient, in both

Table 2
Daytime sleepiness: ESS score and A-PSG findings

	Group A	Group B
ESS score*	14.6 ± 3.7	8.3 ± 4.5
ESS score >10 no. (%) of patients	4 (80)	4 (26)
PSG naps no. (%) of patients	5 (71)	6 (40)
Early afternoon no. (%) of patients	2 (40)	4 (66)
PSG microsleep no. (%) of patients	4 (57)	5 (33)
PSG sleep attack no. (%) of patients	2	0

ESS, Epworth sleepiness scale; *$P < 0.05$

the early and late afternoon in the other, and in all instances during leisure/relaxation time (while playing cards on one occasion). On all occasions, the caregiver witnessed the episodes of sudden sleep, while the patients themselves were unaware of their occurrence.

5.2. Nocturnal sleep: subjective and objective findings

In most subjects, nocturnal sleep lasted from 11.00–11.30 p.m. to 05.30–06.00 a.m.

The main nocturnal PSG findings are reported in Table 3.

In three group A patients and five group B patients, scarcity and/or disruption of spindles and K-complexes and REM alterations (scarcity of REMs, increased number of EMG twitches, transient increase of submental muscle tone, α intrusion on the EEG) were recorded. Slow-wave sleep was reduced in all the patients.

As far as subjective data are concerned, most (77%) of the patients complained of poor sleep due to rigidity and pain (10 patients) or nocturia (7 patients). One patient (14%) from group A and two (13%) from group B reported symptoms suggestive of restless legs syndrome (RLS) in that they complained of recurrent, disagreeable sensations in the legs and an urge to move when relaxed in the evening or in bed at night before falling asleep.

Habitual (every, or almost every night) snoring was present in six of the seven group A patients and in 11 of the 15 group B patients.

Episodes of presumed REM sleep behaviour were reported by three group A and by three group B patients. No objective confirmation of these or other sleep disorders, such as periodic limb movements (PMLs), were obtained because the PSG montages were not suitable for such monitoring and documentation of these disorders was not one of the purposes of this study.

The demographic features, disease characteristics and treatment of patients belonging to groups A and B are compared in Table 1. The values are computed as means ± SD or as percentage values. The daily dose of DAs is expressed as the equivalent L-Dopa dose in mg/day [28]. The percentage of group A patients who were on DAs was significantly higher than the corresponding percentage in group B.

Ergoline DAs (ergolinic derivatives in all but one case) were equally distributed among the two groups of patients (85 vs 86% in group A vs B, respectively).

Illness duration and daily L-Dopa/DA dose were higher, but not significantly so, in group A than in group B patients.

Table 3
Main findings concerning nocturnal sleep

	Group A	Group B
Nocturnal PSG findings		
Sleep latency, min (mean ± SD)	52 ± 46	50 ± 39.8
TST, min (mean ± SD)	366 ± 54	284 ± 104
TIB, min (mean ± SD)	512 ± 50	444 ± 85
SE	72 ± 8	61 ± 18
REM latency, min (mean ± SD)	148 ± 79	135 ± 87
WASO, min (mean ± SD)	64 ± 35	63 ± 64
Clinical findings		
Presumed episodes of RBD (% of patients)	43	20
Habitual snoring (% of patients)	86	65
Symptoms suggestive of RLS (% of patients)		
PMLs prevalence	14	13

TST, total sleep time; TIB, time spent in bed; SE, sleep efficiency (TST/TIB); WASO, wakefulness after sleep onset.

6. Discussion

Based on the patient's and caregiver's reports, daytime episodes of falling asleep interpretable as SAs, occurred in 32% of the PD patients examined. This figure is consistent with that reported in a large series of Caucasian PD patients [21].

The literature contains discussions of whether daytime sleepiness and SAs in PD patients constitute distinct phenomena or a continuum, and whether they are narcoleptic-like phenomena. Among the present PD patients, subjects experiencing SAs showed a higher degree of daytime sleep propensity than those without SA, having higher ESS scores and a higher proportion of microsleeps and intentional naps on A-PSG, indicating that SAs are an extreme manifestation of increased daytime sleepiness. However, it remains controversial why the SAs occurred suddenly and against a background of wakefulness, as was clearly documented by both A-PSG findings and clinical observation in the three episodes we monitored; the question remains whether other mechanisms play a role in the genesis of SAs [23].

Interestingly, we found that nocturnal total sleep time is higher in PD patients with SAs than in the others, making it unlikely that the occurrence of SAs depends simply on the demands of homeostatic mechanisms; this is in keeping with reports by other authors [2–19].

Both narcoleptic [22] and non-narcoleptic-like SAs [23] have been documented during PSG recordings. Our data indicate a non-narcoleptic-like phenomenon; the observed SAs are not featured by SOREMPs.

Further studies are needed to determine whether the different patterns of observed SAs depend on factors such as disease severity, drug regimens and genetic susceptibility.

Since the A-PSG did not include montages suitable for the monitoring of breathing or limb movement, neither sleep-related breathing disorders nor periodic limb movements could be documented with certainty as causes of daytime sleepiness in our study. However, our clinical interviews showed that the rate of presumed REM behaviour disorder and snoring is higher in PD patients with SAs than in the others. Furthermore, these patients had a higher body mass index (BMI) with respect to the others. This finding, along with the higher prevalence of snoring,

suggests that an underlying sleep-disordered breathing, namely obstructive sleep apnea, is likely to play a role in determining increased daytime sleepiness in these patients.

Among various other possible factors contributing to daytime sleepiness in our series of PD patients, the data indicate that DAs and L-Dopa equivalent doses are higher in PD patients with SAs than in the others, while type of DAs (ergoline/non-ergoline derivatives) did not differ substantially between group A and group B.

Finally, males had longer illness duration and were overrepresented among PD patients with SAs.

The small size of the subgroups of PD patients is likely to account for the fact that differences observed did not reach statistical significance.

The present data await further confirmation in a larger series of patients.

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