Predictors of Impaired Daytime Sleep and Wakefulness in Patients With Parkinson Disease Treated With Older (Ergot) vs Newer (Nonergot) Dopamine Agonists

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Background: Patients with Parkinson disease (PD) treated with the nonergot dopamine agonists pramipexole dihydrochloride and ropinirole hydrochloride have been reported to have sleep attacks without warning.

Objective: To perform a systematic evaluation of excessive daytime sleepiness using standard polysomnographic techniques.

Design: Two overnight studies and daytime sleep tests were performed on a prospective sample. Pathologic daytime sleep latency was indexed by a mean Multiple Sleep Latency Test score of no greater than 5 minutes or a mean Maintenance of Wakefulness Test latency of no greater than 20 minutes.

Patients and Setting: Eighty nondemented, independent PD patients treated with dopamine agonists at the Toronto Western Hospital Sleep Research Unit, Toronto, Ontario.

Results: Patients treated with pramipexole dihydrochloride (n=29), ropinirole (n=28), or bromocriptine mesylate or pergolide mesylate (n=23) did not differ with respect to mean Multiple Sleep Latency Test scores (overall, 12.1 minutes [SD, 5.1 minutes], F2,77=0.11; P=.90) or mean Maintenance of Wakefulness Test latencies (overall, 26.7 minutes [SD, 5.4 minutes]; F2,77=1.1; P=.29). Fifteen patients (18.8%) exhibited pathologic daytime sleep latencies. The main risk factor associated with pathologic daytime sleep latency was high levodopa dosage equivalents (>867.5 mg; odds ratio, 4.2; 95% confidence interval, 1.3-13.7). Subjective accounts of daytime sleep and wakefulness, as indexed by scores on the Epworth Sleepiness Scale, were not related to impaired daytime sleepiness or wakefulness (x² [n = 80], 0.13; P=.72).

Conclusions: Total dopaminergic drug dose rather than the specific dopamine agonist used is the best predictor of daytime sleepiness in PD patients receiving dopamine agonist therapy. Physicians concerned with daytime hypersomnolence in PD patients treated with dopamine agonists and receiving high levodopa dosage equivalents should consider polysomnographic monitoring for impaired daytime sleep latency.

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ness in advance of the event, which might have forewarned the patient or the physician, is lacking. It remains unresolved whether episodes of sleepiness can be directly related to the differences in the pharmacodynamics between different agonists or whether this effect can be attributed to the total amount of dopaminergic dose in a patient’s treatment regimen.

**METHODS**

**PATIENTS**

Patients were recruited from the Toronto Western Hospital Movement Disorders Clinic, Toronto, Ontario. Eligibility criteria included an established diagnosis of idiopathic PD according to the criteria of the United Kingdom PD Society Brain Bank, a Schwab and England activities of daily living (ADL) score of at least 70% while in the “on-medication” state, and a Mini-Mental State Examination (MMSE) score of at least 24. Demented and more severely affected patients were not included, as we were interested in choosing highly functioning patients who would be most impaired by daytime somnolence or reduced alertness. This group was considered well representative of similar patients not attending a movement disorder clinic, although the use of dopamine agonists may be more frequent in this specialty care setting. Of 143 candidates contacted, 80 (56%) (52 men [65%] and 28 women [35%]) gave informed consent between April 2000 and April 2001. The most common reasons for not participating were inability to provide the time commitment of 2 days and 2 nights or transportation difficulties. The Ethics Review Board of the University Health Network, Toronto, granted approval for the study.

Patients were categorized on the basis of their primary antiparkinsonian medication, including pramipexole treatment in 29 (17 men; mean ± SD daily dose, 2.8 ± 1.6 mg), ropinirole hydrochloride treatment in 28 (21 men; mean ± SD daily dose, 12.7 ± 8.8 mg), and ergot (bromocriptine mesylate [n = 4] or pergolide mesylate [n = 19]) treatment in 23 (14 men; bromocriptine mesylate mean ± SD daily dose, 24.4 ± 13.0 mg; pergolide mesylate mean ± SD daily dose, 1.9 ± 1.2 mg). No patient had a history of switching from one agonist to another owing to excessive sedation. Patients receiving pergolide and bromocriptine were combined in view of the small number of bromocriptine-treated patients, the similarity of the 2 compounds (older, ergot-derived agonists), and particularly the initial concern that excessive sedation, the risk for sudden-onset sleep, was greater with the newer, nonergot-derived agents than with these older drugs. Concurrent medications that patients were using at the time of study and the number of patients receiving each medication type were as follows: levodopa/carbidopa (n = 73), selective serotonin reuptake inhibitors (n = 10), tolcapone (n = 7), selegiline hydrochloride (n = 7), clonazepam (n = 6), and nonselective monoamine reuptake inhibitors (n = 4). To compare different medications directly at dosages of equivalent efficacy, we converted the dosages to levodopa dosage equivalents (LDEs). The following formula was used:

\[
\text{LDE} = (\text{Regular Levodopa Dose} \times 1) + (\text{Levodopa Controlled Release Dose} \times 0.75) + (\text{Pramipexole Dose} \times 67) + (\text{Ropinirole Dose} \times 16.67) + (\text{Pergolide Dose} \times 100) + (\text{Bromocriptine Dose} \times 10) + [\text{(Regular Levodopa Dose + (Levodopa Controlled Release Dose} \times 0.75))] \times 0.25 \text{ if Taking Tolcapone}.\]

**OVERNIGHT POLYSOMNOGRAPHY**

A standard polysomnographic montage included electroencephalography, electro-oculography, electromyography (at the chin and left and right tibialis muscles), and respiratory monitoring (oxygen saturation, nasal airflow, and breathing efforts). Patients completed 2 consecutive overnight studies followed by the Multiple Sleep Latency Test (MSLT) after the first night and the Maintenance of Wakefulness Test (MWT) after the second. Technical difficulties precluded analysis of the second night of 2 patients (1 pramipexole treated and 1 ropinirole treated).

All recordings were made on REMbrandt software (MEDCARE Diagnostics, Buffalo, NY), with a paper speed of 10 mm/sec. The polysomnograms were scored according to standardized criteria by experienced technologists masked to treatment regimen. We calculated for each patient the following sleep variables: total sleep time, sleep efficiency (total sleep time/time in bed × 100%), the percentage of total sleep time spent in stages 1, 2, 3, 4, and rapid eye movement (REM) sleep, sleep-onset latency, defined as the time until the first 30-second epoch of stage 2 sleep, stage 3 and 4 (slow wave sleep), or REM sleep that was followed by no more than 1 minute of wakefulness during the first 10 minutes of sleep; the latency to the first epoch of REM sleep (REM sleep latency); percentage of wakefulness after sleep onset; and a measure of the number of arousals per hour termed the arousal index. The overnight sleep study extended from 11 PM to 7 AM for a maximum of 8 hours of sleep time. To control for a possible first-night effect, differences between treatment groups were evaluated using polysomnographic variables derived from the second night of study.

**DAYTIME TESTS OF SLEEP LATENCY**

The MSLT was used for the objective assessment of daytime sleepiness. This procedure included 4 or 5 nap opportunities, beginning at 9 AM and repeated every 2 hours subsequently. The patients were asked to lie in a darkened, sound-attenuated room for 20 minutes and attempt to sleep. The time taken to fall asleep was measured with the recording montage that was affixed the previous night. The average latency to sleep onset of all nap opportunities provided an index of sleep propensity. Shorter latencies reflect a higher level of sleepiness; a mean latency of no greater than 5 minutes was considered indicative of an objective level of excessive daytime sleepiness.

The MWT was conducted to measure daytime alertness. This test challenges the patient’s ability to remain awake during soporific circumstances. The MWT is procedurally similar to the MSLT except that the patient is seated in a dark room and instructed to remain awake for 30 minutes. Sleep latencies of no greater than 20 minutes on this version of the test (2 SDs below that observed in healthy individuals) were characterized as evidence of impaired wakefulness.

**SUBJECTIVE TESTS**

A 10-cm visual analog scale was used to estimate perceived sleepiness or diminished alertness before each daytime sleepiness or alertness test. Immediately before the MSLT or MWT, patients completed the visual analog scale indicating low (0 cm) vs high (10 cm) sleepiness or low (0 cm) vs high (10 cm) alertness, respectively.

Before the first night of sleep study, patients were asked to complete the ESS, an assessment of the likelihood of dozing in 8 different circumstances (range for each circumstance, 0 [not likely to doze] to 3 [high likelihood of dozing]; maximum total score, 24). We considered a standard ESS score of at least 7 as high, based on the modal score for the normative data of Johns in a younger population, although higher cutoffs (ie, 10 or 15) can be used in clinical practice.

**DATA ANALYSIS**

Statistical analyses were performed with Statistical Package for the Social Sciences software (version 10.1; SPSS Inc, Chicago, ©2004 American Medical Association. All rights reserved.
Table 1. Characteristics of 80 Subjects With PD Treated With Ergot vs Nonergot Dopamine Agonists

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 80)</th>
<th>Pramipexole Dihydrochloride (n = 29)</th>
<th>Ropinirole Hydrochloride (n = 28)</th>
<th>Bromocriptine Mesylate/Pergolide Mesylate (n = 23)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64.3 (10.3)</td>
<td>65.7 (10.2)</td>
<td>61.0 (11.4)</td>
<td>66.5 (8.2)</td>
<td>.11</td>
</tr>
<tr>
<td>Hoehn and Yahr stage†‡</td>
<td>2.5 (0.68)</td>
<td>2.5 (0.77)</td>
<td>2.4 (0.70)</td>
<td>2.5 (0.55)</td>
<td>.70</td>
</tr>
<tr>
<td>ADL score‡</td>
<td>80.0 (9.6)</td>
<td>79.1 (10.5)</td>
<td>80.4 (8.4)</td>
<td>80.7 (9.5)</td>
<td>.83</td>
</tr>
<tr>
<td>MMSE score</td>
<td>28.9 (1.4)</td>
<td>29.1 (1.3)</td>
<td>28.9 (1.2)</td>
<td>28.5 (1.7)</td>
<td>.28</td>
</tr>
<tr>
<td>Duration of PD, y</td>
<td>9.3 (5.9)</td>
<td>8.4 (6.0)</td>
<td>7.5 (4.4)</td>
<td>12.4 (6.3)</td>
<td>.006†</td>
</tr>
<tr>
<td>LDE, mg</td>
<td>752.2 (394.5)</td>
<td>701.7 (451.2)</td>
<td>755.5 (379.0)</td>
<td>812.0 (340.9)</td>
<td>.61</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, Schwab and England activities of daily living; LDE, levodopa dosage equivalents; MMSE, Mini-Mental State Examination; PD, Parkinson disease.

*Data are expressed as mean (SD).
†Hoehn and Yahr stage.
‡Indicates recorded for the on-medication treatment state.
§Tukey post hoc paired comparisons revealed significant (P < .05) differences between the bromocriptine/pergolide group and the pramipexole and ropinirole groups. Differences between the pramipexole and ropinirole groups were not significant.
||The formula for calculating LDE is given in the “Patients” subsection of the “Methods” section.

Results

Table 1. Characteristics of 80 Subjects With PD Treated With Ergot vs Nonergot Dopamine Agonists

OVERNIGHT POLYSOMNOGRAPHY

Overnight sleep variables were separated into the following 2 categories: sleep continuity and sleep architecture (Table 2). In terms of sleep continuity, no significant differences were observed between treatment groups as a function of sleep-onset latency (F2,75 = 1.7), total sleep time (F2,75 = 0.85), sleep efficiency (F2,75 = 1.4), wakefulness after sleep onset (F2,75 = 1.3), and arousals count (F2,75 = 2.5). The only difference with respect to sleep architecture was the robust increase in slow wave sleep in patients treated with pramipexole compared with ropinirole or bromocriptine/pergolide (F2,75 = 9.5).

DAYTIME SLEEPINESS AND WAKEFULNESS

The overall mean MSLT was 12.1 minutes (5.1 minutes) and did not differ between treatment groups (F2,77 = 0.11; P = .90). Total sleep time was negatively correlated with the mean MSLT (r = −0.23; P = .04), whereas sleep-onset latency was positively correlated (r = 0.41; P = .001). Similarly, with a mean value of 26.7 minutes (5.4 minutes), no differences were observed between patients receiving different dopamine agonists on the mean MWT latency (F2,77 = 1.1; P = .29). The MWT latency correlated negatively with Hoehn and Yahr PD stage (r = −0.23; P = .04) and positively with the Schwab and England ADL (r = 0.34; P = .002) and MMSE scores (r = 0.44; P = .001). There was a positive relationship between the mean MSLT and mean MWT latency (r = 0.49; P = .001).

SUBJECTIVE SLEEPINESS

Overall, mean visual analog scale accounts of sleepiness correlated negatively with mean MSLT scores (r = −0.43; P = .001), whereas mean visual analog scale accounts of alertness correlated positively with mean MWT latencies (r = 0.41; P = .001). This relationship was consistent in patients receiving low and intermediate LDEs but was reversed in patients treated with high LDEs who appeared to misappreciate their subjective vs objective levels of sleepiness (Figure).
Differences between the ropinirole and bromocriptine/perogolide groups were not significant.

objective excessive daytime sleepiness (ESS total score, measured by the MSLT score (F2,77=0.44; P=.65) or category of LDE (F2,77=2.1; P=.13). In addition, the ESS score did not significantly correlate with the mean MSLT score (ρMSLT =0.12; P=.27) or the mean MWT latency (ρMWT =0.09; P=.42).

Furthermore, 34 patients (43%) exhibited high subjective excessive daytime sleepiness (ESS total score, ≥7). However, these individuals were not more likely to display objective pathologic daytime sleep latencies, ie, mean MSLT score of no greater than 5 minutes or mean MWT latency of no greater than 20 minutes (χ2 [n = 80], 0.13; P=.72). We found no relation between objective pathologic daytime sleep latencies and higher cutoff scores on the ESS of 10 (χ2 [n = 80], 0.69; P=.41) or 15 (χ2 [n = 80], 2.3; P=.13).

### Table 3. PREDICTORS OF PATHOLOGIC DAYTIME SLEEPINESS

Fifteen patients (18.8%) exhibited mean daytime sleep latencies of no greater than 5 minutes on the MSLT or no greater than 20 minutes on the MWT. Univariate risk factors (P<.10) associated with these pathologic daytime sleep latencies included the MMSE score (OR, 2.0; 95% CI, 1.3-3.2), Schwab and England ADL rating (OR, 1.1; 95% CI, 1.0-1.2), and LDE (OR, 4.2; 95% CI, 1.3-13.7). Of these 3 risk factors, only high LDEs were found to be independently associated with pathologic daytime sleep latencies (Table 3). The Hosmer-Lemeshow goodness-of-fit test showed that the model was adequately calibrated with P=.36 (a large P value indicating that there is not a large discrepancy between observed and expected episodes of pathologic daytime sleepiness).

To the best of our knowledge, this is the most extensive study to date to use standard polysomnographic techniques to evaluate daytime sleepiness and wakefulness in patients with idiopathic PD receiving dopamine agonist therapy. Objective pathologic sleep latencies as indexed by the MSLT and MWT scores did not differ with respect to treatment group. Moreover, patients taking larger amounts of dopaminergic medication, as measured by a total LDE of greater than 867.5 mg, were 4

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**Table 2. Overnight Sleep Polysomnographic Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 78)</th>
<th>Pramipexole Dihydrochloride (n = 28)</th>
<th>Ropinirole Hydrochloride (n = 27)</th>
<th>Bromocriptine Mesylate/Perogolide Mesylate (n = 23)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep continuity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOL, min</td>
<td>15.4 (14.7)</td>
<td>11.7 (10.0)</td>
<td>16.1 (14.3)</td>
<td>19.2 (19.0)</td>
<td>.19</td>
</tr>
<tr>
<td>TST, min</td>
<td>303.7 (81.8)</td>
<td>310.8 (79.3)</td>
<td>312.2 (85.9)</td>
<td>285.0 (80.3)</td>
<td>.43</td>
</tr>
<tr>
<td>SE, %</td>
<td>64.8 (16.0)</td>
<td>65.4 (15.1)</td>
<td>67.8 (16.3)</td>
<td>60.4 (16.5)</td>
<td>.26</td>
</tr>
<tr>
<td>WASO, %</td>
<td>31.0 (16.3)</td>
<td>31.9 (16.2)</td>
<td>27.1 (15.1)</td>
<td>34.4 (17.5)</td>
<td>.28</td>
</tr>
<tr>
<td>Al per hour</td>
<td>15.0 (8.1)</td>
<td>14.3 (7.4)</td>
<td>13.2 (6.3)</td>
<td>18.0 (10.0)</td>
<td>.09</td>
</tr>
<tr>
<td><strong>Sleep architecture</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Stage 1, %</td>
<td>6.7 (3.7)</td>
<td>6.1 (3.2)</td>
<td>6.3 (3.3)</td>
<td>8.1 (4.6)</td>
<td>.12</td>
</tr>
<tr>
<td>Stage 2, %</td>
<td>43.0 (12.8)</td>
<td>40.4 (10.1)</td>
<td>45.9 (13.3)</td>
<td>42.9 (15.0)</td>
<td>.30</td>
</tr>
<tr>
<td>SWS, %</td>
<td>8.2 (6.1)</td>
<td>11.8 (6.3)</td>
<td>6.9 (4.6)</td>
<td>5.4 (5.6)</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>REM, %</td>
<td>10.9 (7.1)</td>
<td>9.9 (6.2)</td>
<td>13.3 (8.0)</td>
<td>9.3 (6.7)</td>
<td>.09</td>
</tr>
<tr>
<td>REML, min</td>
<td>126.3 (80.9)</td>
<td>123.7 (61.8)</td>
<td>120.4 (76.4)</td>
<td>136.7 (106.1)</td>
<td>.77</td>
</tr>
<tr>
<td><strong>Spearman Correlation Coefficient, ρ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>−0.35†</td>
<td>.09</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>−0.68†</td>
<td>.64†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>−0.74†</td>
<td>.67†</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Abbreviations**: AI, arousal index; REM, rapid eye movement sleep; REML, latency to first REM sleep episode; SE, sleep efficiency; SOL, sleep-onset latency; SWS, slow wave sleep (ie, stages 3 and 4); TST, total sleep time; WASO, wakefulness after sleep onset. *Data are expressed as mean (SD). †Tukey post hoc paired comparisons revealed significant (P<.05) differences between the pramipexole group and the ropinirole and bromocriptine/perogolide groups. Differences between the ropinirole and bromocriptine/perogolide groups were not significant.**

The mean ESS score in our patients was 6.6 (4.9). This score did not differ as a function of treatment group (F2,77=0.44; P=.65) or category of LDE (F2,77=2.1; P=.13). In addition, the ESS score did not significantly correlate with the mean MSLT score (ρMSLT =0.12; P=.27) or the mean MWT latency (ρMWT =0.09; P=.42).

Furthermore, 34 patients (43%) exhibited high subjective excessive daytime sleepiness (ESS total score, ≥7). However, these individuals were not more likely to display objective pathologic daytime sleep latencies, ie, mean MSLT score of no greater than 5 minutes or mean MWT latency of no greater than 20 minutes (χ2 [n = 80], 0.13; P=.72). We found no relation between objective pathologic daytime sleep latencies and higher cutoff scores on the ESS of 10 (χ2 [n = 80], 0.69; P=.41) or 15 (χ2 [n = 80], 2.3; P=.13).
times more likely as those receiving lower LDEs to exhibit pathologic daytime sleep latency. This finding supports a class-effect hypothesis in that shortened daytime sleep latency in PD patients treated with dopamine agonists can be exacerbated with higher levels of LDE.

**PRAMIPEXOLE-RELATED INCREASES IN SLOW WAVE SLEEP**

The increased slow wave sleep observed in our prami- pexole-treated patients appears to be specific to this treatment group. The exact mechanism of this effect, also reported in animals, is unknown, although its absence with ropinirole suggests that dopamine D3 receptor activation common to these agents is not the principle explanation.

**PATHOLOGIC DAYTIME SLEEP LATENCY**

We believe that the most important predisposing factor to exhibiting impaired daytime sleep latency in our sample is the total dopaminergic medication dosage rather than the specific type of dopamine agonist. However, it is important to distinguish between excessive daytime sleepiness and sudden-onset sleep. For example, 1 levodopa-treated patient31 had polysomnographic evidence of sudden daytime sleep onset but a mean MSLT of 7.0 minutes. By our criteria, this patient would not be classified as having pathologic daytime sleep latency. Conversely, none of our 80 patients had documentation of sudden onset of sleep. This may be a rare phenomenon that is difficult to routinely quantify in the sleep laboratory. Thus, we can conclude that objective pathologic daytime sleep latency in PD patients treated with dopamine agonists is related to a high dopaminergic dose, but it remains inconclusive from our data whether sudden-onset sleep has a similar relationship to dopaminergic medication.

**MISAPPRECIATION OF DAYTIME SLEEP AND WAKEFULNESS**

The ESS did not prove useful in our sample in identifying patients at risk for pathologic daytime sleep latency. Furthermore, patients at risk (ie, those treated with high LDEs) were the poorest at predicting their levels of daytime sleepiness or wakefulness. A reasonable interpretation is that patients treated with higher LDEs may be prone to habituate to chronic hypersomnolence and may thus fail to recognize its level of severity, accounting for some descriptions of such sleep episodes as unpredictable or without warning. However, in the original reports by Frucht et al,23 some patients experienced such episodes while receiving low dosages of dopaminergic medications. Thus, misappreciation of objective daytime sleep and wakefulness in PD patients treated with dopamine agonists is likely to be associated with factors other than high LDEs. Recently, Merino-Andreu et al35 reported that 38% of somnolent PD patients did not appreciate at least 1 nap during an MSLT. These naps were of the same duration as perceived naps with the same amount of stage 3 or 4 or REM sleep, in contrast to hypersomnolent non-PD control subjects who had equally frequent unrecognized naps of shorter duration (stages 1 to 3 sleep) than perceived naps. The dosage of dopaminergic medication did not seem to relate to the occurrence of misperceived naps in these patients.

**LIMITATIONS**

We did not evaluate a drug-free PD comparison group. It is possible that patients with de novo PD exhibit decreased objective sleep latencies, because sleep-wake-regulating noradrenergic, serotonergic,34 and cholinergic35 systems also degenerate in PD. Furthermore, none of our patients received dopamine agonist or levodopa monotherapy. Since nearly all were taking levodopa, we cannot exclude the possibility that levodopa somehow masked the contributions of individual dopamine agonists and thus negated differences between agonist types. Concurrent medications were not controlled for and could have influenced overnight and daytime polysomnographic measures. We studied only well-functioning patients with PD and therefore cannot make inferences about the nature of pathologic sleep latencies in more severely affected patients, which should be a focus for future research.

**IMPLICATIONS**

Objective impaired daytime sleep latency is common in well-functioning patients with PD treated with dopamine agonists. From a pharmacological perspective, the total dosage of dopaminergic medication rather than the type of dopaminergic agent appears to be the most important predisposing factor to abnormal daytime sleepiness or wakefulness. In evaluating the presence of excessive daytime somnolence in PD patients who receive dopamine agonist therapy, reliance on subjective measures of sleepiness in those treated with higher LDEs may underestimate the extent of the problem. Future studies should address the issue of sudden sleep onset in this patient population. Our results may provide an explanation of why some PD patients experience sleep events as sudden or attack-like. However, we cannot exclude the possibility that a small proportion of these patients have this sudden onset of sleep without preceding demonstrable drowsiness.

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**Author contributions:** Study concept and design (Drs Lang and Shapiro); acquisition of data (Mr Razmy and Drs Lang and Shapiro); analysis and interpretation of data (Mr
Razmy and Dr Lang); drafting of the manuscript (Mr Razmy and Drs Lang and Shapiro); critical revision of the manuscript for important intellectual content (Drs Lang and Shapiro); statistical expertise (Mr Razmy); obtained funding (Dr Shapiro); administrative, technical, and material support (Dr Shapiro); study supervision (Drs Lang and Shapiro).

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