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ORIGINAL COMMUNICATION

Daytime sleepiness may be an independent symptom unrelated to sleep quality in Parkinson's disease

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Abstract

Excessive daytime sleepiness (EDS) may represent a disabling non-motor symptom in patients affected by Parkinson's disease (PD). This is a secondary analysis of a previous study documenting the improvement of nocturnal sleep in PD patients treated by rotigotine vs placebo. Here we tested the supposition that EDS may represent a distinct PD non-motor symptom occurring independently of other sleep-wake disorders; moreover, we verified whether EDS can be influenced by the improvement of nocturnal sleep in PD. In the present study, we evaluated the daytime sleepiness of PD patients treated with nocturnal administration of rotigotine (PD-Rot) vs placebo (PD-Pla), as measured by both subjective (Epworth Sleepiness Scale—ESS) and objective (Multiple Sleep Latency Test—MSLT) tools. We included 21 PD-Rot compared to 21 PD-Pla patients and documented no significant changes of both ESS and MSLT data between baseline and follow-up visits in both groups. Moreover, we found no correlations between nocturnal sleep improvement and diurnal sleepiness. Therefore, these data suggest that the improvement of nocturnal sleep in PD patients does not modify the daytime sleepiness, thus suggesting that diurnal sleepiness may occur independently of nocturnal sleep disturbances in PD patients.

Keywords Excessive daytime sleepiness · ESS · MSLT · Parkinson's disease · Sleep-wake cycle · Rotigotine

Introduction

Patients affected by Parkinson's disease (PD) frequently experience a wide range of non-motor symptoms (NMS) [1, 2]. Among them, excessive daytime sleepiness (EDS) identifies a disabling PD non-motor symptom consisting in a difficulty in maintaining alertness in daily situations with the impairment of daytime activities [3].

In the last years, increasing experimental and clinical data proved the complex interplay linking EDS to PD pathology and dopaminergic treatment [4–8]. In this view, EDS has been recognized as a common side effect of different dopamine agonists [9–11]. However, there is a general agreement that also PD per se may induce EDS [12, 13]. At the same time, EDS in PD patients has been correlated to nocturnal sleep deprivation, insomnia, circadian sleep–wake rhythm dysregulation, sleep disordered breathing, and narcoleptic-like phenotype [14–19]. However, the effect of disrupted nocturnal sleep on EDS in PD patients is still not completely defined.

This considering, the hypothesis that EDS may represent a distinct PD non-motor symptom occurring independently of other sleep–wake disorders cannot be ruled out [20].

To test this hypothesis, in the present study, we investigated whether EDS, measured via subjective questionnaires and objective assessments, may change in relation to the improvement of nocturnal sleep quality in PD patients. For this purpose, here we report the secondary analysis of

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a previous randomized, double-blind, placebo-controlled, parallel-group experimental study documenting the positive effect of nighttime administration of rotigotine vs placebo on sleep quality and continuity in PD patients [21].

Methods

Study population and design

This is a secondary analysis owing to a previous study performed in moderately advanced PD patients, whose original aim was to determine the efficacy of rotigotine on nocturnal sleep quality in PD [21]. In the present analysis, we evaluated daytime sleepiness of PD patients treated with nocturnal administration of rotigotine (PD-Rot) vs placebo (PD-Pla), as measured by both subjective and objective tools. We also correlated the changes in sleep quality and continuity with daytime sleepiness in both rotigotine and placebo groups. Since the original study was focused on the effect of rotigotine on nocturnal sleep, patches of rotigotine and placebo were positioned from 6:00 pm up to 8:00 am (time of awakening) to not influence patients' daytime, considering that the overall elimination of half-life of rotigotine patches has been reported lasting 5.7 h in Caucasians [22]. The study foresees a 6- to 10-week active/placebo treatment phase, comprising 4–8 weeks of drug titration-to-response, followed by 2 weeks of maintenance. The individual levodopa daily dosage was kept constant throughout the duration of the study and PD patients should not be under other dopamine agonists treatments.

In brief, inclusion criteria for the study were: (i) diagnosis of idiopathic PD according to the UK Parkinson's Disease Society Brain Bank criteria [23], (ii) stable dose of levodopa for at least 4 weeks, (iii) modified Hoehn and Yahr Stage of 2–3, and (iv) no cognitive impairment, defined by Mini-Mental State Exam score ≤ 26. Exclusion criteria were: (i) concomitant neurologic and/or psychiatric diseases, (ii) use of antiparkinsonian drugs, except levodopa, (iii) apnea–hypopnea index ≥ 15 per hour at polysomnography (PSG), and (iv) shift-work, which cannot ensure a stable sleep-wake cycle habits. The whole study design is available by consulting the original publication [21].

All PD patients underwent objective and subjective sleep and daytime sleepiness assessments twice: at baseline (T0) and at the end of the maintenance phase (T1). Objective assessments counted PSG followed by multiple sleep latency test (MLST). Subjective assessments included Parkinson's Disease Sleep Scale (PDSS) and Epworth Sleepiness Scale (ESS) [21].

All patients gave written informed consent and the trial was approved by the local ethic committee (Tor Vergata CE135/2011; code EU 2011/004757/12) and was registered at Clinical Trials and reported according to CONSORT guidelines.

Sleep and daytime sleepiness objective investigations

PSG was performed according to AASM criteria, as previously reported [21]. All PD patients performed the MSLT according to standard criteria [24] the day after the PSG recording. Following the study design, PD patients stopped rotigotine or placebo treatment at awakening to avoid possible drug effects on daytime sleepiness and 2 h later started MSLT assessment.

The following standard MSLT parameters were computed: mean sleep latency (SL) and number of sleep-onset REM periods (SOREMp). MSLT was considered indicative of EDS if SL was ≤ 8 min.

Sleep and daytime sleepiness subjective investigations

PD patients completed PDSS and ESS at T0 and T1. PDSS represents a recommended specific and comprehensive pragmatic clinical tool designed to address the multi-factorial nature and the severity of sleep disturbances in PD [25]. ESS is an 8-item self-reported questionnaire investigating the subjective daytime sleepiness, with a possible score ranging from 0 to 24 and pathological cut-off set at > 10 [26, 27]. We also evaluated the presence of the previously defined narcoleptic-like phenotype [16] at both T0 and T1.

Statistical analysis

The Kolmogorov–Smirnov test was used to check for normal data distribution. All parameters obtained at T0 and T1 in PD-Rot and PD-Pla groups were separately compared using paired *t* test. In addition, objective and subjective daytime sleepiness parameters obtained at T1 were compared between PD-Rot and PD-Pla groups using paired *t* test. Correlations between the mean changes in selected nocturnal sleep variables (sleep efficiency—SE, total sleep time—TST, nocturnal sleep latency—nSL, wakefulness after sleep onset—WASO, stage 3 of non-REM sleep—N3, and REM sleep, defined as the percentage of the TST scored as REM sleep) and the mean change in SL at MSLT and ESS scores were analyzed by Person test. We used these PSG data since they represent the main representative markers of sleep quality and continuity. Normally distributed data were then analyzed with a significant *p* value of 0.05.

Results

Study population

Twenty-one PD patients treated by rotigotine (PD-Rot) and 21 sex- and age-matched PD patients treated by placebo (PD-Pla) were included in this study. Clinical and demographic data of patients and controls are presented in Table 1.

Daytime sleepiness

At MSLT, PD-Rot patients did not show modifications in the mean SL between T0 and T1. We did not observe differences in the number of SOREMp recorded in PD-Rot group at T0 vs T1 (Table 2). ESS scores remained unchanged between T0 and T1 in PD-Rot patients (Table 2). Similarly, PD-Pla patients did not modify SL, number of SOREMp and ESS between T0 and T1. No differences in SL, SOREMp and ESS scores were documented between PD-Rot and PD-Pla at both T0 and T1. Moreover, 2/21 PD-Rot and 1/21 PD-Pla patients showed the narcoleptic-like phenotype at T0 and they did not change their sleep-wake characteristics between T0 and T1.

Finally, MSLT was indicative of EDS in 6/21 PD-ROT and 5/21 PD-Pla patients at T0. At T1 7/21 PD-Rot and 7/21 PD-Pla patients showed EDS at MSLT.

Correlation analysis

Considering the analysis of PSG data, which were previously published, at T1 PD-Rot patients showed the significant increase of SE and REM coupled with the significant reduction of nSL compared to PD-Pla. Comparing data obtained at T1 and T0, PD-Rot patients significantly increased both SE and REM and decreased WASO, whereas PD-Pla patients did not change their sleep.

Starting from these data, we here correlated the mean change of TST, SE, nSL, WASO, N3, and REM obtained at PSG recording (Table 3) with the mean change in objective and subjective daytime sleepiness data between T1 and T0 in both patients' groups. We did not document significant correlations between the mean change of PSG data and the mean change of SL at MSLT or of the ESS scores in both PD-Rot and PD-Pla groups.

Discussion

EDS is a frequent non-motor symptom complained by PD patients, described as the inappropriate and unwanted falling asleep during waking hours. In PD patients, EDS has been ascribed to poor night sleep quality, antiparkinsonian drug side effects, reappearance of nocturnal akinesia or tremor, coexistent medical comorbidities [4–8, 13]. However, EDS may be also directly related to the impairment of the sleep–wake rhythm regulatory areas, which ensure alertness and maintaining vigilance during daytime [16, 17].

Table 1 Demographic and clinical data

	Rotigotine group ($n=21$) (mean ± SD)	Placebo group ($n=21$) (mean ± SD)
Age	63.28 ± 2.98	64.04 ± 2.90
Disease duration (months)	49.57 ± 3.58	51.33 ± 3.13
H&Y	2.28 ± 0.25	2.23 ± 0.25
Levodopa (mg/day)	478.57 ± 66.27	504.76 ± 75.67
MMSE	28.28 ± 0.84	28.47 ± 0.92

H&Y Hoehn and Yahr, *MMSE* Mini-Mental State Examination, *SD* standard deviation

Table 3 PSG data

Mean change between T1 and T0	PD-Rot group ($n=21$) (mean ± SD)	PD-Pla group ($n=21$) (mean ± SD)
SE (%)	8.04 ± 8.29	0.52 ± 2.86
SL (min)	− 10.36 ± 14.00	1.64 ± 7.11
WASO (min)	− 26.21 ± 33.77	4.42 ± 10.11
REM (%)	7.67 ± 8.45	− 1.06 ± 4.36

PSG polysomnogrphy, *SE* sleep efficiency, *SL* sleep latency, *WASO* wakefulness after sleep onset, *REM* rapid eye movements, *Rot* rotigotine, *Pla* placebo, *PD* Parkinson's disease, *SD* standard deviation

Table 2 MSLT and ESS data

	PD-Rot group ($n=21$)		PD-Pla group ($n=21$)	
	T0 (mean ± SD)	T1 (mean ± SD)	T0 (mean ± SD)	T1 (mean ± SD)
SL (min)	11.73 ± 5.16	12.05 ± 5.39	11.22 ± 3.87	10.46 ± 3.40
SOREMp (n)	3/21	3/21	4/21	5/21
ESS	6.71 ± 4.03	6.76 ± 4.02	7.71 ± 4.01	7.95 ± 3.93

SL sleep latency, *SOREMp* periods of sleep-onset REM at MSLT, *MSLT* multiple sleep latency test, *ESS* Epworth Sleepiness Scale, *Rot* rotigotine, *Pla* placebo, *PD* Parkinson's disease, *SD* standard deviation

In this secondary investigation, derived from a previous controlled study focused on the effect of rotigotine vs placebo on objective sleep quality in PD patients, we analyzed MSLT recordings, considered as the gold standard assessment for daytime sleepiness, and ESS data, a validated questionnaire largely used to investigate EDS in PD. By analyzing these specific subjective and objective tools, we found that the improvement of nocturnal sleep parameters documented in PD patients receiving rotigotine did not correlate to the changes of MSLT measures; moreover, we found no changes in daytime sleepiness in both rotigotine-treated and placebo-treated PD patients. Notably, patients complaining for EDS or narcoleptic-like phenotype at baseline still presented the same sleep alterations at the end of the study, regardless of the improvement of their nocturnal sleep.

These data allow to hypothesize that the improvement of nocturnal sleep does not modify the amount of daytime sleepiness in PD, thus suggesting that diurnal sleepiness may occur independently of nocturnal sleep disturbances in PD patients. The present observation is in agreement with previous studies considering that EDS may be a non-motor symptom unrelated to other sleep–wake disturbances [13]. This conjecture derives from post-mortem evidence sustaining that PD pathology may variously affect all the brainstem and midbrain structures, including those controlling the sleep-wake cycle, since the earliest phases of the disease [28]. In keeping with the Braak and co-authors hypothesis about PD pathology, the initial deposition of Lewy bodies in brainstem and midbrain associated with nigral neuron loss is associated with sleep–wake cycle disturbances in PD [27]. In fact, PD pathology may contribute to the sleep–wake cycle dysregulation, either directly through the disruption of sleep–wake regulatory circuits or indirectly by causing motor and non-motor symptoms able to affect the quality of sleep. However, this latter possibility may be reconsidered in the light of previous observations reporting that the association between sleep disturbances and PD pathology is independent of motor and non-motor features, and a host of other medical comorbidities [29]. In support of the hypothesis that PD pathology may directly affect sleep regulatory circuits, individuals with established clinical PD at the post-mortem analysis showed the substantial loss of neurons combined with the spread of α-synuclein pathology in sleep regulatory regions, such as hypothalamus, sublaterodorsal nucleus, peri-locus ceruleus, and magnocellular reticular formation [28, 30, 31].

Daytime sleepiness is a complex phenomenon that needs of the interplay among different brainstem structures regulating the sleep–wake cycle, including the orexinergic and the histaminergic systems, as well as the monoamines networks [7, 30, 32]. If we consider that all these neurotransmitter circuitries may be dysregulated along with the advance of PD neurodegenerative processes, it is feasible that in PD patients EDS may be the clinical expression of the neuropathological involvement of the brain networks regulating not only nocturnal sleep but also controlling daytime alertness [7, 28, 31].

EDS can affect up to 50% of PD patients, being more prominent as the disease progresses [5, 8, 10]. However, EDS may be present in the premotor stages of disease or in de novo PD patients [33–35], before starting dopaminergic therapy. Although dopaminergic treatment may render a subset of PD patients at risk of sudden-onset sleep attacks, and in the past dopamine agonists administration has been associated with severe EDS, in this study we documented no significant increase or changes in daytime sleepiness measured by both objective and subjective instruments in the subgroup of patients taking rotigotine. This result may be related to the fact that rotigotine was administered exclusively in the nighttime period, without influencing the diurnal alertness, although elimination of half-life of rotigotine has been reported lasting 5.7 h after removing the patch [22]. Against the previous supposition that dopamine agonists administration may frequently cause EDS, a recent study evaluating nocturnal sleep measured by the actigraphic 24-h recording documented the improvement of diurnal sleepiness in PD patients treated by rotigotine [36]. Therefore, the lack of changes in daytime sleepiness measures in our report can be also related to the limited population of patients included in this study, which may represent a limitation of this analysis, requiring further investigations to confirm these findings.

Hence, our present data seem to suggest that EDS may be a part of the complex non-motor spectrum of PD, which can be not related to nocturnal sleep alterations. Therefore, we suggest that EDS should be treated differently from the other sleep–wake disturbances. In particular, since the improvement of nocturnal sleep seems to not allow the amelioration of EDS, both non-pharmacological protocols and pharmacological treatments targeting the control of vigilance and alertness merit further investigations to minimize the dramating impact of daytime sleepiness on quality of life of PD patients.

In conclusion, based on the results of this study, we suppose that EDS in PD patients may occur independently of nocturnal sleep dysregulation and may involve different neuroanatomical networks. Furthermore, this study supports the suggestion that diurnal sleepiness deserves more attention in PD patients, since it is a disabling non-motor symptom, which could be not related to other sleep disturbances. The recent increasing attention in treating EDS with novel drugs may enforce the needs of better identify EDS in PD patients.

Compliance with ethical standards

Conflicts of interest This work was supported by an unrestricted grant from UCB. The authors declare no other financial disclosures or conflicts of interest.

Ethical standards The trial was approved by the local ethic committee (Tor Vergata CE135/2011; code EU 2011/004757/12) and was registered at Clinical Trials and reported according to CONSORT guidelines.

Informed consent All patients gave written informed consent.

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