Sleep microstructure in Parkinson's disease: cycling alternating pattern (CAP) as a sensitive marker of early NREM sleep instability

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INTRODUCTION

Sleep disorders are frequent in Parkinson's disease (PD) and have multifactorial origin [1]. These sleep disorders may lead to sleep fragmentation and excessive daytime somnolence [2]. In Parkinson's disease, sleep fragmentation with frequent awakenings and micro-arousals concurrently with excessive daytime somnolence can be caused by REM sleep behavior disorder (RBD) [3], periodic limb movements in sleep (PLM) [4], recurrent parkinsonian symptoms [5], sleep-disordered breathing [6], effect of medications [7,8], psychiatric disorders such as depression or anxiety [9]. Of particular interest is REM behavior disorder (RBD), a parasomnia characterized by violent movements and an increased motor activity during REM sleep that may be either idiopathic or coupled with neurodegenerative disorders, typically synucleinopathies [10, 11].

So far polysomnographic studies have been directed to investigate sleep macrostructure together with disease-related changes [12,13,14, 15, 16, 17, 18, 19,20,21], nocturnal motor symptoms [22,23,24], sleep-related breathing disorders [25, 26, 27, 28], PLM disorder [29,30,31,32] and RBD [33, 34, 35,36,37,38,39]. Case-control polysomnographic studies using sleep standard scoring give inconclusive results [14,15,29,36]. Considering REM sleep, most studies find no difference in percentage of total REM sleep time, although some reduction is reported by some other authors; moreover, NREM sleep including slow wave sleep (SWS) proves to be quantitatively unaffected in majority of the studies, compared to healthy people [12]. Disease severity and medication are all factors that impact macrostructure of sleep. For example dopaminergic drugs promote SWS and REM sleep at low doses, while at higher doses they reduce SWS and promote alertness [40,41,42].

On the contrary, little efforts have been directed to investigate transient EEG phenomena lasting less than the scoring epoch and Cycling Alternating Pattern (CAP), describing what is known as the microstructure of

sleep [43]. In particular, CAP analysis adds important information and gives more insights in sleep disorders pathogenesis, as it reflects the building-up and stability of NREM sleep. Furthermore it is more sensitive in detecting subtle sleep alterations not recognizable by standard scoring of sleep stages [44].
In our study we analyzed sleep microstructure by means of CAP analysis in a group of PD patients compared to age-matched healthy people, in order to provide an objective measure of NREM sleep instability and its relationship with disease severity.

MATERIALS AND METHODS

We recruited 31 PD patients (mean age 59.5 ± 12.4 years; mean Hoehn-Yahr (H-Y) stage: 3.4 ± 1.8) after therapy optimization and 34 age-matched non-parkinsonian subjects (mean age 61.5 ± 15.2 years) as control group. Exclusion criteria for both groups included moderate or severe depression, significant pain disturbances and cognitive impairment.

All patients underwent an adaptation night and then a full-night polysomnography (PSG) in the sleep laboratory in a quiet room with video monitoring. Patients were allowed to maintain their usually sleep habits and timing. Therapy with benzodiazepines and neuroleptics taken by two patients, was discontinued one week before PSG. The following parameters were recorded: EEG using C3-A2, C4-A1, O2-A1, O1-A2 derivations integrated by bipolar montages Fp2-F4, F4-C4, C4-P4, P4-02; Fp1-F3, F3-C3, C3-P3, P3-01; Fz-Cz, Cz-Pz of the 10-20 international placement system; electrooculogram (bipolar montage: right ocular cantus-left ocular cantus); electrocardiogram; respiratory effort by thoracic and abdominal strain gauges, nasal air-flow by nasal cannula, snoring nose by a microphone, arterial oxyhaemoglobin (SaO_2) using a pulse oximeter with finger probe; submental and tibialis anterior muscles elecromyogram. Conventional sleep analysis, respiratory parameters, arousals were performed independently by two evaluators experienced in sleep staging according to literature [45] and on the basis of the guidelines defined by Terzano and colleagues for CAP scoring [46]. Levodopa equivalent dose was calculated and daily motor performances were evaluated using the Unified Parkinson's disease Rating Scale (UPDRS-part III).

We then divided the patients into two groups according to H-Y stage: group 1 (H-Y stage ≤ 2) and group 2 (H-Y stage ≥ 3). Data was examined for normality using visual histograms and the Kolmogorov-Smirnov test. Means were compared using unpaired t-tests or ANOVA (normally distributed data). Correlations were calculated by means of Spearman Rank test and logistic regression analysis was performed to assess predictive variables and to control for covariates (e.g. age). Statistica™ software package, StaSoft Inc. ™ was used for these analyses. Our study is intended to be a preliminary exploratory research, not confirmatory, so that the threshold of significance was set at $p<0.05$.

RESULTS

Compared to controls, polysomnographic analysis in the whole group of PD patients showed significant increase of sleep onset latency, wake periods after sleep onset (WASO), arousal index and N2 sleep stage percentage together with significant decrease of both sleep efficiency and slow wave sleep. PLMs index was increased in PD patients compared to elderly control even if at the limit of statistical significance. In PD patients there was evidence of tremor persistence during N1 and N2 sleep stages in 22.5% of patients. RBD and PLMs disorder were diagnosed in 29% and 6% of PD patients, respectively. Considering the microstructure parameters of sleep in the whole group of PD patients, mean CAP rate was increased compared to controls. Conversely, A1 phase proportion was significantly reduced in PD patients compared to age-matched subjects (Table 1).

The subgroup of 17 patients with more advanced disease stage (group 2), showed, as expected, significant increase of sleep onset latency, decreased sleep efficiency, decreased slow wave sleep, increased CAP rate and decreased A1 phases, compared to controls. Conversely, the subgroup of 14 patients (group 1) with H-Y stage ≤ 2 presented sleep macrostructure parameters not statistically different from controls, even if a tendency to decreased sleep efficiency, decreased slow wave sleep and increased arousal index could be noted. Interestingly, in this group CAP rate was significantly higher than controls, while proportion of A1 phase of CAP was reduced (Table 1).

Considering the whole group of PD patients, sleep efficiency and stage N3 sleep showed mild correlations, with age, H-Y stage, UPDRS or disease duration. CAP rate showed moderate correlation with disease severity and disease duration, while A1 phase of CAP showed moderate negative correlation with disease duration and mild negative correlation with disease severity (Table 2). In our group of PD patients levodopa equivalent dose showed wide dispersion of data and did not correlated with sleep parameters.

Considering only the subgroup of PD patents with H-Y stage ≤ 2, CAP rate and A1 phase of CAP correlated only with disease duration ($r=0.67$, $p=0.03$ and $r= -0.59$, $p=0.04$ respectively). Plots regarding these relations are displayed in Figure 1. Patients with higher CAP rate presented lower A1 phases proportion, this relationship being statistical significant ($r= -0.76$, $p=0.01$). No statistical significant correlation between CAP parameters and disease severity (UPDRS-part III) or age was evidenced.

Multivariate logistic regression showed that disease duration and desease severity (H-Y ≥ 3) emerged as independent predictive factors for CAP rate $\geq 55\%$ (Table 3) and A1 phase of CAP $\leq 40\%$ (Table 4). These CAP parameter cut-offs were chosen, according to published CAP rate distribution in healthy people of comparable age [43].

DISCUSSION

Sleep disorders have a high prevalence in PD patients and, together with the underlying motor symptoms, are one of the main causes of disability having a substantial impact on the quality of life [47].

REM sleep alterations are well documented in PD, while NREM sleep abnormalities, particularly considering sleep microstructure and CAP, still remain poorly investigated.

Cyclic alternating pattern (CAP) constitutes a repetitive biphasic pattern of NREM sleep in which sequences of transient synchronized and/or desynchronized EEG sequences (phase A) recur at intervals from background theta or delta rhythms (phase B). CAP components corresponding to EEG synchrony represent the cortical expression of cortical-subcortical interactions mediated by thalamocortical pathways and modulated by hypothalamic and brainstem nuclei, among which locus coeruleus and raphe nuclei play an important role [44, 51, 52]. Subtype A1 consists of EEG synchronized pattern (intermittent alpha rhythms in S1, K-complex sequences and delta bursts), is most common in the transition from light to SWS and seems to be linked to REM off neurons activity [44]. CAP is supposed to play the main role in the building-up of EEG synchronization during NREM sleep and in the flexible adaptation against perturbations, so that its increase is considered to be related with NREM difficulty to proceed towards stable SWS [44]. In this view, sleep EEG spectral pattern investigations showed alterations during NREM phases in PD patients, even at earlier stages of disease, which may present evidence for altered electrophysiological mechanisms leading to sleep-wake instability [53].

Our study shows, as expected, worse sleep macrostructure parameters, increased CAP rate and decreased A1 phases of CAP in PD patients compared to age-matched controls. CAP alteration in particular are frequent in disease characterized by frequent arousals and primarily suggest sleep instability and difficulty in the building-up of SWS [44]. As shown by subgroup analysis and multivariate logistic regression, considering the whole group of PD patients CAP rate increase and A1 phases decrease in PD patients are mainly correlated with disease duration and severity. Notably, not macrostructure abnormalities but only CAP alterations are detected in the subgroup of patients affected by a milder disease stage, appearing to be mainly related to disease duration, independently from disease severity. These data are the most relevant findings of our study, not yet reported in literature, to our knowledge. Considering neuropathology studies [48], it seems that neurodegenerative process spreads sequentially in caudo-rostral direction (for example, pathological cases with cortical involvement always exhibit brainstem involvement). So, reasonably, patients with more advanced and/or longer duration of Parkinson's disease should display more pronounced NREM alterations.

Our study confirms this hypothesis, suggesting that NREM sleep instability is present even at earlier stages of Parkinson's disease, independently from concurrent motor symptoms or age. These alterations could only be detected by microstructure analysis, as standard sleep stage scoring did not demonstrated to be adequate nor sufficiently sensitive. Precocious NREM sleep instability could reflect early alterations of neural pathways involved in NREM building-up and maintenance. In line with these results, in literature greater sleep fragmentation was found to be associated with PD pathology, particularly Lewy Body deposition in CNS and Substantia Nigra neuron loss, in older adults with pathological diagnosis of PD,

independently of motor features of Parkinsonism, demographic characteristics or medical co-morbidities [54].

Moreover neuropathology studies show that Lewy pathology increases with each advancing stage and progresses caudo-rostrally from dorsal motor nucleus of the vagus nerve and olfactory bulb (stage 1) to lower brainstem (stage 2), mid-forebrain (stage 3) and, eventually, cerebral cortex (stage 4-6) [48]. In neuropathology defined stage 2 and 3, associated to the clinically premotor phase, Lewy body pathology is evident in lower raphe group, gigantocellular nucleus of the reticular formation and coeruleus-subcoeruleus complex. These nuclei are part of NREM and REM sleep network, and its dysfunction could lead to REM sleep behavior disorder, a disease that highly occurs and can predate by decades the occurrence of PD [10]. NREM and REM sleep and wakefulness systems are mutually inhibitory and interact through a flip-flop switch model so, a dysfunction of one system can destabilize activity of the opposing one [49]. From this point of view, dysfunction in NREM promoting cell network as well as of REM and orexyn system could lead to NREM sleep alterations, in line with the REM/NREM instability seen in RBD and PD patients [50].

The dopaminergic medications also may play a role in sleep disruption, even if data in literature are not conclusive about NREM sleep architecture [40,41,42] and EEG spectral power changes [55]. In this context our study is still not conclusive, as it does not evidence any relationship between levodopa equivalent doses and sleep microstructure alterations, possibly due to high dispersion of data and small sample.

In conclusion, polysomnography is a useful tool to evaluate the presence of sleep disorders, but standard sleep stage scoring may be not adequate to detect subtle changes of sleep micro-architecture. In this context, to our knowledge, our study is the first investigation of sleep microstructure, based on CAP analysis, in PD patients. Main result consists in the demonstration of NREM sleep instability even at an earlier stage of the disease and, interestingly, independently from concurrent motor symptoms or age. Further studies are needed to confirm these preliminary data, in particular with the evaluation of a large sample of de-novo patients that are devoid of pharmacological and motor symptoms bias.

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Table 1: Sleep parameters in PD patients, compared to elderly controls

	Elderly controls		PD patients (total)		P	PD patients (group 1)		P[1]	PD patients (group 2)		P[1]
	Mean	SD	Mean	SD		Mean	SD		Mean	SD	
Total sleep time (min)	384.3	78.6	377.5	95.6	NS	395	88.2	NS	353	89.5	NS
Sleep efficiency (%)	81.4	21.6	65.5	31.2	0.04*	75.3	16.2	NS	56.4	26.8	< 0.01*
WASO (min)	58.5	24.9	67.5	37.8	0.04*	64.6	26.8	NS	71.2	36.4	NS
Sleep latency (min)	18.2	14.2	34.6	27.2	0.01*	24.3	23.2	NS	43.6	25.4	< 0.01*
REM sleep latency (min)	81.2	28.8	92.1	44.2	NS	88.8	27.4	NS	95.6	36.7	NS
REM periods (n)	6.3	2.1	8.1	5.8	NS	7.9	4.7	NS	8.6	5.6	NS
Stage N1 (%)	4.7	5.2	4.2	5.3	NS	3.9	4.9	NS	4.5	5.2	NS
Stage N2 (%)	47.4	16.1	61.2	21.3	0.01*	51.2	18.2	NS	68.5	16.2	< 0.01*
Stage N3 (%)	28.4	12.1	15.8	14.6	< 0.01*	23.7	13.6	NS	10.2	12.3	< 0.01*
Stage R (%)	18.5	13.8	18.8	13.6	NS	20.8	11.6	NS	15.8	12.4	NS
Total NREM (%)	80.5	19.5	81.2	23.7	NS	78.8	21.2	NS	83.2	18.4	NS
Arousal index (n/h)	15.8	16.8	28.8	24.9	0.03*	26.8	14.2	NS	33.2	21.5	< 0.01*
PLM index (n/h)	5.7	6.3	11.8	12.4	0.05	11.3	9.6	NS	12.5	11.6	0.04*
AHI (n/h)	2.8	2.3	3.5	1.8	NS	2.7	1.6	NS	3.6	1.6	NS
Central apnea index (n/h)	1	0.8	1.5	1.4	NS	1.2	0.9	NS	1.9	1.3	NS
RBD (n)	1 (0.04%)		9 (29%)			4 (28.5%)			5 (29.4%)		
Tremor persistence in stage 1 and 2 (n)	-		7 (22.5%)			2 (14.2%)			5 (29.4%)		
CAP rate (% of total NREM)	50.8	8.2	57.7	13.2	0.02*	56.8	7.1	0.04*	**59.2**	11.8	0.03*
A1 (% of total A phases)	68.4	13.6	50.5	21.5	< 0.01*	56.7	14.2	0.03*	**40.3**	15.8	< 0.01*

Sleep stages expressed as % of total sleep time. PD: Parkinson's disease. WASO: wake after sleep onset; PLM: periodic limb movements during sleep. RBD: REM behaviour disorder. CAP: cycling alternating pattern. A1: A1 phases of CAP. SD: standard deviation.

Comparisons between control group and the whole parkinsonian group is performed by means of Student t-Test; p value indicated when significant. NS: not significant. (*): $p<0.05$.

Comparisons between control group and parkinsonian group 1 and 2 is performed by means of ANOVA for independent samples and Duncan correction; p^1 values indicate significance between group 1 or group 2 vs control group.

Table 2. Correlations between clinical data and sleep parameters in PD patients

	Age	Hoehn-Yahr stage	Disease duration	UPDRS (on)	UPDRS (off)
Sleep latency	0.27	0.19	0.21	0.28	0.21
REM sleep latency	0.16	0.12	0.09	0.21	0.25
Sleep efficiency	-0.31	-0.4	-0.27	-0.37	-0.36
Stage N3 sleep	-0.34	-0.45*	-0.34	-0.21	-0.33
PLM index	0.26	0.15	0.21	0.11	0.18
CAP rate	0.18	0.64**	0.49*	0.54*	0.51*
A1 phases	-0.23	-0.35	-0.56**	-0.33	-0.36

(*) $p<0.05$; (**) $p<0.01$; Spearman Rank correlation test.

Table 3. Independent predictive factors for CAP rate ≥ 55%

	Exp (B)	95% C.I. (lower – upper)	p
Age	1.02	0.3 - 1.3	NS
H&Y: 3-4	10.7	1.4-14.2	0.002*
Disease duration	7.8	1.2-11.5	0.01*
% REM	0.4	0.1-3.9	NS
Sleep efficiency	0.8	0.2-2.4	NS
RBD	0.3	0.1-4.8	NS
PLM index	1.3	0.5-2.8	NS
Arousal index	2,1	0.9-5.1	0.05*

NS: not significant; binomial logistic regression

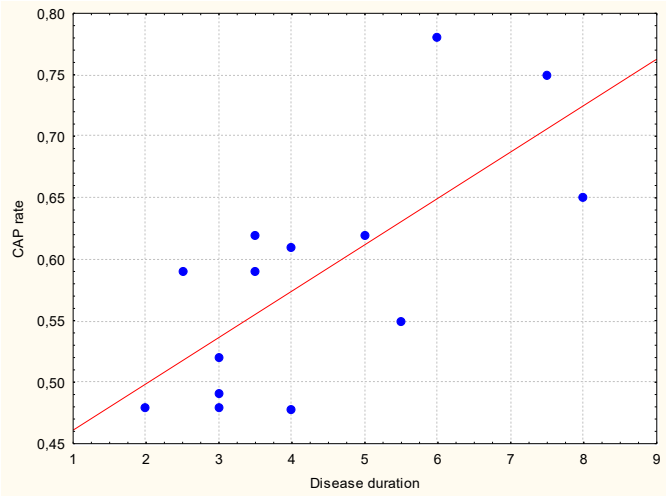
Table 4. Independent predictive factors for A1 proportion ≤ 40%

	Exp (B)	95% C.I. (lower – upper)	p
Age	1.12	0.2 - 1.5	NS
H&Y: 3-4	5.1	1.8-16.2	0.04*
Disease duration	8.7	2.3-11.5	0.001*
% REM	0.7	0.1-5.2	NS
Sleep efficiency	0.5	0.2-2.1	NS
RBD	0.6	0.2-3.5	NS
PLM index	1.7	0.3-3.2	NS
Arousal index	3.1	0.7-7.2	NS

NS: not significant; binomial logistic regression

Figure 1. Relationship of disease duration (in years) with CAP rate (a) or A1 proportion of CAP (b) in the subgroup of PD patients with less advanced disease stage (Group 1, Hoehn-Yahr stage ≤ 2)

(a)



(b)