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Research Article

Macro- and Micro-Structural Aspects of Sleep in Severe Parkinson's Disease

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Abstract

Objectives and background: Sleep disorders are common in Parkinson's Disease (PD) occurring in 60% to 98% of patients. Polysomnographic measures showed that patients with PD had significantly less total sleep time (TST), less sleep period time, increased number of awakenings and wake time after sleep onset (WASO) and, consequently, reduced sleep efficiency. The aim of the study was to explore the sleep pattern of PD patients, focusing on sleep microstructure by analysing the cyclic alternating pattern (CAP).

Methods: Fourteen patients with idiopathic severe PD and fourteen matched healthy volunteers were recruited. All subjects underwent overnight polysomnography and completed Epworth Sleepiness Scale. Macro- and micro-structural sleep variables were evaluated.

Results: Patients with PD had a reduced SE and increased rates of stage shifts and awakenings; the N2 and REM sleep percentages were lower and WASO was higher in patients. Moreover, patients with PD had lower total CAP rate and lower CAP rate in all NREM sleep stages (particularly in N3) than did normal controls. Moreover, the analysis of CAP A subtypes distribution showed a decreased A1 percentage in patients (more pronounced in N3) and a slight, not significant increase of A3 subtypes.

Conclusions: The total CAP rate is reduced in these patients across all sleep stages and this reduction is mainly due to a decrease in CAP A1 subtype. The changes in the micro- and macro-structure of sleep could be only partially explained by the chronic partial sleep deprivation in PD patients.

INTRODUCTION

Sleep disorders are common in Parkinson's disease (PD) occurring in 60% to 98% of patients [1]. Polysomnographic measures showed that patients with PD had significantly less total sleep time (TST), less sleep period time, increased number of awakenings and wake time after sleep onset (WASO) and, consequently, reduced sleep efficiency (SE). Sleep-onset latency (SL), and the relative amounts of non rapid eye movements (NREM) sleep stage 1 and 2, slow wave sleep (SWS) or rapid eye movements (REM) sleep were not significantly different between PD patients and age-matched healthy controls. Moreover, patients with PD had more frequent abnormal REM sleep features and periodic limb movements [2], and an excessive daytime sleepiness (EDS) can affect 20-50% of patients with PD and correlate with disease severity, higher doses of levodopa, and sometimes the use of dopamine agonists [3]. Arnulf et al. [4] observed that the latency to sleep (measured by multiple sleep latency test – MSLT) does not correlate with PSG macrostructural measures. Comparing mild versus severe PD patients with EDS, the severity of illness was not associated with changes in sleep macrostructural parameters [5].

The conventional coding and macrostructural analysis of sleep can underestimate some short-lasting events as the arousals. Most authors consider arousals as transient cortical activations in response to sleep disruptive events, usually associated with activation of vegetative and somato-motor functions. Other slow EEG patterns, such as K-complexes and delta burst, are considered as partial form of arousal, a pre-

activation heralding the classical arousal, or expression of subcortical arousal. In the realm of periodic activities, the cyclic alternating pattern (CAP) is characterized by sustained periods of cyclical arousability in which arousal events are arranged in a biphasic rhythm of 20-40 s: cyclic sequences of cerebral activation (phase A) are followed by periods of deactivation (phase B). According with the EEG rhythm composition different phase A subtypes can be identified: A1 (synchronized events), A2 (mixed synchronized–desynchronized EEG events) and A3 (predominantly desynchronized EEG events).

CAP is present in normal sleepers with specific age-dependent modifications, and the slow, rapid and polyphasic patterns of CAP are differently distributed during the descending and ascending slopes of sleep architecture. These observations suggest that CAP, besides being elicited by perturbing factors, could originate from cerebral sources and could play a physiological role in the development of sleep architecture [6].

In last years, CAP had been investigated in many different diseases, and among others, narcolepsy [7,8] and attention deficit/hyperactivity disorder (ADHD) [9].

The present study aims at exploring the sleep pattern of severe PD patients, focusing on sleep microstructure by analysing the CAP when compared with healthy volunteers.

SUBJECTS AND METHODS

The study was approved by the local hospital ethics committee.

Among the people with severe PD referred to the Movement Disorder Unit of our institution 35 consecutive patients were evaluated. After giving written informed consent, all subjects were interviewed by a neurologist trained in movement disorders and a board-certified sleep medicine physician and instructed on the maintenance of sleep logs.

Exclusion criteria for all subjects enrolled were major not stabilized medical illnesses, known or suspected history of alcoholism, drug dependence or abuse, other neurological disorders, head trauma and mental disorders according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision (DSM-IV-TR), Mini Mental State Examination (MMSE) score <26, diagnosis of dementia according to the Movement Disorder Society clinical diagnostic criteria [10], presence of vascular brain lesions, neoplasms and/or marked cortical and subcortical atrophy at CT and/or MRI scan. Patients were also evaluated through a portable monitoring device (Embletta X100, Natus Medical Inc, Pleasanton, CA, USA), monitoring anterior tibialis electromyogram, airflow (nasal-cannula), respiratory effort (thoracic and abdominal), oxygen saturation and cardiac frequency, body position, and snoring. All subjects with sleep related breathing disorders and sleep related movement disorders according to International Classification of Sleep Disorders III [11] were excluded. Fourteen patients (defined "patients") were recruited and age and gender matched with 14 healthy volunteers (defined "controls").

Each PSG was preceded by an in-laboratory adaptation recording to minimize the first-night effect. Video PSG was performed by Comet XL Lab-based PSG (Grass Telefactor, Astro-Med Inc., RI, U.S.A.) by using four EEG channels (C3, C4, O1, O2), two electrooculogram channels, chin and anterior tibialis electromyogram, electrocardiogram, airflow (nasal-cannula), respiratory effort (thoracic and abdominal), oxygen saturation, body position, and snoring. After the PSG, subjects rated their sleep as the same, worse, or better as compared with usual, and completed the Epworth Sleepiness Scale (ESS) [12].

PSGs were blindly scored by a sleep technician and interpreted by a sleep medicine–certified physician by using standard scoring procedures [13,14], while CAP scoring was based on the rules defined by Terzano et al. [15]. PSG variables included total sleep time (TST), sleep latency (SL), sleep efficiency (SE), REM sleep latency, time spent in stages N1, N2, N3 and REM sleep, wake time after sleep onset (WASO), number of awakenings, stage shifts, apnea–hypopnea index (AHI), respiratory effort related arousals (RERAs), and periodic limb-movement index (PLMI). The measured microstructural variables were: total CAP time, total non-CAP time, CAP rate, non-CAP rate, number, type and distribution across sleep stages of A phases (A1, A2, A3). All of these variables were scored through Hypnolab 1.2 sleep software analysis (SWS Soft, Italy).

All statistical tests were two-tailed and conducted at a 5% significance level. Tests for normality were conducted on all continuous data, which were transformed if appropriate. The objective parameters were submitted to analysis of variance (ANOVA) between-subjects for repeated measures with Bonferroni correction. The data analysis software system SPSS version 23.0 (IBM SPSS Statistics, US) was used for statistical analysis (Table 1).

RESULTS

The table reports the demographic, clinical and sleep macro- and micro-structural characteristics of patients and controls. Patients with PD had a reduced SE, increased rates of stage shifts and awakenings; the S2 and REM sleep percentages were lower, and WASO was higher than in controls.

Most patients were on additional treatments: 9/14 with dopamine agonists, 8/14 with low doses of benzodiazepines (mean daily dose 1.2mg, range 0.5-2.5mg), and 3/14 with low doses of atypical neuroleptics (quetiapine; mean daily dose 25mg).

The polysomnographic monitoring showed loss of the muscle atonia during REM sleep in 5/14 patients, two of them met the diagnostic criteria for REM sleep Behaviour Disorder. In all subjects the AHI and/or RERAs were lower than 5/h and the PLM index was lower than 15. Excessive daytime sleepiness (EDS) was increased in PD patients, but only in 4 of them ESS score was greater than 10.

About the sleep microstructural parameters, patients with PD had lower total CAP rate and lower CAP rates in all NREM sleep stages (particularly in SWS) than did normal controls. Moreover,

Table 1: Demographic, clinical and macro- and micro-structural polysomnographic variables of patients with severe PD and healthy controls.

		Controls		Patients		p ≤
		mean	SD	mean	SD	
Age	(yrs)	64.3	3.1	65.7	3.4	NS
Sex	(m/f)	9/5	-	9/5	-	-
Hoen & Yahr	(stage)	-	-	3.7	0.8	-
LDOPA	(mg)	-	-	1035	318	-
ESS	(score)	4.1	2.6	7.8	3.0	0.001
TIB	(min)	527.6	58.9	513.7	96.8	NS
SPT	(min)	509.9	58.9	450.1	53.1	0.002
TST	(min)	428.9	44.6	288.9	78.6	0.000
SL	(min)	17.8	4.1	12.6	15.3	NS
FRL	(min)	90.6	13.6	158.8	94.1	.015
Stage shifts	(n/h)	7.8	1.4	14.6	5.3	0.001
Awakenings	(n/h)	6.0	1.7	8.1	3.2	0.016
SE	(%)	84.4	6.3	57.9	18.4	0.000
WASO	(%)	14.1	5.5	35.6	18.1	0.001
N1	(%)	9.4	2.6	10.1	5.7	NS
N2	(%)	50.3	4.4	35.5	15.4	0.005
N3 (SWS)	(%)	5.9	2.8	8.8	6.7	NS
REM	(%)	20.4	4.3	10.0	5.4	0.000
AHI	(n/h)	2.9	1.6	2.7	1.3	NS
PLMI	(n/h)	4.3	2.1	5.6	2.7	NS
CAP rate tot	(%)	56.3	7.1	37.4	21.2	0.007
CAP rate S1	(%)	55.9	8.4	43.8	10.3	0.003
CAP rate S2	(%)	58.9	6.9	41.4	20.0	0.007
CAP rate N3 (SWS)	(%)	57.5	7.9	35.5	22.8	0.003
A1	(%)	41.6	11.0	24.2	19.0	0.019
A2	(%)	32.8	10.3	43.6	20.8	NS
A3	(%)	25.6	7.1	32.2	11.7	NS

Abbreviations: LDOPA: Medication Requirement Expressed As Levodopa Equivalent; ESS: Epworth Sleepiness Scale; TIB: Time In Bed; SPT: Sleep Period Time; TST: Total Sleep Time; SL: Sleep-Onset Latency; FRL: First REM Latency; SE: Sleep Efficiency; WASO: Wake After Sleep Onset; N1: Nonrem Sleep Stage 1; N2: Nonrem Sleep Stage 2; N3: Nonrem Sleep Stage 3; SWS: Slow Wave Sleep; REM: Rapid Eye Movement Sleep; AHI: Apnoea-Hypopnea Index; PLMI: Periodic Limb Movement Index; CAP: Cyclic Alternating Pattern; A1: CAP A1 Subtype; A2: CAP A2 Subtype; A3: CAP A3 Subtype

the analysis of CAP A subtypes distribution showed a decreased A1 percentage in patients (more pronounced in SWS) and a slight, not significant increase of A3 subtypes. CAP A subtypes index resembled the distribution, showing a decreased A1 subtypes. The duration of A subtypes was similar in patients and controls.

DISCUSSION

To our knowledge, this study represents the first attempt to evaluate CAP in patients with PD and reveals that the total CAP rate is reduced in these patients across all sleep stages, even if SWS is more affected. This reduction is mediated by a selective decrease in CAP A1 subtypes.

Wetter et al [2] reported that the amount of N1 and N2, N3 (SWS) and REM sleep are similar in PD patients and age matched volunteers. In our study N2 and REM sleep are reduced in PD patients. This difference could be explained by the different severity of disease: 2.2 Hoen and Yahr stage in the Wetter's study, 3.7 in our case. In fact, our findings regarding the macrostructural parameters resemble those reported in literature in severe PD patients [5]. The differences between patients and controls in micro- and macro-structure of sleep could be explained by the chronic partial sleep deprivation in PD patients. In fact, the sleep deprivation might lead to a higher homeostatic sleep pressure and, therefore, both to an increase in N3 percentage, as to a decrease in total CAP rate consequent to the increase in non-CAP sleep.

Some authors [7, 9] found similar CAP changes in ADHD and in narcoleptic patients, and suggested the hypothesis of a deficit of the arousal system. Nevertheless, the A1 distribution is different. In fact, A1 subtypes are reduced in light sleep (N1-N2) and normal in N3 in narcoleptic and ADHD patients, but are normal in light sleep and reduced in N3 in PD patients. Taking in

account that CAP A1 subtypes are involved in the build up and maintenance of deep NREM sleep (N3) and have a protective role for sleep continuity [16], and that N3 percentage is similar in PD patients and in controls, it could be supposed that the decrease of A1 subtypes represents a characteristic feature of PD.

Interestingly, in our study, the analysis of the polysomnographic recordings of the four patients with EDS (ESS score > 10) showed that SL, TST, SE are decreased, stage shifts, awakenings, WASO and REM sleep percentage are increased when compared with PD patients without EDS (ESS score < 10), while N3 and A1 subtypes percentages are similar in both groups. It could be speculated that the EDS might be induced by the increase of sleep disruption that cannot be counter balanced by a further increase of N3, given the lack of synchronizing effect of A1 subtypes.

It has been found that the cortical generators of A1 subtypes are localized over the anterior frontal regions, mostly over the midline [17]. The basal forebrain noradrenergic innervation originates in the locus coeruleus (LC), and electrical or chemical stimulation of the LC is effective in shifting the electrocorticogram from low frequency-high amplitude to high frequency-low amplitude activity [18]. Intriguingly, Braak et Al [19], staging the brain pathology related to sporadic PD, reported that the coeruleus-subcoeruleus complex is affected even in initial stages of disease.

Most of our patients are drug-treated, in particular with benzodiazepines (8/14), and they may influence sleep also macro- and micro-structure [20]. In our study the number of awakening, the number of stage shift as well as the total amount of wake after sleep onset are significantly increased in patients and the CAP rate is reduced (mainly as regards A1 percentage), resembling the sleep pattern observed in insomniac patients with abuse of benzodiazepines [21]. These Authors suggested that, in BDZ abusers, the chronic GABAergic stimulation makes the thalamic filter less adaptive: when exposed to stimuli, abusers either produce no response (and keep sleeping without arousal) or fully awaken. As a consequence, abusers have a marked reduction of arousals associated with increased number of nocturnal awakenings without relevant modifications of sleep macro architecture. Even if the duration of assumption of benzodiazepines were similar in both studies (5,2 yrs and 3,5 yrs), the total daily dose was six times lower in our patients (1,2 mg *vs* 7.8 mg). These data could further support the hypothesis that the arousal system may be dysfunctional in PD patients probably through a degeneration of brainstem structures.

However, these considerations are highly speculative and we should consider some limits of this study. The small sample and the analysis of numerous variables could have introduced type-2 errors. Moreover, ESS correlate with patient's subjective sleepiness, but a poor correlation with objective measures has been reported by some authors [22]. Finally, we could not investigate the relationships between CAP decrease, daytime sleepiness and Hoehn and Yahr staging, given that only severe PD patients were enrolled. Further studies involving larger number of patients with different stage of disease are needed to validate our findings.

REFERENCES

1. Tandberg E, Larsen JP, Karlsen K. A community-based study of sleep disorders in patients with Parkinson's disease. Mov Disord. 1998; 13: 895-899.
2. Wetter TC, Collado-Seidel V, Pollmächer T, Yassouridis A, Trenk walder C. Sleep and periodic leg movement patterns in drug-free patients with Parkinson's disease and multiple system atrophy. Sleep. 2000; 23: 361-367.
3. Arnulf I. Excessive daytime sleepiness in parkinsonism. Sleep Med Rev. 2005; 9: 185-200.
4. Arnulf I, Konofal E, Merino-Andreu M, Houeto JL, Mesnage V, Welter ML, et al. Parkinson's disease and sleepiness: an integral part of PD. Neurology. 2002; 58: 1019-1024.
5. Young A, Home M, Churchward T, Freezer N, Holmes P, Ho M. Comparison of sleep disturbance in mild versus severe Parkinson's disease. Sleep. 2002; 25: 573-577.
6. Terzano MG, Parrino L, Smerieri A, Carli F, Nobili L, Donadio S, et al. CAP and arousals are involved in the homeostatic and ultradian sleep processes. J Sleep Res. 2005; 14: 359-368.
7. Ferri R, Miano S, Bruni O, Vankova J, Nevsimalova S, Vandi S, et al. NREM sleep alterations in narcolepsy/cataplexy. Clin Neurophysiol. 2005; 116: 2675-2684.
8. Terzano MG, Smerieri A, Del Felice A, Giglia F, Palomba V, Parrino L. Cyclic alternating pattern (CAP) alterations in narcolepsy. Sleep Med. 2006; 7: 619-626.
9. Miano S, Donfrancesco R, Bruni O, Ferri R, Galiffa S, Pagani J, et al. NREM sleep instability is reduced in children with attention-deficit/hyperactivity disorder. Sleep. 2006; 29: 797-803.
10. Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord. 2007; 22: 1689-1707.
11. American Academy of Sleep Medicine. International classification of sleep disorders, 3rd ed. Darien, IL: American Academy of Sleep Medicine. 2014
12. Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep 1992;15:376–381.
13. Iber C, Ancoli-Israel S, Chesson AL, Quan F. AASM manual for the scoring of sleep and associated events. 1st ed. Westchester, IL: American Academy of Sleep Medicine; 2007.
14. [No authors listed]. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep. 1992; 15: 173-184.
15. Terzano MG, Parrino L, Smerieri A, Chervin R, Chokroverty S, Guilleminault C, et al. Atlas, rules, and recording techniques for the scoring of cyclic alternating pattern (CAP) in human sleep. Sleep Med. 2002; 3:187-199.
16. Terzano MG, Parrino L. Origin and Significance of the Cyclic Alternating Pattern (CAP). REVIEW ARTICLE. Sleep Med Rev. 2000; 4: 101-123.
17. Ferri R, Bruni O, Miano S, Terzano MG. Topographic mapping of the spectral components of the cyclic alternating pattern (CAP). Sleep Med. 2005;6: 29-36.
18. Zaborszky L, Duque A. Sleep-wake mechanisms and basal forebrain circuitry. Front Biosci. 2003; 8: d1146-1169.
19. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003; 24:197-211.

20. Parrino L, Boselli M, Spaggiari MC, Smerieri A, Terzano MG. Multidrug comparison (lorazepam, triazolam, zolpidem, and zopiclone) in situational insomnia: polysomnographic analysis by means of the cyclic alternating pattern. Clin Neuropharmacol. 1997; 20: 253–263.

21. Mazza M, Losurdo A, Testani E, Marano G, Di Nicola M, Dittoni S, et al. Polysomnographic findings in a cohort of chronic insomnia patients with benzodiazepine abuse. J Clin Sleep Med. 2014; 10: 35-42.

22. Chervin RD, Aldrich MS. The Epworth Sleepiness Scale may not reflect objective measures of sleepiness or sleep apnea. Neurology.1999; 52: 125-131.

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