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Frequency of REM sleep behavior disorders in patients with Parkinson's disease

Učestalost poremećaja REM faze sna kod bolesnika sa Parkinsonovom bolesti

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Abstract

Background/Aim. Sleep is prompted by natural cycles of activity in the brain and consists of two basic states: rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. REM sleep behavior disorder (RBD) is characterized by violent motor and vocal behavior during REM sleep which represents dream enactment. The normal loss of muscle tone, with the exception of respiratory, sphincter, extra ocular and middle ear muscles, is absent in patients with RBD. The origin of RBD is frequently unknown, but can be associated with degenerative neurological disorders, such as Parkinson's disease (PD). PD patients do not necessarily express features of RBD, which is identified in approximately third to a half of them. The aim of this study was to estimate the prevalence of RBD in a cohort of PD patients, as well as to identify risk-factors for its development. **Methods.** In the period from December 2010 to September 2011 we recruited 97 consecutive PD outpatients, treated in the Institute of Neurology, Clinical Center of Serbia, Belgrade. After establishing the diagnosis, all the patients filled out a specially constructed questionnaire with the following items: actual age, sex, age at disease onset, disease duration, form of the disease, type of treatment, duration of treatment, the presence of constipation, lessening of smell sense, and family history of PD. At entring the study, patients disability was scored using the Unified Parkinson's Disease Rating Scale (motor part – UPDRS). Cognitive abilities were assessed by the Mini Mental Status Examination (MMSE) scale, and depression symptoms by the 21-item Hamilton Depression Rating Scale (HDRS). The patients with PD were dichotomized to those with and without RBD using the RBD Questionnaire – Hong Kong (RBDQ-HK) in the manner of an interview. Forms of PD, mode of treatment, sex, constipation and family history were investigated using the Fishers χ^2 test. Symptoms and treatment duration, the presence of smell disturbances, MMSE score, UPDRS motor score and HDRS score were analyzed by implementation of the Z-test. Actual age and age at disease onset were evaluated by the unpaired *t*-test. **Results.** The RBD-positive group contained 15 (15.5%) patients, while in the rest of them (82/97), RBD was not identified (non-RBD group). There was no difference between the two groups considering gender distribution ($p = 0.847$), age ($p = 0.577$), age at disease onset ($p = 0.141$), duration of PD ($p = 0.069$), family history ($p = 0.591$), type of initial symptoms ($p = 0.899$), constipation ($p = 0.353$), olfaction ($p = 0.32$) and MMSE scores ($p = 0.217$). The duration of treatment in the RBD group was longer than in the non-RBD group (9.4 ± 5.3 and 6.3 ± 3.9 years, respectively; $p = 0.029$), and the UPDRS motor score in the RBD group was higher (19.1 ± 9.4 and 12.7 ± 8.2, respectively; $p = 0.013$). Also, HDRS scores were higher in patients expressing RBD (10.1 ± 6.0 and 6.4 ± 4.5, respectively; $p = 0.019$). **Conclusion.** We found that 15.5% of the consecutive PD patients had RBD, and that the patients with RBD differed from the non-RBD ones regarding duration of treatment, disease and depressive symptoms severity.

Key words:
parkinson disease; sleep, rem; sleep disorders; prevalence; risk factors.

Apstrakt

Uvod/Cilj. San je izazvan prirodnim ciklusima aktivnosti u mozgu i sastoji se od dva osnovna stanja: sna sa brzim kretanjem očiju (REM faza) i sna bez brzog kretanja očiju (NREM faza). Poremećaj REM faze sna (RBD) karakteriše se izraženim motornim i vokalnim manifestacijama u toku REM faze sna koje predstavljaju 'odigravanje' događaja u snovima. Normalan gubitak mišićnog tonusa, sa izuzetkom respiratornih, ekstraokularnih, sfinkternih mišića i mišića srednjeg uva odsutan je kod bolesnika sa RBD. Poreklo RBD često je nepoznato, ali se dovodi u vezu sa degenerativnim neurološkim poremećajima kao što je Parkinsonova bolest (PB). Bolesnici sa PB ne moraju uvek ispoljiti odlike koje prate RBD, koji se identifikuje kod približno jedne trećine do jedne polovine ovih bolesnika. **Metode.** U periodu od decembra 2010. do septembra 2011. ambulantno smo pregledali 97 bolesnika sa PB, lečenih u Institutu za neurologiju Kliničkog Centra Srbije u Beogradu. Nakon što je ustanovljena dijagnoza, svi bolesnici popunili su posebno konstruisani upitnik sa sledećim varijablama: starost, pol, godine života na početku bolesti, dužina trajanja bolesti od pojave simptoma, forma bolesti, način lečenja, dužina trajanja lečenja, prisustvo opstipacije, smanjenje čula mirisa i porodična anamneza PB. Na početku pregleda, motorna sposobnost bolesnika ocenjivana je pomoću skale *Unified Parkinson's Disease Rating Scale* (*motor part*)

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(UPDRS). Kognitivne sposobnosti procenjivane su pomoću skale *Mini Mental Status Examination* (MMSE) (*Mini mental test*), a simptomi depresije bodovani su uz pomoć skale Hamilton-ove *Depression Rating Scale* (HDRS). Bolesnici sa PB podeljeni su na one sa i bez RBD koristeći RBD *Questionnaire* – Hong Kong (RBDQ-HK) upitnik u vidu intervjua. Forma PB, način lečenja, pol, opstipacija i porodična anamneza PD su statistički računate Fišerovim χ^2 testom. Dužina trajanja simptoma i lečenja, prisustvo olfaktivnih promena, MMSE skor, UPDRS skor i HDRS skor analizirani su primenom Z-testa. Starost i godine života na početku bolesti procenjene su neuparenim *t*-testom. **Rezultati.** RBD pozitivnu grupu činilo je 15 (15,5%) bolesnika, dok kod ostalih (82/97) RBD nije bio identifikovan. Između RBD pozitivne i negativne grupe kada je u pitanju pol ($p = 0,847$), starost ($p = 0,577$), uzrast na početku bolesti ($p = 0,141$), dužine trajanja bolesti od pojave simptoma ($p = 0,069$), porodična anamneza ($p = 0,591$), forma bolesti ($p = 0,899$), prisustva opstipacije ($p = 0,353$), smanjenje čula mirisa ($p = 0,32$) i MMSE skor ($p = 0,217$) nije bilo razlike. Dužina trajanja lečenja u grupi RBD pozitivnih bila je značajno duža nego u grupi RBD negativnih ($9,4 \pm 5,3$ i $6,3 \pm 3,9$ godina, respektivno; $p = 0,029$), što je utvrđeno i za UPDRS motorni skor ($19,1 \pm 9,4$ i $12,7 \pm 8,2$, respektivno; $p = 0,013$). Takođe, HDRS skor bio je viši kod bolesnika kod kojih je utvrđen RBD, za razliku od bolesnika u grupi u kojoj je ovo oboljenje bilo odsutno ($10,1 \pm 6,0$ i $6,4 \pm 4,5$, respektivno; $p = 0,019$). **Zaključak.** Dobijeni rezultati pokazuju da 15,5% bolesnika sa PB ima i RBD, kao i da se bolesnici sa RBD razlikuju od onih bez tog oboljenja po dužini trajanja lečenja, težini bolesti (utvrđenoj UPDRS skorom) i težini depresivnih simptoma.

Ključne reči:
parkinsonova bolest; spavanje, rem; spavanje, poremećaji; prevalenca; faktori rizika.

Introduction

Sleep is prompted by natural cycles of activity in the brain and consists of two basic states: rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep, which consists of stages N 1 through 3 [1]. Intense dreaming occurs during REM sleep as a result of heightened brain activity, but paralysis occurs simultaneously in the major voluntary muscle groups. However, fascinating REM sleep behavior disorder (RBD) paradoxically represents acting out of vivid, action-filled dreams and is characterized by violent motor and vocal behavior during REM sleep [2]. In the course of REM sleep there is a loss of muscle tone, with exception of respiratory, sphincter, extraocular and middle ear muscles [3]. In contrast, in the course of RBD muscle activity is preserved. The origin of RBD is frequently unknown (idiopathic RBD), but it can be associated with degenerative neurological disorders mainly classified as synucleinopathies, such as multiple-system atrophy, dementia with Lewy bodies (DLB) and Parkinson's disease (PD) [4]. Expression of RBD is probably due to a lesion of the sleep atonia system, mainly located in the pontomedullary brainstem region.

According to the Braak et al. [5] theory of PD progression, pathological process in PD initially appears not in the substantia nigra, but in the olfactory bulbs and medulla oblongata, which can explain emergence of RBD early in the course of PD, frequently before motor signs. Therefore, RBD may be a prodromal marker for PD, with higher sensitivity in comparison to other proposed markers, such as hyposmia, constipation, excessive daytime sleepiness or depression. However, the PD patients did not necessarily express features of RBD, which was identified in approximately third to a half of them [4].

The aim of this study was to estimate the prevalence of RBD in our cohort of PD patients, as well as to identify risk factors for its development.

Methods

Between December 2010 and September 2011 we recruited 97 consecutive PD outpatients treated in the Institute of Neurology, Clinical Center of Serbia, Belgrade, who gave informed and written consent for their participation. The study was approved by the Ethical Committee of our institution.

Only patients who fulfilled the Brain Bank criteria for clinical diagnosis of PD [6] were included. After establishing the diagnosis, all the patients filled out a specially constructed questionnaire with the following items: actual age, sex, age at disease onset, disease duration, form of the disease [7] (tremor predominant or rigidity predominant), type of treatment, duration of treatment, the presence of constipation, lessening of smell sense (quality of olfaction, i.e. hyposmia and/or anosmia, was assessed using the Pocket Smell test (PST) [8] and anamnestic data concerning common etiologies of possible lessening or absence of smell), and family history of PD. At the study entry, patients disability was scored using the Unified Parkinson's Disease Rating Scale (motor part) (UPDRS) [9]. Cognitive abilities were assessed by the Mini Mental Status Examination (MMSE) scale [10], while depressive symptoms by the 21-item Hamilton Depression Rating Scale (HDRS) [11].

The patients with PD were dichotomized to those with and those without RBD, by using the RBD Questionnaire – Hong Kong (RBDQ-HK) [12] in the manner of an interview. The questionnaire comprises 13 queries with a score ranging from 0 to 100. The questions considered various clinical features of RBD defined by the International Classification of Sleep Disorders [13] (ICSD-II) and derived from clinical observations by the authors of the questionnaire and previous empirical work (i.e. frequent dreams, frequent nightmares, emotional, violent or aggressive or frightening dreams, disturbed sleep, sleep talking, shouting or yelling in sleep, dream-related movements, falling out of bed, sleep-related injuries (SRI), attempts to assault/injure and SRI related to dream content). The cut-off score for disproving/proving RBD was 18/19.

The forms of PD, mode of treatment, sex, constipation and family history were investigated using the Fishers χ^2 test. Symptoms and treatment duration, the presence of smell disturbances, MMSE score, UPDRS motor score and HDRS

score were analyzed by implementation of the Z-test. Actual age and age at disease onset were evaluated by an unpaired *t*-test.

Results

The cohort comprised of 41 female and 56 male subjects. The mean age of our patients was 62.1 ± 8.8 years, with the age at disease onset 54.3 ± 9.4 years. The duration of symptoms was 8.3 ± 4.9 years. Concerning the form of the disease by which the symptoms first manifested themselves, 59 (60.8%) of the patients had the tremor-predominant form, 37 (38.1%) akinetic-rigid form, while only 1 (1%) of the patients presented with mixed symptoms. The duration of treatment was 6.8 ± 4.3 years, with levodopa as the most frequently used drug. Other centrally active medications included levodopa, amantadine, ropinirole, clonazepam, pramipexole, diazepam, clozapine, alprazolam, lorazepam, fluoxetine, and selegiline. Therapy-wise, 11 (11.3%) of the patients had undergone monotherapy, while 86 (88.7%) used more than one medication (polytherapy). In regards to constipation, 62 (63.9%) of the patients had, and 35 (36.1%) of them did not have this symptom. The sense of smell was normal, reduced or absent in 11 (11.3%), 19 (19.6%) and 67 (69.1%) of the examinees, respectively. A family history of PD was positive in 6 (6.2%), negative in 87 (89.7%), and unknown in the rest of the patients – 4 (4.1%). The MMSE score was 27.2 ± 3.8, UPDRS motor score 13.7 ± 8.6, Hamilton Depression Rating Scale score 7.0 ± 4.8, and the RBDQ-HK score was 8.8 ± 9.5.

The RBD-positive group contained 15 (15.5%) patients, while in the rest of them (82/97), RBD was not identified (non-RBD group) (Table 1).

There was no difference between the two groups considering gender distribution ($p = 0.847$), age ($p = 0.577$), age at disease onset ($p = 0.141$), duration of PD ($p = 0.069$), family history ($p = 0.591$), type of initial symptoms ($p = 0.899$), constipation ($p = 0.353$), olfaction ($p = 0.32$) and MMSE scores ($p = 0.217$).

The duration of treatment in the RBD group was longer than in the non-RBD group (9.4 ± 5.3 and 6.3 ± 3.9 years, respectively; $p = 0.029$), and the UPDRS motor score in the RBD group was higher (19.1 ± 9.4 and 12.7 ± 8.2, respectively; $p = 0.013$). Also, HDRS scores were higher in the patients expressing RBD (10.1 ± 6.0 and 6.4 ± 4.5, respectively; $p = 0.019$).

Discussion

In this study we detected RBD in 15.5% of the patients with PD, using RBDQ-HK [12], without detailed neurophysiological studies. Briefly, the patients with RBD did not differentiate from the non-RBD patients according to sex, age, age at disease onset, duration of symptoms, family history, form of the disease, constipation, olfaction, mode of treatment and MMS, but they were statistically different regarding duration of treatment, disease severity and the presence of depression.

Our results are quite similar to the results of Vibha et al. [14], with the prevalence of RBD of 19.4% in their PD cohort, and Comella et al. [15] whose estimates were even closer (15%). Overall, the reported prevalence of RBD in PD population varies from 15 to 60%, most probably due to different methods of patient selection and disorder ascertainment (spouses' interview, nocturnal video, etc.) [16].

Cross-sectional studies failed to find the difference in

Table 1

Comparison of the patients with Parkinson's disease with (n = 15) and without REM sleep behavior disorder (RBD) (n = 87)

Variables	RBD	Non-RBD	*p*
Age (years), $\bar{x} \pm SD$	60.9 ± 8.6	62.3 ± 8.9	0.577
Sex (m/f), n (%)	9 (60)/6 (40)	47 (57.3)/35 (42.7)	0.847
Age at disease onset (years), $\bar{x} \pm SD$	51.0 ± 10.9	54.9 ± 9.1	0.141
Symptoms duration (years), $\bar{x} \pm SD$	10.6 ± 5.6	7.8 ± 4.7	0.069
Form of the disease, n (%)			0.899
tremor-predominant	9 (15.3)	50 (84.7)	
akinetic-rigid form	6 (16.2)	31 (83.8)	
mixed		1 (1)	
Mode of treatment, n (%) (Monotherapy / polytherapy)	3 (27.3)/12 (14)	8 (72.7)/74 (86)	0.250
Constipation (Yes/No), n (%)	8 (12.9)/7 (20)	54 (87.1)/28 (80)	0.353
Sense of smell, n (%)			0.32
normal	1(9.1)	10 (90.9)	
reduced	2(10.5)	17 (89.5)	
absent	12 (17.9)	55 (82.1)	
Family history (Yes/No), n (%)	0(0)/15(17.2)	6 (100)/72 (82.8)	0.591
Duration of treatment (years), $\bar{x} \pm SD$	9.4 ± 5.3	6.3 ± 3.9	0.029*
MMSE scores, $\bar{x} \pm SD$	25.0 ± 6.8	27.6 ± 2.9	0.217
UPDRS motor scores, $\bar{x} \pm SD$	19.1 ± 9.4	12.7 ± 8.2	0.013*
HDRS scores, $\bar{x} \pm SD$	10.1 ± 6.0	6.4 ± 4.5	0.019*
RBDQ-HK scores, $\bar{x} \pm SD$	27.5 ± 5.6	5.4 ± 4.9	N/A

REM – rapid eye movement; MMSE – Mini Mental State Examination; UPDRS – Unified Parkinson's Disease Rating Scale; HDRS – Hamilton Depression Rating Scale; RBDQ-HK – REM Sleep Behavior Disorder Questionnaire–Hong Kong; *statistically significant.

age at disease onset between RBD and non-RBD PD patients [17]. In our study, initial Parkinson's disease symptoms started earlier in the patients with RBD than in those without RBD, but the observed difference did not reach statistical significance.

In contrast with our and the study of Arnulf [17], other authors reported a striking male predominance in chronic RBD patients [18]. In the first series of RBD patients described in 1985 by Schenck et al. [19] more than 90% of them were males. Other studies also found male predominance (87% and 83.3%) [20]. One of the possible explanations for such gender predominance is that milder forms of RBD occurs in females as subclinical, non-aggressive behaviors, and therefore are not reported.

In several studies dealing with smaller cohorts of PD patients, RBD was more frequent in patients with akinetic-rigid form of the disease [17]. Romenets et al. [21] reported a relationship between RBD and non-tremor predominant subtype of PD ($p = 0.04$). However, in this study tremor was an initial symptom in 31% of the patients, while in our study PD started with tremor in 60% of the cases. Lack of association of RBD to any type of PD we found in our study was in accordance with the data obtained from a larger cohort of PD patients [22].

Concerning family history, no difference was obtained between the RBD and non-RBD groups of PD patients, in accordance to previous reports [18, 23]. Lack of difference was also noted for constipation and olfactory function.

We assessed cognition with robust instrument, MMSE, and found no statistically significant difference between RBD and non-RBD group. However, some cross-sectional studies gave evidence of mild cognitive impairment in PD patients with RBD, as opposed to those without this sleep disorder [24] (the instrument we used was not sensitive enough to detect mild cognitive impairment in our patients). In a study of PD patients with RBD progression to dementia was documented in 48% of them during a period of 4 years, compared to none in the non-RBD group [24]. Cognition was lower in PD patients with RBD than those without it. Also, the existence of RBD had strong anticipatory value for the development of hallucinations over a 12-year follow-up [25]. However, careful follow-up is needed for a suggestion that the presence of RBD predisposed patients for developing dementia [26].

Contrary to some previous data [16] the presence of RBD in PD in our study correlated with the disease severity (UPDRS motor scores), and HDRS scores. Also, the longer the treatment of PD patients was, the chances they had to develop RBD were larger. Our data are in partial accordance with several cross-sectional studies where RBD was associated with older age, longer disease duration, higher Hoehn and Yahr score, lower amplitude of response to their medication, more frequent falls, more fluctuations, more psychiatric comorbidity, and higher doses of levodopa [22, 26, 27–32]. A population-based prevalence study that evaluated 231 PD patients for RBD during a follow-up period of 8 years found an increased prevalence of probable RBD from 14.6% to 27% during the study period.

In our work, definitive validation of RBD in the patient cohort remains with the RBD-HK questionnaire. Although 10 patients underwent polysomnographic testing (PSG), a larger number is needed in order to yield more precise results, which would make this the main limitation of our study.

Behaviors during RBD were complex and sometimes dramatic. They included arm and leg movements (93.3%), falling out of bed (20%), assaulting the bed-partner (26.6%) etc., and occasionally resulted in trauma of the patient or the partner (26.6%). In some patients violent behavior was associated with variable forms of vocalization (93.3%). Finally, all of our patients remembered the content of dreams.

Conclusion

In our study, we found that 15.5% of the consecutive PD patients had RBD, and that the patients with RBD differed from the non-RBD ones regarding duration of treatment, disease and depressive symptoms severity.

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