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Fragmentary myoclonus in idiopathic rapid eye movement sleep behaviour disorder

Jiri Nepozitek[1] | Simona Dostalova[1] | David Kemlink[1] | Latica Friedrich[1,2] | Iva Prihodova[1] | Veronika Ibarburu Lorenzo y Losada[1] | Petr Dusek[1] | Ondrej Bezdicek[1] | Tomas Nikolai[1] | Pavla Perinova[1] | Irene Dall'Antonia[1] | Pavel Dusek[1] | Martin Ruml[1] | Evzen Ruzicka[1] | Karel Sonka[1]

[1]Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic

[2]University Department of Neurology, Sveti Duh University Hospital, Zagreb, Croatia

Correspondence
Jiri Nepozitek, Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University and General University Hospital, Prague, The Czech Republic.
Email: jiri.nepozitek@lf1.cuni.cz

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Summary

Fragmentary myoclonus is a result of muscle activity consisting of brief potentials in surface electromyography during polysomnography. Excessive fragmentary myoclonus is defined by increased intensity of the potentials. A few studies report excessive fragmentary myoclonus occurrence in neurodegenerative diseases. Because idiopathic rapid eye movement sleep behaviour disorder is considered as an early stage of neurodegeneration with involvement of the brainstem, we charted the prevalence and quantified the intensity of excessive fragmentary myoclonus in idiopathic rapid eye movement sleep behaviour disorder. Twenty-nine patients (one woman, 28 men, mean age 68 years, *SD* 6.2) and 29 controls (two women, 27 men, mean age 65.6 years, *SD* 8.6) underwent polysomnography. Fragmentary myoclonus potentials were identified and counted according to internationally used criteria. Fragmentary myoclonus intensity was quantified by the fragmentary myoclonus index. Excessive fragmentary myoclonus was diagnosed in 75.9% (22 subjects) in idiopathic rapid eye movement sleep behaviour disorder, while in 34.5% (10 subjects) among the controls ($p = 0.003$). Quantitative analysis showed a wide-range fragmentary myoclonus index in idiopathic rapid eye movement sleep behaviour disorder (4.0–632.4; median 60.7) and in the controls (0.8–938.1; median 34.3). The overall difference in fragmentary myoclonus index was not significant between the groups; however, patients with idiopathic rapid eye movement sleep behaviour disorder showed trends for higher fragmentary myoclonus index scores in wakefulness ($p = 0.027$), N1 ($p = 0.032$), N3 ($p = 0.046$) and R ($p = 0.007$). Fragmentary myoclonus index does not correlate with age, idiopathic rapid eye movement sleep behaviour disorder duration or R stage atonia deficiency. The prevalence of excessive fragmentary myoclonus is higher in idiopathic rapid eye movement sleep behaviour disorder compared with the controls, so fragmentary myoclonus should be taken into account in future research of rapid eye movement sleep behaviour disorder and motor control in sleep.

KEYWORDS

electromyographic activity, excessive fragmentary myoclonus, motor dyscontrol, rapid eye movement sleep atonia loss, twitch

1 | INTRODUCTION

Fragmentary myoclonus (FM) is a polysomnographic (PSG) phenomenon discovered incidentally in sleep. FM is defined as a result of muscle activity, consisting of sudden, isolated, arrhythmic, asynchronous and asymmetric brief twitches, jerks or twitch-like movements of muscles or muscle fibres, which is registered as potentials by surface electromyography (EMG) during PSG (American Academy of Sleep Medicine, 2014).

In 1985, Broughton and co-workers referred the presence of abnormal amounts of FM potentials during sleep in 38 individuals (Broughton, Tolentino, & Krelina, 1985). The condition was described as *excessive fragmentary myoclonus* (EFM), and was contrasted with the physiological form of FM (Broughton & Tolentino, 1984). EFM persists with pathologically increased frequency throughout all stages of non-rapid eye movement (NREM) and rapid eye movement sleep (R). Additionally, association between EFM and other sleep disorders was observed. These disorders include: obstructive sleep apnea, primary central sleep apnea, sleep-related hypoxaemic and hypoventilation syndromes, periodic limb movements disorder, narcolepsy and various causes of insomnia (Broughton et al., 1985).

In a healthy population, FM potentials were found in 100% of healthy subjects, whereas the prevalence of EFM was reported to be 9% (Frauscher et al., 2014).

Excessive fragmentary myoclonus was also observed in several neurodegenerative diseases, such as Parkinson's disease (PD; Sobreira-Neto et al., 2015), multiple system atrophy (Vetrugno et al., 2007), amyotrophic lateral sclerosis (Sonka et al., 2004), spinocerebellar ataxia type 3 (dos Santos et al., 2014), Niemann–Pick disease type C (Vankova et al., 2003) and mitochondrial encephalopathy (Pincherle, Mantoani, Villani, Confalonieri, & Erbetta, 2006).

Rapid eye movement sleep behaviour disorder (RBD) is a parasomnia, characterized by abnormal behaviour during the R stage corresponding to the content of the current dream in the absence of normal muscle atonia (Arnulf, 2012). The idiopathic form of RBD (iRBD) is known to be associated with later development of neurodegenerative diseases characterized by abnormal alpha-synuclein aggregation and storage, such as PD, Lewy body disease and multiple system atrophy (Claassen et al., 2010; Iranzo et al., 2006; Postuma et al., 2009; Schenck, 2013; Schenck, Bundlie, & Mahowald,1996).

Based on the observations of higher prevalence of EFM in alpha-synucleinopathies, an elevated occurrence of EFM in iRBD can be expected as well. Considering dysregulation of muscle tone in sleep as the main feature of RBD, it is reasonable to focus research on the phenomenon of FM in iRBD. Vetrugno et al. in 2002 presented a case report of a single RBD patient in whom EFM was observed (Vetrugno et al., 2002). To our knowledge, no group studies on this topic have so far been published.

The goals of this study were to chart the prevalence of EFM in patients with iRBD, to quantify the intensity of FM and to describe the clinical and PSG profiles of patients with iRBD and concurrent EFM in a comparison with a control group.

2 | METHODS

The patients were recruited by a stepwise media and internet survey (Bušková, Ibarburu, Šonka, & Růžička, 2016), and they were included consecutively in the study. All patients were diagnosed with iRBD according to the latest version of the International Classification of Sleep Disorders, third edition (ICSD-3; American Academy of Sleep Medicine, 2014). The diagnosis of RBD was based on their history of dream-enacting behaviours and nocturnal video-PSG demonstrating prominent EMG activity during R stage (American Academy of Sleep Medicine, 2014). The exclusion criteria were as follows: age under 50 years, clinical signs of dementia or parkinsonism, RBD associated with narcolepsy, encephalitis, head injury or focal brain lesion found on magnetic resonance imaging (MRI) indicative of secondary RBD.

The controls were healthy volunteers aged 50 years or more with no medical history of sleep or neurological disorders.

Participants were not treated with drugs with the potential to influence the sleep structure, peripheral nerve activity and muscle activity during the study and prior to the study except for antidepressants and anxiolytics. Five of the patients with iRBD were using antidepressants, six were using anxiolytics, and two were on both antidepressants and anxiolytics. The patients who used antidepressants referred the beginning of RBD symptoms before they started using this medication.

The study was approved by the local Ethics Committee, and participants signed informed consents before the study in accordance with the Helsinki Declaration.

All study participants underwent a comprehensive clinical evaluation, including medical history, standard neurological examination, a Movement Disorders Society-sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), nocturnal video-PSG, high-resolution brain MRI (whole brain T2-weighted 0.7 mm^3 isotropic scan, TE/TR = 566/3200 ms), and dopamine transporter single-photon emission computed tomography scan (DAT-SPECT) using the [^{123}I]-Ioflupane (DaTscan®, GE Healthcare) tracer. Specific tracer binding indices in the putamen were calculated in both hemispheres using the BasGan V2 software (Calvini et al., 2007). In order to exclude patients with any clinical signs of dementia, a neuropsychological examination was performed. All participants also completed questionnaires to assess laterality (Edinburgh Handedness Inventory [EHI]; Oldfield, 1971), autonomic dysfunction (Scales for Outcomes in Parkinson's Disease-Autonomic [SCOPA-AUT]; Visser, Marinus, Stiggelbout, & Van Hilten, 2004), depression (Beck Depression Inventory, Second Edition [BDI-II]; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), anxiety (State-Trait Anxiety Inventory [STAI]; Spielberger, Gorsuch, & Lushene, 1970; state anxiety [STAI X1], trait anxiety [STAI X2]), daytime sleepiness (Epworth Sleepiness Scale [ESS]; Johns, 1991) and insomnia (Insomnia Severity Index [ISI]; Morin, 1993) (Table 1).

Nocturnal video-PSG was performed using a digital PSG system (RemLogic, version 3.4.1, Embla Systems), and consisted of electrooculography (EOG), electroencephalography (F3-M2, C3-M2, O1-M2, F4-M1, C4-M1, O2-M1), surface EMG of the bilateral mentalis

TABLE 1 Demographic and clinical characteristics

	iRBD		Controls		
	Mean	*SD*	Mean	*SD*	*p*-value
EHI	87.9	30.0	86.8	31.5	0.993
BMI	27.5	3.6	27.4	4.1	0.768
iRBD duration (years)	8.3	7.0	NA	NA	NA
MDS-UPDRS total	18.2	14.5	7.3	5.5	<0.001[a]
MDS-UPDRS I	8.5	5.6	2.6	2.5	<0.001[a]
MDS-UPDRS II	3.3	5.7	1.0	1.8	0.037
MDS-UPDRS III	7.0	6.3	3.8	4.2	0.019
MDS-UPDRS IV	0.1	0.8	0.0	0.0	0.818
SCOPA-AUT	11.3	7.9	6.4	4.1	0.010
ESS	6.7	3.8	6.0	3.8	0.518
ISI	8.8	5.3	2.8	3.0	<0.001[a]
BDI-II	11.2	9.6	5.0	4.9	0.012
STAI X1	37.5	11.1	32.2	7.4	0.086
STAI X2	41.1	10.5	32.5	8.3	0.002[a]

Data presented as mean and *SD* unless otherwise noted. All between-group comparisons were based on the Mann–Whitney *U*-test. The Bonferroni correction for 25 comparisons was applied.

BDI-II, Beck Depression Inventory, Second Edition; BMI, body mass index; EHI, Edinburgh Handedness Inventory; ESS, Epworth Sleepiness Scale; iRBD, idiopathic rapid eye movement sleep behaviour disorder; ISI, Insomnia Severity Index; MDS-UPDRS, Movement Disorders Society-sponsored Revision of the Unified Parkinson's Disease Rating Scale; NA, not applicable; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease: Autonomic; *SD*, standard deviation; STAI, State-Trait Anxiety Inventory (state anxiety – X1; trait anxiety – X2).

[a]Remains significant after the Bonferroni correction. Bold for trends.

muscle, the bilateral flexor digitorum superficialis muscle and the bilateral tibialis anterior muscle, electrocardiography, nasal pressure, nasal air flow, thoracic and abdominal respiratory effort, oxygen saturation, microphone and digitally synchronized video monitoring from 22:00 hours to 06:00 hours according to the American Academy of Sleep Medicine (AASM) recommendation (Berry et al., 2015).

All features on video-PSG including FM were analysed visually. Sleep stages, arousals, respiratory events and limb movements were scored according to AASM Manual for the Scoring of Sleep and Associated Events version 2.2 (Berry et al., 2015), with an exception for the R rules allowing to score R stage despite the prominent EMG activity in the mentalis muscle channel (Schenck & Mahowald, 2005). The beginning and the end of the R stage episode were scored according to the SINBAR (Sleep Innsbruck Barcelona) rules (Frauscher et al., 2012): the occurrence of the first rapid eye movements in the EOG channel was used to determine the onset of the R stage period. The end of the R stage period was determined when either no REMs were detected in 3 consecutive minutes or an awakening, K complexes or spindles were observed. A new R stage episode was scored when it occurred 30 min or more after the previous one, otherwise it was considered to be part of the same R stage episode (Frauscher et al., 2012).

2.1 | Analysis of fragmentary myoclonus

In each participant the quantification of FM intensity and the presence of EFM were evaluated.

The FM potentials were identified according to the criteria determined by ICSD-3 as EMG potentials with a maximal duration of 150 ms and an amplitude over 50 μV rarely rising above 200 μV to several hundred μV (American Academy of Sleep Medicine, 2014). These potentials were not associated with any visible movement on the video recording.

The EFM was clinically diagnosed according to the AASM Manual for the Scoring of Sleep and Associated Events (2015) by the presence of 5 potentials per minute during at least 20 min of recorded NREM sleep at the tibialis anterior muscle channels regardless of the side (Berry et al., 2015).

The intensity of FM was evaluated visually in EMG of both tibialis anterior muscles, each side separately. For quantitative evaluation, the FM index (FMI) was used as defined by Lins, Castonguay, Dunham, Nevsimalova, and Broughton (1993): each 30-s scoring epoch was divided into 10 × 3-s mini-epochs. EMG potentials fulfilling criteria of minimal amplitude 50 μV and maximal duration 150 ms were identified as FM (American Academy of Sleep Medicine, 2014). The number of 3-s mini-epochs with one or more FM potentials fulfilling these criteria present was counted in all sleep stages. Then the count was referenced to the duration of individual sleep stages in hours (Lins et al., 1993).

2.2 | Analysis of electromyographic activity in R

Electromyographic activity in R was scored according to the recommendation defined by SINBAR montage: all artefacts and increases in EMG tone due to arousals from respiratory events were excluded from the quantitative scoring before the analysis of EMG activity. R-related EMG activity was scored in the mentalis muscle and flexor digitorum superficialis muscle channels (Frauscher et al., 2012).

The recording was divided into 3-s mini-epochs. Each 3-s mini-epoch was scored as having or not having any EMG activity, irrespective of whether it contained tonic, phasic (including phasic EMG activity between 5 and 15 s that is not measured with current scoring systems) or a combination of both types of EMG activities. Tonic EMG activity was scored only in the mentalis muscle channels, and it was defined as an increased sustained EMG activity present in more than 50% of the total 30-s epoch duration with an amplitude of at least twice the background EMG muscle tone or more than 10 μV. Phasic EMG activity was defined as any burst of EMG activity lasting between 0.1 and 5.0 s with amplitude exceeding twice the background EMG activity irrespective of its morphology. The end of each phasic EMG burst was defined, when there was observed an identifiable return to the baseline or an interburst interval of more than 250 ms. After scoring of "any" EMG activity in the mentalis muscle channels using 3-s mini-epochs,

we scored the phasic EMG activity in the flexor digitorum superficialis muscle channels also in 3-s mini-epochs as not having "any" EMG activity already scored in the mentalis muscle channels according to the SINBAR scoring rules recommendation (Frauscher et al., 2012). Thus, we obtained a SINBAR index expressing the percentage of R referring to the amount of R stage-related EMG activity.

With regard to the rules for scoring phasic EMG activity in R, periodic limb movements (PLMs) during R stage were identified only when having a periodic pattern (Frauscher et al., 2012).

2.3 | Statistical analysis

Statistical analyses were performed using the STATISTICA 13 software package (Dell 2016 software.dell.com). To assess the normality of demographic, clinical and PSG variables, a Shapiro–Wilks test was performed. Except for age, body mass index (BMI) and time in bed in PSG, all the other data showed a non-parametric nature. For the comparison of the between-group differences in qualitative data, Fischer's exact two-tailed test was used. The Mann–Whitney *U*-test was applied to evaluate between-group differences in quantitative data. Given the non-parametric nature of the data, a Spearman Rank Correlation Coefficient (rho) was calculated to evaluate correlations between variables. We used a cut-off absolute value of rho > 0.4 and/or $p < 0.001$ for significant signal in the exploratory phase.

The Bonferroni correction for multiple comparisons was applied to correct family-wise error, and the post-correction cut-off for statistical significance was set at $p < 0.05$ for quantitative data.

3 | RESULTS

A total of 29 patients with iRBD (one woman and 28 men) with a mean age of 68 years (*SD* 6.2) and 29 controls (two women and 27 men) with a mean age of 65.6 years (*SD* 8.6) were included in the study. Comparing iRBD and control groups, higher scores were found in total MDS-UPDRS as well as in MDS-UPDRS parts I in the patient group, and II, III and SCOPA-AUT also showed similar trends. Patients with iRBD showed higher ISI as well as STAI X2 scores compared with the controls, there was also a trend towards higher BDI-II. Other clinical parameters were not different in the two groups. Detailed characteristics can be seen in Table 1.

No differences in the proportions of the sleep stages and arousal index were found (Table 2). Compared with the controls, patients with iRBD showed trends towards higher sleep latency and PLM index (PLMI), and lower apnea–hypopnea index (AHI). The SINBAR indexes as well as phasic, tonic and any REM sleep without atonia were significantly higher in the iRBD group.

3.1 | Prevalence of excessive fragmentary myoclonus

Excessive fragmentary myoclonus was diagnosed in 75.9% (22 subjects) among patients with iRBD, while in the control group EFM was found in 34.5% (10 subjects; $p = 0.003$).

TABLE 2 PSG characteristics

	iRBD		Controls		
	Mean	*SD*	Mean	*SD*	*p*-value
Total sleep time (min)	327.8	71.7	319.7	1.4	0.907
Sleep period time (min)	420.5	47.7	427.7	1.1	0.635
Sleep efficiency (%)	73.9	15.2	72.1	1.4	0.624
Sleep latency (min)	24.3	9.9	13.6	5.4	**0.031**
R latency (min)	120.0	89.6	99.0	60.3	0.446
Arousal index	15.0	9.5	18.4	9.7	0.064
Wake (%)	21.9	12.2	25.4	14.6	0.343
N1 (%)	10.6	5.6	9.2	5.2	0.392
N2 (%)	35.5	12.9	33.3	9.8	0.331
N3 (%)	16.7	11.9	16.1	8.2	0.703
R (%)	15.2	5.4	16.0	7.5	0.608
AHI	10.9	11.9	18.6	15.7	**0.017**
Oxygen desaturation index	10.3	10.6	16.6	13.6	0.059
PLMI	36.6	38.7	13.9	23.9	**0.005**
SINBAR index (%)	50.4	24.4	5.7	4.2	**<0.001**[a]
REM sleep without atonia: phasic (%)	24.8	13.2	3.1	2.5	**<0.001**[a]
REM sleep without atonia: tonic (%)	12.9	12.6	0.5	0.8	**<0.001**[a]
REM sleep without atonia: any (%)	45.4	30.0	3.9	3.0	**<0.001**[a]

Data presented as mean and *SD*. All between-groups comparisons were based on the Mann–Whitney *U*-test. The Bonferroni correction for 25 comparisons was applied.

AHI, apnea-hypopnea index; iRBD, idiopathic rapid eye movement sleep behaviour disorder; N1, non-rapid eye movement sleep stage one; N2, non-rapid eye movement sleep stage two; N3, non-rapid eye movement sleep stage three; PLMI, periodic limb movement index; R, rapid eye movement sleep; REM, rapid eye movement; *SD*, standard deviation; SINBAR, Sleep Innsbruck Barcelona.

[a]Remains significant after the Bonferroni correction. Bold for trends.

3.2 | Clinical-polysomnographic profile differences in subjects with and without excessive fragmentary myoclonus

Clinical and PSG parameters were compared between the subjects with EFM present and EFM absent in both iRBD and control groups. In the iRBD group, lower N2 and higher R stage percentages were

TABLE 3 FMI results

	iRBD			Controls			
	Median	Min	Max	Median	Min	Max	*p*-value
FMI both limbs	60.7	4	632.4	34.3	0.8	938.1	0.051
FMI mean	66.1	7.6	490.4	43.3	1.4	730.8	0.140
FMI limb difference (right – left)	−10.3	−545.9	386.2	0.6	−929.5	277.3	0.534
FMI NREM both limbs	43.0	1.8	553.8	23.8	0.2	700.3	0.059
FMI NREM mean	44.2	2.9	421.8	34.9	0.7	353.1	0.171
FMI wake both limbs	50.7	0.0	766.0	29.5	1.3	698.8	0.027
FMI N1 both limbs	44.7	3.0	550.3	25.4	0.0	699.8	0.032
FMI N2 both limbs	48.4	1.2	555.0	27.1	0.4	714.1	0.073
FMI N3 both limbs	38.1	0.0	556.5	24.2	0.0	664.4	0.046
FMI R both limbs	65.6	3.6	552.2	27.9	0.0	667.3	0.007

Due to high dispersion and non-parametrical layout, data are presented as median, minimum and maximum. All between-group comparisons were based on the Mann–Whitney *U*-test. The Bonferroni correction for 25 comparisons was applied. No *p*-value remained significant after the Bonferroni correction.

Bold for trends.

FMI, fragmentary myoclonus index; iRBD, idiopathic rapid eye movement sleep behaviour disorder; Max, maximum; Min, minimum; N1, non-rapid eye movement sleep stage one; N2, non-rapid eye movement sleep stage two; N3, non-rapid eye movement sleep stage three; NREM, non-rapid eye movement sleep; R, rapid eye movement sleep.

found in the EFM-positive subjects compared with the EFM-negative subjects (Supporting Information Table S1).

No significant differences were found between EFM-positive and EFM-negative subjects in the control group (Table S2).

We performed the analysis of FMI, antidepressants and anxiolytics use with no significant differences among the groups (Tables S3 and S4).

3.3 | Quantitative analysis of fragmentary myoclonus

The results of the quantitative analysis of FM showed a wide range of FMI values in iRBD (4.0–632.4; median 60.7) as well as in the controls (0.8–938.1; median 34.3). The difference in FM intensity between right and left lower limbs was conspicuously high in iRBD (−545.9 to 386.2; median −10.3) as well as in controls (−929.5 to 277.3; median 0.6).

The overall difference in FMI values in both limbs was not significant between the two groups; however, differences in FMI for separate sleep stages were found. Patients with iRBD showed trends for higher FMI scores in wakefulness, N1, N3 and R. No other differences were found between patients with iRBD and controls in the quantitative analysis. Detailed results are presented in Table 3.

3.4 | Association of fragmentary myoclonus with other parameters

No correlations of FMI with age, iRBD duration, MDS-UPDRS scores, SCOPA-AUT scores, BDI-II, STAI X1 and STAI X2 scores, ESS scores and ISI, arousal index, sleep efficiency, AHI or PLMI were found. Correlations of FMI with the SINBAR index, phasic, tonic and "any" EMG activity separately were performed with insignificant results. Because the difference of FM intensity between the limbs was distinctively high, we correlated it with EHI scores but with insignificant results. FMI values were not related to the use of antidepressants or anxiolytics (Tables S3 and S4). Because FM occurs in lower limb EMG channels, we were interested in its association with specific autonomic functions coming predominantly from the lower spinal cord autonomic nervous system, thus we correlated FMI and particular SCOPA-AUT items focused on constipation and sexual dysfunction separately, and the results were insignificant.

The correlations between DAT-SPECT mean putaminal binding index from both hemispheres and FMI as well as the correlation between putaminal binding indexes from each hemisphere and FMI from the corresponding side of the body were not significant.

4 | DISCUSSION

The present study renders the results of the qualitative and quantitative analysis of FM in patients with iRBD.

According to a previous study, the prevalence of EFM in healthy subjects aged 19–77 years is 9% (Frauscher et al., 2014). The prevalence of EFM in controls aged 50–86 years in our study was 34.5%, which confirms the previous report that FM tends to intensify with age (Frauscher et al., 2011). However, in quantitative analysis the correlation of FMI and age was not significant, in contrast to the results of the Innsbruck group.

In our cohort, 75.9% of iRBD had EFM, which is a significantly higher prevalence compared with the age-matched controls (34.5%);

however, a quantitative analysis searching for the connection of FM intensity with R atonia deficiency was not significant. Although our results are not entirely unequivocal, the difference of the EFM prevalence between the iRBD and control groups is so distinct that FM should be taken in account in future research of RBD and motor control in sleep.

The aetiology of FM remains unclear. The exact origin of the FM potentials is unknown, and the results of the existing studies are quite inconsistent so far (Nepozitek & Sonka, 2017). The remark that the appearance of the FM potentials resembles fasciculations (Frauscher et al., 2014; Montagna et al., 1988; Raccagni et al., 2016; Sonka et al., 2004) points to the possibility that the generator of FM could be located at the level of the spinal cord or peripheral nerves, and Raccagni et al. presented 50% prevalence of electrophysiological abnormalities corresponding to polyneuropathy, root lesions and benign fasciculations in a group of patients with EFM (Raccagni et al., 2016). Other studies suggest that supraspinal structures could be involved as the site of origin (Frauscher et al., 2011; Merlino & Gigli, 2012; Sobreira-Neto et al., 2015; Vetrugno et al., 2002). This hypothesis is supported by the work of Gassel et al., who showed the effect of deafferentation on myoclonic twitches in cats (Gassel, Marchiafava, & Pompeiano,1964), and in addition by reports of the occurrence of EFM in neurodegenerative diseases associated with the lesions of the brainstem structures, including synucleinopathies such as PD and multiple system atrophy (Pincherle et al., 2006; dos Santos et al., 2014; Sobreira-Neto et al., 2015; Vankova et al., 2003; Vetrugno et al., 2007). Our observations of EFM in iRBD support this hypothesis, because alpha-synuclein abnormalities in the brainstem are assumed to disinhibit the motor activity in iRBD (Braak, Ghebremedhin, Rub, Bratzke, & Del Tredici, 2004).

Aggregation of alpha-synuclein in iRBD is considered to start in autonomic nerve terminals, and subsequently spread via autonomic nerves to the spinal cord and brainstem (Borghammer, 2018; Uchihara & Giasson, 2016). Most patients with PD exhibit alpha-synuclein pathology in the dorsal motor nucleus of the vagus post mortem, which testifies to the idea that the spread goes via the vagus, while the spinal cord is spared. Only in a minority of patients are the locus coeruleus and raphe nuclei affected, and these observations are explained by the idea of sympathetic system involvement through the preganglionic sympathetic neurons of the intermediolateral cell column spreading, which would bypass the vagus path (Borghammer, 2018). Based on the knowledge that alpha-synuclein spread mostly via the vagus path leaving the spinal cord intact, and the intermediolateral cell column path does not explain the damage of the anterior spinal cord horns, we incline to the hypothesis that the brainstem is more likely than the spinal cord to contain the generator of FM.

In accordance with the concept of autonomic system spread, we tested the association of FMI with autonomic functions via SCOPA-AUT scores, with negative results. Because FM occurs in lower limb EMG channels, we also tested autonomic dysfunction coming predominantly from the lower spinal cord autonomic nervous system via processing the items of the SCOPA-AUT focused on constipation and sexual dysfunction scores separately, and no association was found with the intensity of FM in accordance with our hypotheses.

In the case of presumed brainstem origin of EFM, abnormalities in brainstem MRI and DAT-SPECT could be expected. However, morphological brain MRI was normal in all subjects, and there were no associations between FMI and DAT-SPECT results. Lack of association between EFM and substantia nigra degeneration does not necessarily rule out the existence of the relationship between EFM and brainstem; EFM pathogenesis may be related to degeneration of other brainstem regions located caudally to the substantia nigra. Future quantitative MRI studies based on, for example, diffusion weighted imaging may elucidate this relationship.

In iRBD with EFM, lower N2 sleep stage percentage and higher R stage percentage trends were found. These sleep differences were not present in the control group. One reason could be R stage control and R stage atonia control abnormalities, which cause facilitation of R stage together with increase of FM intensity. The other reason could be that EFM resembles phasic muscle activity physiologically present in R, which falsely indicated R stage differentiation. There was no association found of FM intensity with PLM or sleep-related breathing disorders, unlike the results of the various Innsbruck patient groups (Frauscher et al., 2011).

Quantitative analysis showed a major dispersion of FMI values and a high difference in FM intensity between the limbs in both participant groups. The difference in FM intensity between the lower limbs had not been assessed in earlier studies. We find it difficult to find an explanation for such a difference in the context of current knowledge. Correlations of the differences with EHI scores were not found.

The intensity of FM was highest in R, followed by relaxed wakefulness, N2 and N1, and was lowest in N3. The same distribution was detected in the controls. The fact that changes in the FM intensity are dependent on the sleep stage supports the concept that the generator of FM is influenced by sleep (Frauscher et al., 2011). Higher FMI scores were found in all sleep stages with suggestive results in wakefulness, N1, N3 and R in iRBD compared with the controls.

Because little is known about changes in EMG activity in NREM sleep in iRBD, EFM, which persists with high intensity in NREM sleep stages, could be a form of motor control impairment similar to phasic atonia deficiency as we see in R. We suppose that the research of FM could help to understand the general modification of motor control in sleep in RBD.

The limitations of this study are the small number of subjects and the high mean AHI scores in both participant groups. Antidepressant and anxiolytic intake by a minority of patients with iRBD must also be considered a limitation, but no association of this medication use with FMI intensity was found in our subjects.

It needs to be noted that there is an overlap in the current definition of EMG potentials of FM (0–150 ms) and phasic R stage-related muscle activity as the result of insufficient atonia in R (100–5,000 ms). Consequently, the values of FMI in R could be overrated. On the

other hand, qualitative analysis of EFM was performed only in NREM sleep stages according to the criteria. Also FMIs in R did not correlate with SINBAR indexes in either group.

The present research has brought up the remark that EFM occurs in iRBD with high prevalence, presumably along with the lesion of the brainstem, thereby mildly supporting the notion that the predominant generator of EFM is located in this site of the central nervous system.

5 | CONCLUSIONS

The main outcome of this study is that we found a higher occurrence of EFM in patients with iRBD (75.9%) compared with the controls (34.5%). This finding points out that FM should be taken into account in future research of RBD and motor control in sleep.

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CONFLICT OF INTERESTS

Jiri Nepozitek, Simona Dostalova, David Kemlink, Latica Friedrich, Iva Prihodova, Veronika Ibarburu Lorenzo y Losada, Petr Dusek, Ondrej Bezdicek, Tomas Nikolai, Pavla Perinova, Irene Dall'Antonia, Pavel Dusek, Martin Ruml, Evzen Ruzicka and Karel Sonka have no conflict of interest to disclose.

ORCID

Jiri Nepozitek https://orcid.org/0000-0002-3339-5286

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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ORIGINAL ARTICLE

Simultaneous tonic and phasic REM sleep without atonia best predicts early phenoconversion to neurodegenerative disease in idiopathic REM sleep behavior disorder

Jiri Nepozitek[1,*], Simona Dostalova[1], Petr Dusek[1], David Kemlink[1], Iva Prihodova[1], Veronika Ibarburu Lorenzo y Losada[1], Latica Friedrich[1,2], Ondrej Bezdicek[1], Tomas Nikolai[1], Pavla Perinova[1], Irene Dall'Antonia[1], Pavel Dusek[1], Martin Ruml[1], Evzen Ruzicka[1] and Karel Sonka[1]

[1]Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic and [2]University Department of Neurology, Sveti Duh University Hospital, Zagreb, Croatia

*Corresponding author. Jiri Nepozitek, Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University and General University Hospital in Prague, Katerinska 30, Prague, 120 00, Czech Republic. Email: jiri.nepozitek@vfn.cz.

Abstract

Study Objectives: Rapid eye movement (REM) sleep without atonia (RWA) is the main polysomnographic feature of idiopathic REM sleep behavior disorder (iRBD) and is considered to be a promising biomarker predicting conversion to manifested synucleinopathy. Besides conventionally evaluated tonic, phasic and any RWA, we took into consideration also periods, when phasic and tonic RWA appeared simultaneously and we called this activity "mixed RWA." The study aimed to evaluate different types of RWA, to reveal the most relevant biomarker to the conversion.

Methods: A total of 55 patients with confirmed iRBD were recruited with mean follow-up duration 2.3 ± 0.7 years. Scoring of RWA was based on Sleep Innsbruck Barcelona rules. Positive phenocoversion was ascertained according to standard diagnostic criteria during follow-up. Receiver operator characteristic analysis was applied to evaluate predictive performance of different RWA types.

Results: A total of nine patients (16%) developed neurodegenerative diseases. Yearly phenoconversion rate was 5.5%. Significantly higher amounts of mixed ($p = 0.009$), tonic ($p = 0.020$), and any RWA ($p = 0.049$) were found in converters. Optimal cutoffs differentiating the prediction were 16.4% (sensitivity 88.9; specificity 69.6) for tonic, 4.4% (sensitivity 88.9; specificity 60.9) for mixed, and 36.8% (sensitivity 77.8; specificity 65.2) for any RWA. With area under the curve (AUC) 0.778, mixed RWA has proven to be the best predictive test followed by tonic (AUC 0.749) and any (AUC 0.710).

Conclusions: Mixed, tonic and any RWA may serve as biomarkers predicting the conversion into neurodegenerative disease in iRBD. The best predictive value lies within mixed RWA, thus it should be considered as standard biomarker.

Statement of Significance

Idiopathic rapid eye movement sleep behavior disorder is considered to be prodromal stage of neurodegenerative diseases associated with alpha-synuclein aggregation. Amount of muscle activity in rapid eye movement sleep, when muscle atonia is supposed to occur physiologically, is a promising biomarker predicting early phenoconversion according to current knowledge. Tonic and phasic muscle activity are distinguished conventionally. The present study tests the hypothesis that simultaneous occurrence of tonic and phasic muscle activity, which could reflect more severe alpha-synuclein involvement, predicts the phenoconversion, and answers the question which type of muscle activity has the best predictive value.

Key words: REM sleep behavior disorder; movement disorders; sleep and neurodegenerative disorders; REM sleep; parasomnias

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Introduction

Rapid eye movement sleep behavior disorder (RBD) is a parasomnia, characterized by abnormal behavior during the rapid eye movement (REM) sleep corresponding to the content of the current dream [1, 2]. The idiopathic form of RBD (iRBD) is known to be a manifestation of prodromal neurodegenerative diseases characterized by abnormal alpha-synuclein aggregation and storage such as Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, and pure autonomic failure [3–7]. There is a need for reliable biological markers predicting the risk of early phenoconversion into manifest synucleinopathy.

The loss of physiological atonia in REM sleep represents the main polysomnographic (PSG) feature of RBD, manifesting as excessive muscle activity in the electromyographic (EMG) channels and is referred to as REM sleep without atonia (RWA) [8]. To describe the characteristics of muscle activity in RBD, tonic and phasic type of RWA are conventionally distinguished [9]. In a previous study, it was reported that increased tonic EMG muscle activity in iRBD was associated with early phenoconversion to Parkinson's disease [10] and the observation of tonic RWA as a stable biomarker was confirmed by recent work [11]. Very recently it was further presented that higher amounts of RWA at the baseline evaluated in certain combinations of chin and tibialis anterior EMG channels (chin tonic RWA, tibialis phasic RWA, combination of chin and tibialis phasic, and any RWA) were observed in patients with iRBD, who developed neurodegenerative disorder [12]. Another earlier study shows that excessive tonic and phasic RWA increases over time in subjects with iRBD, but does not comment on the relationship to the conversion [13]. These studies document that the intensity of REM sleep atonia loss and its differentiation may serve as quantifiable biomarker reflecting the severity of neurodegenerative changes in the brainstem [14, 15].

According to current guidelines, when analyzing muscle activity during REM sleep, tonic and phasic activities are classified as if they occurred separately as independent types. The term "any RWA" was introduced to describe every period containing any EMG activity irrespective of whether it contained tonic, phasic, or a combination of both EMG activities [16].

However, in RWA, phasic activity bursts often appear over a background of tonic activity. This is not taken into account by any scoring classification of RWA. We believe that the simultaneous tonic and phasic muscle activity in REM sleep could represent more severe involvement of the brainstem and hence the higher risk of early phenoconversion. To quantify this superimposed EMG activity as a specific entity, we introduced the term "mixed RWA."

In this study, we aimed to quantify different types of RWA including the mixed RWA and to determine whether amounts of these RWA types are predictive of phenoconversion to neurodegenerative disorders in iRBD.

Methods

Study subjects

The patients were recruited by a stepwise media and internet survey [17]. A total of 55 iRBD patients (5 women and 50 men) with a mean age 65.7 ± standard deviation (SD) 9.1 years were included in the study. All patients were diagnosed with iRBD according to the latest version of the International Classification of Sleep Disorders, third edition (ICSD-3). The diagnosis of RBD was based on their history of dream-enacting behaviors and nocturnal video-PSG demonstrating prominent EMG activity during REM sleep [8]. The exclusion criteria were as follows: age under 50 years, clinical signs of overt dementia or parkinsonism, RBD associated with narcolepsy, encephalitis, head injury, or focal brain lesion found on magnetic resonance imaging (MRI) indicative of secondary RBD.

Thirteen of the iRBD patients were using antidepressants, however, the patients who used antidepressants referred the beginning of RBD symptoms before they started using this medication. Otherwise participants were not treated with drugs with a potential to influence sleep structure, peripheral nerve activity, and muscle activity during the study and prior to the study.

The study was approved by the local Ethics Committee and participants signed informed consents before the study in accordance with the Helsinki Declaration.

Clinical examination

All study participants underwent a comprehensive clinical evaluation including medical history, a neurological examination including the Movement Disorders Society-sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS UPDRS), olfactory examination using University of Pennsylvania Smell Identification Test (UPSIT), video-PSG, high-resolution brain MRI (whole brain T2-weighted 0.7 mm^3 isotropic scan, TE/TR = 566/3,200 ms), and neuropsychological examination including Montreal Cognitive Assessment (MoCA) testing at the baseline. The MoCA cutoff for the diagnosis of mild cognitive impairment (MCI) was set according to Czech normative data study as below 1.5 SD from the normative mean [18]. All participants also completed questionnaires to assess the severity of RBD (RBD screening questionnaire—RBD SQ) and autonomic dysfunction (Scales for Outcomes in Parkinson's Disease-Autonomic—SCOPA-AUT).

All patients had in-person follow-up examinations on a yearly basis that included MDS-UPDRS scoring and MoCA. Hereby in 21 patients (38.2%) the follow-up examination was performed three times, in 27 patients (49.1%) twice and in 7 patients (12.7%) once. Mean follow-up duration was 2.3 ± 0.7 years. Positive phenocoversion was recorded upon the presence of parkinsonism, dementia, and/or autonomic failure. Parkinsonism was diagnosed according to the MDS criteria [19], which is presence of bradykinesia in association with resting tremor and/or rigidity. Dementia was diagnosed according to the MDS criteria [20]. For diagnosis of dementia with Lewy bodies, the consensual criteria were used [21]. Diagnosis of multiple system atrophy was made according to the consensus criteria [22] and pure autonomic failure was diagnosed in cases with clinical signs compatible with chronic sympathetic deficiency, without associated parkinsonism, dementia, or cerebellar symptoms [23].

Video-polysomnography

Nocturnal video-PSG was performed using a digital PSG system (RemLogic, version 3.4.1, Embla Systems) and consisted of electrooculography (EOG), electroencephalography (F3-M2, C3-M2, O1-M2, F4-M1, C4-M1, O2-M1), surface EMG of

the bilateral mentalis muscle, the bilateral flexor digitorum superficialis muscle (FDS), and the bilateral tibialis anterior muscle, electrocardiography, nasal pressure, nasal and oral air flow, thoracic and abdominal respiratory effort, oxygen saturation, microphone, and digitally synchronized video monitoring from 10 pm to 6 am according to the American Academy of Sleep Medicine (AASM) recommendation [24].

All features on video-PSG were analyzed visually. Sleep stages, arousals, respiratory events, and limb movements were scored according to AASM Manual for the Scoring of Sleep and Associated Events version 2.2 2015 [24] with an exception for the REM sleep rules allowing to score REM sleep stage despite the prominent EMG activity in the mentalis muscle channel [25]. The beginning and the end of the REM sleep episode were scored according to the Sleep Innsbruck Barcelona (SINBAR) rules [16]: the occurrence of the first rapid eye movements (REMs) in the EOG channel was used to determine the onset of the REM sleep period. The end of the REM sleep period was determined when either no REMs were detected in 3 consecutive minutes or an awakening, K complexes or spindles were observed [16].

The scoring method of RWA was based on the SINBAR montage: REM sleep-related EMG activity was scored in the mentalis muscle and FDS channels. All artifacts and increases in EMG tone due to arousals from respiratory events were excluded from the quantitative scoring before the analysis of EMG activity [16].

For scoring of the EMG activity, each 30-second epoch was divided into ten 3-second miniepochs [26].

Phasic EMG activity was defined as any burst of EMG activity lasting between 0.1 and 5.0 seconds with amplitude exceeding twice the background EMG activity irrespective of its morphology. The end of each phasic EMG burst was defined, by an identifiable return to the baseline or by an interburst interval lasting more than 250 milliseconds.

Tonic EMG activity was defined as a sustained increase in EMG activity exceeding 50% of the total 30-second epoch duration with amplitude of at least twice the background EMG muscle tone or more than 10 μV.

Mixed EMG activity, which is a new concept introduced in this paper, was scored when burst of phasic EMG activity had at least twice the amplitude of the background tonic EMG activity within that same 3-second miniepoch. EMG activity with a duration of 5–15 seconds, which could not be classified as neither tonic or phasic and had a character of sustained elevated baseline EMG activity with superimposed phasic activity exceeding at least twice the baseline activity amplitude, was counted into mixed EMG activity as well.

Each 3-second mini-epoch was scored as having or not having "any" EMG activity, irrespective of containing phasic, tonic, or mixed EMG activity [16].

In order to compare the amounts of different types of RWA, 3-second mini-epochs were used in the mentalis muscle channels for quantification of each type. The amounts of each RWA type were expressed as the percentage of REM sleep.

Overall RWA was quantified according to the SINBAR recommendations: after scoring any EMG activity in the mentalis muscle channels using 3-second mini-epochs, we scored the phasic EMG activity in the FDS channels also in 3-second mini-epochs not having any EMG activity already scored in the mentalis muscle channels [16]. Thus, we obtained a SINBAR score expressing the percentage of REM sleep referring to the amount of REM sleep-related EMG activity.

With regard to the rules for scoring phasic EMG activity in REM sleep, periodic limb movements during REM sleep were identified only when having a periodic pattern [16].

Motor behaviors and/or vocalizations in REM sleep with a complex purposeful component other than comfort moves were identified as REM sleep behavioral events (RBE). Two or more events had to be present to be classified as RBE positive [27].

Statistical analysis

Statistical analyses were performed using the STATISTICA 13 software package (Dell Inc. 2016 software.dell.com). To assess the normality of demographic, clinical, and polysomnographic variables, a Shapiro–Wilks test was performed. Except for age all the other data showed a nonparametric nature. For the comparison of the between-group differences in qualitative data, Fischer's exact two-tailed test was used. Mann–Whitney *U* test was applied to evaluate between-group differences in quantitative data. Spearman Rank Correlation Coefficient (rho) was calculated to evaluate correlations between variables. We used a cutoff value of rho > 0.4 and/or $p < 0.001$ for significant signal in the exploratory phase. The Bonferroni correction for multiple comparisons was applied to correct family-wise error (FWE) and the postcorrection cutoff for statistical significance was set at $p < 0.05$ for quantitative data. Receiver operator characteristic (ROC) analysis was performed for tonic, mixed and any RWA. For each RWA type, ROC curve was plotted and optimal cutoff points with resulting sensitivity and specificity values were obtained. The area under the curve (AUC) was calculated.

Results

Baseline clinical and PSG results of all subjects as well as the comparison between converter and nonconverter groups are displayed in Table 1.

Yearly phenoconversion rate in our cohort was 5.45%. In 2.3 ± 0.7 years of follow-up examinations, nine patients (16.3%) developed neurodegenerative phenotype; six patients developed Parkinson's disease, two patients developed probable Lewy body disease, and one patient developed pure autonomic failure.

Comparing converted and nonconverted iRBD patients, significantly higher MDS UPDRS III and significantly lower UPSIT scores were found among converters. Any, tonic and mixed RWA was significantly higher in converters than in nonconverters while difference in phasic RWA was not significant.

The contribution of mixed to other RWA types needed to be investigated. In order to obtain that, the amounts of any, phasic, and tonic RWA were evaluated separately with subtracted mixed RWA. The differences between converters and nonconverters in either RWA type after the subtraction of mixed RWA turned out to be insignificant.

The optimal cutoff points with resulting sensitivities/specificities for differentiation of converters and nonconverters were 16.4% (sensitivity = 88.9; specificity = 69.6) for tonic RWA, 4.4% (sensitivity = 88.9; specificity = 60.9) for mixed RWA, and 36.8% (sensitivity = 77.8; specificity = 65.2) for any RWA (Figure 2). Results of the ROC analysis are presented in Table 2. Mixed RWA had the highest AUC value (0.778), followed by tonic (0.749) and any (0.710) RWA.

Table 1. Clinical-polysomnographic profiles of all subjects, converted and nonconverted iRBD patients and their comparison

	All iRBD patients (*N* = 55)		Nonconverters (*N* = 46)		Converters (*N* = 9)		
	Mean	*SD*	Mean	*SD*	Mean	*SD*	*P* value
Age	65.7	9.1	65.0	9.5	68.9	6.5	0.152
RBD SQ	10.2	2.1	10.2	2.2	10.2	1.5	0.936
MDS UPDRS III	6.0	5.5	5.4	5.4	8.7	6.2	**0.040**
UPSIT	24.4	8.8	26.1	8.5	16.0	3.3	**0.008**
SCOPA-AUT	12.3	7.0	12.3	6.6	12.4	8.8	0.865
MoCA	24.0	2.9	24.0	3.0	24.3	2.6	0.749
iRBD duration (years)	9.9	9.3	10.0	9.9	9.2	6.2	0.963
Observation (years)	2.25	0.67	2.26	0.67	2.22	0.63	0.877
AHI	10.2	12.6	11.3	13.5	4.4	3.1	0.649
ODI	11.2	14.7	12.5	15.8	4.4	3.9	0.406
PLMI	32.4	37.4	29.4	35.0	48.0	49.3	0.269
REM sleep (minutes)	68.1	26.8	69.8	27.5	59.4	24.3	0.275
Excluded amount of REM sleep (%)	1.7	3.3	1.8	3.6	0.8	1.6	0.622
SINBAR score (%)	45.2	23.1	42.7	23.0	58.3	20.7	0.073
Any RWA (%)	36.3	23.5	33.6	22.5	50.1	23.5	**0.049**
Phasic RWA (%)	23.5	13.0	22.5	11.8	28.8	17.0	0.638
Tonic RWA (%)	19.2	20.5	16.6	19.1	32.8	22.2	**0.020**
Mixed RWA (%)	8.4	11.6	7.0	10.4	15.3	15.8	**0.009**
Any without mixed RWA (%)	27.9	15.4	26.5	15.4	34.9	13.0	0.549
Phasic without mixed RWA (%)	15.1	8.0	15.4	7.9	13.5	8.4	0.960
Tonic without mixed RWA (%)	10.9	11.6	9.6	11.6	17.6	8.8	0.368
Arousals (number)	73.0	49.1	75.9	51.9	58.1	33.3	0.345
Arousal index	13.1	8.1	13.4	8.5	11.4	6.5	0.569

Data presented as mean and *SD*. All between-group comparisons except age were performed using the Mann–Whitney *U* test. Comparison of age and observation time was performed using Student *t*-test. The Bonferroni correction for 13 comparisons was applied. iRBD duration expresses the time from the subjective beginning of first signs of RBD to the time of disease conversion or the last clinical re-examination.
AHI, apnea-hypopnea index; *N*, number; ODI, oxygen desaturation index; PLMI, periodic limb movement index. Bold for trends.

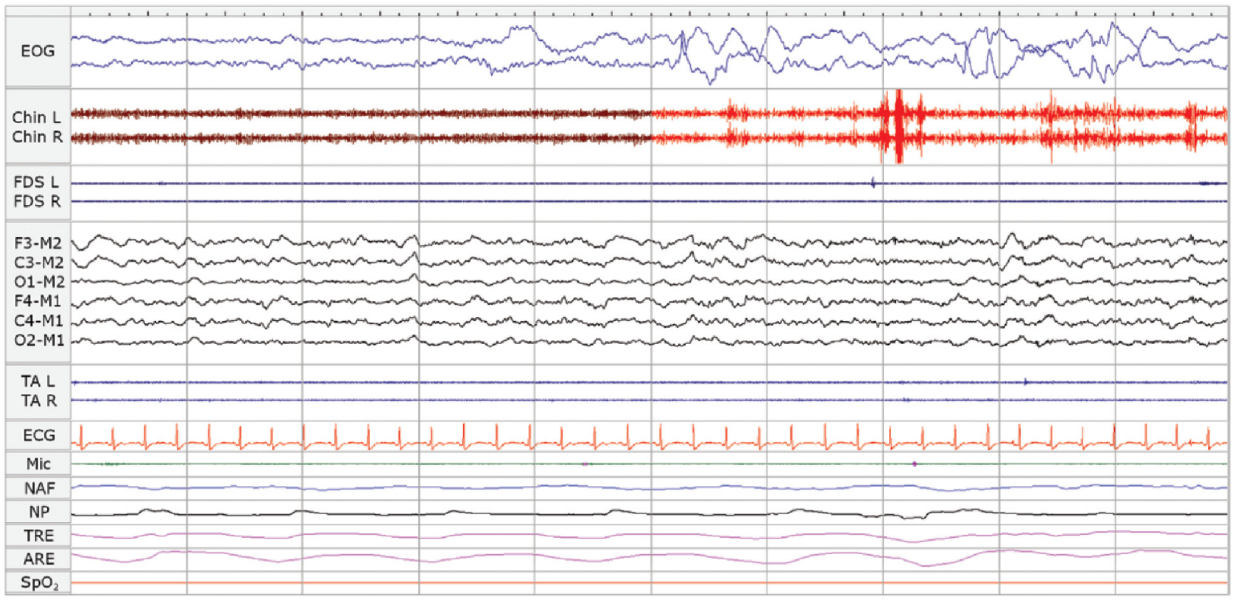

Figure 1. Example of simultaneous tonic and phasic muscle activity during REM sleep referred as "mixed RWA". First five 3-second miniepochs of displayed 30-second epoch of REM sleep show tonic activity, from 6th to 10th miniepoch (highlighted in bright red) bursts of phasic activity occur over a background of persisting tonic activity, thus representing "mixed RWA". ARE, abdominal respiratory effort; Chin L, left mentalis muscle electromyography; Chin R, right mentalis muscle electromyography; ECG, electrocardiography; FDS L, left flexor digitorum superficialis muscle electromyography; FDS R, right flexor digitorum superficialis muscle electromyography; F3-M2, C3-M2, O1-M2, F4-M1, C4-M1, O2-M1, referenced electroencephalography channels; Mic, microphone; NAF, nasal air flow; NP, nasal pressure; SpO_2, oxygen saturation; TA L, left tibialis anterior muscle electromyography; TA R, right tibialis anterior muscle electromyography; TRE, thoracic respiratory effort.

MCI was detected in 11 patients (20% of the whole group), 2 in the converted group and 7 in the nonconverted group. Results of the qualitative analysis evaluating the presence of MCI in relation to conversion were nonsignificant.

RBE were captured in 38 patients (69%), 6 in the converted and 32 in the nonconverted group. The comparative analysis in qualitative data showed no association of RBE with conversion.

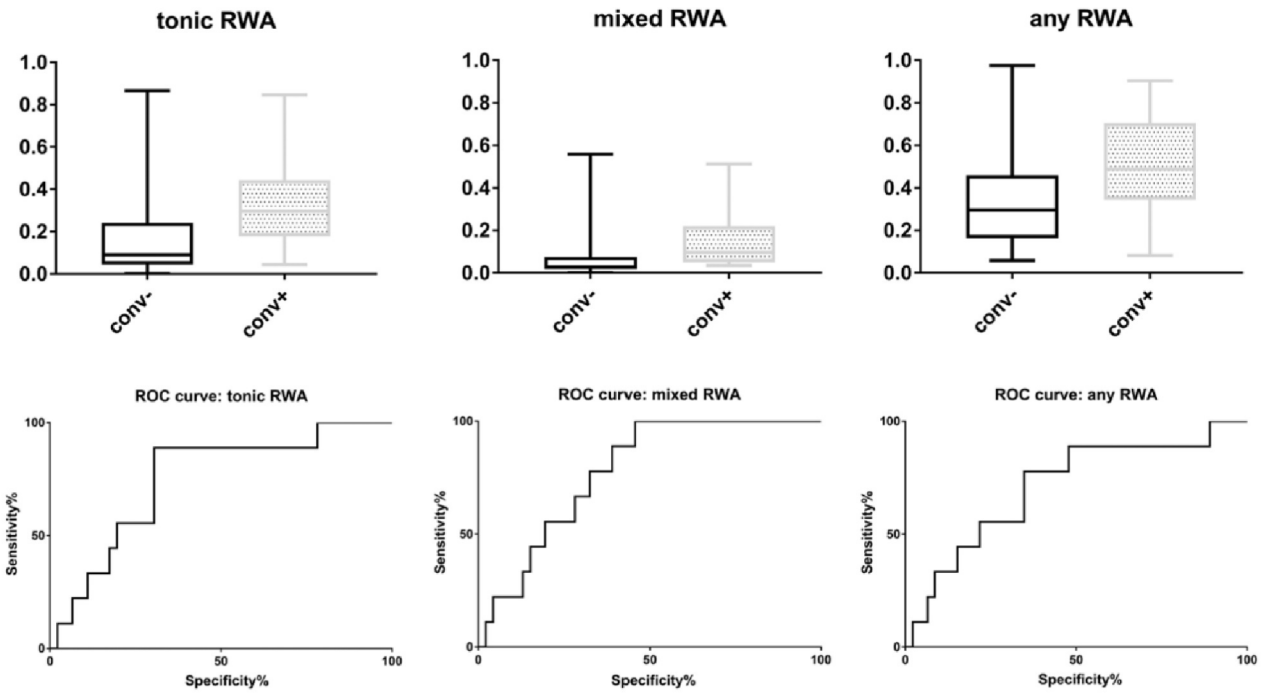

Figure 2. Boxplot representation of the amounts of different types of RWA (tonic, mixed, any) in nonconverted and converted iRBD patients, and corresponding receiver operating characteristic curves. conv-, nonconverters; conv+, converters.

Table 2. Receiver operator characteristic analysis results of tonic, mixed, and any RWA

	AUC	95% CI	*P* value	RR	95% CI	*P* value
Tonic RWA	0.749	0.585 to 0.912	0.019	12.0	2.1 to 71.4	0.001
Mixed RWA	0.778	0.648 to 0.908	0.009	8.9	1.6 to 53.3	0.006
Any RWA	0.710	0.524 to 0.896	0.048	4.9	1.3 to 19.5	0.017

CI, confidence interval; RR, relative risk.

The comparative analysis showed that use of antidepressants was not associated with an increase of either type of muscle activity in REM sleep (Supplementary Table S1). None of the iRBD patients on antidepressants converted to the neurodegeneration, however, results of the analysis comparing use of antidepressants in the converted and nonconverted group did not reach statistical significance (Supplementary Table S2).

Correlation analysis showed no significant associations of either RWA type with RBD SQ, MDS UPDRS III, SCOPA-AUT, MoCA, UPSIT scores, subjectively perceived RBD duration, sleep respiration parameters, periodic limb movement index, and arousals.

Discussion

This observational study presents the new concept of mixed RWA referring to simultaneous appearance of phasic and tonic EMG activity.

The results show that tonic, mixed, and any RWA are useful predictive factors of phenoconversion in iRBD patients. No difference of phasic RWA was observed between the converted and nonconverted patients. The observation of tonic but not phasic EMG muscle activity in iRBD associated with early phenoconversion is in accordance with previous reports [10, 11].

It has been suggested that phasic and tonic muscle activity during REM sleep in RBD have different underlying neural mechanisms [10]. Phasic activity was reported to be generated by cortical and spinal motor neurons [28] and depends upon alteration of pathways in the ventromedial medulla (VMM) [10, 29, 30]. Tonic activity is considered to be caused by degeneration of sublaterodorsal (SLD) nucleus (or analogous subcoeruleus nucleus in humans) [10, 29, 31]. It has been determined that REM-active neurons of SLD are generally important for generation of REM sleep atonia by projection to inhibitory premotor neurons both in the spinal cord and the VMM [32]. According to this concept, the sole degeneration of SLD would fittingly explain the concurrent occurrence of phasic and tonic activity, represented by mixed RWA. Indeed, it is reasonable to expect the pathophysiological substrate of mixed RWA to be more complex. The global degeneration of SLD itself would hardly leave a margin for explanation of isolated tonic RWA. Instead, different subpopulations of neurons within SLD could be involved, so mixed EMG activity would be the expression of overlap involvement of several functional subsections of the nucleus. It has been further hypothesized that difference between separate types of motor activity may be more quantitative than qualitative, depending on the excitatory drive breaking through the inhibitory modulation as a continuum [32]. Mixed EMG activity can also be the expression of overlap neurodegeneration involving multiple brainstem areas and control of REM sleep atonia on multiple different levels [30]. Under this assumption, mixed RWA would be giving a nice picture about the severity of the disease and presumably about its future progression.

Performing ROC analysis for comparison of tonic, mixed, and any RWA, the "mixed RWA" parameter appears to be strong predictive marker with slightly higher AUC compared to those observed in tonic and any RWA. Results in any RWA appeared to be

influenced by the inclusion of phasic activity, which seemed to decrease the statistical significance of the "any RWA" parameter. The results of our study support previous findings showing that simple phasic muscle activity in REM sleep is nonspecific factor with regard to the conversion [10, 11].

In order to reveal the counterpart of the mixed RWA, we have evaluated any, phasic and tonic RWA with subtracted mixed RWA separately. The differences between converters and nonconverters in either RWA type were insignificant after the subtraction. These results suggest that the predictive value of EMG activity lies precisely within the mixed RWA. In other words, mixed RWA is the phenomenon that is worth evaluating in order to estimate the risk of upcoming conversion.

The phenoconversion rate of 16% observed in the present study is in accordance with previous studies which yielded approximately 15–35% of patients converting to overt neurodegeneration over 2–5 years [33, 34].

Interestingly, the results show no differences in SINBAR score between convertors and nonconvertors. SINBAR score comprise mentalis muscle tone together with FDS tone, which suggests that FDS activity may serve as parameter useful just to improve diagnostic sensitivity, but not as biomarker of short-term conversion.

One of the earlier studies shows that tonic and phasic RWA increases over time in subjects with iRBD [13]. The prediction value of mixed RWA with regard to the conversion would also empirically suggest that the amount of muscle activity increases over time, and thus, it can be a marker of iRBD progression as well. However, such implication cannot be inferred from the present results, since only cross-sectional data are available. On the other hand, the study mentioned above does not comment on the relationship of tonic and phasic RWA amounts to the conversion. Further research with a repeated follow-up polysomnographic examinations need to be performed in order to confirm the hypothesis that mixed RWA is also a marker of progression of the synucleinopathy.

The scores of RBD SQ did not show any difference between the converters and nonconverters or correlation with quantitative RWA measures, suggesting that RBD SQ is less likely to be used as a surrogate marker for RBD severity or early phenoconversion risk.

Higher MDS UPDRS III scores found in early converters supports previous observations that clinical examination is sensitive to capture discrete motor manifestations present in prodromal stage of synucleinopathies [14, 35].

The results of UPSIT scores confirm the findings from previous studies that olfactory deficit predict the phenoconversion to neurodegenerative disease [35–37].

As to autonomic dysfunction and cognitive decline, no relationship to the conversion was found in the present study, although it is reported by earlier studies [35, 38]. One of the reasons could be a relatively short time of follow-up.

In earlier study on RBE in early Parkinson's disease, it was shown that presence of RBE is a marker of neurodegeneration and it was hypothesized that it may precede iRBD [27]. In line with this idea, it would be expected that presence of RBE at the baseline involves subjects showing later early conversion. Surprisingly, qualitative analysis of RBE showed no association with the conversion. Shorter follow-up and potential bias due to the use of the cover might influence the present result. Further studies need to be performed in order to confirm the previous observation.

The major limitation of the present study is low number of converters despite the study has replicated the results of previous studies on the relationship of specific RWA types and phenoconversion [10, 11]. Rather broad variability of RWA parameters reflect this limitation. The evaluation of mixed RWA and validation of the present results in larger cohorts is needed. The inclusion of subjects with only 1 year follow-up is another limitation that should be mentioned, as RWA measures of these patients might have biased the results and they could be less prone to convert due to a shorter the follow-up time. To confirm that RWA scores at baseline did not differ between subjects with longer vs. shorter follow-up, subanalysis was performed (Supplementary Table S3). Antidepressant use by a minority of patients must also be considered a limitation. Despite antidepressants are reported to cause increase of muscle activity in REM sleep [39, 40], the medication showed not to be associated with an increase of muscle activity in REM sleep in the current cohort.

Conclusions

The severity of mixed, tonic, and any type of RWA at the baseline in iRBD predict the phenoconversion to fully manifested synucleinopathy. Mixed RWA, as the new concept representing simultaneous occurrence of phasic and tonic EMG activity appears to be the best predictive RWA parameter and thus consideration should be given to its use as a standard indicator of impending phenoconversion.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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Conflict of interest statement. None declared.

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Titulní strana

Název článku:

Profil behaviorálních projevů u idiopatické poruchy chování v REM spánku.

Autoři:

Jiří Nepožitek[1], Canan Ünalp[1,2], Simona Dostálová[1], Iva Příhodová[1], Veronika Ibarburu Lorenzo y Losada[1], Petr Dušek[1], Karel Šonka[1]

Pracoviště:

1) Neurologická klinika a Centrum klinických neurověd, 1. lékařská fakulta, Univerzita Karlova a Všeobecná fakultní nemocnice v Praze

2) Ankara University Faculty of Medicine, Turkey

Korespondující autor: Jiří Nepožitek

Poděkování:

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Souhrn

Abnormálně zvýšená motorická aktivita v REM spánku je hlavním polysomnografickým znakem idiopatické poruchy chování v REM spánku. Podmínkou stanovení této diagnózy je komplexní charakter pohybů, avšak na videozáznamu během polysomnografie lze pozorovat i diskrétnější motorické projevy. Cílem práce bylo provést systematickou videoanalýzu pohybů v REM spánku.

Motorické projevy identifikované na videozáznamu při polysomnografii u 32 pacientů ve věku 67,4±7,3 let byly klasifikovány podle klinické tíže do čtyř kategorií (elementární, excesivní, scénické a násilné). U každé motorické události byla dále určena topografická distribuce, rozlišen briskní a pomalý charakter pohybu, zaznamenána asociace s vokalizací, následným probuzením do bdělosti a s emočním nábojem.

Bylo identifikováno průměrně 114,6±85,1 motorických jevů. Z těchto 67,8% bylo klasifikováno jako elementárních, 9,1% jako excesivních, 22,3% jako scénických a 0,7% jako násilných. Přitom násilné projevy se vyskytly u 31,3% pacientů. Briskní pohyby byly častější než pomalé (p=0,001). Vokalizace se vyskytla u 34,4% pacientů. Pohyb způsobil probuzení u 9,4% pacientů a u 21,9% pacientů byl alespoň jednou spojen se zřetelnou emocí.

Tato studie ukazuje velké množství motorických jevů v REM spánku s velkou variabilitou. Elementární projevy představují naprostou většinu. Násilné projevy jsou sice zastoupeny poměrně minoritně, ale byly zachyceny u 31% pacientů.

Klíčová slova: Porucha chování v REM spánku, motorická aktivita, REM spánek

Abstract

Abnormally prominent motor activity in REM sleep is a major polysomnographic feature of idiopathic REM sleep behavior disorder. The diagnosis is based on the complex nature of the movements, but more discreet motor manifestations can be seen in the video recording during polysomnography. The aim of this work was to perform a systematic video analysis of REM sleep movements.

The motor manifestations identified in the video recording of polysomnography in 32 patients aged 67.4 ± 7.3 years were classified into four categories according to clinical severity (elementary, excessive, scenic and violent). In addition, topographic distribution, brief and slow character of movement, association with vocalization, subsequent wakefulness and emotional subtext were determined for each motor event.

An average of 114.6 ± 85.1 motor phenomena were identified. Of these, 67.8% were classified as elementary, 9.1% as excessive, 22.3% as scenic, and 0.7% as violent. However, 31.3% of patients experienced violent manifestations. Brief movements were more frequent than slow ($p = 0.001$). Vocalization occurred in 34.4% of patients. Movement caused wakefulness in 9.4% of patients and in 21.9% was at least once associated with distinct emotion.

This study shows a large number of motor phenomena in REM sleep with extensive variability. Elementary events represent the vast majority. Although violent manifestations are captured in relative minority, they were detected in 31% of patients.

Key words: REM sleep behavior disorder, motor activity, REM sleep

Vlastní text

Úvod

Porucha chování v REM spánku (rapid eye movement sleep behavior disorder – RBD) je parasomnie, charakterizovaná abnormálními motorickými projevy během REM fáze spánku, které odpovídají obsahu právě probíhajícího snu [1, 2]. Onemocnění je většinou způsobeno postižením kmenových struktur, které za fyziologického stavu zajišťují svalovou atonii v REM spánku. K tomu u člověka nejčastěji dochází v rámci neurodegenerativních onemocnění s hromaděním alfa-synukleinu jako je Parkinsonova nemoc, nemoc s Lewyho tělísky a multisystémová atrofie [3]. RBD o mnoho let předchází rozvoji klasických příznaků těchto nemocí [4] a do jejich eventuálního propuknutí se nazývá idiopatická RBD (iRBD) [2].

Diagnostika RBD je založena na anamnéze behaviorálních projevů ve spánku, tj. komplexních pohybů a/nebo vokalizací, a na průkazu poruchy svalové atonie v REM spánku při video-polysomnografii (PSG). Behaviorální projevy, které považujeme za komplexní, mohou mít velmi pestrý obraz: gestikulace napodobující běžné denní činnosti, šátravé a úchopové pohyby, máchání horními končetinami, výpady, údery, výkopy, ale i posazování či vrhání se z lůžka [5]. Pohyby ve spánku znamenají pro pacienty i jejich partnery sdílející lůžko riziko zranění [5, 6], které představuje další významný klinický dopad.

Přestože podmínkou stanovení diagnózy RBD je komplexní charakter pohybů, lze na videozáznamu během video-PSG pozorovat i další motorické projevy v průběhu REM spánku, které nemají komplexní charakter. Dosud nebyla stanovena jednotná klasifikace behaviorálních projevů, ale řada autorů již použila jimi vytvořená rozdělení zohledňující polysomnografické či anamnestické parametry pohybů ve spánku [5, 7-10]. S ohledem na klinickou závažnost u pacientů s potvrzenou iRBD jsme vytvořili 4-stupňovou

klasifikaci motorických projevů dle videozáznamu. Jednotlivé kategorie byly optimalizovány pro klinické hodnocení.

Cílem práce bylo zmapovat výskyt motorických projevů v rámci jednotlivých kategorií klasifikace u skupiny pacientů s iRBD.

Metodika

Studijní soubor

Pacienti byli zváni do studie prostřednictvím médií a internetu. Celkem bylo zařazeno do studie 32 pacientů (čtyři ženy a 28 mužů) s polysomnograficky prokázanou iRBD. Průměrný věk subjektů činil 67,4 ± (směrodatná odchylka) 7,3 let. Diagnóza iRBD byla stanovena podle doporučení poslední verze Mezinárodní klasifikace spánkových poruch (International Classification of Sleep Disorders, third edition – ICSD-3) [2]. Vylučovací kritéria byla následující: věk pod 50 let, přítomné klinické známky počínající demence nebo parkinsonského syndromu, RBD asociované s narkolepsií, encefalitidou, kraniotraumatem či strukturální lézí mozku zjištěné magnetickou rezonancí, která by naznačovala sekundární původ RBD.

Studie byla schválena lokální etickou komisí a účastníci podepsali informovaný souhlas před začátkem vyšetření.

Hodnocení PSG

Pacienti podstoupili noční video-PSG za použití digitálního polysomnografického systému (RemLogic, version 3.4.1, Embla Systems), sestávajícího z elektrookulografie (EOG), EEG (F3-M2, C3-M2, O1-M2, F4-M1, C4-M1, O2-M1), oboustranného povrchového EMG musculus mentalis, musculus flexor digitorum superficialis a musculus tibialis anterior, elektrokardiografie (EKG), záznamu z nosního tlakového a proudového čidla, hrudního a břišního dechového úsilí, saturace hemoglobinu kyslíkem, mikrofonu a digitálně synchronizovaného videozáznamu od 22:00 do 6:00 hodin podle doporučení Americké akademie spánkové medicíny (American Academy of Sleep Medicine – AASM) [11]. Polysomnografický záznam byl hodnocen vizuálně. Spánková

stadia, respirační události a pohyby končetinami byly hodnoceny podle Manuálu AASM (Manual for the Scoring of Sleep and Associated Events, verze 2.2 2015) [11] s výjimkou kritérií pro hodnocení REM spánku, kdy jako REM spánek byly skórovány i epochy obsahující prominentní EMG aktivitu musculus mentalis, pokud epocha jinak splňovala kritéria REM spánku.

Hodnocení motorických jevů

Klasifikace motorických projevů byla založena na rozdělení podle Frauscherové et al. [7] a upravena s ohledem na klinickou závažnost a diagnostickou použitelnost s vybranými prvky z rozdělení referovaných v dalších studiích [5, 8-10]. Motorické jevy byly hodnoceny podle videozáznamu při noční video-PSG v REM spánku. Následující čtyři kategorie určily klinickou závažnost pohybu: 1) elementární, 2) excesivní, 3) scénické a 4) násilné. Klasifikace motorických projevů RBD je podrobně prezentována v tabulce 1. Zvlášť byly kvantifikovány pohyby vázané na probouzecí reakci (přetočení, škrábání, protažení), respirační události a periodické pohyby končetinami. Byla kvantifikována četnost motorických jevů i trvání každého z nich. Nový motorický jev byl započítán, pokud se vyskytl nejméně po 10 sekundách od předchozího. V případě, že byl interval menší, byla událost brána jako součást jednoho motorického projevu. Frekvence jevů byla získána vztažením jejich četnosti k době trvání REM spánku.

Ke každému motorickému projevu RBD byla přiřazena lokalizace těla: obličej/mimické svaly, hlava, pravá horní končetina, levá horní končetina, pravá dolní končetina, levá dolní končetina. Vzhledem ke klinické zkušenosti, že behaviorální projevy RBD mají prudký či trhaný charakter, což má význam na klinickou závažnost s ohledem na riziko poranění pacienta či partnera, byl rozlišen briskní a pomalý charakter pohybu. Byla zaznamenána asociace s vokalizací, následným probuzením do minimálně jedné celé

30-sekundové epochy bdělosti, a s emočním nábojem. Zvlášť byl diferencován pozitivní (úsměv v obličeji, smích) a negativní (smutný či vyděšený výraz v obličeji, křik, pláč, agrese) emoční náboj, pokud toto bylo možné hodnotit.

Statistická analýza

Četnost motorických jevů je vyjádřena v procentech a směrodatnou odchylkou. Normalita dat byla ověřována Shapiro-Wilksovým testem, který ukázal nenormální rozdělení. Srovnávací analýza kvantitativních dat byla tedy provedena za použití Mann-Whitneyho U testu. Pro výpočet korelací byl použit Spearmanův korelační koeficient. Z důvodu omezení rizika chyby 1. druhu při paralelním testování více hypotéz byla použita Bonferroniho korekce při stanovené základní hladině významnosti 5%.

Výsledky

V celém souboru byla v REM spánku videem zaznamenána a kategorizována 4141 motorická událost (průměrně 114,6±85,1 na jednoho nemocného). Ve 173 případech se tyto vyskytly v souvislosti s probouzecí reakcí a ve 12 v souvislosti s respirační událostí. Celkem 3965 motorických projevů RBD, které nebyly jinak z PSG etiologicky vysvětleny a určeny, jsme rozdělili dle klinické tíže do 4 kategorií (tabulka 1) v celkovém počtu takto: elementární 2681 (67,8%), excesivní 361 (9,1%), scénické 886 (22,3%) a násilné 28 (0,7%). Násilné projevy se vyskytly u 10 pacientů (31,3%).

Briskní pohyby v celkovém počtu 2131 (53,7%) byly téměř dvakrát častější, než pomalé, jejichž součet činil 1120 (28,2%) ($p=0,001$).

Rozdíl v motorické aktivitě mezi pravou a levou horní končetinou nebyl statisticky signifikantní ($p=0,522$), stejně tak mezi pravou a levou dolní končetinou ($p=0,589$). Na horních končetinách byla pozorována vyšší motorická aktivita než na dolních ($p<0,001$).

Vokalizace se vyskytla u 11 pacientů (34,4%), u těchto všech nesrozumitelná, u tří z nich současně přítomna také srozumitelná (9,4%). Celkem motorických událostí s vokalizací bylo pozorováno 59 (1,5%).

U tří pacientů (9,4%) se jednou vyskytla situace, kdy motorický projev RBD způsobil probuzení do plné bdělosti.

U sedmi pacientů (21,9%) byl alespoň jeden motorický projev spojen se zřetelnou emocí. Celkem bylo zaznamenáno 19 emočně zabarvených motorických událostí. Všechny měly negativní charakter.

Celková doba pohybů vůči trvání REM spánku činila 16,0±35,3%.

Klinická a polysomnografická data jsou prezentována v tabulce 2. Podrobné výsledky o četnosti motorických událostí prezentuje tabulka 3, údaje o trvání jsou v tabulce 4.

Korelace mezi četností motorických projevů RBD i v rámci jednotlivých kategorií, trvání a podílu vůči celkové době REM spánku s věkem a anamnesticky referovaným trváním nemoci nebyly statisticky signifikantní.

Diskuse

Tato studie mapuje profil motorických projevů v REM spánku u iRBD s ohledem na jejich klinickou tíži. Hlavním výsledkem je nález vysokého počtu motorických událostí za noc (109,6±84/h) ve srovnání s množstvím udávaným v literatuře u zdravých subjektů v odpovídající věkové skupině (3,6±2,3) [10].

Většina motorických projevů měla elementární charakter (67,8%), zatímco komplexní chování bylo méně časté (22,3%). Pouze malý podíl zaznamenaných událostí (0,7%) měl násilný charakter. Nicméně násilné projevy byly zachyceny u 31% pacientů, což odpovídá údaji v literatuře o anamnesticky referovaných zraněních pacienta (32-38%) a partnera (17-64%) [6, 12].

Klinická diagnóza RBD podle standardních kritérií vyžaduje anamnestický či polysomnografický údaj o komplexitě motorických projevů v REM spánku [2]. Bylo však zaznamenáno velké množství pohybů, které zdaleka neměly charakter komplexnosti, a nejvíce bylo těch, které jsme označili jako elementární. Jejich zmnožení má jistě s onemocněním iRBD souvislost, i když část elementárních pohybů na videozáznamu může mít jiný původ. Do této kategorie spadají i projevy probouzecí reakce a krátké záškuby, vyskytující se fyziologicky jako fázické projevy REM spánku. EMG zaznamenává porušenou atonii v REM spánku, což je citlivější metoda, než prosté pozorování videozáznamu [13]. Navíc porucha svalové atonie bez behaviorálních projevů se považuje za subklinické stádium RBD [14], takže je přijímán názor, že se nejpravděpodobněji jedná o kontinuum mezi izolovanou poruchou atonie v REM spánku u RBD a RBD s plně manifestními behaviorálními projevy. Z tohoto důvodu je důležité všímat si i diskrétnějších motorických projevů ve videozáznamu. [10].

Převažující briskní charakter motorických událostí oproti pomalým, potvrzuje klinickou zkušenost, že ráz pohybů asociovaných s RBD je odlišný od fyziologických a bdělostních pohybů.

Převažující motorická aktivita pozorovaná na horních končetinách mohla být ovlivněna přítomností pokrývky, která skryla část pohybů dolních končetin. Jiné vysvětlení může být facilitace motorických drah pro jemnou motoriku týkající se jen horních končetin, zapojených při uskutečňování snové aktivity.

Jen malý podíl (1,5%) motorických událostí doprovázela vokalizace. I přes intenzivní motorické projevy byla asociace motorického projevu s úplným probuzením do minimálně jedné celé epochy bdělosti spíše sporadická.

Hlavní limitací této studie je analýza pohybů u pacientů, kteří více či méně byli pod přikrývkou. Množství registrovaných pohybů a trvání videozáznamů však tento nedostatek zmenšují. Bohužel není možné uskutečnit záznamy bez přikrývky u pacientů, kteří jsou zvyklí ji používat. Absence kontrolní skupiny je jistě další nedostatek, kterého jsme si vědomi, na druhou stranu polysomnografické parametry včetně pohybů vázaných na spánek u zdravé populace jsou dobře zdokumentovány v literatuře [10, 15].

Dalším krokem by měla být navazující longitudinální studie, která by odpověděla na otázky, zda klinická tíže motorických projevů v REM spánku patrných na videozáznamu svědčí též o progresi nemoci a zda je některý typ motorických jevů parametrem predikujícím konverzi do plně vyjádřené neurodegenerativní nemoci.

Závěr

Tato průřezová studie ukazuje, že pacienti s RBD vykazují velké množství motorických jevů v REM spánku pozorovatelných na videozáznamu při PSG s velkou variabilitou. Elementární záškuby, které představují naprostou většinou pohybů zachycených ve video-PSG, sice nemohou být podkladem stanovení diagnózy, ale jejich výskyt je podstatně vyšší než u zdravé populace dle literárních údajů. Scénické a násilné pohyby jsou komplexní motorické projevy, odrážející snovou aktivitu a jsou nutným diagnostickým kritériem. Násilné behaviorální projevy, které jsou vůči ostatním kategoriím pohybů zastoupeny poměrně minoritně, se však vyskytly s poměrně vysokou prevalencí 31%.

Seznam zkratek

AASM – American Academy of Sleep Medicine

EEG – elektroencefalografie

EKG – elektrokardiografie

EMG – elektromyografie

EOG – elektrookulografie

ICSD-3 – International Classification of Sleep Disorders, third edition

iRBD – idiopatická RBD

PSG – polysomnografie

RBD – porucha chování v REM spánku

REM – rychlé oční pohyby

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Tabulky

Tabulka 1: Klasifikace motorických projevů RBD

Kategorie		Definice	Příklady
1	Elementární	Drobné, jednoduché pohyby s malými exkurzemi charakteru záškubů zahrnující izolovaně jednu část těla, při běžném pozorování by zůstaly bez povšimnutí	Záškuby prstů, drobné záškuby končetin/y, otevírání úst
2	Excesivní	Větší izolované exkurze jedné končetiny a hrubé záškuby celého těla	Zvedání končetin/y, hrubé záškuby končetin/y a celého těla
3	Scénické	Komplexní pohybová aktivita sugestivně naznačující uskutečňování snové aktivity, která nemá silový nebo agresivní charakter	Gestikulace, šátrání, tápání, úchopy, grimasování, somnilokvie, smích, pláč, zpěv, posazování v lůžku
4	Násilné	Silové a vehementní pohyby s potenciálem zranění pacienta nebo partnera	Údery, výpady, boxování, kopy, skoky z postele, souboj, pokus o vstávání a chůzi

Tabulka 2: Klinicko-polysomnografický profil souboru

	Průměr	SD	Medián	První kvartil	Třetí kvartil
Věk	67,4	7,3	67,8	64	71,3
BMI	28,7	4	28,5	27	29,8
Trvání RBD (roky)	8	6,6	6	3	10
SPT (min)	421,4	43,4	419	396,9	458,4
SE (%)	73,5	12,1	74	68	82,7
Bdělost (% SPT)	22,5	11,8	22,1	13,1	27,6
N1 (% SPT)	10,3	5,8	9,4	6,5	11,9
N2 (% SPT)	33,8	13,4	32,4	25,5	42,6
N3 (% SPT)	15,6	11,4	14,9	5,8	19,8
R (% SPT)	16	5,4	16,7	12,1	19,7
Trvání R (min)	66,4	24,4	62,8	50,8	84,3
AHI	9,4	11,8	5,4	0,9	12,8

BMI – body mass index; RBD (REM sleep behavior disorder) – porucha chování v REM spánku; SPT (sleep period time) – trvání periody spánku; SE – spánková efektivita, vyjadřující podíl spánku vůči celkové době strávené v lůžku; N1, N2, N3 – non-REM spánek, fáze 1, 2, 3; R – REM spánek; AHI – apnoe-hypopnoe index; SD – směrodatná odchylka.

Tabulka 3: Behaviorální události

Četnosti behaviorálních jevů a jednotlivých jejich typů na pacienta, vyjádřených jako frekvence pohybů za 1 hodinu REM spánku.

	Průměr	SD	Medián	První kvartil	Třetí kvartil
Behaviorální projevy celkem	109,6	84	82,6	43,1	145,3
Základní rozdělení na 4 kategorie					
Elementární	74,1	54,7	59,7	29,4	103,6
Excesivní	10,4	9,5	9,5	2,4	16,7
Scénické	24,4	26,3	17	6,7	33,1
Násilné	0,7	1,3	0	0	1,3
Rychlost pohybu					
Briskní pohyby	60,8	43,4	49,9	26,7	91,8
Pomalé pohyby	28,4	34,6	15	5,6	33,5
Lokalizace					
Mimické svaly	17,6	19,6	9,8	4,2	23,5
Hlava	5,8	6	3	0,9	8,8
Pravá horní končetina	34,4	27,5	29	10,6	51,3
Levá horní končetina	26,4	20,5	23,3	11,2	40,4
Pravá dolní končetina	12	12,9	5,3	2,5	17,5
Levá dolní končetina	13,2	14,3	9,4	3,4	17,4
Celé tělo	4,8	5	3,2	1,7	5,3
Vokalizace					
Vokalizace	1,6	3,6	0	0	1,5
Vokalizace – srozumitelná	0,2	0,8	0	0	0,0
Vokalizace – nesrozumitelná	1,4	3,2	0	0	1,5
Probuzení	0,1	0,3	0	0	0
Emoční náboj	0,5	1,2	0	0	0

SD – směrodatná odchylka.

Tabulka 4: Trvání motorických událostí RBD

Celkový součet doby trvání motorických projevů RBD a jejich jednotlivých kategorií na pacienta.

	Průměr	SD	Medián	První kvartil	Třetí kvartil
Celkové trvání (min)	10,5	22	3,5	1,5	10,0
Elementární (min)	7,6	21,4	2,0	1,1	6,1
Excesivní (min)	0,8	0,8	0,4	0,1	1,4
Scénické (min)	2,9	3,7	1,4	0,6	3,7
Násilné (min)	0,2	0,3	0,1	0,1	0,2

SD – směrodatná odchylka.

Excessive Fragmentary Myoclonus: What Do We Know?

Jiří Nepožitek, Karel Šonka
Centre for Sleep and Wake Disorders, Department of Neurology,
First Faculty of Medicine, Charles University and General University Hospital
in Prague, Prague, Czech Republic

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Key words: Fragmentary myoclonus – Excessive fragmentary myoclonus – Twitch – Polysomnography – Electromyography – Sleep disorders

Abstract: Excessive fragmentary myoclonus (EFM) is a polysomnographic finding registered by the surface electromyography (EMG) and characterized as a result of the muscle activity consisting of sudden, isolated, arrhythmic, asynchronous and asymmetric brief twitches. The EMG potentials are defined by the exact criteria in The International Classification of the Sleep Disorders, 3rd edition and they appear with high intensity in all sleep stages. Clinical significance of EFM is unclear. It was observed in combination with other diseases and features such as obstructive and central sleep apnea, narcolepsy, periodic limb movements, insomnia, neurodegenerative disorders and peripheral nerve dysfunction. Relation to such wide range of diseases supports the opinion that EFM is nor a specific sleep disorder nor a specific polysomnographic sign. The option that EFM is a normal variant has also not been ruled out so far.

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Mailing Address: Jiří Nepožitek, MD., Department of Neurology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Kateřinská 30, 120 00 Prague 2, Czech Republic; Phone: +420 224 965 009; e-mail: jiri.nepozitek@lf1.cuni.cz

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Definition and characteristics

Fragmentary myoclonus (FM) is a polysomnographic phenomenon incidentally discovered in sleep. According to the latest official version of The International Classification of Sleep Disorders, 3rd edition (ICSD-3; American Academy of Sleep Medicine, 2014) by The American Academy of Sleep Medicine (AASM) FM is defined as a result of the muscle activity registered by the surface electromyography (EMG) during polysomnography (PSG). This activity consists of sudden, isolated, arrhythmic, asynchronous and asymmetric brief twitches, jerks or twitch-like movements of muscles or muscle fibers involving various body areas, in particular corners of the mouth, fingers or toes (American Academy of Sleep Medicine, 2014). They do not have to lead to the visible movement every time (Broughton and Tolentino, 1984). The expression "fragmentary" emphasizes the multifocal appearance of the muscle activity. The term *fragmentary myoclonus in sleep* was first introduced by Broughton and Tolentino in 1984. In ICSD-3 FM is not classified as a nosological entity, it is included among isolated symptoms and normal variants of the sleep related movement disorders (American Academy of Sleep Medicine, 2014). Two forms of FM are being distinguished: the physiologic form and the abnormal (excessive) form.

Physiologic fragmentary myoclonus (PFM) was described by Montagna et al. (1988). This form is called *non-excessive fragmentary myoclonus* by some authors (Frauscher et al., 2014). The PFM appears as a sporadic phenomenon in rapid eye movement sleep (R) and it is also observed during sleep stage non-REM 1 (N1) with lower rates in wakefulness and stages non-REM 2 (N2) and non-REM 3 (N3 – formerly divided at N3 and non-REM 4) (Montagna et al., 1988).

Excessive fragmentary myoclonus (EFM) is the term first used by Broughton et al. in 1985 in a report of 38 cases. The EFM is described by Broughton et al. (1985) as abnormal amounts of FM potentials, which in contrast to PFM persist throughout all stages of non-REM and REM sleep (Broughton et al., 1985; Mizuma and Sakamoto, 1997; American Academy of Sleep Medicine, 2014).

Criteria determined by the latest official version of ICSD-3 identify the FM as EMG potentials with maximal duration of 150 ms and amplitude over 50 μV rarely rising above 200 μV to several hundred μV (American Academy of Sleep Medicine, 2014). The EFM is clinically diagnosed by presence of 5 potentials per minute during at least 20 minutes of recorded non-REM sleep according to the most recent version of the AASM Manual for the Scoring of Sleep and Associated Events 2015 (AASM Manual; Berry et al., 2015).

The EFM during sleep is generally seen in the tibialis anterior muscle surface EMG (Figure 1). It does not tend to appear in bursts unlike phasic REM twitches, which are generally clustered within small groups. The potentials are more universally dispersed throughout a sleep epoch (American Academy of Sleep Medicine, 2014). Patients are usually not aware of the muscle twitches (Lins et al., 1993). EFM is predominantly found in males (Broughton et al., 1985). Although it

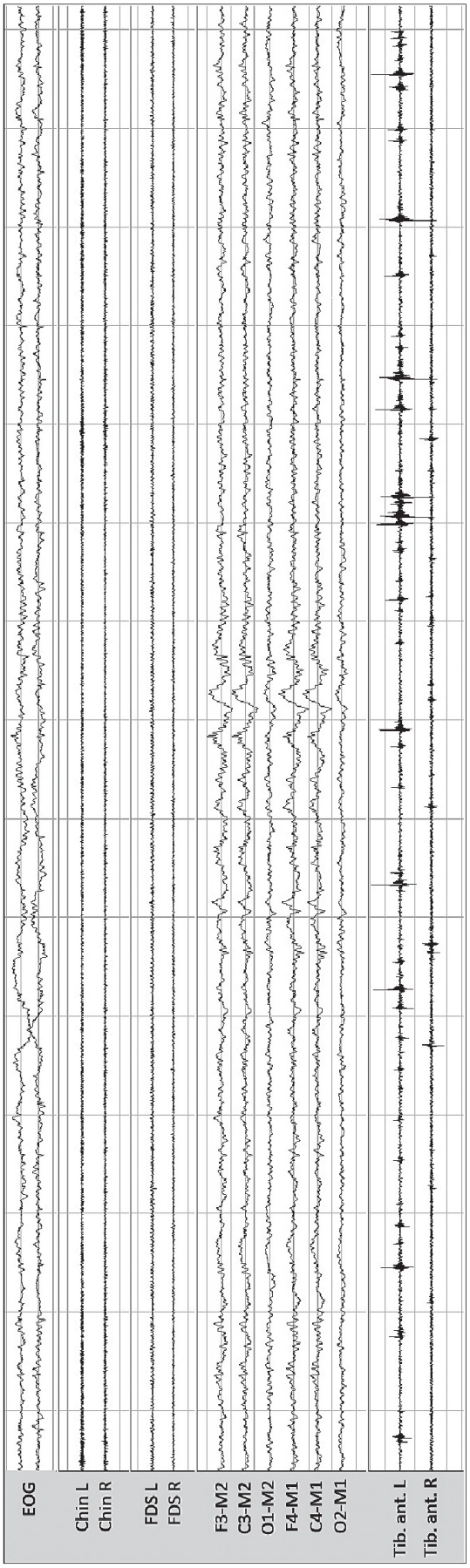

Figure 1 – Typical polysomnographic finding of the excessive fragmentary myoclonus during the sleep stage N2. Brief EMG potentials appear with high intensity asynchronously in both channels registering the activity of the tibialis anterior muscle. Legend: EOG; Chin L – left mentalis muscle EMG; Chin R – right mentalis muscle EMG; FDS L – left flexor digitorum superficialis muscle EMG; FDS R – right flexor digitorum superficialis muscle EMG; F3-M2, C3-M2, O1-M2, F4-M1, C4-M1, O2-M1 – EEG; Tib. ant. L – left tibialis anterior muscle EMG; Tib. ant. R – right tibialis anterior muscle EMG.

has been described that FM intensity increases with age (Frauscher et al., 2011), it has not yet been confirmed in EFM (Lins et al., 1993).

Occurrence of EFM in wakefulness is not quite clear. In the most recent study Raccagni et al. (2016) report that the EFM potentials extend into wakefulness in a group of 98 patients. FM present in relaxed wakefulness was previously observed by Montagna et al. (1988) and Frauscher et al. (2011). Contradictory to these results is the study with two patients by Vetrugno et al. (2002) who observed EFM purely in sleep.

The results referring about the sleep stage distribution of EFM vary from study to study. It can be summarized that the highest EFM amounts occur in R and the lowest in N3 (Lins et al., 1993; Mizuma and Sakamoto, 1997), while the abnormal intensity in contrast with PFM, is kept. In the recent work by Hoque et al. (2013) the sleep stage distribution was assessed for the different amplitude criteria. For the potentials with lower amplitude criteria (≥25 μV) the EFM rates increased from wakefulness to stage N1, 2, 3 and R. With the higher criteria (40 μV and 50 μV) EFM occurred less often in N3 than other sleep stages, in which the rate still had an increasing tendency through wakefulness, stages N1, N2 and R (Hoque et al., 2013). Based on the Hoque's results it can be concluded that the EFM intensity increases with N3 and R, while the amplitude of the potentials in non-REM decreases with the fall of muscle tone under the level of the scoring criteria.

The time of night distribution has been studied as well, the number of potentials rise sharply after the initial lower level in the first hour of sleep and remains unchanged across the rest of the night (Lins et al., 1993).

Only one study refers about the prevalence of EFM so far. Frauscher et al. (2014) reported non-excessive FM in every single subject in the group of 100 healthy subjects, whereas 9% met the criteria for the excessive form.

Development of terminology and assessment

Sudden, arrhythmic, brief twitches occurring during sleep in various body muscles in men and animals were observed for the first time by De Lisi in 1932, who called the phenomenon *physiological hypnic myoclonus*. It probably was fragmentary myoclonus.

In 1969, Dagnino et al. used the term *hypnic myoclonus* for sudden arrhythmic brief twitches observed in sleep at PSG in 18 patients. No amplitude and duration criteria were used in the study. Part of the observed twitches was most likely FM, according to the actual terminology.

Broughton and Tolentino published a case report in 1984, where they used the term *sleep related fragmentary pathological multifocal myoclonus* and as mentioned above, one year later introduced the term *excessive fragmentary myoclonus* (Broughton et al., 1985).

In 1988, Montagna et al. used the same term as De Lisi – *physiological hypnic myoclonus*. Montagna exerted a quantification method, which has not been followed by other authors.

In 1993, Lins et al. presented a scoring method for the assessment of EFM intensity, called fragmentary myoclonus index (FMI). Each 30-second scoring epoch was divided into ten 3-second mini-epochs. Then the number of mini-epochs with one or more FM potentials exceeding 50 μV was counted. Thus this count led to the number ranging from 0 to 10 for each 30-second epoch. The count then could be referenced to the hours of night and to the duration of individual sleep stages (Lins et al., 1993).

Vetrugno et al. called the phenomenon *excessive fragmentary hypnic myoclonus* in the case report in 2002. The quantitative analysis was performed only on the left tibialis anterior muscle EMG channel (Vetrugno et al., 2002).

So far, no quantification criteria have been accepted worldwide.

Clinical significance

A study by Frausher et al. (2011) found FM in 100% of 62 patients with a variety of sleep disorders. The EFM can be according to the present findings conceivably considered as an abnormal intensification of the PFM however its clinical consequences are unclear. The option that EFM is a normal variant has also not been ruled out so far.

The phenomenon was first noted in the 42-year-old patient suffering from the excessive daytime sleepiness and sleep fragmentation, which was not explained by other sleep disturbances (Broughton and Tolentino, 1984). The EFM has also been described in combination with other sleep disorders such as obstructive sleep apnea, primary central sleep apnea, sleep related hypoxemic and hypoventilation syndromes (Broughton et al., 1985), periodic limb movements disorder (Broughton et al., 1985), narcolepsy (Broughton et al., 1985) and various causes of insomnia (Broughton et al., 1985). In patients with the sleep apnea, the EFM intensifies during periods of increased hypoxemia (American Academy of Sleep Medicine, 2014).

Due to the occurrence of EFM in relation to such sleep comorbidities, the specificity and the causality of EFM as a sole disorder is questionable (American Academy of Sleep Medicine, 2014). A very recent work by Raccagni et al. (2016) confirmed the wide range of coexistent sleep disorders associated with EFM and the findings support the opinion that EFM is not a specific sleep disorder.

A few works have reported the occurrence of EFM in some neurodegenerative diseases. The EFM was observed in Parkinson's disease (Sobreira-Neto et al., 2015), multiple system atrophy (Vetrugno et al., 2007), amyotrophic lateral sclerosis (Sonka et al., 2004), Machado-Joseph disease (dos Santos et al., 2014), Niemann-Pick disease type C (Vankova et al., 2003) and mitochondrial encephalopathy (Pincherle et al., 2006).

The EFM must be taken into account in differential diagnosis of the following sleep related movement disorders and polysomnographic features: RLS, periodic limb movements in sleep, epileptic myoclonus, sleep related leg cramps, hypnagogic foot tremor, alternating leg muscle activation, and propriospinal myoclonus.

The RLS are associated with a nocturnal or evening urge to move the legs, uncomfortable and unpleasant sensations in the legs, worsening during periods of rest or inactivity and leading to the limb movements associated with relieving sensations. None of these symptoms is present in EFM (American Academy of Sleep Medicine, 2014).

The periodic limb movements in sleep have in contrast with EFM periodic character. The duration of each movement is longer (0.5 to 10 seconds) than FM potentials (American Academy of Sleep Medicine, 2014).

Epileptic myoclonus as an expression of epilepsy in sleep is always associated with an EEG discharge (Lins et al., 1993).

Sleep related leg cramps are sudden and intense involuntary contractions of muscles occurring during the time in bed, unlike EFM lasting much longer (for a few seconds up to several minutes), associated with painful sensations, muscle spasm and hardness (American Academy of Sleep Medicine, 2014).

Hypnagogic foot tremor is rhythmic movement of the feet or toes that occurs at the transition between wake and sleep or during stages N1 and N2 (American Academy of Sleep Medicine, 2014). EFM lacks the rhythmic character and predominant occurrence in mentioned sleep stages.

Alternating leg muscle activation consists of brief repeated activation of the anterior tibialis muscle in one leg in alternation with similar activation in the other leg (American Academy of Sleep Medicine, 2014), they appear in sequences and may recur periodically (Merlino and Gigli, 2012), while EFM lacks the alternating pattern, rhythmicity and periodic occurrence in sequences.

Propriospinal myoclonus consists of sudden jerks, mainly of the abdomen, trunk, and neck. These myoclonic jerks of propriospinal myoclonus irregularly recur when alpha activity is present on the EEG and they disappear with EEG desynchronization and the occurrence of sleep spindles and K-complexes. Myoclonic jerks of propriospinal myoclonus are absent throughout sleep, even if these movements might reappear during intrasleep wakefulness, while EFM is present throughout sleep. The propriospinal myoclonus shows different EMG characteristics than EFM, myoclonic jerks last from 100 to 300 ms (Merlino and Gigli, 2012).

Neurophysiology

Until 2002 no other neurophysiological investigations of FM except for PSG had been reported. In 2002 Vetrugno et al. performed concentric needle EMG, motor and sensory nerve conduction velocity studies and EEG back-averaging studies. They did not find any neuromuscular abnormalities which could indicate a disorder of integrity of the peripheral nervous system, and they also demonstrated that no cortical EEG potentials preceded the EFM twitches (Vetrugno et al., 2002).

Another work by Gassel et al. (1964) showed the effect of deafferentation on myoclonic twitches in cats. Partial section affecting the dorsal half of the

lateral funiculus of spinal cord caused a conspicuous reduction in frequency and amplitude of the myoclonic twitches in sleep. The abolition was a global one, not concerning in isolation either extensor or flexor muscle groups, which suggest that neither the pyramidal nor the rubrospinal tract were essential in this regard. The explanation was that reticulospinal tract, as the third important descending system in dorsolateral funiculus, is the effective pathway (Gassel et al., 1964).

Since this excitatory descending volley is physiologically under suppressive control of other structures involved in the active process of sleep, namely rostral and caudal pontine reticular nucleus projecting to gigantocellular reticular nucleus (Chase and Babb, 1973; Chase, 1983; Chase et al., 1986; Takakusaki et al., 1989), the damage or malfunction of these structures and their connections are most likely involved in the etiopathogenesis of EFM. The same structures were identified as the site of origin of the physiological phasic twitches in REM sleep (Kohyama et al., 1994) which implies that both phenomena might have the similar genesis.

The hypothesis that brainstem is the site of origin of EFM is moreover supported by reports of the occurrence of EFM in neurodegenerative diseases associated with the lesions of the brainstem structures (Vankova et al., 2003; Pincherle et al., 2006; Vetrugno et al., 2007; dos Santos et al., 2014; Sobreira-Neto et al., 2015).

Very recently a study by Raccagni et al. (2016) the incidental finding of EFM in 98 patients has shown contradictory results to Vetrugno's conclusions. Fifty percent of the patients in this study presented electrophysiological abnormalities such as polyneuropathy, root lesions and benign fasciculations. Such high prevalence of abnormal neurophysiological findings in patients with EFM points to the possibility that peripheral nerve pathology could be the cause of EFM at least in part of the cases (Raccagni et al., 2016).

Another point of view on the substantiality of EFM was mentioned in the study on amyotrophic lateral sclerosis (Sonka et al., 2004). It was noticed that the characteristics of FM appear to be very similar or identical to the polysomnographic picture of fasciculations. No difference found between particular sleep stages is a feature that resembles the EFM. The fact that hypnic myoclonus displays the characteristics of fasciculation potentials has been noted also by Montagna et al. (1988). A few studies have reported electrophysiologically confirmed benign fasciculation syndrome in the group of EFM patients (Frauscher et al., 2014; Raccagni et al., 2016).

The exact origin of the EFM remains unknown and the results of the existing studies are quite inconsistent so far. Brainstem lesion and peripheral nerve dysfunction considered as the cause of EFM are the two main contradictory hypotheses.

Summary

The EFM is a challenging phenomenon and there are few existing neurophysiological and clinical studies making a background for the future

investigations. Its relation to the wide range of sleep disorders supports the opinion that EFM is not a specific sleep disorder and probably not even a specific polysomnographic sign. The option that it is a normal variant has not been disproved yet. Existing results on the pathophysiology of EFM are inconsistent. Observations of EFM in neurodegenerative diseases support the idea that brainstem structures could be involved as the site of EFM origin. Furthermore, it was pointed out that peripheral lesions are associated with EFM as well. Polysomnographic picture of fasciculations has almost identical characteristics with EFM. There is no doubt that more research has to be done on this topic before the pathophysiological mechanisms and clinical significance of the EFM can be reliably concluded.

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Prospective memory impairment in idiopathic REM sleep behavior disorder

Ondrej Bezdicek[a], Tomáš Nikolai[a], Jiří Nepožitek[a], Pavla Peřinová[a], David Kemlink[a], Pavel Dušek[a], Iva Příhodová[a], Simona Dostálová[a], Veronika Ibarburu[a], Jiří Trnka[b], Karel Kupka[b], Zuzana Mecková[c], Jiří Keller[d], Josef Vymazal[d], Evžen Růžička[a], Karel Šonka[a] and Petr Dušek[a,b]

[a]First Faculty of Medicine, Department of Neurology and Center of Clinical Neuroscience, Charles University and General University Hospital, Prague, Czech Republic; [b]First Faculty of Medicine, Institute of Nuclear Medicine, Charles University and General University Hospital, Prague, Czech Republic; [c]First Faculty of Medicine, Department of Medical Physics, Charles University and General University Hospital, Prague, Czech Republic; [d]Department of Radiology, Na Homolce Hospital, Prague, Czech Republic

ABSTRACT

Objective: The aim of the present study was to investigate if prospective memory (PM) is impaired in idiopathic rapid eye movement (REM) sleep behavior disorder (iRBD). RBD is a parasomnia characterized by dream enactment and by REM sleep without muscle atonia. iRBD is considered as the initial stage of neurodegeneration with pathological storage of alpha-synuclein. **Method**: Sixty iRBD patients with polysomnography-confirmed RBD without parkinsonism and dementia and 30 demographically matched normal controls (NC) were enrolled in the present study. Clinical assessment included Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), dopamine transporter single-photon emission computed tomography (DaT-SPECT) for imaging synapses of dopaminergic neurons in the striatum and a neuropsychological battery with embedded time-based and event-based PM measures. **Results**: iRBD differed significantly from NC in event-based PM, a number of event-based failures to recall intention and total PM performance (all $p < .001$) but did not differ in time-based PM and recognition. PM did not contribute to impairment of instrumental activities of daily living in iRBD. Despite being preserved in iRBD in comparison to NC, time-based PM correlated significantly with dopaminergic neuronal loss measured by DaT-SPECT. **Conclusions**: We show evidence for a differential pattern of PM impairment in iRBD with severe impairment of event-based and concurrent preservation of time-based PM. We theorize that event-based PM impairment in iRBD is caused by severe impairment of retention and recognition mechanisms in episodic memory whereas time-based PM seems to be affected by reduced striatal dopaminergic synapses.

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CONTACT Ondrej Bezdicek ondrej.bezdicek@gmail.com

Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by dream enactment and by REM sleep without muscle atonia (Boeve, 2010; Ferini-Strambi, Rinaldi, Giora, Marelli, & Galbiati, 2016; Schenck, Bundlie, Ettinger, & Mahowald, 1986). In the absence of significant neurological signs or lesion in the central nervous system, RBD is defined as idiopathic. RBD is labeled as symptomatic when it occurs with neurodegenerative disorders such as Parkinson's disease (PD), Lewy body dementia (LBD), multiple system atrophy (MSA), focal brainstem lesions, narcolepsy, and more rarely with other neurological conditions. Idiopathic REM sleep behavior disorder (iRBD) is considered as the initial stage of neurodegeneration with pathological storage of alpha-synuclein in the brain (Boeve et al., 1998, 2013; Gagnon et al., 2002; Hu et al., 2015; Iranzo et al., 2005, 2006; Mahowald & Schenck, 2013; Postuma, Gagnon, & Montplaisir, 2013). Dopaminergic transporter single-photon emission computed tomography (DaT-SPECT) in iRBD shows that there is a continuum from normal finding to definitely reduced striatal uptake suggesting subclinical degeneration of dopaminergic neurons (Iranzo et al., 2010). Striatal uptake reduction was associated with increased muscle activity during REM sleep (Eisensehr et al., 2000, 2003). The prevalence of RBD is about 2% of people aged 60 and over and approximately from .5 to 1.6% in the general population with a strong disproportion regarding men (85%) vs. women (15%) (Bodkin & Schenck, 2009; Kang et al., 2013; Ohayon, Caulet, & Priest, 1997; Ohayon & Schenck, 2010). The risk estimates of iRBD conversion to diseases with dementia and parkinsonism increase each year from approximately 18–33% at 5 years to 75% at 10 years, and 90% at 14 years after onset (Iranzo et al., 2014; Youn et al., 2016).

The frequency of mild cognitive impairment (MCI) was estimated to be 33–50% in iRBD patients seen in sleep clinics and 63–73% in PD patients with RBD, respectively (Gagnon et al., 2009; Zhang et al., 2016). The high conversion rate of iRBD is interconnected with a 2.2-fold increased risk of developing MCI in a population-based sample (Boot et al., 2012; Gagnon, Bertrand, & Genier Marchand, 2012; Manni et al., 2013). Subsequently, MCI status in subjects with RBD strongly predicts conversion to dementia (Marchand, Montplaisir, Postuma, Rahayel, & Gagnon, 2017; Terzaghi, Zucchella, Rustioni, Sinforiani, & Manni, 2013). Cross-sectional studies indicate that a proportion of iRBD patients show a pattern of cognitive deficits similar to those typically found in patients with synucleinopathies, especially in LBD or PD with MCI or PD with dementia (Boeve et al., 1998; Manni et al., 2013; Marchand et al., 2017; Terzaghi et al., 2013). In addition to structural changes in cortical and subcortical brain areas (Rahayel et al., 2015), dysfunction of cholinergic, noradrenergic, and dopaminergic neurotransmitter networks can potentially play a role in the genesis of MCI in iRBD patients (Arnaldi et al., 2015; Brunetti et al., 2014). In iRBD selective attention, executive functions and episodic verbal and non-verbal memory are the most affected memory domains (Fantini et al., 2011; Ferini-Strambi et al., 2004; Massicotte-Marquez et al., 2008; Terzaghi et al., 2008). However, the presence of visuospatial and visuoconstructional deficits has also been reported by some studies (Fantini et al., 2011; Iranzo et al., 2006; Molano et al., 2010), especially in those iRBD subgroups who later convert to PD with dementia or DLB. On the other hand, according to Gagnon et al. (2009), praxis and language seem to be relatively spared in RBD. Recently, new studies have emerged, e.g. Rusz et al. (2016) found detectable speech impairment based on acoustic analysis in 88% of RBD subjects.

The identification of cognitive markers at initial stages of brain degeneration with pathological storage of synuclein is essential, as they could provide predictive information and

outcome measures for future trials with disease-modifying therapies (Boeve, 2010; Marchand et al., 2017; Postuma, Gagnon, Bertrand, Genier Marchand, & Montplaisir, 2015; Schenck et al., 2013). Episodic memory seems to play a significant role in the functional independence in instrumental activities of daily living (IADL) of iRBD patients. However, previous studies focused only on its retrospective component (Ferini-Strambi et al., 2016; Massicotte-Marquez et al., 2008; Terzaghi et al., 2008). We argue that prospective memory (PM) functioning is also essential for independence of iRBD patients as is the case within the framework of PD (Costa et al., 2015; Di Fabio, Poryazova, Oberholzer, Baumann, & Bassetti, 2013; Einstein & McDaniel, 1996; Foster, McDaniel, Repovs, & Hershey, 2009; Marcone et al., 2017). PM refers to the ability to carry out intentions after a delay; for instance, to phone someone at a particular time in the future (Kliegel, McDaniel, & Einstein, 2008). PM is a subsystem of declarative, and in particular, episodic memory (Kliegel, Altgassen, Hering, & Rose, 2011; Squire, 2004; Tulving, 2002). It is comprised of several cognitive processes, namely intention formation, intention retention, intention initiation, and intention execution (Kliegel et al., 2011; McDaniel & Einstein, 2007). To the best of our knowledge, studies investigating episodic memory in more depth and more specifically PM impairments in iRBD have not been performed up until now.

The aim of the present study was, therefore, to better characterize PM functioning in a large cohort of iRBD patients by comparing them with a demographically matched normal control sample. Second, we aimed at investigating if PM performance in iRBD is related to MCI and IADL or can be predicted by cognitive or clinical variables. Third, we were looking for a possible association between PM functioning and markers of reduced striatal dopamine transporters using DaT-SPECT. More broadly, our goal was to contribute to the literature regarding the structure of memory impairment in iRBD patients.

Method

Study participants

The patients were recruited by a stepwise media and internet survey in 2014 and 2015 (Buskova, Ibarburu, Sonka, & Ruzicka, 2016). The clinical sample consisted of a total of 60 iRBD patients and 30 healthy controls (Table 1). All patients were diagnosed with RBD according to the International classification of sleep disorders, third edition (*American academy of sleep medicine. International classification of sleep disorders*, 2014) including videopolysomnography with the recording of superficial electromyography of flexor digitorum superficialis muscles of both sides by a trained sleep specialist (KŠ, SD, IP and VI). All patients fulfilled the following inclusion criteria: age >40 years; >8 years of education. Exclusion criteria were as follows: clinical signs of neurodegenerative disease, i.e. overt dementia or parkinsonism, RBD associated with narcolepsy, untreated major depression, encephalitis, EEG abnormalities suggesting epilepsy, severe sleep apnea (defined as apnea–hypopnoea index (AHI) ≥30), drug-induced RBD, head injury, or focal brain lesion indicative of secondary RBD. Dementia was defined according to the DSM-V criteria for major neurocognitive disorder. Parkinsonism was defined according to the MDS clinical diagnostic criteria as clearly present bradykinesia, in combination with either rest tremor, rigidity, or both (Postuma, Berg et al., 2015). RBD patients underwent a comprehensive clinical evaluation that included medical history, evaluation of functional abilities using the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part II, and motor status using the MDS-UPDRS part III by a neurologist experienced in movement disorders (VI, PD, ER). We have classified iRBD patients into iRBD-MCI and

Table 1. Socio-demographic and clinical characteristics of iRBD patients and controls.

	NC ($N = 30$)	iRBD ($N = 60$)	p value (NC vs. iRBD)
Age (years)	66.63 (69; 7.43)	68.08 (69; 7.91)	.53
Education (years)	13.57 (12; 2.91)	12.88 (12; 3.26)	.41
Gender (men %)	87	92	.51
Caucasian (%)	100	100	–
iRBD duration (years)	–	4.49 (6; 5.33)	–
Depression level (BDI-II)	5.60 (5; 3.58)	8.12 (7; 5.65)	.12
State anxiety (STAI-X1)	32.67 (32; 6.14)	36.26 (34.5; 7.71)	.06
Trait anxiety (STAI-X2)	36.95(35; 6.92)	39.02 (37; 8.35)	.30
ESS	–	7.60 (8; 3.94)	–
AHI	–	11.50 (5.5; 13.06)	–
MDS-UPDRS-III	–	5.58 (4; 5.32)	–
MDS-UPDRS-II	–	1.91 (1; 2.05)	–
DaTscan (n/ua/ba/nd)	–	32/5/17/6	–
Antidepressants only (%)	0	10 (17)	–
Anxiolytics only (%)	0	2 (3)	–
Combined (Ad+Ax; %)	0	3 (5)	–

Notes: Data presented as mean (median and SD) unless otherwise noted. NC = normal controls, iRBD = idiopathic rapid eye movement sleep behavior disorder; MoCA = Montreal Cognitive Assessment Czech version; BDI-II = the Beck Depression Inventory, Second Edition; STAI = the State-Trait Anxiety Inventory (state anxiety, X1) and (trait anxiety, X2); ESS = Epworth Sleepiness Scale; AHI, apnea–hypopnoea index; UPDRS-II and III, Unified Parkinson's Disease Rating Scale, Part II and III. DaTscan = dopamine transporter imaging using single-photon emission computed tomography; n = normal; ua = unilaterally abnormal; ba = bilaterally abnormal; nd = not done; Ad = antidepressants; Ax = anxiolytics. All between-groups comparisons are based on Mann–Whitney U Test except for gender which was based on a Chi-square test for independence (with Yates continuity correction).

iRBD-normal cognition (NC) groups using the MoCA total score (Kopecek et al., 2017) and a cutoff of 2.0 SD below the normative mean as suggested by Goldman (Goldman et al., 2013; Petersen, 2004; Petersen et al., 1999). All clinical participants also completed questionnaires to assess depression (Beck Depression Inventory, Second Edition (BDI-II), anxiety (the State-Trait Anxiety Inventory (STAI); Spielberger, Gorsuch, & Lushene, 1970) and daytime sleepiness (Epworth Sleepiness Scale) (Beck, Steer, & Brown, 1999; Johns, 1991), see Table 1.

The clinical sample ($N = 60$) was matched for age, gender, and education with normal controls (NC; $N = 30$; Table 1). Controls were recruited from the general community through advertisements and a brief medical history for each subject was obtained via telephone. Afterward, a detailed interview excluded all participants with a history of major head trauma, stroke, abuse of alcohol or other psychoactive substances, and individuals with a history of neurological or psychiatric disease (e.g. epilepsy, multiple sclerosis, schizophrenia, or delirium), individuals currently undergoing radio- or chemotherapy, with a major somatic illness (myocardial infarction, diabetes mellitus, etc.), or with uncompensated sensory deficits. Moreover, to exclude control subjects with cognitive impairment, limits for enrollment were set on the MoCA below 1.5 SD in comparison to Czech normative data (Kopecek et al., 2017). To exclude subjects with a higher level of depression, the BDI-II score was limited to <13 (Beck, Steer, & Brown, 1999). Demographic and clinical cohort characteristics are presented in Table 1. All tests were administered under standard neuropsychological laboratory conditions and were conducted by trained psychologists (OB, TN).

The hospital's IRB approved the study, and all subjects signed a written consent before their inclusion in the study.

Materials

Both participants (NC and iRBD) underwent a flexible neuropsychological battery (Kane, 1991). The battery consisted of one global screening measure and six tests in four cognitive domains:

the Montreal Cognitive Assessment (MoCA) (Kopecek et al., 2017; Nasreddine et al., 2005), (1) attention and working memory (Trail Making Test, Part A and Letter-Number Sequencing from Wechsler Adult Intelligence Scale, Third Revision) (Bezdicek et al., 2012; Reitan & Wolfson, 1985; Wechsler, 2010), (2) executive function (Trail Making Test, Part B and Prague Stroop Test interference condition) (Bezdicek et al., 2012, 2015; Reitan & Wolfson, 1985) (3) episodic memory (Rey Auditory Verbal Learning Test total immediate recall, delayed recall and total recognition) (Bezdicek, Stepankova et al., 2014; Schmidt, 1996), and (4) psychomotor and motor speed of upper limbs (Symbol Digit Modalities Test and Grooved Pegboard Test) (Bezdicek, Nikolai et al., 2014; Kløve, 1963; Smith, 1982). Both samples were assessed with a brief measure of PM functioning differentiating time-based and event-based PM (each on a six-point scale with a total of twelve points indicating perfect PM functioning). The brief PM measure was derived from the Memory for Intentions Screening Test (MIST). MIST was previously validated in the Czech version (Bezdicek, Raskin, Altgassen, & Ruzicka, 2014). Our validation study indicated very similar psychometric properties in comparison to other studies (Kamat et al., 2014; Raskin, 2009; Raskin, Buckheit, & Sherrod, 2010; Woods, Moran, Dawson, Carey, & Grant, 2008). The PM measure in the present study consists of three consecutive tasks for time-based PM (in 15 min, tell me that it is time to take a break; ask me what time this session ends today; use that paper to write the number of medications you are currently taking) and another consecutive three tasks for event-based PM (when I hand you a red pen, sign your name on your paper; when I hand you a post-card, self-address it; when I hand you a Request for Records Form, write your Doctors' names on it), all tasks were intersected with 1 min latency during encoding. As for the ongoing task, we administered other tests in the battery in a fixed order (Trails, Stroop, Symbol Digit and Grooved Pegboard). However, for brevity of the PM functioning tool in clinical settings, we aimed at increasing the level of interference in memory by ordering time-based and event-based tasks in a row during encoding and recall (Lewandowsky, Duncan, & Brown, 2004; Underwood, 1957). We scored several types of errors during the PM reproduction phase (loss of time, loss of content and task substitution). The measure also contained six forced-choice recognition questions (PM recognition).

Neuroimaging

Patients were examined on a 3T whole-body MRI system (Skyra, Siemens Healthcare, Erlangen, Germany) using a standard clinical T1-weighted and T2-weighted MRI protocol. Images were reviewed by experienced neuro-radiologists (JK, PeD) and focal lesions that may cause secondary RBD were excluded. Additionally, iRBD patients underwent dopamine transporter imaging using the ^{123}I-FP-CIT/Ioflupane (DaTscan^{TM}) SPECT in order to assess the degree of nigrostriatal degeneration. The scanning followed three hours after the application of 185 MBq (5 mCi) ^{123}I-FP-CIT and the 'uptake index' was calculated for putamen and the whole striatum bilaterally using occipital reference area based on the formula: (AROI-AOCC)/(AOCC). Three DaTscan markers were used for analyses: sum of striatal uptake indexes from both sides (DaTscan total), the lower striatal and putaminal uptake index (DaTscan striatum and DaTscan putamen respectively).

Statistical analysis

Statistical analyses were performed using IBM SPSS 22.0. To assess the normality of socio-demographic, clinical and cognitive variables, we examined Q-Q plots and performed the

Kolmogorov–Smirnov test, and in the case of two groups, we used Levene's test to assess the equality of variances. Given the non-parametric nature of the data, we used the Spearman Rank Correlation Coefficient (rho) to evaluate correlations between variables and point-biserial correlation coefficient for dichotomous variables (gender). The chi-square (χ^2) test was used to compare proportions by gender. The Mann–Whitney *U* test was applied to evaluate between-group differences. A one-way between-group ANCOVA was conducted to compare group differences without the influence of demographic (age and education), and general cognitive performance measure (MoCA) and retrospective episodic memory measures (RAVLT immediate, retention and recognition). These were taken as covariates in the model (Tabachnick & Fidell, 2012). Preliminary checks were conducted to ensure that there was no violation of the assumptions of normality, linearity, homogeneity of regression slopes, and reliable measurement of covariates (Pituch & Stevens, 2015). To show if any of demographic and clinical variables can predict PM measures or if PM measures can predict the impairment in IADL, we used standard and hierarchical multiple regression analysis. Statistical significance was set at $\alpha = .05$. The Bonferroni correction for multiple comparisons was applied in PM analyses. The magnitude of effect size in non-parametric tests (*r*) was estimated according to Cohen's effect sizes (Cohen, 1988) as small (>.1), medium (>.3), or large (>.5) and as partial eta squared in parametric analyses.

Results

Descriptive and neuropsychological analyses

Sociodemographic and clinical characteristics of iRBD and NC can be seen in Table 1. A comparison of both samples (iRBD vs. NC) has shown a statistical difference and medium effect size in the MoCA, Stroop interference and all RAVLT measures (Table 2). Furthermore, there was a significant difference in event-based PM and the number of PM event-based failures between iRBD and NC (forgetting to perform the intended action; Table 3 and Figure 1). It is noteworthy that a comparison between time-based and event-based PM performance within iRBD subjects provided a non-significant result. Furthermore, we see several highly significant medium associations between PM measures and demographic variables (the highest between PM recognition and age); medium associations between motor and PM performance (the highest between MDS-UPDRS III and PM total) and between PM and IADL (the highest between event-based PM and MDS-UPDRS II) and between daytime sleepiness and PM. The relation of depression level and PM was not significant in any of the PM measures, however, there were significant association between PM measures and state as well as trait anxiety (Table 4). There were significant correlations between prospective and retrospective episodic memory measures; the highest correlation was between RAVLT recognition and time-based PM (Table 4). No significant correlation was observed between AHI and any PM measure or between AHI and the MoCA.

Parametric analyses as a corollary of non-parametric neuropsychological analyses (iRBD vs. NC)

In the case of time-based PM, PM total and PM recognition Levene's Tests of Equality of Error Variances have not violated the assumption of equality of variance (for time-based PM $p = .55$, for PM total $p = .56$ and PM recognition $p = .54$), however, not in the case of event-based PM

Table 2. Cognitive performance on neuropsychological tests of all iRBD patients and NC.

	NC ($N = 30$)	iRBD ($N = 60$)	p value (effect size) in NC vs. iRBD
MoCA (screening)	25.53 (26; 1.64)	23.98 (24; 2.77)	<.01 (<.0005)* (.40)
1. *Attention and WM*			
TMT-A	39.40 (39; 9.66)	43.72 (38; 19.57)	.76
LNS (WAIS-III)	8.07 (7; 2.55)	7.50 (7; 2.59)	.06
2. *Executive functions*			
TMT-B	98.00 (94; 29.31)	113.86 (96; 69.14)	.61
PST interference	32.00 (33; (6.54)	38.60 (36; 11.56)	<.01 (<.001)* (.34)
3. *Episodic memory*			
RAVLT immediate recall	43.93 (43; 5.97)	37.41 (38; 8.24)	<.01 (<.0005)* (.39)
RAVLT retention	7.93 (7; 2.28)	6.19 (6; 2.78)	<.01 (<.0005)* (.37)
RAVLT recognition	44.67 (45; 2.72)	41.91 (43; 5.23)	<.01 (.003)* (.31)
4. *Psychomotor speed*			
SDMT	46.20 (44; 4.91)	39.60 (38; 10.30)	.10
GPT upper limbs	174.1 (167; 30.45)	178.84 (165; 44.67)	.75

Notes: Data presented as mean (median and SD) unless otherwise noted. MoCA = Montreal Cognitive Assessment; (1) attention and WM = working memory (TMT-A = Trail Making Test, Part A and LNS = Letter-Number Sequencing from Wechsler Adult Intelligence Scale, Third Revision); (2) executive function (TMT-B = Trail Making Test, Part B and PST = Prague Stroop test interference condition); (3) episodic memory (RAVLT = Rey Auditory Verbal Learning Test total immediate recall (the sum of all correct responses given over the five consecutive trials (T1 + T2 + T3 + T4 + T5), retention (delayed recall after 30 min) and total recognition), and (4) psychomotor and motor speed of upper limbs (SDMT = Symbol Digit Modalities Test and GPT = Grooved Pegboard Test). All between-groups comparisons are based on Mann–Whitney *U* Test. By p levels in parentheses we aimed at showing that the comparisons would still survive Bonferroni correction for ten comparisons ($\alpha < .005$).

*Still significant after Bonferroni correction.

Table 3. Prospective memory performance of iRBD patients and controls.

	NC ($N = 30$)	iRBD ($N = 60$)	p value (effect size) in NC vs. iRBD
PM time-based	4.17 (4; 1.46)	3.77 (4; 1.71)	.32
PM event-based	5.37 (6; 1.19)	3.76 (4; 1.73)	<.01 (<.0005)* (.46)
PM total	9.53 (10; 2.16)	7.53 (8; 2.24)	<.01 (<.0005)* (.43)
PM recognition	5.86 (6; .14)	5.63 (6; .71)	.29
PM time-based failures	.43 (0; .73)	.62 (0; .87)	.33
PM event-based failures	.10 (0; .40)	.73 (1; .82)	<.01 (<.0005)* (.43)
Loss of time errors	.23 (0; .57)	.50 (0; .98)	.30
Loss of content errors	.67 (1; .66)	.75 (1; .84)	.88
Task substitution errors	.33 (0; .71)	.27 (0; .55)	.82

Notes: Data presented as mean (median and SD) unless otherwise noted. PM = prospective memory. PM total = (time-based PM + event-based PM). All between-groups comparisons are based on Mann–Whitney *U* Test. Bonferroni correction for nine PM comparisons was applied ($\alpha < .0055$).

*Still significant after Bonferroni correction.

($p = .02$). After adjusting for covariates (age, education, MoCA, RAVLT immediate, retention and recognition), we have found a significant difference between iRBD vs. NC only in event-based PM $F(1, 77) = 10.84$, $p < .01$ (.002), partial eta squared = .13; other comparisons of PM scores were not significant: PM time-based $F(1, 77) = 2.51$, $p = .12$, partial eta squared = .04, PM total $F(1, 77) = 2.21$, $p = .14$, partial eta squared = .03, however, there was a trend in PM recognition $F(1, 77) = 3.87$, $p > .05$ (.053), partial eta squared = .05 (Appendix 1).

Standard multiple regression analysis (iRBD only)

Regarding the results of correlational analyses (Table 4), we aimed at addressing the question of how well demographic: age, education; clinical: iRBD duration, AHI, UPDRS-II and III; cognitive: MoCA, RAVLT immediate, retention, recognition, and affective variables: STAI (X1, X2)

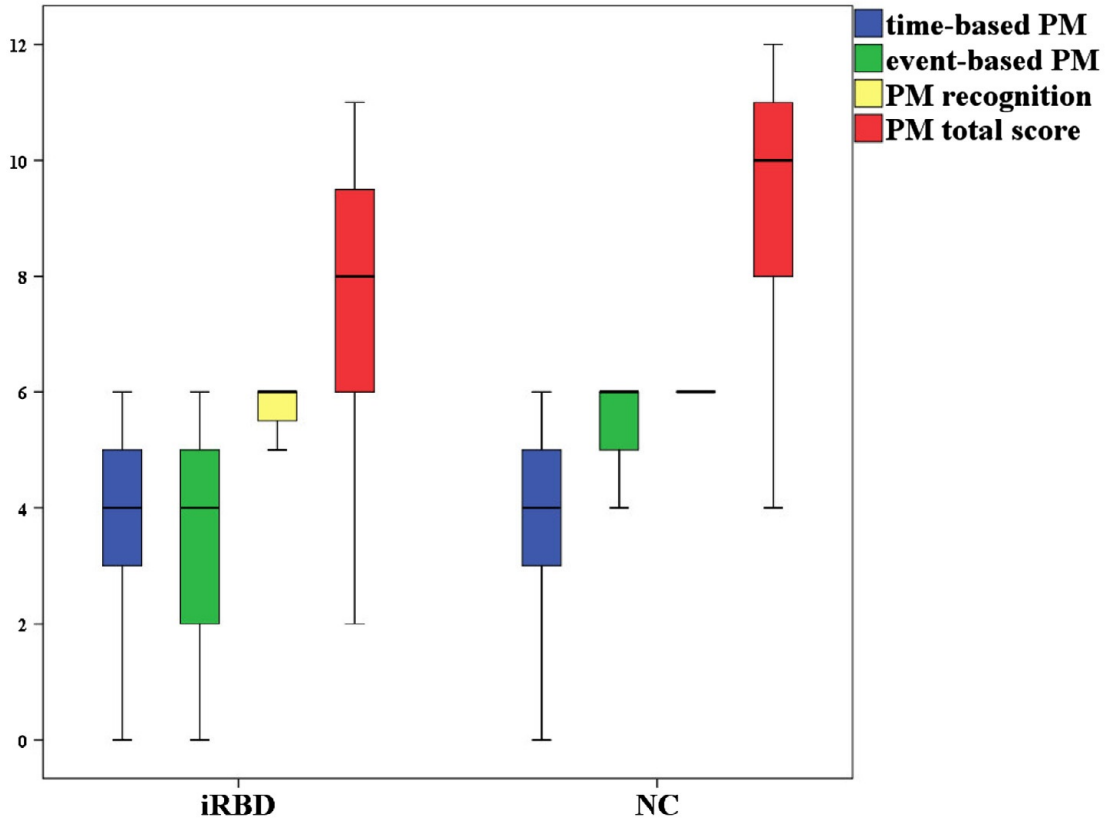

Figure 1. Boxplots showing prospective memory performance of iRBD patients and controls.
Notes: The length of the box is interquartile range and contains 50% of cases, the line inside of the box represents median and the whiskers represent the smallest and largest values. PM = prospective memory. PM total score = (time-based PM + event-based PM; min—max. 0–12 points). Time-based and event-based PM and PM recognition are sub-scores with min—max. 0–6 points. NC = normal controls, iRBD = idiopathic rapid eye movement sleep behavior disorder.

predict PM and which is the best predictor of PM performance in iRBD. The total variance explained by the model as a whole was 51.0% in PM total $F(13, 38) = 3.04$, $p < .01$ (.004) with the largest beta coefficient –.41 for STAI X1 and –.37 for age and .37 for RAVLT retention; the total variance explained was 42.7% in PM time-based $F(13, 38) = 2.18$, $p = .03$ with the largest beta coefficient .28 for RAVLT immediate; MoCA .23 and RAVLT recognition .21; the total variance explained was 58.7% in PM recognition $F(13, 38) = 4.16$, $p < .01$ (<.0005) with the largest beta coefficient –.36 for UPDRS-III, education .35 and STAI X1 –.26; however, non-significant in PM event-based $F(13, 38) = 1.44$, $p = .19$.

iRBD and MCI

The prevalence of MCI in our sample of iRBD was 15% (i.e. 9 out of 60 patients). There were significant trends for between-group differences in PM Total, PM Recognition, and a number of PM event-based failures that, however, did not survive Bonferroni correction (Table 5). Besides PM measures, the most discriminative tests were MoCA score (of note is that MoCA was used as an MCI status criterion) and TMT-B (Table 6).

iRBD and IADL

In addition, we used hierarchical multiple regression to assess the ability of event-based PM to predict levels of IADL (MDS-UPDRS II) in iRBD after controlling for the influence of age

Table 4. Correlations between demographic, clinical and prospective and retrospective memory measures.

	PM time-based	PM event-based	PM total	PM recognition
Age (years)	−.27**	−.13	−.28***	−.38****
Education (years)	.15	.23**	.30***	.32***
Gender	−.19	−.17	.04	−.25**
iRBD duration (years)	−.13	−.40****	−.38****	−.03
MoCA	.38****	.28***	.45****	.41****
BDI-II	−.07	−.13	−.17	−.14
ESS	−.02	−.43****	−.33***	−.03
State anxiety (STAI-X1)	.07	−.35****	−.21*	−.25**
Trait anxiety (STAI X2)	.07	−.14	−.08	−.25**
AHI	−.24*	.10	.05	−.08
UPDRS-II	−.04	−.36***	−.31***	−.18
UPDRS-III	−.19	−.40****	−.44****	−.20****
DaTscan total	.30**	.12	.09	.03
DaTscan striatum	.33**	−.06	.14	−.03
DaTscan putamen	.26*	−.08	.10	−.02
RAVLT immediate	.36****	.27**	.44****	.22**
RAVLT retention	.37****	.35***	.49****	.21*
RAVLT recognition	.45****	.25**	.46****	.19*

Notes: All correlations are based on Spearman rank order correlation except for gender (based on point-biserial correlation) and all correlations are based on both samples except for iRBD duration, ESS, UPDRS-II and III, and DaTscan which are based only on iRBD sample; PM = prospective memory; MoCA = Montreal Cognitive Assessment Czech version; BDI-II = the Beck Depression Inventory, Second Edition; STAI = the State-Trait Anxiety Inventory (state anxiety, X1) and (trait anxiety, X2); ESS = Epworth Sleepiness Scale; AHI, apnea–hypopnoea index; UPDRS-II and III, Unified Parkinson's Disease Rating Scale, Part II and III; DaTscan total = sum of striatal indexes from both sides; DaTscan striatum, DaTscan putamen = lower value of striatal and putaminal index respectively . RAVLT = Rey Auditory Verbal Learning Test.
*$p < .10$; **$p < .05$; ***$p < .01$; ****$p < .001$.

Table 5. Prospective memory performance of iRBD with MCI (iRBD-MCI) and iRBD without MCI (iRBD-NC).

	iRBD-NC ($N = 51$)	iRBD-MCI ($N = 9$)	p value
PM time-based	2.67 (4; 1.57)	3.96 (3; 2.12)	.09
PM event-based	3.84 (4; 1.74)	3.33 (2; 1.73)	.30
PM total	7.80 (8; 2.15)	6.00 (6; 2.24)	.03 (.026)
PM recognition	5.71 (6; .67)	5.22 (5; .83)	.03 (.032)
PM time-based failures	.55 (0; .76)	1.00 (0; 1.32)	.49
PM event-based failures	.65 (0; .80)	1.22 (1; .83)	.04 (.041)
Loss of time errors	.39 (0; .85)	1.11 (0; 1.45)	.09
Loss of content errors	.82 (1; .87)	.33 (0; .80)	.11
Task substitution errors	.27 (0; .57)	.22 (0; .44)	.97

Notes: Data presented as mean (median and SD) unless otherwise noted. iRBD-MCI = iRBD with mild cognitive impairment; iRBD-NC = iRBD without mild cognitive impairment; PM = prospective memory. PM total = (time-based PM + event-based PM). All between-group comparisons are based on Mann–Whitney U Test. Bonferroni correction for nine PM comparisons was applied ($\alpha < .0055$).

and motor performance (MDS-UPDRS III). Preliminary analyses were conducted to assess possible violations of the assumptions of linearity, multicollinearity, and homoscedasticity. However, the data violated the assumption of normality. Age (beta value non-significant) and MDS-UPDRS III (beta value .55) were entered in Step 1 explaining 29.5% of the variance in MDS-UPDRS II. After entry of event-based PM at Step 2, the total variance explained by the model as a whole was 29.9%, $F(3, 83) < 11.80$, $p < .01$. Event-based PM explained only an additional .4% of the variance in IADL, after controlling for age and MDS-UPDRS III. The association between UPDRS-III and UPDRS-II total scores in iRBD was significant ($r = .542$ $p < .001$).

Table 6. Cognitive performance on neuropsychological tests of iRBD-NC vs. iRBD-MCI.

	iRBD-NC ($N = 51$)	iRBD-MCI ($N = 9$)	p value (effect size) iRBD-NC vs iRBD-MCI
MoCA (screening)	24.74 (24.50; 1.89)	19.25 (19.50; 2.77)	<.01 (<.0005)* (0.61)
1. *Attention and WM*			
TMT-A	42.54 (37; 20.17)	51.13 (50; 14.05)	.10
LNS (WAIS-III)	7.58 (7; 2.56)	7.00 (7; 2.88)	.85
2. *Executive functions*			
TMT-B	99.68 (87.50; 52.18)	202.50 (160; 97.24)	<.01 (<.0005)* (0.48)
PST interference	37.20 (35.50; 8.23)	47.38 (40.50; 22.65)	.15
3. *Episodic memory*			
RAVLT immediate recall	38.56 (39; 7.89)	30.25 (30; 7.03)	.03 (.032)
RAVLT retention	6.38 (6.50; 2.86)	5.00 (5; 2.00)	.14
RAVLT recognition	42.06 (43; 5.16)	41.00 (41.50; 5.93)	.89
4. *Psychomotor speed*			
SDMT	39.35 (38; 6.85)	34.12 (35; 14.16)	.05 (.045)
GPT upper limbs	177.34 (164.50; 46.66)	188.25 (198.50; 29.81)	.28

Notes: Data presented as mean (median and SD) unless otherwise noted. MoCA = Montreal Cognitive Assessment; (1) attention and WM = working memory (TMT-A = Trail Making Test, Part A and LNS = Letter-Number Sequencing from Wechsler Adult Intelligence Scale, Third Revision); (2) executive function (TMT-B = Trail Making Test, Part B and PST = Prague Stroop test interference condition); (3) episodic memory (RAVLT = Rey Auditory Verbal Learning Test total immediate recall (the sum of all correct responses given over the five consecutive trials (T1 + T2 + T3 + T4 + T5), retention (delayed recall after 30 min) and total recognition), and (4) psychomotor and motor speed of upper limbs (SDMT = Symbol Digit Modalities Test and GPT = Grooved Pegboard Test). All between-group comparisons are based on Mann–Whitney *U* Test. By p levels in parentheses we aimed at showing that the comparisons would still survive Bonferroni correction for ten comparisons ($\alpha < .005$).

*Still significant after Bonferroni correction.

Imaging analyses

After showing a significant correlation between reduction in striatal and putaminal ^{123}I-FP-CIT uptake indices and time-based PM (Table 4), we investigated whether there are between-group differences in time-based PM in iRBD divided into a group in the first quartile (Q_1) with the lowest DaTscan sum striatal (DaTscan total) indices (i.e. patients with highest dopaminergic cell loss) and the rest ($Q_2 + Q_3 + Q_4$). This analysis did not show a significant difference in time-based PM in iRBD based on the Mann-Whitney *U* Test ($p = .29$).

Discussion

The present study aimed at investigating the relationship between explicit memory functioning and demographic, clinical, and imaging findings in iRBD. In general, we showed significant differences in cognitive functioning (memory, executive functions) between iRBD and NC which is in accordance with previous studies (Ferini-Strambi et al., 2004; Massicotte-Marquez et al., 2008; Terzaghi et al., 2008). Furthermore, our results indicate that MCI status in iRBD is not significantly related to PM performance despite a trend towards significance.

More specifically, we focused on the relationship between retrospective and prospective components of explicit memory and especially whether there is a differential impairment of time-based versus event-based PM. Regarding the retrospective component of explicit memory we found a significant impairment of each of basic explicit memory mechanisms in iRBD in comparison to controls in verbal learning (immediate recall), retention and recognition in RAVLT, which is in accordance with previous studies (Ferini-Strambi et al., 2004; Gagnon et al., 2009; Massicotte-Marquez et al., 2008; Terzaghi et al., 2008); only Massicotte-Marquez et al. (2008) have not found a deficit in retention in iRBD patients.

A novel piece of information in this respect is a differential impairment of event-based but not time-based PM in iRBD in the present study. Furthermore, iRBD patients showed significantly more event-based PM failures (true prospective component deficits) in comparison to controls. We surmise that a selective event-based PM impairment is interconnected with frank retrospective component deficits in retention and especially in recognition. This is because the stimulus presented during intention formation and retention that triggers the action to be performed in future in the event-based PM paradigm is presented again before intention initiation and execution. Consequently, when retrospective retention and recognition are impaired as indicated by more event-based PM failures, the same processes are recruited during event-based PM intention execution. We assume in accordance with dual-store models of memory that rehearsal is critical for encoding and retention of information in PM (Atkinson & Shiffrin, 1968; Raaijmakers & Shiffrin, 1980). However, the reason for selective event-based PM impairment that does not extend to time-based PM impairment as is the case in PD (Ramanan & Kumar, 2013) is not clear. We present two convergent explanations. We suppose that the first possible mechanism appeals to external cues. Cues encountered in the environment during the retention interval (a watch on the table in the time-based condition) prompted retrieval of the intended action creating Intention Superiority Effect, in which reaction times were more efficient to intention in a subsequent time-based rather than event-based task (Goschke & Kuhl, 1993; Kvavilashvili & Fisher, 2007; Sellen, Louie, Harris, & Wilkins, 1997). The second mechanism appears to converge nicely with findings that PM performance significantly improves when the retention interval contains breaks, particularly when the breaks are unfilled (Hicks, Marsh, & Russell, 2000). The time-based condition was in our design always presented first, so it did not suffer from proactive interference as did event-based from time-based condition and event-based condition was always presented directly after time-based condition, so there was no preceding break; time-based condition was therefore boosted by the primacy effect (Hicks et al., 2000; Murdock, 1962; Postman & Keppel, 1977; Underwood, 1957).

Furthermore, our results remained stable even after we considered important variables (covariates) that could influence the results of our non-parametric analyses, such as age, education, global cognitive performance (MoCA), and retrospective episodic memory measures (RAVLT). However, the results of this parametric analysis based on ANCOVA should be taken with caution and were done only for justification of the results of non-parametric analyses; the distribution of some variables is not normal and e.g. event-based PM does not fulfill the homogeneity of variance requirement. In the case of the standard regression, cognitive and clinical variables explained a large proportion (43–59%) of the variance in PM total, time-based and recognition. However, in PM event-based, the model was non-significant which is indicative that the difference in event-based PM in NC vs. iRBD was not influenced by those variables.

Hierarchical multiple regression provided negative results regarding the question of whether PM explains the variability in IADL in iRBD. It is MDS-UPDRS, Part III (beta value .55) but not age (beta value non-significant) that explained about one-third of the variability in IADL as measured by MDS-UPDRS, Part II. Hence, we conclude that the severity of motor impairment, although very mild, is related to IADL impairment in iRBD whereas cognitive factors such as PM functioning do not affect IADL. It remains an open question whether MDS-UPDRS, Part II can be taken as a representative measure of IADL in iRBD which leads several authors in PD research to the development of more sensitive and comprehensive measures for IADL measurement (Brennan et al., 2016; Shulman et al., 2016).

In the imaging part of the study, we have found a positive correlation between time-based PM performance and reduced striatal dopamine uptake on the more affected side. However, a between-group comparison in PM functioning of iRBD patients with more severe and less severe dopaminergic cell loss was not significant. This finding could be related to the idea that there is a direct connection between the dopaminergic system and the speed of an internal clock in early PD patients and that RBD associated with PD is a marker of worse cognitive functioning (Chahine et al., 2016; Malapani et al., 1998). Time-based PM is dependent on the integrity of the internal clock for interval timing estimates and may underlie the association observed in the present data (Buhusi & Meck, 2005; Costa et al., 2008; Labelle, Graf, Grondin, & Gagne-Roy, 2009; Smith, Harper, Gittings, & Abernethy, 2007). We believe, therefore that this association reflects an early internal clock impairment related to a dopaminergic deficit in iRBD patients and this interval timing deficit causes a selective dissociation between time-based and event-based PM and DaTscan results.

In general, the analysis of iRBD-NC vs. iRBD-MCI showed significant differences in the neuropsychological battery in set shifting (TMT-B) with medium effect size, and a trend for differences in learning (RAVLT immediate recall) and psychomotor speed (SDMT). These results are consistent with previous findings in which iRBD performed worse than controls and even than PD without RBD in these measures (Gagnon et al., 2009). Regarding PM performance iRBD-MCI were worse than iRBD-NC on PM measures assessing total PM delayed recall performance (with a non-significant trend favoring time-based rather than event-based PM impairment), PM recognition, and event-based PM failures. The results are in accordance with previous studies showing that iRBD-MCI has delayed memory as well as prospective and retrospective memory deficits (Gagnon et al., 2009; Marcone et al., 2017; Zhang et al., 2016). A recent study showed that cognitive tests assessing attention and executive functions predicted early conversion to dementia in RBD patients (Marchand et al., 2017). It would be intriguing to study whether prospective memory deficit is a risk factor for conversion into a specific subtype of synucleinopathy (Iranzo et al., 2010).

The present study has several limitations. First, DaTscan, MRI, and polysomnography were not performed in NC. However, none of NC indicated sleep problems, psychiatric, or neurological disease. Second, patients with periodic leg movements in REM sleep (PLMS) were not excluded because OSA and PLMS exclusion would lead to a significant reduction of the sample size (e.g. 46% of our iRBD patients had PLMS). However, PLMS frequency was associated with greater decline in cognition and neurocognitive dysfunction is commonly observed in patients with OSA (Leng et al., 2016; Zhou, Camacho, Tang, & Kushida, 2016). Third, our PM examination was performed in clinical settings and is an abbreviated version of a standard clinimetric tool for PM measurement (Bezdicek, Raskin et al., 2014; Raskin, 2009; Raskin et al., 2010). We could not estimate important variables in PM performance, such as exact time response accuracy, whether PM performance declines with higher cognitive load (interference effects), and whether a longer retention interval or distinctiveness of stimuli or focal or non-focal conditions play an important role in intention execution (Kliegel et al., 2011; Kvavilashvili & Fisher, 2007). Fourth, our parametric analyses should be taken just as support of non-parametric findings because the data violated some of the assumptions for ANCOVA or multiple regression (Tabachnick & Fidell, 2012).

In conclusion, the current study provides new clinical insights into the impaired mechanisms involved in PM functioning of iRBD patients. We argue for differential impairment of event-based PM functioning in iRBD which may be related to severely impaired retention

and recognition mechanisms that were observed also in early PD patients (Bronnick, Alves, Aarsland, Tysnes, & Larsen, 2011; Chahine et al., 2016; Chiaravalloti et al., 2014; Cohn, Giannoylis, De Belder, Saint-Cyr, & McAndrews, 2016). On the other hand, we have shown a medium association between time-based PM and dopaminergic depletion in iRBD which may reflect early signs of internal clock dysregulation (Malapani et al., 1998). Most importantly, the study has generated several interesting avenues for future clinical research of cognitive impairment in iRBD.

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The authors have no financial interests in the present research and have nothing to disclose. A proprietary test (Memory for Intentions Screening Test; MIST) was legally purchased by Psychological Assessment Resources (PAR) and an official Czech translation and back-translation of the MIST authorized by PAR and Professor S Raskin, PhD. MIST Czech version is the property of PAR, and the authors of the study have no financial interest in the test.

Authorship statement

Drs Ondřej Bezdíček, Petr Dušek, Evžen Růžička and Karel Šonka designed the study. Dr. Ondřej Bezdíček conducted the statistical analyses. Drs Tomáš Nikolai, Jiří Nepožitek, Pavla Peřinová, David Kemlink, Pavel Dušek, Iva Příhodová, Simona Dostálová, Veronika Ibarburu Lorenzo y Losada, and Bezdíček conducted the study recruitment, data collection, and clinical intervention. Drs Jiří Trnka, Karel Kupka, Zuzana Mecková, Jiří Keller, and Josef Vymazal, provided the expertise and data collection and interpretation of DaTscan and MRI. Dr Ondřej Bezdíček drafted the manuscript while all co-authors provided feedback and approved the final version.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Appendix 1

Table A1. Correlations between demographic, clinical and prospective and retrospective memory measures for NC (N = 30) and iRBD (N = 60) separately.

	PM time-based (NC vs iRBD)	PM event-based (NC vs iRBD)	PM total (NC vs iRBD)	PM recognition (NC vs iRBD)
Age (years)	**−.24 vs −.25**	**−.16 vs −.12**	**−.19 vs −.29***	**−.49† vs −.34†**
Education (years)	**.27 vs .11**	**.48† vs .10**	**.51† vs .20**	**−.01 vs .43‡**
Gender	**−.23 vs −.15**	**−.22 vs −.11**	**−.27 vs −.20**	**.08 vs .05**
iRBD duration (years)	−.13	−.40‡	−.38‡	−.03
MoCA	**.30 vs .46‡**	**.27 vs .01**	**.37* vs .36†**	**.01 vs .46‡**
BDI-II	**.29 vs −.12**	**.07 vs −.08**	**.25 vs −.18**	**−.08 vs −.15**
State anxiety (STAI-X1)	**.06 vs .09**	**.05 vs −34†**	**.12 vs −12**	**−.20 vs −.28***
Trait anxiety (STAI-X2)	**.39↑ vs −.01**	**.02 vs −.15**	**.38↑ vs −12**	**−.09 vs −.29***
ESS	−.02	−.43‡	−.33†	−.03
AHI	−.24↑	.10	.05	−.08
UPDRS-II	−.04	−.36†	−.31†	−.18
UPDRS-III	−.19	−.40‡	−.44‡	−.20‡
DaTscan total	.30*	.12	.09	.03
DaTscan striatum	.33*	−.06	.14	−.03
DaTscan putamen	.26↑	−.08	.10	−.02
RAVLT immediate	**.02 vs .49‡**	**.37* vs .03**	**.21 vs .38***	**.04 vs .30†**
RAVLT retention	**.19 vs .44‡**	**.34 vs .17**	**.32 vs .43***	**−.09 vs .27‡**
RAVLT recognition	**.21 vs .51‡**	**.25 vs .06**	**.26 vs .40†**	**−.05 vs .23**

Note. All correlations are based on Spearman rank order correlation except for gender (based on point-biserial correlation) and all correlations are based on both samples except for iRBD duration, ESS, UPDRS-II and III and DatScan which are based only on iRBD sample; PM = prospective memory; MoCA = Montreal Cognitive Assessment Czech version; BDI-II = the Beck Depression Inventory, Second Edition; STAI = the State-Trait Anxiety Inventory (state anxiety, X1) and (trait anxiety, X2); ESS = Epworth Sleepiness Scale; AHI, apnea–hypopnoea index; UPDRS-II and III, Unified Parkinson's Disease Rating Scale, Part II and III; DaTscan total = sum of striatal indexes from both sides; DaTscan striatum, DaTscan putamen = lower value of striatal and putaminal index, respectively. RAVLT = Rey Auditory Verbal Learning Test. Separate correlations in bold.

↑ $p < .10$; * $p < .05$; † $p < .01$; ‡ $p < .001$

Olfactory dysfunction in a Czech idiopathic REM sleep behaviour disorder patient cohort

Čichová dysfunkce u české skupiny pacientů s idiopatickou poruchu chování v REM spánku

Authors: Irene Dall'Antonia, Petr Dušek, Adam Tesař, Jiří Nepožitek, Simona Dostálová, Veronika Ibarburu Lorenzo y Losada, Iva Příhodová, Ondrej Bezdicek, Tomáš Nikolai, Pavla Peřinová, Pavel Dušek, Evžen Růžička, Karel Šonka

Affiliations: Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic

Abstract

REM sleep behaviour disorder (RBD) is a sleep abnormality heralded by the absence of physiological atonia in REM sleep and dream enactment behaviour. Idiopathic RBD (iRBD), diagnosed when no primary RBD cause can be identified, is a marker of prodromal synucleinopathy with a high conversion rate to overt neurodegenerative disorders from the synucleinopathy group. The aim of this cross-sectional study was to investigate olfactory function in iRBD patients and its relation to other symptoms.

This study included 54-iRBD patients with a median age of 67 (interquartile range 63-72) years; the 37-control subjects, matched by sex and age, had a median age of 67 (57.5-70) years. All subjects underwent a complex examination, which included olfactory testing using the University of Pennsylvania Smell Identification Test (UPSIT).

In total, 62.9 % of iRBD patients had either total loss of olfactory function or severe hyposmia. In contrast, only 8.1% of controls showed such a degree of olfactory dysfunction. Furthermore, we found that the percentage of REM sleep without atonia on polysomnography negatively correlates with the UPSIT score ($p < 0.01$).

This study demonstrated a significantly lower olfactory function in the iRBD group compared to controls.

Key words: Parkinson´s disease, phenoconversion, hyposmia, synucleinopathy, REM sleep behavior disorder.

Abstrakt

Porucha chování v REM spánku (REM sleep behavior disorder; RBD) je parasomnie charakterizovaná nepřítomností fyziologické atonie a chováním uskutečňování snu v REM spánku. Jako idiopatická RBD (iRBD) je RBD označena v nepřítomnosti jiné nemoci, která RBD obvykle vyvolává. iRBD je známkou prodromální fáze synucleinopatie a má vysokou míru fenokonverze do nemocí ze skupiny synucleinopatií. Cíl této průřezové studie byl zjistit stav čichové funkce u iRBD pacientů a její vztah k jiným symptomům.

Do studie bylo zahrnuto 54 pacientů s mediánem věku 67 let (mezikvartilové rozpětí 63-72); a 37 kontrolních subjektů s mediánem věku 67 (57.5-70) let, které byly spárovány podle věku a pohlaví. Všichni účastníci studie absolvovali komplexní vyšetření, které obsahovalo identifikační čichový test Pensylvánské univerzity (University of Pennsylvania Identifaction test; UPSIT).

Úplnou ztrátu čichu anebo jeho těžkou dysfunkci mělo 62.9% iRBD pacientů, přitom u kontrolních subjektů to bylo pouze 8.1%.

Porucha atonie v REM spánku v polysomnografii nepřímo korelovala se skóre UPSIT ($p < 0.01$).

Studie prokázala významně horší čich u iRBD pacientů než u kontrolních osob.

Kličová slova: Parkinsonova nemoc, fenokonverze, hyposmie, synucleinopatie, porucha chování v REM spánku.

Introduction

REM sleep behaviour disorder (RBD) is a parasomnia manifesting with a loss of physiological atonia in REM sleep associated with dream enactment [1]. The prevalence of RBD is estimated as 1-2% in the population over 50 years of age [2, 3]. In the majority of RBD patients, no cause of this abnormality can be identified and this disorder is considered as idiopathic RBD (iRBD) [4]. Following the discovery of RBD, it became clear that the vast majority of iRBD subjects convert to overt synucleinopathy disorders, such as Parkinson's disease (PD) or dementia with Lewy bodies (DLB) and multiple system atrophy; iRBD is therefore considered as a marker of prodromal phase of neurodegeneration [5]. A high rate of phenoconversion to synucleinopathies has been confirmed in several longitudinal studies with RBD patients [6-8], including our recent study, where a conversion rate of 32.4% within 5 (median, range 1-14) years follow-up was observed [9].

In addition to RBD, a wide array of symptoms, including olfactory and autonomic impairment, have been shown to precede or occur in parallel with the manifestation of motor symptoms in PD and other synucleinopathies. Olfactory threshold has been shown to correlate with the Hoehn and Yahr classification of disease progression in PD patients [10]. Given the extensive clinical evidence, olfactory dysfunction is included in the supportive diagnostic criteria for PD by the European Federation of Neurological Societies [11]. Furthermore, hyposmia has been shown to precede other markers of prodromal neurodegeneration by several years [12], allowing the early identification of patients at a high risk of future synucleinopathy diagnosis. The recent largest multicentre study of iRBD phenoconversion predictors has shown that impaired olfaction represents the hazard ratio of phenoconversion into PD or DLB of 2.62 (1.7-4.1) in the mean follow-up of 4.6 (range 1 – 19) years [13]. The aim of this cross-sectional study was to detail properties of olfactory dysfunction and its associations with other relevant symptoms in a cohort of iRBD patients compared to control subjects.

Method of investigation

Patients were screened in a stepwise manner following a public advertisement and internet survey [14]; RBD was diagnosed following the International Classification of Sleep Disorders, third edition [15]. Exclusion criteria were: overt parkinsonism (diagnosed according to the MDS criteria [16]) or dementia (diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders [17]), severe obstructive sleep apnea defined by apnea-hypopnea index (AHI) ≥ 30, and the presence of other disorders that could cause secondary RBD (for example narcolepsy or lesions in the brainstem on brain MRI).

Patients in the study underwent a single night video-polysomnography (PSG), which was performed according to the 2014 Academy of Sleep Medicine (AASM) guidelines including the superficial electromyography of bilateral flexor digitorum superficialis muscles. Sleep analysis was done in standard 30-second epochs. Increased tonic or phasic activity recorded on the electromyography (EMG) of the mentalis muscle during PSG, known as REM sleep without atonia (RWA), was thoroughly investigated. A 30-second epoch of REM sleep was scored positive for RWA when, at least 50% of its duration had a chin EMG amplitude greater than the minimum amplitude in NREM sleep or excessive transient muscle activity was found in at least 50% of the epoch divided into three-second mini epochs [18]. RWA is presented as the percentage of epochs scored as RWA from the total number of epochs scored as REM sleep. Sleep efficacy (SE), the proportion of total sleep time relative to the time in bed, was used as a simple marker of sleep quality. AHI represents the mean number of apnea and hypopnea events in one hour of sleep.

The cognitive performance was evaluated by the Montreal Cognitive Assessment (MoCA) Czech version [19], which was administered by a clinical neuropsychologist. The autonomic symptom questionnaire, SCOPA-AUT (Scales for Outcomes in Parkinson's Disease-Autonomic), was completed by participants and consisted of a 23-item questionnaire with a maximum score of 69 points [20, 21]. To assess motor function, patients were examined by a certified neurologist using the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), part III [22].

To analyse olfaction the University of Pennsylvania Smell Identification Test (UPSIT) was used. It entails the identification of 40 different smells in a multiple-choice manner [23]. The UPSIT has been validated for detection of olfactory dysfunction and proved to possess high sensitivity and high reliability in various populations and disorders [24]. The Czech translation of the German version of the UPSIT (manufactured by Sensonics International, USA) was administered in a standard examination room in the morning hours. The total score ranging from 0 to 40 points was calculated using an answer key from the supplier. The results were then evaluated using the administration manual obtained from the manufacturer, according to age and sex specific cut-off scores. Subjects were divided into five categories according to their UPSIT score: normosmic (men: >33, women: >34), mild microsmic (men: 30-33, women: 31-34), moderate microsmic (men: 26-29, women: 26-30), severe microsmic (men: 19-25, women: 19-25), and anosmic (men: <19, women: <19) [25].

Age and sex matched controls underwent the same protocol as RBD patients. The control group was composed of healthy volunteers without a history of major neurological or sleep disorders. RBD in control subjects was excluded by PSG.

The protocol was approved by the Hospital Ethics Committee, all participants gave written consent before being enrolled in the study.

Statistical analysis

The Statistical Package for the Social Sciences 20 was used to perform all statistical analysis. First, we applied Shapiro-Wilk test of normality. Depending on their distribution, data are presented as mean and standard deviation or median and interquartile range. For between-group comparison we used t-test for variables with normal distribution and Mann-Whitney U test for non-normally distributed variables. P-values below 0.05 were regarded as significant. We also studied Pearson correlation coefficients to identify linear correlation between individual variables or Spearman correlation analysis for variables with non-normal distribution in both groups.

Results

A total of 54 RBD patients and 37 healthy controls were included in the study; their demography and clinical characteristics are summarized in Table 1. Several statistically significant variables were calculated in iRBD patients compared to controls. RBD patients had a higher median MDS UPDRS III and a higher median SCOPA-AUT score than control subjects ($p < 0.01$). The median MoCA score was found to be lower in iRBD patients ($p = 0.02$). Of note, the median RWA was considerably higher in iRBD patients at 50.7% compared to 2.0% in controls ($p < 0.01$). Lastly, the median AHI and BMI in iRBD patients was considerably lower than in controls ($p < 0.01$).

UPSIT scores for patients and controls are shown in Table 2. A lower UPSIT score was observed in iRBD patients.

Classification of olfactory function into five groups according to UPSIT scores is shown in Table 3. Markedly, 37.0% of iRBD patients were found to be anosmic, whereas only 2.7% of controls were anosmic. Similarly, 25.9% of iRBD patients suffered from severe microsmia, compared to 5.4% of control subjects.

The associations between UPSIT and other relevant clinical parameters are displayed in Table 4.

A negative correlation was found between the UPSIT score and RWA (Figure 1). The associations between UPSIT and other examined parameters were not statistically significant.

Table 1. Clinical characteristics of iRBD and control subjects. Variables are expressed as mean and standard deviation or as median and interquartile range. Statistically significant results (p <0.05) are marked in bold text.
Legend: p= probability, n= number, BMI= body mass index, MoCA = Montreal Cognitive Assessment, MDS UPDRS III = Movement Disorder Society Unified Parkinson's Disease Rating Scale, part III, SE= sleep efficacy, AHI: apnoe-hypopnoe index, RWA= REM sleep without atonia, iRBD= idiopathic REM sleep behaviour disorder, SCOPA AUT=

	iRBD patients n=54	**Controls n=37**	**p value**
Males / Females (n)	48 / 6	30 / 7	0.31
Age (years)	67 (63.0-72.0)	67 (57.5-70.0)	0.23
BMI	24.6 ±3.5	26.9 ±3.8	**<0.01**
MDS UPDRS III score	4.0 (2.0-7.0)	2.5 (1.0-4.5)	**<0.01**
MoCA score	24.0 (23.0-26.0)	25.0 (24.0-27.0)	**0.02**
Duration of RBD symptoms (years)	7.6 ±9.0	N/A	N/A
SE (%)	77.3 (68.2-84.8)	76.5 (65.1-84.9)	0.90
AHI	7.8 (1.0-14.4)	14.1 (5.8-19.1)	**<0.01**
RWA (%)	50.7 (28.2-70.1)	2.0 (0.1-3.6)	**<0.01**
SCOPA-AUT score	9.0 (6.0-14.0)	6.0 (4.0-8.0)	**<0.01**

Scales for Outcomes in Parkinson's Disease-Autonomic, N/A= not applicable.

Table 2. UPSIT score. Statistically significant results (p < 0.05) are marked in bold text.

	iRBD patients n=54	**Controls n=37**	**p value**
UPSIT score both sexes	21 (16-30)	32 (29-34)	**<0.01**
UPSIT score males	20.5 (15.5-30)	31.5 (29-34)	**<0.01**
UPSIT score females	25.5 (24-32)	33 (32-34)	0.06

Legend: p= probability, n= number, UPSIT= University of Pennsylvania Smell Identification Test

Table 3. Classification of UPSIT results.

Legend: n= number, iRBD= idiopathic REM sleep behaviour disorder.

Classification of olfactory function	iRBD patients		Controls	
	n (total=54)	% (total=100)	n (total=37)	% (total=100)
normosmia	4	7.4	9	24.3
mild microsmia	11	20.4	18	48.6
moderate microsmia	5	9.3	7	18.9
severe microsmia	14	25.9	2	5.4
anosmia	20	37.0	1	2.7

Table 4. Correlation of the UPSIT score and other clinical variables in iRBD patients. Statistically significant results are marked in bold text.

Legend: n= number of patients, MoCA = Montreal Cognitive Assessment, MDS-UPDRS III = Movement Disorder Society Unified Parkinson's Disease Rating Scale, part III, RWA = percentage of REM sleep without atonia, SCOPA-AUT = Scales for Outcomes in Parkinson's Disease-Autonomic, vs = versus.

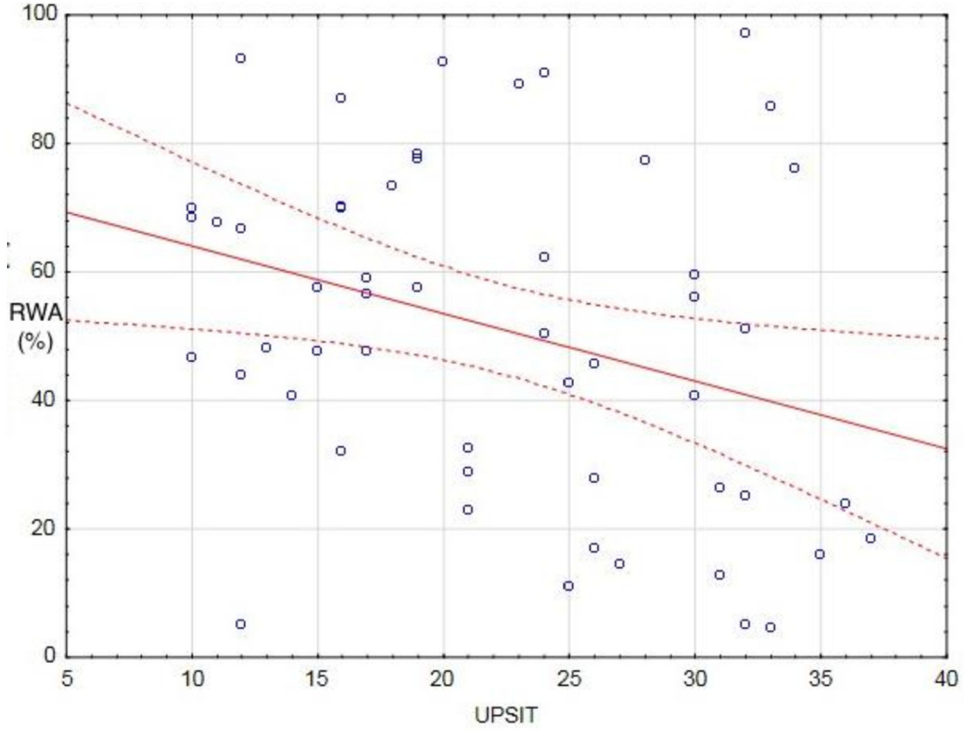
UPSIT score vs	RWA	MoCA score	SCOPA AUT score	MDS-UPDRS III score	Log years of RBD	PSG sleep efficacy (%)
Spearman correlation coefficient	**-0.30**	0.07	0.10	-0.04	0.05	0.15
t(N-2)	**-2.32**	0.52	0.73	-0.26	0.33	1.10
P value	**0.03**	0.60	0.47	0.78	0.75	0.28

Figure 1. Scatter graph of Spearman correlation between RWA and UPSIT.

Legend: RWA = percentage of REM sleep without atonia out of total REM sleep duration, UPSIT = University of Pennsylvania Smell Identification Test score.

Obrázek 1. Bodový graf znázorňující korelaci mezi RWA a UPSIT skóre.

Legenda: RWA = podíl REM spánku bez svalové atonie vzhledem k celkovému trvání REM spánku v procentech, UPSIT = skóre identifikačního čichového testu Pennslyvanské Univerzity


100
80
60
40
20
0
RWA
(%)
5
10
15
20
25
30
35
40
UPSIT

Discussion

This study found lower olfactory identification capabilities in iRBD patients compared to controls. In the iRBD group, 62.9 % of patients were classified as having severe microsmia or anosmia. In contrast, only 8.1% of our control subjects had either severe microsmia or anosmia. These results are in line with a previous Italian and French Canadian study, where 61.1% of iRBD patients versus 16.6% of controls showed abnormal olfactory function [26]. Similarly, in the Japanese population, a significant olfactory dysfunction in iRBD patients compared to that of control subjects was found [27]. Of note, iRBD patients with olfactory function in the lowest tercile compared to other iRBD patients, have been shown to have a significantly higher relative risk of conversion to DLB and therefore can predict phenoconversion into overt synucleinopathies in a relatively short time frame [28]. More pronounced brain abnormalities typical for synucleinopathies were found in iRBD patients with hyposmia compared to those with normal olfactory function using fluorodeoxyglucose positron emission tomography imaging [29].

As expected, olfactory function differed between sexes in our study. The median UPSIT score was higher for females in both the control and iRBD groups. This is in accordance with studies in various ethnic groups, which have consistently shown that olfactory identification capabilities are higher in women than in men [30]. This implicates that different UPSIT cut-off values for identification of high phenoconversion risk have to be defined for men and women.

A lower UPSIT score was associated with a decreased ability to maintain REM sleep atonia. This finding supports the theory postulated by Braak et al stating that in the first stage of the spread of synuclein pathology, the anterior olfactory nucleus and lower parts of brainstem are affected, followed by affliction of areas in the rostral pons [31] responsible for maintenance of REM sleep atonia. The negative association between olfactory function and severity of RWA indicates that areas of the brain ensuring olfaction and sleep are affected in close succession and/or similar intensity in the early phases of the synucleinopathy disease process. The relevance of RWA as an early sign of synuclein-mediated neurodegeneration has been highlighted as an intriguing area for further investigation [32]. We found no significant correlation between UPSIT and the duration of RBD symptoms. This could be influenced by unreliable recall of the RBD duration by patients.

Some limitations of the study should be noted. Firstly, the iRBD and control group contained a low number of female subjects and thus results for the female cohort have a limited validity. A further limitation is the statistically lower AHI in iRBD patients compared to control subjects despite the inclusion criteria concerning AHI were in both groups identical. This difference can be explained by the statistically higher BMI in control subjects compared to iRBD patients. A higher BMI is associated with the presence and severity of obstructive sleep apnea [33]. Lastly, this study did not include odour threshold testing, which could theoretically bring additional information regarding olfactory function.

In summary, this study shows that Czech iRBD patients have significantly impaired olfaction compared to control subjects, supporting results from previous studies in other populations.

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Prevalence kouření u středoevropských pacientů s narkolepsií s kataplexií, narkolepsií bez kataplexie a idiopatickou hypersomnií

Smoking Prevalence in Group of Central--European Patients with Narcolepsy-cataplexy, Narcolepsy without Cataplexy and Idiopathic Hypersomnia

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.
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P. Peřinová[1], A. Wierzbicka[2], E. Feketeová[3], D. Kemlink[4], P. Kovalská[1], J. Nepožitek[1], V. Ibarburu[1], E. Králíková[5], S. Nevšímalová[1], K.Šonka[1]

[1] Centrum pro poruchy spánku a bdění, Neurologická klinika a Centrum klinických neurověd 1. LF UK a VFN v Praze
[2] Department of Clinical Neurophysiology, Institute of Psychiatry and Neurology, Warsaw, Poland
[3] Neurologická klinika LF UPJŠ a UN L. Pasteura Košice
[4] Neurologická klinika a Centrum klinických neurověd 1. LF UK a VFN v Praze
[5] Centrum pro závislé na tabáku, 3. interní klinika – klinika endokrinologie a metabolizmu 1. LF UK a VFN v Praze

✉
MUDr. Pavla Peřinová
Centrum pro poruchy spánku a bdění
Neurologická klinika a Centrum klinických neurověd
1. LF UK a VFN v Praze
Kateřinská 30
128 21 Praha
e-mail: pavla-perinova@seznam.cz

Přijato k recenzi: 2. 1. 2017
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Souhrn
Cíl: Zmapování závislosti na tabáku u osob s narkolepsií s kataplexií (NC), s narkolepsií bez kataplexie (N) a s idiopatickou hypersomnií (IH). Ověření hypotézy, že ve střední Evropě je prevalence kouření u NC proti N a IH vyšší. *Soubor a metodika:* Podle vlastního strukturovaného dotazníku jsme se ptali na kouření 172 dospělých pacientů, z toho 111 s NC, 37 N a 24 IH v průběhu ambulantního vyšetření nebo telefonického pohovoru. *Výsledky:* Pravidelnými kuřáky ve skupině NC je 46,8 % pacientů, ve skupině N 18,9 % pacientů a ve skupině IH 12,5 % pacientů. Zastoupení kuřáků ve skupině NC je významně vyšší oproti hodnotě 16,4 % kuřáků ve skupině N a IH dohromady (p = 0,0006; two-sided Fischer test). *Závěr:* Zastoupení kuřáků je u NC oproti běžné populaci více než dvojnásobné (prevalence aktivních denních kuřáků v České republice je 18 %) a je vyšší než u nemocných s N a IH dohromady.

Abstract
Aim: To map the prevalence of smoking among patients with narcolepsy-cataplexy (NC), narcolepsy without cataplexy (N) and idiopathic hypersomnia (IH) and verify whether smoking prevalence in NC patients is higher than in N and IH patients in Central Europe. *Methods:* We asked 172 adult patients about smoking (111 of them with NC, 37 with N and 24 with IH) using our own structured questionnaire during their outpatient examination or during phone interview. *Results:* Daily smokers represented 46.8% in the NC group, 18.9% in N and 12.5% in the IH group. The prevalence of smoking in the N and IH group together is 16.4%, i.e. significantly lower than the prevalence in the NC group (p = 0.0006, two-sided Fisher test). *Conclusion:* The prevalence of daily smoking among patients with NC is more than twice as high as in the Czech general adult population (18%), and higher than smoking prevalence among N and IH patients together.

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Klíčová slova
narkolepsie s kataplexií – narkolepsie bez kataplexie – idiopatická hypersomnie – hypocretin/orexin – závislost – kouření – nikotin

Key words
narcolepsy-cataplexy – narcolepsy without cataplexy – idiopathic hypersomnia – hypocretin/orexin – addiction – smoking – nicotine

Úvod

Narkolepsie s kataplexií (NC), narkolepsie bez kataplexie (N) a idiopatická hypersomnie (IH) jsou chronická neurologická onemocnění řadící se mezi centrální hypersomnie. Jejich společným projevem je nadměrná denní spavost.

NC je onemocnění s prevalencí přibližně 0,045 % v Severní Americe a Evropě [1]. Prvním vrcholem manifestace je věk 15–20 let, druhým pak období 35–40 let, ale nástup příznaků se může objevit kdykoli v rozmezí od dětství do přibližně 60 let [2]. Vedle nadměrné denní spavosti jsou pro NC typické kataplexie (opakované stavy svalové atonie během bdělosti, zpravidla vyvolané náhlou situací s emotivním významem, např. smíchem, pláčem nebo momentem překvapení) a dále spánková obrna a hypnagogické halucinace objevující se typicky na přechodu spánku a bdělosti a postihující přibližně polovinu nemocných. Většina pacientů má navíc fragmentovaný noční spánek. Při denním i nočním spánku se často podaří zachytit REM spánek v prvních 15 min od usnutí (Sleep Onset REM period; SOREMp). Etiopatogeneze nemoci spočívá ve vymizení neuronů produkujících hypokretin (Hcrt) v laterálním hypothalamu [3]. Ačkoli mechanizmus jejich úbytku není přesně znám, poznatky z posledních 20 let shodně ukazují na autoimunitní inzult zprostředkovaný T buňkami cílený specificky proti hypokretinovým neuronům u geneticky predisponovaných jedinců [4]. Svědčí pro to mimo jiné velmi silná asociace s HLA třídy I, zvláště pak s alelou HLA-DQB1*06:02, která je u nemocných s NC přítomna ve více než 85 % [5]. Dosavadní poznatky také uvádějí, že je tento specifický autoimunitní proces u geneticky vnímavých jedinců spuštěn různými environmentálními podněty, např. streptokokovou infekcí [6] nebo H1N1 vakcinací či samotnou H1N1 infekcí [7].

O etiopatogenezi N je známo velmi málo; nejsou dostatečné doklady o chybění hypokretinových neuronů a hladina Hcrt 1 v mozkomíšním moku je normální. Výskyt alely HLA-DQB1*06:02 se pohybuje asi kolem 40 %, přičemž v běžné populaci je to kolem 25 %. Vedoucím klinickým příznakem je nadměrná denní spavost, kataplexie se nevyskytují, rovněž spánková obrna a hypnagogické halucinace jsou přítomny podstatně méně často. Výskyt SOREMp je součástí diagnostických kritérií [8].

IH je vzácná nemoc s nadměrnou denní spavostí, která stejně jako N není vyvolána deficitem hypokretinu. Nemocní mívají obtíže s ranním probouzením, které je protrahované a často spojené s příznaky spánkové opilosti. Kataplexie chybí a nevyskytuje se SOREMp [9].

Závislost na tabáku patří celosvětově mezi nejrozšířenější závislosti, Českou a Slovenskou republiku a Polsko nevyjímaje. Prevalence současných kuřáků je podle výsledků z roku 2015 24 %, přičemž 18,2 % české populace nad 15 let je kuřáky pravidelnými (denními) [10]. Vzhledem k tomu, že nikotin má v malé dávce stimulační účinky na centrální nervový systém (CNS), je zajímavé sledovat jeho roli u nemocí, jejichž hlavním klinickým rysem je nadměrná denní spavost, zejména u centrálních hypersomnií. Jelikož jsou dosavadní data týkající se kouření u těchto nemocí omezená, rozhodli jsme se výskyt kuřáctví zmapovat na našem souboru českých, slovenských a polských pacientů. Zároveň jsme chtěli ověřit hypotézu, že je prevalence kouření u NC (Hcrt-deficientní onemocnění) oproti N s IH (Hcrt-non-deficientní onemocnění) vyšší i ve střední Evropě s dominantně slovanským obyvatelstvem podobně, jako prokázali Barateau et al ve Francii [11]. Šlo by tak o posílení domněnky, že se na vzniku závislosti na nikotinu u NC podílí odlišný patofyziologický mechanizmus související s nedostatkem Hcrt.

Tab. 1. Klinické a kuřácké charakteristiky souboru.

	NC (n = 111) průměr (SD)	N (n = 37) průměr (SD)	IH (n = 24) průměr (SD)
věk (roky)	43,5 (16,2)	40,2 (14,8)	38,4 (13,4)
muži/ženy (n/n)	53/58	16/21	9/15
BMI	28,7 (5,2)	26,1 (4,3)	24,6 (4,1)
věk vzniku nemoci (roky)	22,7 (10,0)	23,6 (12,2)	25,0 (12,6)
ESS	17,9 (3,6)	16,8 (3,6)	14,4 (3,6)
spánková efektivita (%)	83,4 (9,2)	90,9 (7,2)	91,0 (5,4)
kuřácké zvyklosti			
pravidelní kuřáci (%)	46,8	18,9	12,5
bývalí kuřáci (%)	15,4	18,9	20,8
celoživotní nekuřáci (%)	37,8	62,2	66,7
věk první cigarety (roky)	15,9 (4,2)	14,1 (2,8)	19,3 (4,9)
věk zahájení pravidelného kouření (roky)	19,5 (5,5)	16,1 (3,0)	22,3 (5,0)
počet vykouřených cigaret denně	14,0 (10,0)	16,7 (5,3)	13,9 (12,2)

NC – narkolepsie s kataplexií, N – narkolepsie bez kataplexie, IH – idiopatická hypersomnie, SD – standardní odchylka, BMI – body mass index, ESS – Epworth sleepiness scale, pravidelní kuřáci – v době dotazování alespoň jedna vykouřená cigareta denně, bývalí kuřáci – za život vykouřili více než 100 cigaret, ale v době dotazování již nekouří, celoživotní nekuřáci – méně než 100 vykouřených cigaret za život.

Soubor a metodika

Do studie bylo zařazeno celkem 172 dospělých pacientů, kteří jsou sledováni v Centru pro poruchy spánku a bdění při Neurologické klinice 1. LF UK a VFN v Praze (121 pacientů), na Neurologické klinice LF UPJŠ a UNLP v Košicích (11 pacientů) a Institutu neurologie a psychiatrie ve Varšavě (40 pacientů). Jednalo se o pacienty s jednoznačnou diagnózou NC, N, nebo IH. Všichni splnili diagnostická kritéria podle třetího vydání Mezinárodní klasifikace poruch spánku z roku 2014 (ICSD3). U nemocných, kteří byli diagnostikováni před rokem 2014, kdy byla vydána ICSD3, byla pečlivě zkontrolována konformita s ICSD3. Relevantní klinické údaje společně s výsledkem spánkové efektivity (tj. poměru mezi souhrnným trváním všech spánkových stadií a dobou strávenou na lůžku vyjádřeného v procentech) z noční polysomnografie byly doplněny z lékařské dokumentace pacientů.

Data týkající se kouření byla získána anamnesticky v průběhu ambulantního vyšetření nebo pomocí telefonického kontaktu, během nichž byly respondentům pokládány otázky z námi sestaveného strukturovaného dotazníku. Po úvodním dotazu na kuřáckou anamnézu byli účastníci studie rozděleni na

současné pravidelné kuřáky (tj. osoby kouřící alespoň 1 cigaretu denně), bývalé kuřáky (tj. osoby, které za svůj život vykouřily více než 100 cigaret, ale v současné době již nekouří) a na nekuřáky (celoživotně nevykouřili 100 a více cigaret), tedy ve shodě s terminologií WHO [12]. U bývalých a současných kuřáků byly otázky dále cíleny na věk první cigarety, věk zahájení pravidelného kouření a počet denně vykouřených cigaret. Rovněž bylo dotazem ověřeno, jaký typ kuřiva pacient preferoval.

Výsledná data zjištěná u jednotlivých skupin NC, N a IH byla nejprve porovnána s údaji platnými pro běžnou českou populaci, vycházejícími ze sociodemografického výzkumu pro Státní zdravotní ústav z roku 2015. Následně byly posouzeny výsledky skupiny NC oproti skupině N + IH.

Všechny statistické testy byly prováděny pomocí programu STATISTICA 12 CZ (StatSoft, Inc. 2013, www.statsoft.com). Kvalitativní znaky byly hodnoceny Fischerovým přesným dvoustranným testem, kvantitativní parametry vzhledem k jejich normálnímu rozdělení pak Studentovým t-testem s korekcí pro nestejné rozptyly.

Studii schválila Etická komise VFN a nemocní písemně vyjádřili souhlas s výzkumným zpracováním svých dat.

Výsledky

Klinická charakteristika a kuřácké zvyklosti

Soubor tvořilo 172 pacientů, z nichž 111 splňovalo diagnostická kritéria NC, 37 N a 24 IH. Charakteristika jednotlivých skupin vč. kuřáckých návyků je uvedena v tab. 1. Žádné signifikantní rozdíly v demografických parametrech nebyly nalezeny.

Srovnání NC oproti N + IH

Průměrný věk skupiny NC (n = 111) a skupiny N + IH (n = 61) se nelišil (p = 0,89). Na rozdíl od prevalence pravidelných kuřáků ve skupině NC (46,8 %) je prevalence pravidelných kuřáků ve skupině Hcrt-non-deficientních hypersomnií (N + IH) výrazně nižší (16,4 %; p = 0,0006; two-sided Fischer test). V počtu denně vykouřených cigaret, věku první cigarety a věku zahájení pravidelného kouření statisticky významný rozdíl nebyl prokázán.

Diskuze

Prevalence pravidelných kuřáků v české populaci nad 15 let je 18,2 % [10]. Prevalence pravidelných kuřáků ve skupině NC našeho souboru je tak více než dvojnásobně vyšší (46,8 %) než v běžné české populaci. Není však rozdíl v zastoupení bývalých kuřáků – 17,2 % v české populaci oproti 15,4 % u NC. Podíl kuřáků zastoupený u dalších dvou skupin nemocných je s českou populací srovnatelný (18,9 % v případě N) nebo dokonce nižší (12,5 % v případě IH).

Srovnání NC (onemocnění s chybějícím Hcrt 1) s N a IH (nemoci, které nemají alterovanou hypocretinovou transmisi) přineslo zjištění, že nemocní ve skupině NC referují pravidelné užívání tabáku statisticky významně častěji než nemocní ve skupině N + IH. Jedná se o výsledek podporující tvrzení, že mechanizmus vzniku závislosti je u NC od ostatních hypersomnií odlišný a mohl by souviset se snížením Hcrt transmise. Role Hcrt při vzniku závislostí je stále posuzována. Studie uvádějí vyšší míru impulzivity a vyhledávání smyslové zkušenosti u NC, která může vysvětlovat vyšší tendenci kouřit [13]. Naše výsledky jsou však odlišné oproti výsledkům pokusů na zvířatech, které naznačují, že stav nedostatku Hcrt představuje spíše protektivní faktor vzniku závislostí [14–16] a oproti klinické zkušenosti, že u pacientů medikovaných stimulancii nevzniká závislost [17,18]. Náš výsledek je ve shodě s francouzskou multicentrickou studií [11] a zdá se tedy, že není ovlivněn kulturními nebo etnickými rozdíly v přístupu ke kouření.

Limitem této práce je malý počet nemocných v jednotlivých skupinách, daný ovšem prevalencí sledovaných diagnóz.

Závěr

V našem souboru nemocných jsme prokázali více než dvojnásobně vyšší prevalenci kuřáků ve skupině NC oproti běžné české populaci a signifikantně vyšší prevalenci kuřáků ve skupině NC oproti skupině N a IH dohromady.

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Smoking Prevalence and Its Clinical Correlations in Patients with Narcolepsy-cataplexy

Pavla Peřinová[1], Eva Feketeová[2], David Kemlink[1], Petra Kovalská[1], Karolína Chlebušová[1], Jiří Nepožitek[1], Veronika Ibarburu[1], Eva Králíková[3,4], Soňa Nevšímalová[1], Karel Šonka[1]

[1]Centre for Sleep and Wake Disorders, Department of Neurology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic;
[2]Department of Neurology, Faculty of Medicine, Pavol Jozef Šafárik University in Košice and Louis Pasteur University Hospital, Košice, Slovak Republic;
[3]Institute of Hygiene and Epidemiology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic;
[4]Centre for Tobacco-Dependent, 3rd Department of Medicine – Department of Endocrinology and Metabolism, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic

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Abstract: Narcolepsy-cataplexy (NC) is a chronic neurological disease with suggested autoimmune etiopathogenesis. Nicotine stimulates central nervous system and smoking increases the risk of autoimmune diseases. Assessment of smoking habits and its correlation to clinical parameters among 87 adult NC patients (38 male, 49 female) included night polysomnography and multiple sleep latency test. In our sample, 43.7% NC patients were regular smokers, and 19.5% former smokers compared to 22.2%, and 12.6%, respectively, in the general population. Patients started to smoke in the mean age of 20.0 (SD ±6.0) years. 72.2% of NC smokers started to smoke before the onset of NC and the mean of the delay between smoking onset and NC onset was 9.1 (±5.8) years. We found

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Mailing Address: Prof. Karel Šonka, MD., DSc., Department of Neurology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Kateřinská 30, 120 00 Prague 2, Czech Republic; Phone: +420 224 965 568; e-mail: ksonka@lf1.cuni.cz

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a direct correlation between smoking duration and the number of awakenings, duration of N1 sleep, REM sleep latency, and apnoea/hypopnoea index (AHI), and, on the contrary, indirect correlation between smoking duration and N3 sleep duration, showing that smoking duration consistently correlates with sleep macrostructure. Smoking is highly prevalent in NC and has relationship with clinical features of NC.

Introduction

Narcolepsy-cataplexy (NC) is a chronic neurological disease with a prevalence of approximately 0.045% in North America and Europe (Ohayon et al., 2002). The manifestations of NC are excessive daytime sleepiness (EDS) and cataplexy, and roughly half of patients experience hypnagogic hallucinations and sleep paralysis. Additionally, most patients have fragmented night-time sleep. Dysregulation of REM sleep is typical, with REM sleep occurring within the first 15 minutes of sleep onset, termed sleep onset REM periods (SOREMp), during the day and at night (Dauvilliers et al., 2007). The age at onset varies from childhood to approximately 60 years of age, with manifestation most often at 15–20 years of age, and a second peak between 35 and 40 years of age (Dauvilliers et al., 2001).

The pathologic basis of the disease is a deficiency of neurons in the lateral hypothalamus that produce hypocretin (Thannickal et al., 2000). Although the exact mechanism of hypocretin deficiency is unknown, evidence from the past 20 years strongly favours an immune-mediated or autoimmune attack, targeting specifically hypocretin neurons in genetically predisposed individuals (Liblau et al., 2015). The hypothesis that a targeted immune-mediated or autoimmune attack causes the specific degeneration of hypocretin neurons arose mainly through the discovery of genetic associations, first with the HLA DQB1*06:02 allele (Mignot, 1998) and then with the T-cell receptor α locus (Hallmayer et al., 2009). It is suggested that specific autoimmune process is triggered by different environmental stimuli like streptococcal infection or anti H1N1 vaccination or H1N1 infection itself in genetically disposed subjects and is time limited (Partinen et al., 2014).

Dependency on tobacco is one of the most common dependencies in today's society, including the Czech Republic and Slovak Republic, with prevalence of about 30% in the population 15–64 years (Sovinová and Csémy, 2015). Smoking as related to NC deserves our interest for several reasons. Nicotine exhibits stimulatory effects (Boutrel and Koob, 2004), so patients might use it in attempt to suppress their EDS. Some studies report that NC is associated with higher levels of impulsiveness and the so-called sensation-seeking behaviour in this condition (Dimitrova et al., 2011), which might explain increased tendency to smoke. Smoking is a risk factor for development and progression of multiple sclerosis (Carlens et al., 2010; Wingerchuk, 2012; Hedstrom et al., 2013) and other inflammatory diseases such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, and

sarcoidosis (Carlens et al., 2010). It is thus possible to assume that smoking plays a role in the development of NC, even when smoking appears to cause multiple sclerosis in other ways than through the mediation of nicotine (Carlens et al., 2010).

This led us to find out about the proportion of our patients with NC who are smokers, and whether there is a relationship between smoking and the clinical parameters of NC.

Sample and Methods

Our study included 87 adult patients with NC we were able to contact over the course of 2015. All patients fulfilled the diagnostic criteria of the International Classification of Sleep Disorders, 2nd Edition (ICSD2; American Academy of Sleep Medicine, 2005). The records of subjects diagnosed before 2005 (the year of ICSD2 publication) were carefully checked and conformity with ICSD2 was verified. The study included 49 women and 38 men aged from 19 to 83 years, mean age of study participants was 46.6 (SD ±16.3) years. Mean age of onset of narcolepsy symptoms was 23.5 (±10.4) years. HLA DQB1*0602 genotyping was available for 83 patients 82 of whom were positive corresponding to commonly reported representation in NC (Liblau et al., 2015). Relevant clinical data including the results of polysomnography analysed according to American Academy of Sleep Medicine (AASM) guidelines (Iber et al., 2007) and Multiple Sleep Latency Test (MSLT) conducted according to AASM recommendations (Arand et al., 2005) and Epworth sleepiness scale (Johns, 1991) were completed based on patient medical records. Night polysomnography and MSLT were performed in patients who have had not been treated before or who were not taking drugs influencing sleep and mood ≥ 2 weeks.

The patients were asked about smoking according to our own structured questionnaire during their outpatient examination or in the form of phone interview. The questionnaire included the following items: classification into non-smokers (less than 100 cigarettes in life course), former smokers and current smokers (WHO, 2008). Former and present smokers were additionally subjected to targeted questions regarding age at the first cigarette, age of regular smoking onset, number of cigarettes smoked in one day and attempts to stop smoking.

All categorical data were compared using two sided chi-squared statistics. Since polysomnographic parameters are by their nature not normally distributed, we used for inter-group comparisons Mann-Whitney U-test, other parameter were compared using parametric T-tests. Correlations were calculated as Pearson's correlations coefficients.

All statistical analyses were conducted using STATISTICA (data analysis software system), version 12. www.statsoft.com, StatSoft, Inc. (2013).

This study was part of a large study on narcolepsy approved by the Ethical Committee of the General University Hospital in Prague and all patients provided signed informed consent with this study.

Results

Regular smokers (one or more cigarettes daily) represented 43.7% patients, while 19.5% were former regular smokers. Prevalence of smoking present in any period of life was thus 63.2% (55 patients). The patients smoked only cigarettes, no other tobacco product was recorded. Mean age at initiating smoking was 20.0 (±6.0) years and mean number of cigarettes smoked daily was 13.6 (±10.7). Forty (72.2%) smokers started smoking prior to their first symptoms of narcolepsy, and mean recorded latency of onset of narcolepsy since smoking initiation was 9.1 (±5.8) years. Mean age of NC onset in patients who started smoking prior to developing NC was 27.8 (±9.0) years, while patients who commenced smoking after developing NC or had never smoked developed NC at 20.5 (±10.2) years of age ($p<0.001$).

Table 1 – Clinical data on subjects suffering from NC under study expressed as mean (SD)

	All	Non-smokers	Smokers	P-value
Number (%)	87.0 (100)	32.0 (36.8)	55.0 (63.2)	NA
Age at smoking interview (years)	46.6 (16.3)	42.2 (13.8)	49.1 (17.2)	0.043
Age at NC onset (years)	23.5 (10.4)	21.8 (12.0)	24.5 (9.2)	NS
BMI	29.2 (5.1)	28.3 (4.5)	29.7 (5.4)	NS
Epworth sleepiness scale	18.0 (3.6)	17.0 (4.1)	18.5 (3.1)	NS
Number of patients with restless legs syndrome (%)	15.0 (17.2)	4.0 (12.5)	11.0 (20)	NS
Latency between night polysomnography and MSLT and smoking interview (years)	5.4 (5.2)	6.3 (6.9)	4.9 (3.9)	NS
Night polysomnography				
Sleep efficiency (%)	82.6 (9.9)	86.0 (7.8)	80.7 (10.2)	0.022
Sleep N1 duration (%)	11.9 (9.2)	9.0 (6.0)	13.6 (10.3)	0.034
Sleep N2 duration (%)	39.0 (10.8)	38.6 (9.6)	32.3 (11.4)	NS
Sleep N3 duration (%)	15.8 (8.2)	19.6 (7.0)	13.6 (8.2)	0.002
REM sleep duration (%)	19.5 (7.1)	21.0 (5.8)	18.6 (7.6)	NS
REM sleep latency (min)	40.1 (60.9)	30.3 (63.7)	45.6 (59.2)	NS
PLMI	17.8 (22.6)	9.3 (13.8)	22.5 (25.1)	0.016
AHI	8.8 (16.6)	3.8 (5.5)	11.8 (20.0)	0.041
MSLT				
Sleep latency – MSLT (min)	2.9 (2.2)	2.2 (1.6)	3.3 (2.4)	0.031
SOREM MSLT (number)	3.6 (1.2)	3.6 (1.2)	3.6 (1.2)	NS

Non-smokers are defined as individuals who have smoked less than 100 cigarettes in their whole life, and smokers are patients smoking at the time of questioning, taken together with those who have already quitted smoking (but had smoked more than 100 cigarettes in their life). SD – standard deviation; NA – non applicable; NC – narcolepsy with cataplexy; NS – nonsignificant; BMI – body mass index; MSLT – multiple sleep latency test; N1, N2, N3 – non rapid eye movement sleep stage 1, 2, 3 respectively; REM – rapid eye movement; PLMI – periodic leg movements index (number of periodic leg movements/1 hour); AHI – apnoea/hypopnoea index (number of apnoea/hypopnoea episodes/1 hour of sleep); SOREM – sleep onset REM period

Relevant clinical parameters for the whole patient group and the group of smokers (i.e. former smokers and those who smoked at the time of study interview of all actively smoking taken together) and non-smokers (i.e. individuals who had smoked less than 100 cigarettes in their whole life) including statistical comparisons are shown in Table 1.

We found direct correlation between age at NC onset and the latency between onset of symptoms of narcolepsy and the age of initiating regular smoking (0.822, $p<0.001$, N=30). Secondly we found negative correlation between age at NC onset and the time delay (both positive and negative) from smoking initiation to NC onset (–0.7936, $p<0.001$, N=45) in all NC patients.

Smoking duration correlates rather consistently with the parameters of night sleep macrostructure. We found correlation with the number of awakenings (0.5217, $p=0.001$, N=39), duration of NREM 1 sleep (0.3573, $p<0.015$, N=46), REM sleep latency (0.3511, $p<0.016$, N=47) and also AHI (apnoea/hypopnoea index) (0.5059, $p=0.001$, N=43). Smoking duration was negatively correlated with sleep efficiency (–0.5145, $p<0.001$, N=47), duration of NREM 3 sleep (–0.6142, $p<0.001$, N=46). No correlation was found between smoking duration and subjective or objective evaluation of sleepiness during the day.

The number of cigarettes smoked in one day did not correlate with any NC parameter of interest.

Discussion

There are 23.5% active regular smokers in the age group of those above 15 years in the Czech Republic (Sovinová and Csémy, 2015) while the rate recorded in our sample of patients with NC was 43.7%. Occurrence of active regular smoking in NC is thus twice as high as in general Czech population. A similar difference concerns the rate of former regular smoking, specifically 12.6% of former smokers in the whole Czech population against 19.5% of former regular smokers among patients with NC. Regarding the number of cigarettes smoked, our patients with NC (13.6 cigarettes daily) come close to this number in common population where regular smokers smoke around 15 cigarettes daily (Sovinová and Csémy, 2015). We assume that smoking habits are similar in Slovakia. The proportion of smokers in our NC population is about 50% higher than in an Italian study where, however, was the same percentage of smokers in the control group as is reported for the Czech population, so also the Italian study has shown higher frequency of smoking among patients with NC, the authors explain this higher rate with the stimulatory action of nicotine (Palaia et al., 2011). Higher proportion of current smokers in NC than in controls (37.2% vs. 21.7%) was also reported in recent large French study (Barateau et al., 2016).

Our data do not allow any conclusion regarding a possible relationship between smoking and the etiopathogenesis of narcolepsy, the differing ages of patients who started smoking prior to NC symptom onset and the age of other patients with

NC is rather due to the age at NC onset than to its relationship to smoking. The relationship between smoking initiation, albeit passive, and the development of NC is suggested by the finding that in individuals with HLA DQB1*0602 positivity passive smoking was a risk factor of narcolepsy. The authors of this study explain why passive smoking was a risk factor, unlike active smoking, with the fact that narcolepsy symptoms in many patients begin in their childhood where exposure to active smoking is negligible (Ton et al., 2009).

Our results showing worse quality of sleep in patients with NC suggest that nicotine worsens the quality of sleep in NC as well, in the same way as in general population (Jaehne et al., 2009). The results, however, have to be taken as only approximate in this respect as smokers in our sample were older than non-smokers, and smokers had higher AHI and PLMI (periodic leg movements index). Sleep apnoea and periodic limb movements during sleep participate in disturbing the quality of night sleep, and this is also the case in NC (Sansa et al., 2010).

In our sample, smoking duration correlated clearly with objective parameters of night sleep quality. To some degree, this might be explained with ageing – the changes described develop also as a result of ageing as such (Šonka et al., 1993). This finding might also suggest that smoking has a cumulative rather than immediate effect on quality of sleep which has not been described yet and should be tested by a more elaborated study.

The fact that the number of cigarettes smoked does not correlate with subjective or objective sleepiness, may be rather interpreted as suggesting that our patients do not use cigarette smoking as self-indicated drug against EDS but this relationship is far to be excluded. Shorter mean sleep latency in MSLT in patients – non-smokers may be interpreted only with difficulty as patients undergoing MSLT are prohibited to smoke (Arand et al., 2005) and smokers should thus rather have shorter latency of falling asleep as is the case in smoking abstinence in smokers in the general population (Prosise et al., 1994). More severe sleepiness of smokers in MSLT, however, might have been influenced by worse quality night sleep related to obstructive apnoeas and periodic limb movements that may accentuate sleepiness during the day by itself, though no clear evidence for this exists in NC, unlike in general population (Engleman and Douglas, 2004; Hornyak et al., 2006). Case reports suggest that nicotine may mask or relieve symptoms of narcolepsy, including EDS and even cataplexy (Krahn et al., 2009; Ebben and Krieger, 2012). Such an interaction is supported by limited data suggesting that nicotine addiction may be mediated by hypocretin pathways (Corrigall, 2009).

Nicotine exhibits antidepressant action (Tizabi et al., 1999), so higher-degree smoking might also be related to increased prevalence of several depressive symptoms (Vourdas et al., 2002; Fortuyn et al., 2010). Higher rate of smokers among narcolepsy patients is not connected to hypocretin deficiency because from animal models it seems that hypocretin system's role is to reduce drug seeking behaviours. Hypocretin knockout mice showed reduced signs of withdrawal from

nicotine (Plaza-Zabala et al., 2013). All other reasons possibly leading to smoking in NC should be tested by more sophisticated research.

Not negligible is certainly also the impact of smoking on the general health of a patient with NC. Smoking is a risk factor for many cardiovascular and metabolic diseases. Literary data and our unpublished results show that patients with NC suffer from higher rates of arterial hypertension, type 2 diabetes and obesity (Sonka et al., 2010; Jennum et al., 2013; Ohayon, 2013), which may also be related to higher rate of smoking in NC.

Although narcolepsy symptom relief may be viewed as a benefit of nicotine and may thus be a barrier to smoking cessation in narcoleptics, the act of smoking is itself of concern because of many reasons. First is the risk of falling asleep while smoking resulting in injury and damage (Krahn et al., 2009) and second is the already mentioned risk factor of many other diseases. Third reason is based on the fact that nicotine is a highly addictive substance (Benowitz, 2008), and this obviously applies to the narcolepsy population as well.

This study has several limitations that were mostly mentioned in the discussion above. The limitation is not only a small number of patients, but also the latency between complete clinical examination and interview regarding smoking, limited information about smoking and missing personality profiles of the respondents. Larger prospective studies of smoking in NC are certainly worth considering. In any case, patients with NC should be instructed not to start smoking, and if this has already happened, to quit smoking.

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