

Olfactory dysfunction in a cohort of Czech patients with idiopathic REM sleep behaviour disorder

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

Abstract

Aim: Rapid eye movement (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. **Patients and methods:** This study included 54 iRBD patients with a median age of 67 (IQR 63–72) years; the 37 control subjects, matched by gender and age, had a median age of 67 (57.5–70.0) years. All subjects underwent a complex examination, which included olfactory testing using the University of Pennsylvania Smell Identification Test (UPSIT). **Results:** 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 ($P < 0.01$). **Conclusion:** This study demonstrated a significantly lower olfactory function in the iRBD group compared to controls.

Souhrn

Cíl: Porucha chování v REM (rapid eye movement) 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. Idiopatická RBD je známkou prodromální fáze synukleinopatie a má vysokou míru fenokonverze do neurodegenerativních nemocí ze skupiny synukleinopatií. Cílem této průřezové studie bylo zjistit stav čichové funkce u pacientů s iRBD a její vztah k jiným symptomům. **Materiál a metody:** Do studie bylo zahrnuto 54 pacientů s iRBD s mediánem věku 67 (IQR 63–72) let a 37 kontrolních subjektů s mediánem věku 67 (57,5–70,0) let, které byly spárovány podle věku a pohlaví. Všichni účastníci studie absolvovali komplexní vyšetření, které obsahovalo identifikační čichový test Pensylvánské univerzity (University of Pennsylvania Identification Test; UPSIT). **Výsledky:** Úplnou ztrátu čichu anebo jeho těžkou dysfunkcí mělo 62,9 % pacientů s iRBD, přitom u kontrolních subjektů to bylo pouze 8,1 %. Porucha atonie v REM spánku v polysomnografii nepřímo korelovala se skóre UPSIT ($p < 0,01$). **Závěr:** Studie prokázala významně horší čich u pacientů s iRBD než u kontrolních osob.

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Introduction

Rapid eye movement (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% of 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 the 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.

Methods

Patients were screened in a stepwise manner following a public advertisement and internet survey [14]; RBD was diagnosed in accordance with the International Classification

of Sleep Disorders, third edition [15]. Exclusion criteria were: overt parkinsonism (diagnosed according to the Movement Disorder Society [MDS] criteria [16]) or dementia (diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders [17]), severe obstructive sleep apnea defined by the Apnea-Hypopnea Index (AHI) \geq 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 EMG of bilateral flexor digitorum superficialis muscles. Sleep analysis was done in standard 30-s epochs. Increased tonic or phasic activity recorded on the EMG of the mentalis muscle during PSG, known as REM sleep without atonia (RWA), was thoroughly investigated. A 30-s 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 non-REM sleep or excessive transient muscle activity was found in at least 50% of the epoch divided into 3-s 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 1 h 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, Scales for Outcomes in Parkinson's Disease-Autonomic (SCOPA-AUT), 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, Haddon Heights, NJ, 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 gender 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 gender-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.

The SPSS 20 (IBM, Armonk, NY, USA) was used to perform all statistical analysis. First, we applied the 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 the t-test for variables with normal distribution and the 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 Tab. 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 body mass index (BMI) in iRBD patients was considerably lower than in controls ($P < 0.01$).

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

Classification of olfactory function into five groups according to UPSIT scores is shown in Tab. 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 Tab. 4.

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

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 vs. 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 PET imaging [29].

As expected, olfactory function differed between genders 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

Tab. 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.

	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

AHI – apnoe-hypopnoe index; BMI – body mass index; iRBD – idiopathic REM sleep behaviour disorder; MDS-UPDRS III – Movement Disorder Society Unified Parkinson’s Disease Rating Scale, part III; MoCA – Montreal Cognitive Assessment; N – number; N/A – not applicable; RWA – REM sleep without atonia; SE – sleep efficacy; SCOPA-AUT – Scales for Outcomes in Parkinson’s Disease-Autonomic

Tab. 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

iRBD – idiopathic REM sleep behaviour disorder; N – number; UPSIT – University of Pennsylvania Smell Identification Test

Tab. 3. Classification of UPSIT results.

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

iRBD – idiopathic REM sleep behaviour disorder; N – number

that olfactory identification capabilities are higher in women than in men [30]. This implicates that different UPSIT cut-off values for identification of a high phenocon-

version risk have to be defined for men and women.

A lower UPSIT score was associated with a decreased ability to maintain REM sleep

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

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

iRBD – idiopathic REM sleep behaviour disorder; MDS-UPDRS III score – Movement Disorder Society Unified Parkinson's Disease Rating Scale, part III; MoCA – Montreal Cognitive Assessment; N – number; PSG – polysomnography; RBD – REM sleep behaviour disorder; RWA – percentage of REM sleep without atonia; SCOPA-AUT – Scales for Outcomes in Parkinson's Disease-Autonomic; UPSIT – University of Pennsylvania Smell Identification Test

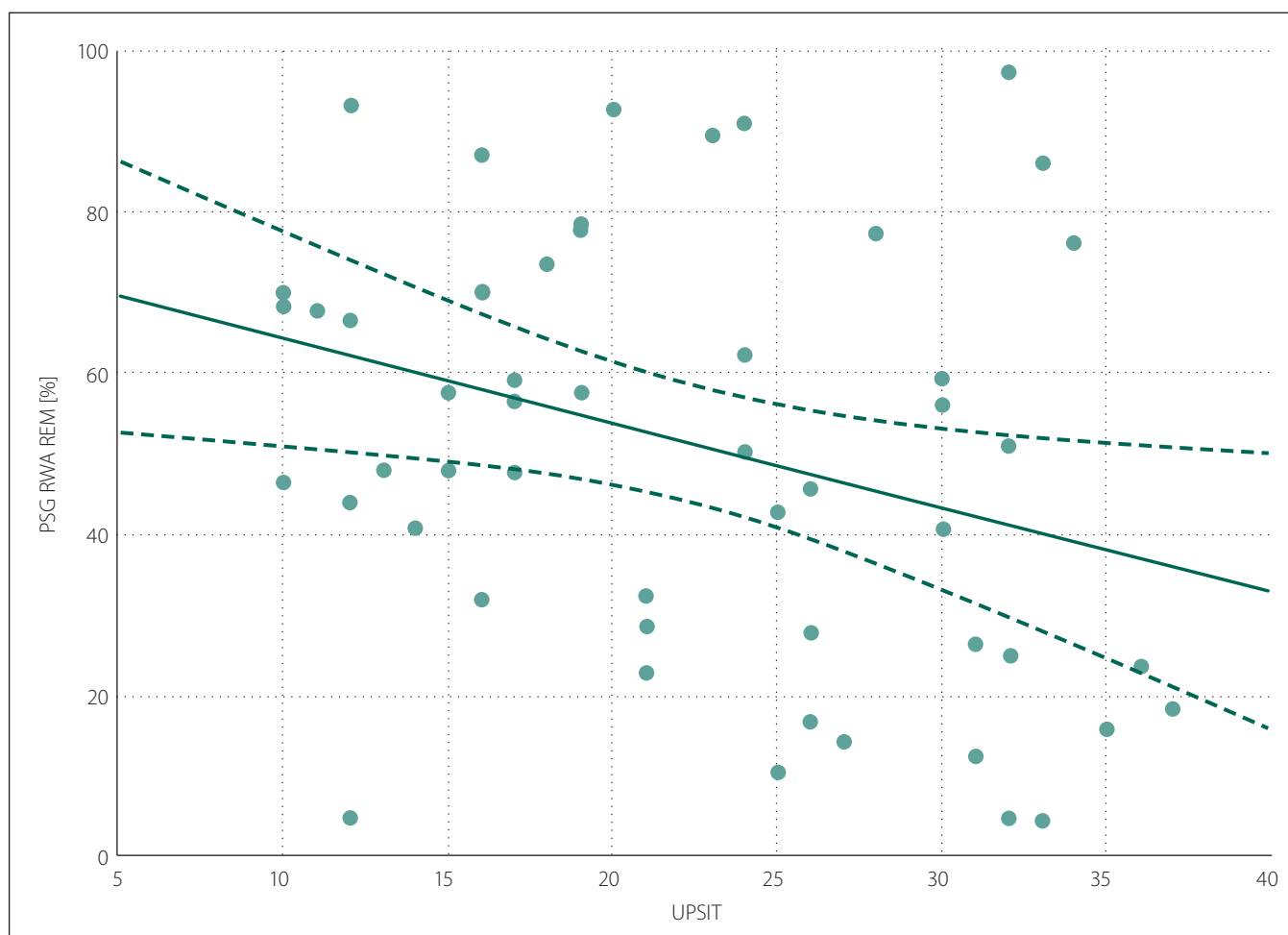


Fig. 1. Scatter graph of Spearman correlation between RWA and UPSIT.

RWA – percentage of REM sleep without atonia out of total REM sleep duration; UPSIT – University of Pennsylvania Smell Identification Test score

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

RWA – podíl REM spánku bez svalové atonie vzhledem k celkovému trvání REM spánku v procentech; UPSIT – skóre University of Pennsylvania Smell Identification Test

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 the brainstem are affected, followed by affliction of areas in the rostral pons [31] responsible for maintenance of REM sleep atonia. The negative association between olfac-

tory 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 AHL in iRBD patients compared to control subjects despite the inclusion criteria concerning AHL in both groups were 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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