Progressive Olfactory Impairment and Cardiac Sympathetic Denervation in REM sleep behavior disorder

Supplementary Material

Methods

Statistical Analysis

Variables were tested for normal distribution using the Shapiro-Wilk test at the whole group level. All normally distributed variables (striatal DAT-binding values, age, follow-up time, TDI baseline and follow-up, MoCA baseline, identification subscore) are given in mean ± standard deviation (SD). For the non-parametric values ([^{123}I]MIBG uptake values, UPDRS-III, MoCA follow-up, discrimination/threshold subscores, duration times [diagnosis to baseline/follow-up; start of symptoms to follow-up]), median and interquartile range (IQR) are used. The Mann-Whitney-U-test was used to analyze changes between the subgroups at baseline and at last follow-up. A one-sample Wilcoxon signed-rank test was used to analyze changes within subgroups from baseline to last follow-up. A two-sided Spearman's rank correlation coefficient was used for correlation analysis. Values were considered significant if $p < 0.05$.

Results

Baseline - whole group of 37 iRBD subjects

31/37 (86.1%) RBD patients were male. The mean age at diagnosis was 63.5 ± 6.7 years. Regarding UPDRS-III scores, there were minor motor findings at baseline: 2 (0-4). The olfactory function test showed a severe hyposmia (TDI: 19.5 (12.1-25.4)). The cognitive testing with MoCA showed normal cognitive performance (27.0 (25.0-28.8)). 12/37 (32.4%) RBD

patients were treated with antidepressants at the time of diagnosis: SSRI (citalopram, paroxetine or fluoxetine; n=4), NSRI (venlafaxine or duloxetine; n=4), trimipramine plus citalopram (n=1), trimipramine plus duloxetine (n=1), agomelatine plus venlafaxine (n=1) and quetiapine plus citalopram (n=1). See also Table S1.

Follow up – at whole group level

35 RBD patients were followed over a time period of 49.1 ± 18.6 months (see Table S1). At whole group level, motor function, nonmotor symptoms and odor threshold score worsened significantly while a trend was seen for TDI sum score (UPDRS-III BL: 2 (0 - 4), FU: 3 (2 - 6), p = 0.017; PDNMS BL: 7.0 (4.0 – 9.0), FU: 8.0 (5.0 – 11.0), p = 0.012; odor threshold score BL: 3.0 (0.0 - 5.5), FU: 1.5 (0.0 - 4.5), p = 0.010; TDI BL: 18.1 ± 10.1, 16.9 ± 9.6, p = 0.050). Cognitive testing improved significantly (MoCA BL: 27.0 (25.0 - 28.75), FU: 28.0 (27.0 - 29.0), p = 0.025) compared to baseline. 7/35 (20%) subjects converted to PD, all of which had a pathological [^{123} I]MIBG uptake and [^{123} I]FP-CIT-SPECT at baseline. Interestingly, the olfactory function of one RBD patient who converted to PD was completely normal at baseline, but worsened about 5 points in TDI at the time of phenoconversion. None of the RBD patients with both normal [^{123}I]MIBG and [^{123} I]FP-CIT-SPECT or reduced [^{123}I]MIBG uptake but normal [^{123}I]FP-CIT-SPECT converted to a manifest aSYN.

When considering [^{123} I]MIBG as the first procedure performed, 29/37 (78.4 %) subjects had a pathological [^{123} I]MIBG uptake, of whom 86.2% presented at least with a moderate hyposmia (TDI ≤25) at baseline. When considering olfactory testing with Sniffin' Sticks as the first procedure performed, 28/37 (75.7%) RBD subjects suffered from at least moderate hyposmia (i.e. TDI ≤25) at baseline, of which 92.9% additionally presented a pathological [^{123}I]MIBG. The quantitative analysis of [^{123} I]FP-CIT-SPECT showed a reduced striatal DAT-binding in 20/37 (54.1%) subjects. In all 20 subjects, the pathological [^{123}I]FP-CIT-SPECT was combined with an abnormal [^{123} I]MIBG and in 17/20 (85.0%) subjects with at least moderate hyposmia.

Table S1: A: Overview of the demographic data of all subjects at baseline and follow-up. B: Results of [^{123}I]MIBG scintigraphy and [^{123}I]FP-CIT-SPECT

A: Overview of the demographic data of all subjects at baseline (Bl) and follow-up (Fu)			
	All patients n=37	**All patients n=35**	**Bl vs. Fu Statistical analysis $p < 0.05$ p value**
Male (%)	31 (86.1%)		
Age at Bl (years)	63.5 ± 6.7		
Age at Fu (years)	64.2 ± 6.6	68.3 ± 6.8	
Fu time (months)		49.1 ± 18.6	
Duration of RBD at time of diagnosis (months)	59.0 (22.0-106.0)		
Antidepressants (%)	12 (32.4)		
UPDRS-III	2 (0 - 4)	3 (2 - 6)	**0.017**
TDI score	18.1 ± 10.1	16.9 ± 9.6	0.050
Threshold score	3.0 (0.0 - 5.5)	1.5 (0.0 - 4.5)	**0.010**
Discrimination score	9.0 (6.5 - 11.0)	8.0 (4.0 -10.0)	0.057
Identification score	6.9 ± 4.1	7.4 ± 4.4	n.s.
MOCA	27.0 (25.0 - 28.75)	28.0 (27.0 - 29.0)	**0.025**
PDNMS	7.0 (4.0 – 9.0)	8.0 (5.0 – 11.0)	**0.012**
Phenoconversion to PD (%)		7 (20)	
B: Results of [^{123}I]MIBG scintigraphy and FP-CIT-SPECT			
pathological [^{123}I]MIBG (%)	29 (78.4)		
[^{123}I]MIBG uptake value (cut off <1.5)	1.2 (1.1 - 1.5)		
pathological [^{123}I]FP-CIT-SPECT (%)	20 (54.0%)		
Caudate nucleus right	2.3 ± 0.6		
Caudate nucleus left	2.3 ± 0.5		
Putamen right	1.9 ± 0.5		
Putamen left	1.9 ± 0.5		

Conversion Rates

Conversion rates (CR) to Parkinson's disease (PD) are shown according to the stratifying conditions (olfactory function, [^{123}I]MIBG, [^{123}I]FP-CIT-SPECT) in Table S2. CRs are calculated for the duration from the start of symptoms to phenoconversion (PC), from diagnosis to PC and follow-up time (=duration from baseline to PC). In the upper part of the table the CRs for the diagnosis RBD are demonstrated whereas the lower part of the table shows the CRs only for patients fulfilling criteria of isolated RBD (iRBD).

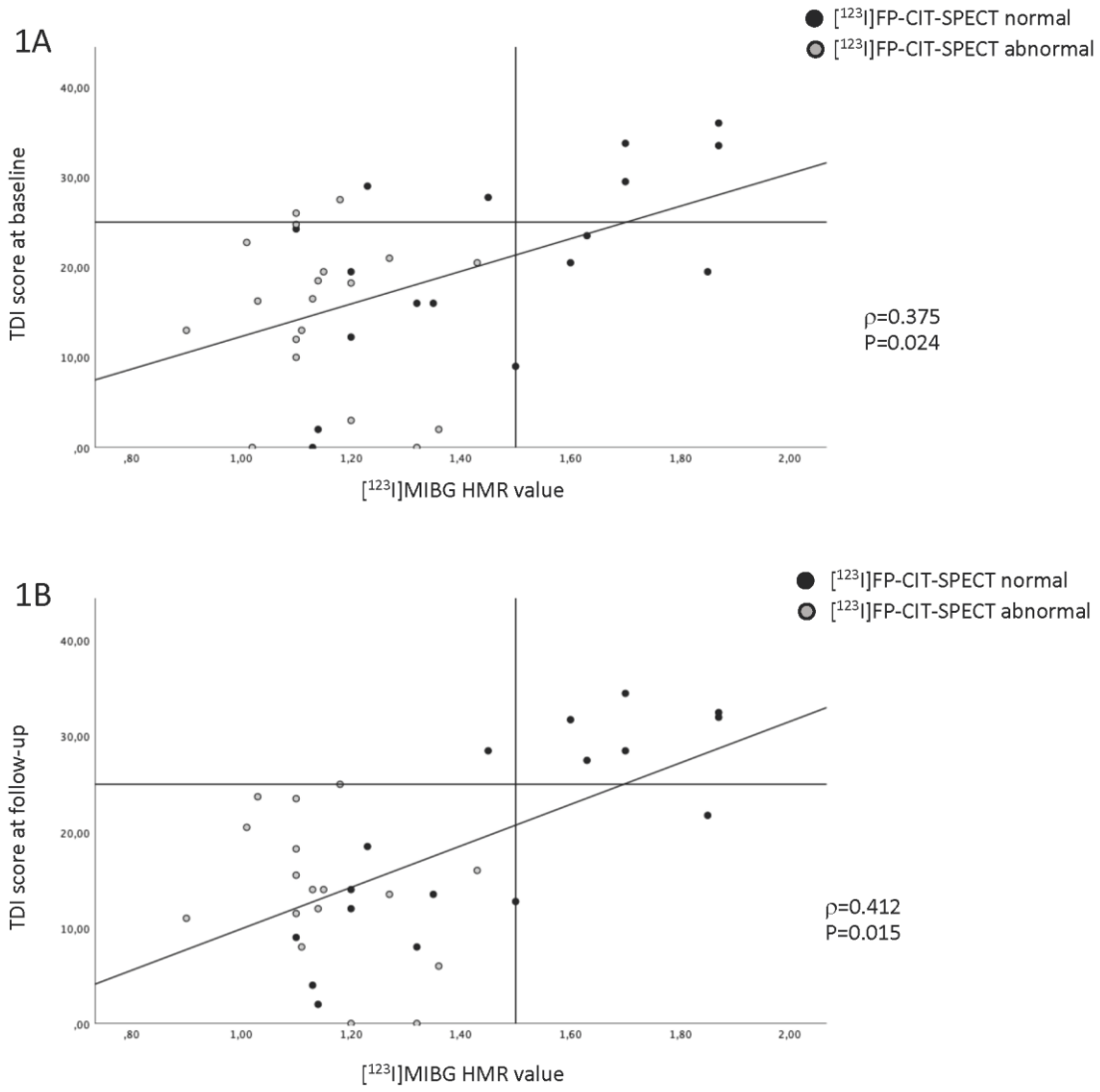
Table S2: Conversion rates to Parkinson's disease

Stratifying conditions	n (Bl)	converters/ n (Fu) (%)	time diagnosis to PC (y)	follow-up time (y)	CR symptoms to PC (%/y)	CR diagnosis to PC (%/y)	CR baseline to PC (%/y)	conv missed
RBD	37	7/35 (20.0)	4.5 (3.3 – 5.7)	4.0 (3.0 - 5.3)	2.2	4.4	5.0	0/7
RBD + TDI ≤25	28	6/26 (23.1)	4.4 (3.2 – 5.4)	3.9 (3.0 – 5.1)	2.2	5.3	5.9	1/7
RBD + TDI <18	16	2/15 (13.3)	4.8 (3.3 – 5.7)	4.0 (3.0 – 5.2)	1.3	2.8	3.3	5/7
RBD + TDI ≤25 + MIBG^{P}	25	6/23 (26.1)	4.5 (3.3 – 5.7)	3.9 (3.0 - 5.2)	2.7	5.8	6.7	1/7
RBD + MIBG^{P}	29	7/27 (25.9)	4.5 (3.3 – 5.7)	4.0 (3.0 - 5.2)	2.8	5.8	6.5	0/7
RBD + FP-CIT-SPECT^{P}	20	7/18 (38.9)	4.6 (3.7 – 6.1)	4.0 (3.0 - 5.2)	4.1	8.5	9.7	0/7
RBD + TDI ≤25 + FP-CIT-SPECT^{P}	17	6/15 (40.0)	4.8 (3.9 – 5.7)	3.9 (3.0 - 5.2)	4.0	8.3	10.3	1/7
iRBD	30	7/28 (25.0)	4.8 (3.3 – 5.7)	4.3 (3.1 - 5.3)	2.4	5.2	5.8	0/7
iRBD + TDI ≤25	25	6/23 (26.1)	4.5 (3.0 – 5.7)	3.9 (3.0 - 5.2)	2.6	5.8	6.7	1/7
iRBD + TDI <18	16	2/15 (13.3)	4.8 (3.3 – 5.7)	4.0 (3.0 - 5.2)	1.3	2.8	3.3	5/7
iRBD + TDI ≤25 + MIBG^{P}	24	6/22 (27.3)	4.7 (3.2 – 5.7)	4.0 (3.0 - 5.2)	2.8	5.8	6.8	1/7
iRBD + MIBG^{P}	27	7/25 (28.0)	4.8 (3.3 – 5.7)	4.2 (3.1 - 5.2)	2.8	5.8	6.7	0/7
iRBD + FP-CIT-SPECT^{P}	18	7/16 (43.8)	5.0 (3.9 – 7.0)	4.3 (3.2 - 5.2)	4.2	8.8	10.2	0/7
iRBD + TDI ≤25 + FP-CIT-SPECT^{P}	16	6/14 (42.9)	5.0 (3.7 – 6.1)	4.1 (3.0 - 5.2)	4.1	8.6	10.5	1/7

The follow-up time is given in median (interquartile range). Conversion rates (CR) were calculated as follows: percentage of phenoconverted patients was divided by median of duration from symptoms to PC in years, duration of diagnosis to PC in years and follow-up time in years. Bl, baseline; Fu, follow-up; y, year; conv, converters.

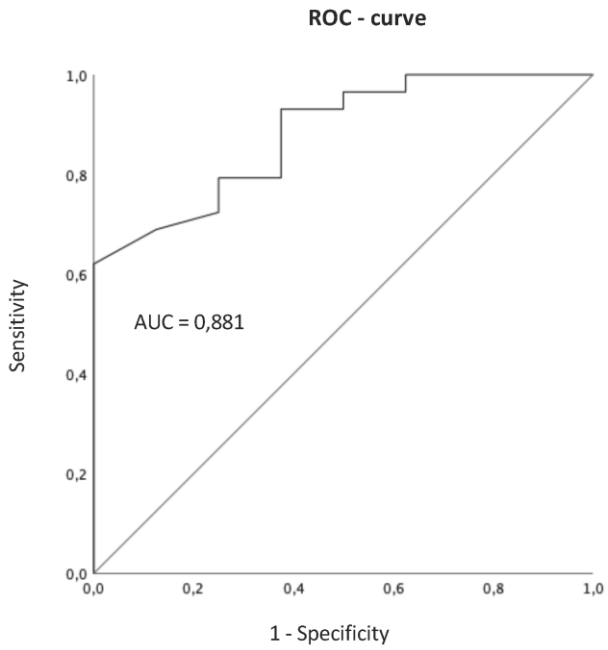
Correlations

The [^{123}I]MIBG uptake values and the TDI-scores were correlated at baseline (r = 0.375, p = 0.024) and follow-up (r = 0.412, p = 0.015) (See Supplementary Figure 1). [^{123}I]MIBG values correlated with the lowest putaminal (r = 0.527, p = 0.001) and lowest caudatal DAT-binding value (r = 0.389, p = 0.019). The lowest putaminal DAT-binding value correlated inversely with the UPDRS-III value at follow-up (r = -0.395, p = 0.019).



Supplementary Figure1: Correlation between [^{123}I]MIBG-HMR (abnormal <1.5) and TDI-score at baseline (1A) and follow-up (1B).

ROC-analysis for olfactory testing to predict the [^{123}I]MIBG result showed an area under the curve of 0.881 (Standard Error 0.060), p = 0.001, (CI: 0.764-0.999) (see Supplementary Figure 2).



Supplementary Figure 2: ROC-analysis for olfactory testing to predict the [^{123}I]MIBG result showed an area under the curve of 0.881, p = 0.001, (CI: 0.764 - 0.999). According to ROC-analysis, a TDI ≤ 25 has a sensitivity of 86.2% and a specificity of 62.5%. 100% specificity with a sensitivity of 62.1% is reached for a TDI ≤ 19.