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Rapid Eye Movement Sleep Behavior Disorder: Abnormal Cardiac Image and Progressive Abnormal Metabolic Brain Pattern

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ABSTRACT: Background: Isolated rapid eye movement sleep behavior disorder (iRBD) is prodromal for α-synucleinopathies.

Objective: The aim of this study was to determine whether pathological cardiac [^{123}I]meta-iodobenzylguanidine scintigraphy ([^{123}I]MIBG) is associated with progression of [^{18}F]fluorodeoxyglucose-positron emission tomography–based Parkinson's disease (PD)-related brain pattern (PDRP) expression in iRBD.

Methods: Seventeen subjects with iRBD underwent [^{18}F]fluorodeoxyglucose-positron emission tomography brain imaging twice ~3.6 years apart. In addition, [^{123}I]MIBG and [^{123}I]*N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane single-photon emission computed tomography ([^{123}I]FP-CIT-SPECT) at baseline were performed. Olfactory, cognitive, and motor functions were tested annually.

Results: Twelve of 17 subjects had pathological [^{123}I]MIBG. At baseline, 6 of 12 of these expressed the PDRP (suprathreshold PDRP *z* score). At follow-up, 12 of 17 subjects had suprathreshold PDRP *z* scores, associated with pathological [^{123}I]MIBG in 92% and with pathological [^{123}I]FP-CIT-SPECT in 75%. Subjects with pathological [^{123}I]MIBG had higher PDRP *z* score change per year (P = 0.027). Three subjects phenoconverted to PD; all had pathological [^{123}I]MIBG and [^{123}I]FP-CIT-SPECT, suprathreshold baseline PDRP *z* scores, and hyposmia.

Conclusions: Pathological [^{123}I]MIBG was associated with progressive and suprathreshold PDRP *z* scores at follow-up. Abnormal [^{123}I]MIBG likely identifies iRBD as prodromal PD earlier than pathological [^{123}I]FP-CIT-SPECT. © 2021 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: isolated rapid eye movement sleep behavior disorder; [^{123}I]MIBG scintigraphy; [^{18}F]FDG-PET-derived Parkinson's disease–related pattern; hyposmia; prodromal progression biomarker

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Isolated rapid eye movement sleep behavior disorder (iRBD) is prodromal for α-synucleinopathies (Parkinson's disease [PD], dementia with Lewy bodies [DLB], multiple system atrophy [MSA]) in 80%–90% of cases.[1,2]

Most patients with iRBD will convert to PD or DLB, and this will be important for future disease-modifying therapies at premotor stages. This necessitates biomarkers for the prediction and monitoring of disease progression. Equally important, such biomarkers should identify patients with iRBD who will *not* phenoconvert.

iRBD is associated with abnormalities in cognition,[3] olfaction,[4,5] motor function,[3] autonomic functions,[3] cardiac noradrenergic innervation as assessed by [^{123}I]meta-iodobenzylguanidine scintigraphy ([^{123}I]MIBG),[6,7] striatal dopaminergic innervation as visualized by [^{123}I]*N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane single-photon emission computed tomography ([^{123}I]FP-CIT-SPECT),[8,9] and cerebral glucose metabolism as visualized by [^{18}F]fluorodeoxyglucose-positron emission tomography ([^{18}F]FDG-PET).[10,11] By combining [^{18}F]FDG-PET with the computational algorithm Scaled Subprofile Model/principal component analysis, a robust pattern of altered brain glucose

metabolism has been identified in PD: the PD-related pattern (PDRP).[12,13] This technique allows quantification of PDRP expression on a case-by-case basis, denoted by a z score.[12–15] PDRP expression can be considered a PD progression marker and was also observed in independent iRBD cohorts (ie, in prodromal PD).[10,16,17]

Recently, we reported that the degree of PDRP expression, and changes therein, may be suitable as a nondopaminergic progression biomarker in iRBD. In that study, 4 of 8 subjects with suprathreshold baseline PDRP z scores ($z > 1.98$; for details, see Kogan et al.[18]) converted to PD, and 6 of 12 subjects with lower baseline PDRP z scores progressed to suprathreshold PDRP z scores at 3.6-year-follow-up.[18]

Therefore, we investigated whether [^{123}I]MIBG[6,7,19] could stratify patients with iRBD into those with a fast rate of PDRP z score progression and imminent phenoconversion to PD/DLB versus those with a slower progression rate. [^{123}I]MIBG has been reported to be impaired early in the course of iRBD before nigrostriatal degeneration.[20–22] In addition, pathological [^{123}I]MIBG has been shown to correlate with olfactory dysfunction in PD.[23,24] Because hyposmia is one of the earliest prodromal PD/DLB symptoms,[4,5] we also studied the correlation of cardiac [^{123}I]MIBG uptake with olfactory function. Complementarily, we used [^{123}I]FP-CIT-SPECT.[8] Cognitive and motor functions were clinically assessed to detect phenoconversion.

Patients and Methods

Study Design

The study design, details of enrolled subjects, and criteria of phenoconversion to PD/DLB have been published previously.[18] The study protocols were approved by both institutional review boards (University Medical Center Groningen, the Netherlands; University Marburg, Germany). According to the Declaration of Helsinki, all subjects gave their voluntary informed consent after verbal and written explanation of the study (Netherlands Trial Register: NL8057). This report focuses on the previously described 17 German subjects with iRBD.[18]

Imaging

All 17 subjects with iRBD underwent serial [^{18}F]FDG-PET brain imaging and baseline [^{123}I]FP-CIT-SPECT, with scanning, reconstruction, and analysis protocols as previously published.[10,18] Fifteen [^{123}I]MIBGs were performed at baseline, and another 2 after the second [^{18}F]FDG-PET. For details, see Supporting Information.

Clinical Tests

The Sniffin' Sticks 16-item odor identification test (pathological: scores $\leq 10/16$),[25] the Montreal Cognitive Assessment (MoCA; pathological: scores $\leq 25/30$),[26] and the Unified Parkinson's Disease Rating Scale-motor, Part III (UPDRS-III)[27] were performed annually.

Statistical Analysis

Variables were tested for normality of distribution with the Shapiro-Wilk test. Normally distributed variables are given in mean $\pm$ standard deviation, and nonparametric variables as median and interquartile range. Due to small subgroup size, nonparametric tests were used: the Mann-Whitney U test to examine changes between both subgroups (iRBD with reduced versus normal [^{123}I]MIBG) and a one-sample Wilcoxon signed-rank test for changes within subgroups. Values were considered to be significant at $P < 0.05$. All analyses were performed using SPSS v27 (SPSS, Chicago, IL). See also Supporting Information Methods.

Results

Clinical, demographic, and imaging data of all subjects are summarized in the Supporting Information Results and Table S1.

[^{123}I]MIBG

Twelve of 17 subjects had an abnormal [^{123}I]MIBG (11 at baseline, 1 after the follow-up [^{18}F]FDG-PET), and 5 of 17 subjects had a normal [^{123}I]MIBG (4 at baseline, 1 after follow-up [^{18}F]FDG-PET; see Supporting Information). For the demographic, clinical, and imaging data of the two subgroups and the statistical analysis, see Table 1.

[^{18}F]FDG-PET

At baseline, 6 of 12 (50%) subjects with abnormal [^{123}I]MIBG expressed suprathreshold PDRP z scores. Of these, five subjects had abnormal baseline [^{123}I]FP-CIT-SPECT (Fig. 1B,C; Supporting Information Table S1). At follow-up [^{18}F]FDG-PET, 11 of 12 (92%) subjects with abnormal [^{123}I]MIBG had suprathreshold PDRP z scores, of whom 9 had pathological baseline [^{123}I]FP-CIT-SPECTs. Of the three subjects with pathological [^{123}I]MIBG and normal baseline [^{123}I]FP-CIT-SPECT, one had subthreshold PDRP z scores at baseline and follow-up, one progressed from subthreshold to suprathreshold z score at follow-up, and one had suprathreshold z scores at baseline and follow-up (Fig. 1B; Supporting Information Table S1).

All five subjects with normal [^{123}I]MIBG had subthreshold baseline PDRP z scores, with all but one still

TABLE 1 *Demographic and clinical data: subgroup analysis*

RBD subjects with normal [^{123}I]MIBG vs. RBD subjects with abnormal [^{123}I]MIBG[a]			
	RBD Subjects with Normal [^{123}I] MIBG (n = 5)	**RBD Subjects with Abnormal [^{123}I] MIBG (n = 12)**	***P* Value**
Male sex, n (%)	4 (80)	11 (92)	
Age (y)			
Baseline	60.9 ± 6.4	63.5 ± 5.3	0.646
Follow-up	64.6 ± 6.3	67.1 ± 5.5	0.721
RBD duration at follow-up (y)	10.0 (7.6–19.2)	7.8 (6.2–9.6)	0.184
PDRP *z* score			
Baseline	−0.44 ± 1.31	1.85 ± 2.07	**0.048**
Follow-up	0.95 ± 1.09	4.3 ± 2.67	**0.006**
Change from baseline to follow-up	1.39 ± 0.95	2.45 ± 1.15	0.104
Change per year	0.35 ± 0.21	0.69 ± 0.31	**0.027**
[^{123}I]MIBG-HMR value	1.6 (1.56–1.73)	1.17 (1.10–1.22)	**0.001**
Lowest putaminal DAT binding value	2.38 ± 0.18	1.66 ± 0.51	**0.010**
Lowest caudatal DAT binding value	2.87 ± 0.28	2.19 ± 0.52	**0.004**
UPDRS-III score			
Baseline	4.0 (1.0–5.0)	2.0 (1.0–4.0)	0.600
Follow-up	2.0 (0.5–5.0)	3.5 (2.3–6.3)	0.282
Odor identification score			
Baseline	10.6 ± 3.2	6.3 ± 4.1	0.053
Follow-up	12.0 ± 2.4	5.3 ± 4.2	**0.003**
MoCA			
Baseline	27.0 (24.5–29.0)	27.0 (26.0–28.0)	0.884
Follow-up	28.0 (27.5–29.5)	28 (27.0–29.0)	0.528

Baseline vs. follow-up in RBD subjects with normal or abnormal [^{123}I]MIBG[b]		
	RBD Subjects with Normal [^{123}I]MIBG (n = 5), *P* Value	**RBD Subjects with Abnormal [^{123}I]MIBG (n = 12), *P* Value**
PDRP *z* score: baseline vs. follow-up	0.063	**<0.001**
UPDRS-III: baseline vs. follow-up	1.000	0.324
Odor identification score: baseline vs. follow-up	0.250	0.063
MoCA: baseline vs. follow-up	0.500	0.059

Bold values denote significant *P* values.
[a]Normally distributed values are shown as mean ± standard deviation and nonparametric values as median (interquartile range). Nonparametric Mann-Whitney *U* test was used to compare subgroups with normal versus abnormal [^{123}I]MIBG.
[b]Wilcoxon test was used to compare baseline and follow-up results within each group.
RBD, rapid eye movement sleep behavior disorder; [^{123}I]MIBG, [^{123}I]meta-iodobenzylguanidine scintigraphy; PDRP, Parkinson's disease–related brain pattern; HMR, heart-to-mediastinum ratio; DAT, dopamine transporter; UPDRS-III, Unified Parkinson's Disease Rating Scale-motor, Part III; MoCA, Montreal Cognitive Assessment.

having subthreshold PDRP *z* scores at follow-up. This one subject (*z* = 2.07 at follow-up) was the second oldest of the iRBD cohort (72.5 years old at follow-up).

The 12 subjects with abnormal [^{123}I]MIBG had higher PDRP *z* score change per year (*P* = 0.027) and higher PDRP *z* scores at baseline (*P* = 0.048) and follow-up (*P* = 0.006) compared with those with normal [^{123}I]MIBG. PDRP expression in the subjects with abnormal [^{123}I]MIBG was higher at follow-up than at baseline (*P* < 0.001). Only a trend of higher follow-up

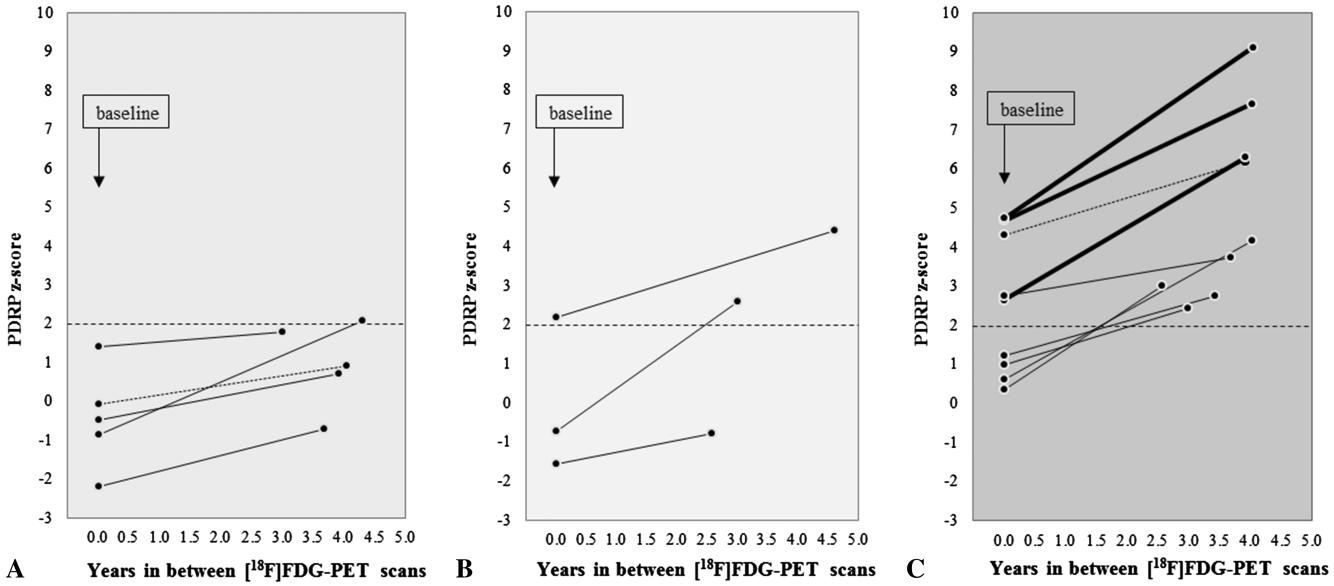

FIG. 1. Parkinson's disease–related brain pattern (PDRP) *z* score (baseline to follow-up). (**A**) Subjects with normal [^{123}I]meta-iodobenzylguanidine scintigraphy ([^{123}I]MIBG) and [^{123}I]*N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane single-photon emission computed tomography ([^{123}I]FP-CIT-SPECT). (**B**) Subjects with abnormal [^{123}I]MIBG and normal [^{123}I]FP-CIT-SPECT. (**C**) Subjects with abnormal [^{123}I]MIBG and [^{123}I]FP-CIT-SPECT; bold line marks the phenoconverted subjects (range: −2.0 to 5.0 months after follow-up [^{18}F]fluorodeoxyglucose-positron emission tomography ([^{18}F]FDG-PET)).

PDRP *z* scores was observed in the subjects with normal [^{123}I]MIBG ($P = 0.063$).

[^{123}I]FP-CIT-SPECT

Nine of 12 (75%) subjects with pathological [^{123}I]MIBG had pathological baseline [^{123}I]FP-CIT-SPECTs. All subjects with normal [^{123}I]MIBG had normal baseline [^{123}I]FP-CIT-SPECT. Dopamine transporter (DAT)-binding ratios were lower in subjects with abnormal [^{123}I]MIBG (lowest putaminal value: $P = 0.010$; lowest caudatal value: $P = 0.004$).

Olfaction

Subjects with abnormal [^{123}I]MIBG had lower odor identification scores at baseline compared with subjects with normal [^{123}I]MIBG, although this was not statistically significant ($P = 0.053$). The olfactory function in subjects with abnormal [^{123}I]MIBG deteriorated from baseline to follow-up, but this change did not reach statistical significance ($P = 0.063$). At follow-up, subjects with abnormal [^{123}I]MIBG had lower odor identification scores compared with subjects with normal [^{123}I]MIBG ($P = 0.003$). See also Supporting Information Fig. S2. Baseline and follow-up UPDRS-III and MoCA scores did not differ significantly between the two subgroups. At follow-up, two subjects with iRBD fulfilled the research criteria of probable mild cognitive impairment-Lewy body type.[28]

PD Phenoconverters

All three subjects who phenoconverted to PD during the study had abnormal [^{123}I]MIBG and [^{123}I]FP-CIT-SPECT, suprathreshold PDRP *z* scores, and hyposmia at baseline and follow-up (Fig. 1C; Supporting Information Table S1). Their baseline PDRP expressions were among the highest six PDRP *z* scores. At follow-up, they exhibited the highest PDRP *z* scores of the iRBD cohort.

For correlation analysis and the individual UPDRS-III scores at baseline and follow-up, see the Supporting Information.

Discussion

This longitudinal pilot study demonstrates that [^{123}I]MIBG, a proxy for cardiac noradrenergic innervation, is associated with the prodromal progression of PDRP expression in iRBD, the latter was recently reported by our group.[18] According to [^{123}I]MIBG results, we identified two subgroups.

In the first, defined by a pathological [^{123}I]MIBG, the majority (75%) had a pathological [^{123}I]FP-CIT-SPECT, 92% presented with suprathreshold follow-up PDRP *z* scores and 83% had hyposmia. Conversely, the second subgroup with normal [^{123}I]MIBG always had normal [^{123}I]FP-CIT-SPECT, exhibited only mild PDRP *z* score progression, and mostly had normosmia. Olfactory function correlated to [^{123}I]MIBG–heart-to-mediastinum ratio values and PDRP *z* scores at baseline

and follow-up. Cognitive and motor scores did not change significantly in either subgroup because of short follow-up time.

Studies of iRBD cohorts showed cardiac noradrenergic denervation in >80% of subjects[20,22] that has been observed before dopaminergic denervation, in concordance with Braak's PD staging model.[21,22,29]

Accordingly, we identified three cases with pathological [^{123}I]MIBG but normal [^{123}I]FP-CIT-SPECT. All subjects with reduced DAT binding had pathological [^{123}I]MIBG. As previously published,[30] [^{123}I]MIBG and [^{123}I]FP-CIT-SPECT results were found to highly correlate to each other. Patients with iRBD with pathological [^{123}I]MIBG but normal [^{123}I]FP-CIT-SPECT may represent an early stage of prodromal PD in which brainstem structures at the level of the vagal nuclei and/or locus coeruleus have already been affected, but the nigrostriatal pathway is undisturbed or only mildly disturbed. Our findings are in line with the literature[21,22] and the hypothesis of a "body-first" PD of which iRBD represents a prodromal stage subtype.[31] Alternatively, some early DLB cases have been known to present with normal striatal DAT binding.[21,32]

The PDRP is very similar to the [^{18}F]FDG-PET–derived DLB-related pattern (unpublished data).[10] However, it may not detect metabolic changes present in prodromal MSA. Therefore, some subjects with normal [^{123}I]MIBG (and normal [^{123}I]FP-CIT-SPECT) and subthreshold PDRP expression may possibly be in the prenigrostriatal MSA stages. Alternatively, they could represent nonphenoconverters or subjects with slow disease progression. The borderline suprathreshold PDRP expression at follow-up in one of this subgroup may be attributable to advancing age (for details, see Supporting Information).

[^{123}I]MIBG seems to be superior to [^{123}I]FP-CIT-SPECT in identifying subjects with suprathreshold follow-up PDRP z score in an earlier disease stage. This is illustrated by the fact that pathological [^{123}I]MIBG identified more subjects (92%) with suprathreshold follow-up PDRP z score than pathological [^{123}I]FP-CIT-SPECT alone (75%). Because the effectiveness of disease-modifying therapy may be higher in a prodromal "prenigral" stage of PD/DLB, [^{123}I]MIBG could function as a state marker to identify subjects with iRBD presenting the prodromal "peripheral" PD/DLB type. Complementarily, the cerebral [^{18}F]FDG-PET is a state marker[10] that may be able to differentiate between parkinsonian disorders[14] and is a prodromal progression marker[18] that is needed to measure the therapy effect. In contrast, [^{123}I]FP-CIT-SPECT is a state[8,9,33] and a progression marker[34] but detects converters later when nigrostriatal degeneration has occurred. Based on the three phenoconverted subjects, pathological [^{123}I]MIBG, pathological [^{123}I]FP-CIT-SPECT, suprathreshold PDRP z score, and hyposmia together indicate a high risk for phenoconversion to manifest PD.

This study has several limitations: (1) the small sample size, (2) the lack of repeated [^{123}I]MIBGs and [^{123}I]FP-CIT-SPECTs, and (3) the need of a longer follow-up period to clarify the etiology and course of subjects with normal imaging and low PDRP z score. As discussed earlier, those subjects may represent prodromal MSA, slow disease developers, or nonphenoconverters. Finally, this study focuses on a subtype of prodromal α-synucleinopathies, iRBD. Thus, our findings may not be generalizable to other prodromal PD subtypes.

In conclusion, pathological [^{123}I]MIBG appears to indicate prodromal progression of PDRP expression earlier than [^{123}I]FP-CIT-SPECT and is associated with hyposmia in iRBD. Therefore, we propose cardiac [^{123}I]MIBG as an early stratifying variable in iRBD research, provided that our results are confirmed by a larger, prospective, multicenter study.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Comparison of Transcranial Sonography and [^{18}F]-Fluorodopa PET Imaging in *GBA1* Mutation Carriers

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