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Imaging progressive peripheral and central dysfunction in isolated REM sleep behaviour disorder after 3 years of follow-up

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A B S T R A C T

Introduction: Most patients with isolated rapid eye movement sleep behaviour disorder (iRBD) convert to Parkinson's disease (PD), dementia with Lewy bodies, or multiple system atrophy within 15 years of diagnosis. Furthermore, iRBD patients develop non-motor symptoms similar to those of manifest PD patients and display dysfunction of the sympathetic and parasympathetic nervous system, comparable to that seen in PD. However, progression rates of autonomic dysfunction in iRBD have not been studied with objective measures in detail, which is the aim of this study.

Methods: Twenty-two iRBD patients were included at baseline and 14 participated in follow-up after 3 years. Colonic transit time (CTT) was examined using radio opaque markers, colonic volume was defined on abdominal computed tomography (CT) scans, Iodine-123-metaiodobenzylguanidine ([123I]MIBG) scintigraphy was performed to assess cardiac sympathetic innervation, and 3,4-dihydroxy-6-(18F) fluoro-L-phenylalanine ([18F]FDOPA) positron emission tomography (PET) scan determined nigrostriatal dopamine storage capacity. All examinations were performed at baseline and after 3 years.

Results: iRBD patients displayed increased CTT ($p = 0.001$) and colonic volume ($p = 0.01$) at follow-up compared to baseline. Furthermore, [123I]MIBG uptake and [18F]FDOPA uptake showed progressive reductions at follow-up ($p = 0.02$ and $p = 0.002$, respectively). No correlations were seen between changes in intestinal or cardiac measurements and dopaminergic function.

Conclusion: Using objective markers, the present study documented that intestinal dysfunction and cardiac sympathetic degeneration worsen in the majority of iRBD patients over a 3-year period. The absent correlation between these markers and nigrostriatal dopaminergic dysfunction suggests that progressive gastrointestinal and cardiac dysfunction in iRBD is caused mainly by non-dopaminergic mechanisms.

1. Background

Isolated rapid eye movement (REM) sleep behavior disorder (iRBD) is a parasomnia characterized by REM sleep without atonia and vivid dream enactment [1]. A majority of patients with iRBD convert to either Parkinson's disease (PD), dementia with Lewy bodies (DLB), or rarely multiple system atrophy (MSA) within 14 years of diagnosis [2]. Furthermore, iRBD patients show many non-motor symptoms similar to those of diagnosed PD patients including gastrointestinal dysfunction, orthostatic hypotension, and hyposmia [3]. Also, alpha-synuclein (α-syn) rich inclusions, the pathological hallmark of Lewy body disease, are present in the brain and peripheral autonomic nervous system of patients with iRBD [2].

iRBD in humans is believed to be caused by damage to several structures, including the locus coeruleus, subceruleus, sublaterodorsal nucleus, STN, and magnocellular reticular formation. Most of these nuclei are situated at the level of pons, above the dorsal motor nucleus of the vagus (DMV), but below substantia nigra [4]. It has been suggested that iRBD represents a body-first prodromal phenotype of PD, caused by gut-to-brain propagation of α-syn pathology, explaining the appearance of various autonomic symptoms prior to onset of motor symptoms [5].

A recent study substantiated this idea by demonstrating a caudo-rostral gradient of neuronal dysfunction in iRBD patients using positron emission tomography (PET) imaging to assess function of the

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autonomic nervous system, locus coeruleus, and substantia nigra [6]. iRBD patients displayed severe damage in both branches of the autonomic nervous system in some cases at the same level as manifest PD patients. Objective colonic function was assessed in the same iRBD cohort, and although a substantial fraction of iRBD patients had colonic dysfunction, the degree was less pronounced compared to de novo RBD-positive PD patients [3]. Thus, it remains an open question whether progressive gastrointestinal dysfunction in iRBD develops independent of nigrostriatal dopaminergic damage, or alternatively, whether it arises in synchrony with nigrostriatal denervation, which would suggest that the dopaminergic damage is in part responsible for constipation and colonic dysfunction, as has been suggested by observations in animal models [7].

Several studies have investigated evolution of non-motor symptoms and integrity of the dopaminergic system in iRBD, but the study of progression rates of autonomic dysfunction in iRBD using objective measures has received less attention [8]. Furthermore, progression of autonomic symptoms, motor symptoms and cognitive decline as possible disease modifying trial end points were shown to require sample sizes of hundreds or thousands of iRBD patients, elucidating the need for additional markers of disease progression [9]. The objective of this study was to image progression of intestinal dysfunction, cardiac sympathetic denervation, and dopaminergic nigrostriatal damage in patients with iRBD.

2. Materials and methods

2.1. Subjects

Twenty-two iRBD patients were included at baseline and 14 participated at follow-up after 3 years. Baseline examinations were performed between June 2016, and December 2017. Follow-up examinations were performed between October 2019, and September 2020. All participants provided written informed consent according to the Declaration of Helsinki. The study was approved by the Central Denmark Region Committee on Health Research Ethics (No. 1-10-72-160-16). All participants had a polysomnography (PSG) -confirmed iRBD diagnosis. Identical exclusion criteria were in effect at baseline and follow-up visits: PD or DLB diagnosis, previous or current cancer and/or major abdominal surgery, inflammatory bowel disease, diabetes mellitus, severe psychiatric disease, substance abuse, heart, liver, or kidney failure, and use of cholinesterase inhibitors. One patient had a moderate depression and was treated with Venlafaxin (150 mg x 2). Three iRBD patients converted to neurological disease before 3 years of follow-up and were not able to participate in the follow-up visit. Furthermore, one patient had died and four neurologically intact iRBD patients did not wish to participate in follow-up. Patient flow between baseline and follow-up flow is illustrated in Fig. 1. Previously published imaging data from healthy controls and PD patients are used for visual comparison in Fig. 2 [10].

2.2. Clinical assessments

iRBD diagnosis was confirmed in all participants after overnight video-PSG, as previously described, and RBD symptoms were additionally assessed with RBD screening questionnaire (RBDSQ) [6,11]. Daytime sleepiness was evaluated with Epworth sleepiness scale (ESS) [12]. Blood pressure was assessed after 15 min of supine rest and after 1, 2, and 3 min of standing. Orthostatic hypotension (OH) was defined as systolic blood pressure drop of 20 mmHg or diastolic blood pressure drop of 10 mmHg. Motor symptoms were assessed with Movement Disorder Society (MDS) Unified Parkinson's disease Rating Scale part III (MDS-UPDRS III) [13]. Olfaction was tested using Sniffin' Sticks 16-item identification test (Burghart, Wedel, Germany) [14]. Cognition was evaluated using Montreal Cognitive Assessment battery (MoCA) [15]. Depressive symptoms were assessed with the Major Depression Inventory (MDI) [16]. Constipation and gastrointestinal symptoms were scored with ROME III functional constipation and nausea-vomiting questionnaires [17]. Other non-motor symptoms were scored using the scales for outcomes in PD - autonomic (SCOPA-AUT), and the non-motor symptoms scale (NMSS) [18,19].

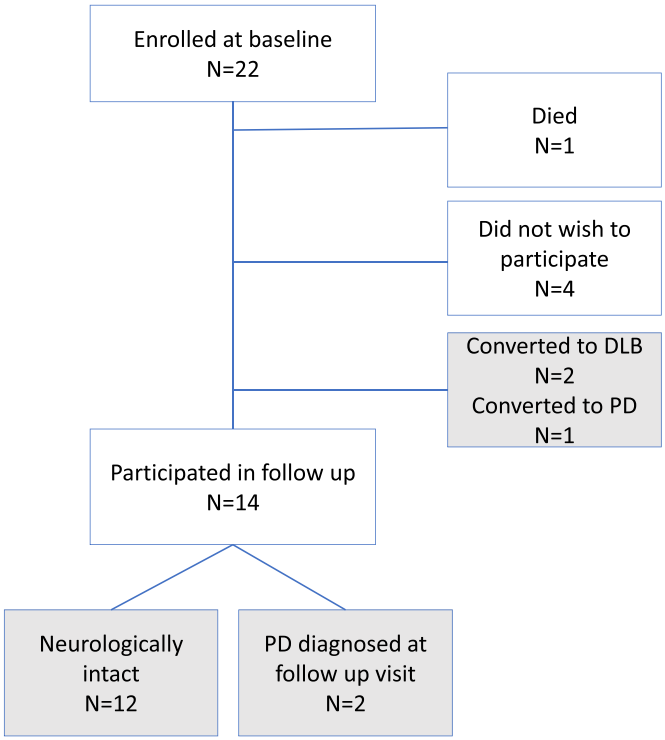

Fig. 1. Patient flow at baseline and follow up. Grey boxes signify the subjects whose assessments are reported in the paper.

2.3. Gastrointestinal transit time and colonic volume

Colonic transit time (CTT) was examined using radio opaque markers (ROM) and colonic volume was assessed on abdominal CT scans as previously described [20]. In short, participants were instructed to ingest six capsules each morning containing 10 ROM. The capsules were ingested at day 1–6 and a CT scan was performed at day 7 to determine the number of retained ROM. Total and segmental colonic volumes were also defined on the abdominal CT scan using PMOD Software (PMOD Technologies, Zürich, Switzerland). Volumes of interest (VOI) were drawn manually to outline the total colon as well as separate segments: coecum, ascendens, transversum, descendens, and rectosigmoideum. Colonic air was detected by segmenting VOIs at a threshold of −300 Hounsfield units and air volume was subtracted from total volume. Furthermore, the colonic volumes were adjusted for gender as previously described [20].

2.4. [123I]MIBG imaging, [18F]FDOPA, and MRI

[123I]MIBG heart scintigraphy, as a measure of cardiac sympathetic innervation, was performed on all subjects who participated in follow-up. A dual-head gamma camera (Siemens Symbia T16 SPECT/CT, Erlangen, Germany) with a LEHR (low-energy high-resolution) collimator was used. 110 MBq of [123I]MIBG was injected intravenously and 15 min planar imaging were performed at 15 min and 3.5 h post-injection resulting in an early and late image for each participant. Hermes software (Hermes, Stockholm, Sweden) was used to outline regions of interest on the heart and mediastinum. Mean heart uptake/mediastinum uptake (H/M) ratios were calculated on early and late

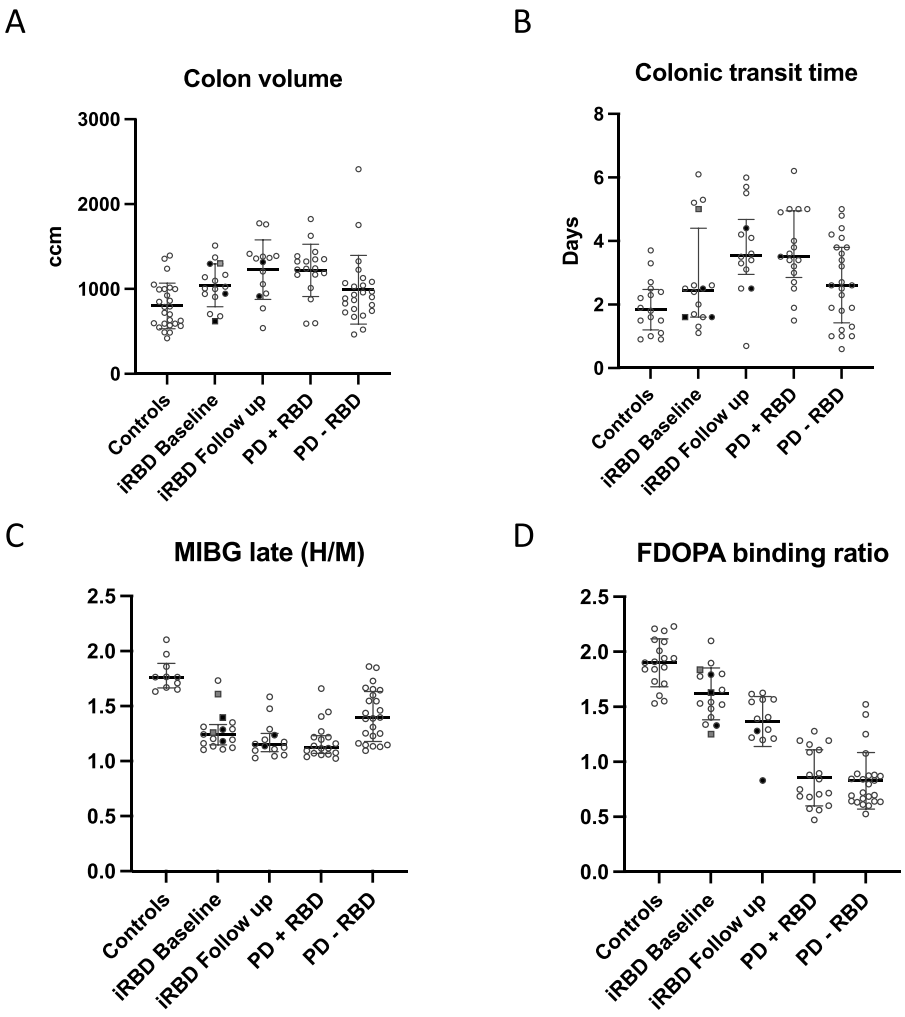

Fig. 2. Imaging results from 14 iRBD patients who completed 3 year follow up and an additional 3 iRBD patients who only had baseline data, since they converted to DLB (n = 2) or PD (n = 1) before the follow-up date. For visual comparison, previously published data are also shown from healthy controls, de novo PD with RBD (PD + RBD), and de novo PD without RBD (PD - RBD). Black circles signify patients who converted to PD at follow-up. Black square converted to PD and grey squares converted to DLB in between baseline and follow-up. One of the DLB converters did not have an abdominal CT scan due to claustrophobia. A. Colon volumes are given as mean ± SD. B. Colonic transit time is presented as median ± IQR. C. Heart/mediastinum (H/M) ratio on the late [123I]MIBG images is given as median ± IQR. D. The minimum (left or right) [18F]FDOPA PET specific-to-nonspecific binding ratio in the putamen is presented as mean ± SD.

images and washout rate was defined as $H/M_{late} - H/M_{early}$.

[18F]FDOPA PET was used to assess nigrostriatal dopamine storage capacity as previously described [6]. A dose of 120 MBq of [18F]FDOPA was injected intravenously approx. 1 h after ingestion of 150 mg carbidopa. Participants were placed in an ECAT high-resolution research tomograph (HRRT; Siemens/CTI, Knoxville, TN). A transmission scan was performed, and dynamic PET data was acquired at 70–90 min post-injection. PET images were normalized to MNI space and rigidly matched to each subjects anatomical MRI using PMOD Software NeuroTool. Hammers N30R83 atlas was used for MR segmentation of putamen and occipital cortex. [18F]FDOPA signal was analyzed using a simple ratio approach with specific-to-non-specific binding defined as (putamen-occipital cortex)/occipital cortex on summed 70–90 min PET images.

Subjects had an MRI scan including T1 and fluid-attenuated inversion recovery (FLAIR) images on either a 3T SIEMENS MAGNETOM TRIO or a 3T SIEMENS SKYRA magnet, as previously described [21]. [18F]FDOPA PET was performed on all subjects participating in follow-up visits, however four subjects did not receive MRI (two due to metallic foreign bodies, and two due to severe claustrophobia). [18F]FDOPA analysis was performed without MRI matching.

Previously published In-house imaging data from healthy subjects and PD patients [10] is presented for visual comparison.

2.5. Statistical analysis

Statistical analyses were conducted with Prism version 9 (GraphPad Software, La Jolla, USA) and Stata 13 (College Station, TX: StataCorp LP). Distribution of data was tested for normality with Q-Q plots, and D'Agostino & Pearson normality test. We used paired *t*-test to compare baseline results with follow up results for numerical variables with normal distribution and Wilcoxon matched-pairs signed rank test for numerical variables without normal distribution and ordinal variables (UPDRS, MoCA, Sniffin Sticks, questionnaires). Chi-squared test was used for nominal variables (presence/absence of OH). The applied test type is stated in Table 1 for each variable. Correlations were assessed with the Pearson correlation coefficient for numerical variables with normal distribution and Spearman rank correlation analysis for ordinal variables and numerical variables without normal distribution. Normally distributed variables are expressed as mean ± SD, the rest are expressed as median (range). Statistical significance was defined as $p < 0.05$, without correction for multiple comparison; exact p-values as well as relevant scatter plots are presented.

3. Results

Demographic and clinical data are reported in Table 1. Full baseline data on our iRBD cohort was published previously [3,6]. Mean follow-up time was 3.1 ± 0.3 years. No differences were seen in severity of sleep symptoms, olfactory dysfunction, or gastrointestinal symptoms according to ROME questionnaires. The number of participants suffering from orthostatic hypotension had doubled from three at baseline to six at follow-up. Depressive symptoms had not worsened during the follow-up period. Autonomic symptoms assessed with SCOPA-AUT had not

Table 1
Demographic, clinical, and imaging characteristics of iRBD patients at baseline and follow up.

	Baseline (n = 14)	Follow up (n = 14)	p-value
Age	67 ± 9	70 ± 8	N/A
Gender (male/female)	11/3	11/3	N/A
RBD symptom duration (years)	5.4 ± 4.2	8.5 ± 4.3	N/A
RBDSQ[a]	10 (0–12)	9.5 (4–13)	0.72
ESS[a]	5.5 (0–21)	5.5 (0–15)	0.70
MoCA[a]	27.5 (24–30)	27.5 (25–30)	0.56
MDS-UPDRS (part III)[a]	1 (0–5)	1.5 (0–21)	**0.03**
Sniffin' Sticks[a]	6 (2–13)	6 (1–13)	0.84
ROME III – constipation[a]	3.5 (0–24)	5.5 (0–24)	0.09
ROME III – nausea[a]	0 (0–4)	0 (0–6)	0.25
NMSS[a]	6 (2–15)	20 (0–97)	**<0.001***
SCOPA-AUT[a]	11.5 (2–28)	12.5 (5–29)	0.57
Major ICD-10	4 (0–24)	5 (0–39)	0.35
OH (yes/no)[b]	3/10	6/7	0.06*
Colonic volume, cm^3[c]	1056 ± 233	1228 ± 351	**p = 0.01**
ROM, total number[a]	19.5 (6–56)	30.5 (2–55)	**p = 0.002**
CTT, days[a]	2.45 (1.1–6.1)	3.55 (0.7–6.0)	**p = 0.002**
MIBG early (H/M)[a]	1.34 (1.16–1.69)	1.25 (1.15–1.70)	p = 0.07
MIBG late (H/M)[a]	1.20 (1.10–1.73)	1.15 (1.03–1.59)	**p = 0.02**
MIBG washout rate[c]	−0.09 ± 0.07	−0.09 ± 0.07	p = 1.0
FDOPA specific binding ratio[c]	1.63 ± 0.23	1.37 ± 0.23	**p = 0.001**

* Data for 13 patients only, since one subject failed to complete the full examination.

[a] Wilcoxon matched-pairs signed rank test.

[b] Binomial test, one-tailed.

[c] Paired *t*-test. Data is presented as mean ± SD or median (range). Abbreviations: RBD = REM sleep behavior disorder, RBDSQ = REM Sleep Behavior Disorder Questionnaire, MoCA = Montreal Cognitive Assessment battery, MDS-UPDRS (part III) Movement Disorder Society Unified Parkinson's Disease Rating Scale, NMSS = Non-motor Symptoms Scale, SCOPA-AUT = Scales for Outcomes in PD – Autonomic, OH = orthostatic hypotension. ROM = radio opaque markers, CTT = colonic transit time, H/M = heart uptake/mediastinum uptake ratio.

worsened, however, global non-motor symptoms assessed with NMSS had increased significantly. No patients had clinical dementia at baseline or follow-up and the average MoCA scores were unaltered. A significant, albeit slight worsening of motor symptoms was detected using MDS-UPDRS III.

Imaging results are presented in Table 1 and Fig. 2. Patients displayed increased CTT (p = 0.001), and colonic volume (p = 0.01) at follow-up compared to baseline. CTT had progressed in 13/14 patients and colonic volume increased in 11/14 iRBD patients at follow-up compared to baseline. Furthermore, the [123I]MIBG uptake showed progressive reductions in 12/14 patients at follow-up (p < 0.02) and the putaminal [18F]FDOPA uptake showed progressive reductions in 10/14 patients (p = 0.002) with an annual decline of approximately 5%. 3/14 iRBD patients had pathological [18F]FDOPA scans (>2 SD below control mean) at baseline without showing symptoms of PD and this number increased to 8/14 at follow up. Differences in colonic volume, colonic transit time, MIBG late (H/M), and FDOPA specific binding ratios were calculated for each patient. We found no correlation between [18F]FDOPA binding ratio differences and differences in cardiac and intestinal parameters. As previously reported, PD patients without RBD have less severe peripheral dysfunction compared to PD patients with RBD and iRBD patients [10]. However, whereas iRBD patients displayed less severe dysfunction than de novo PD with RBD at baseline on the three markers of peripheral dysfunction (Fig. 2A–C), the iRBD group showed similar levels of dysfunction at follow-up.

Between baseline and follow up visits, one patient converted to PD and two patients converted to DLB. Baseline data from these subjects are shown in Fig. 2 and Supplemental Fig. 1.

Additionally, two patients were found to fulfil diagnostic criteria for PD at follow-up, and were diagnosed with PD. The small sample size prevented a proper statistical analysis of converters vs. non-converters in this study. However, we noted that the two converted subjects showed large reductions in FDOPA binding ratios. The two converters also had the highest difference in MDS-UPDRS III scores between the visits with increases of 15 and 16 points, respectively. Changes from baseline to follow-up in colonic volume, CTT, and MIBG heart signal were similar between converters and non-converters (Supplemental Fig. 2).

4. Discussion

The present study documents that intestinal dysfunction as well as cardiac sympathetic innervation and striatal dopaminergic innervation show marked deterioration in the majority of iRBD patients over a 3-year period. To our knowledge this is the first study to assess progression of peripheral intestinal dysfunction in iRBD with imaging markers. Our findings suggest a certain pattern in the progression of peripheral dysfunction in iRBD, starting with measurable denervation of cardiac noradrenergic fibers, followed by progressive objective intestinal dysfunction at a time when nigrostriatal degeneration is still insufficient to cause parkinsonism (Fig. 3).

Follow-up of motor and non-motor symptoms in subjects with iRBD and risk of conversion to movement disorders have been studied in large multi-center cohorts [22]. However, these studies focused mainly on baseline evaluations of symptoms, cognition, and dopaminergic imaging to predict later conversion to PD, DLB, or MSA.

A study with 24 cognitively intact iRBD patients showed no global cognitive impairment after two years of follow-up, which is in line with our findings [23]. We also found no progressive decline in olfactory function, which is in accordance with previous findings in 20 iRBD patients after 4 years of follow-up [24]. Fereshtehnejad et al. followed a large cohort of iRBD patients for 2–12 years and reported a slight worsening of constipation, urinary symptoms, and erectile dysfunction over time [25]. Another large study assessed progression markers in iRBD patients and found modest progression rates of cognitive and autonomic symptoms during 3 years of follow-up [9]. However, the authors concluded that future trials of disease-modifying drugs would require sample sizes in the hundreds or thousands if an effect was to be assessed based solely on symptomatic progression. These observations highlight the need for reliable objective techniques to evaluate disease progression. Furthermore, subjective assessments of intestinal dysfunction show large discrepancies and yield different estimates in the same subjects depending on the choice of questionnaire [20]. Also, objective measurements reveal a much larger prevalence of colonic dysfunction compared to symptom-based evaluations [20].

Recent follow-up imaging studies assessed dopamine transporter integrity in the striatum of cohorts of iRBD patients, and reported an annual mean decrease of 3–6% in the striatum and putamen, [26,27]. This is in accordance with our finding of a 5% annual decrease of FDOPA SBR.

To our knowledge, only one study by Miyamoto et al. has evaluated follow up [123I]MIBG scintigraphies in iRBD patients. Fifteen subjects were examined at baseline and after 2.5 years with a mean RBD symptom duration of 5.2 years at baseline. Miyamoto et al. only reported the late H/M ratio, which was not significantly decreased at follow up although a trend towards decrease was found (p = 0.06). The iRBD patients in our study may have been further advanced in their disease course, which is supported by the fact that Miyamoto et al. did not see any converted iRBD subjects at follow up. Furthermore, they reported no change in UPDRS motor examination at follow up, whereas we detected a small, but significant increase in motor symptoms. Also, a slightly longer average follow up duration could explain the ability to detect a significant decrease in our study [28]. A case report by the same group

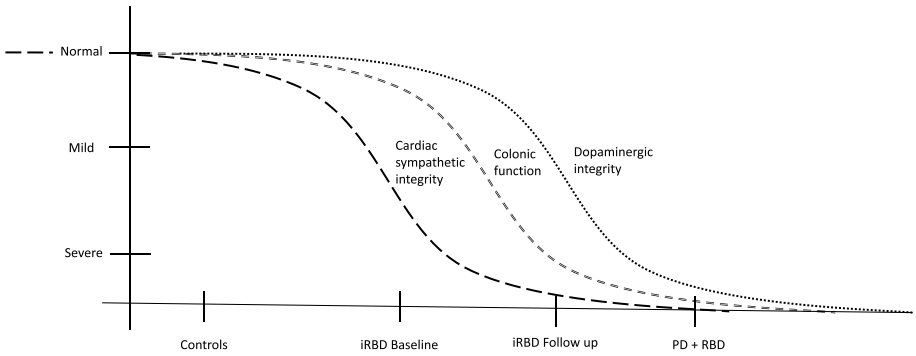

Fig. 3. Schematic illustration of gradual development of dysfunction in patients with iRBD. The graph is a hypothetical depiction shown for visual clarification.

followed an iRBD patient from the first symptom development and found that MIBG signal was normal at first but decreased after 2 years suggesting that cardiac sympathetic denervation is a very early occurrence [29].

To our knowledge, this is the first study to evaluate progression of intestinal dysfunction in iRBD patients using objective measures. We found progressively increased colonic transit time and colonic volume after 3 years of follow-up. Recently, we published results from a cohort of newly diagnosed PD patients, who were divided into subgroups depending on the presence of RBD (+RBD/- RBD). These patients were compared to our iRBD cohort at baseline and even though iRBD subjects showed increased colonic transit and colonic volume compared to healthy controls they were not as severely affected as PD + RBD patients [10]. However, these same iRBD subjects, now assessed 3 years later, displayed a degree of intestinal dysfunction, comparable to the de novo PD + RBD subjects (Fig. 2). Interestingly, the two converted subjects in the present study had some of the smallest increases in colonic volume but showed some of the largest progressive reductions in FDOPA binding ratio suggesting that the intestinal dysfunction may reach a plateau prior to the degeneration of the dopaminergic system (Fig. 3). Furthermore, the absent correlation between objective intestinal dysfunction and nigrostriatal dopaminergic dysfunction suggests that progressive intestinal dysfunction in iRBD is caused mainly by non-dopaminergic mechanisms.

There are several limitations to this study. First, the baseline sample size was small, and only two thirds of the patients participated in follow-up. Furthermore, the patients who converted to neurodegenerative disease before the follow up visit were not assessed at time of conversion. This could lead to potential confounding since the subjects participating in follow up may have been less affected by various symptoms and thus have slower disease progression in general. However, that would lead us to underestimate rather than overestimate the ability of the imaging techniques to capture disease progression. Second, colonic volume measurement requires an abdominal-pelvic CT scan and when used as a progression marker this will lead to repeated radiation exposure of the patient. A low-dose CT scan is sufficient, but the manual outline of the colon becomes time-consuming and requires specialized training. On the other hand, the assessment of CTT is performed with cheap and widely available radio-opaque markers and a simple x-ray of the abdomen is adequate minimizing the radiation dose and risk of side effects. There are no contraindications to either imaging technique, but previous major abdominal surgery can complicate the evaluations. Third, we evaluated the patients during a follow up period of 3 years and trials evaluating disease-modifying drugs usually aim to detect an effect during a shorter time window. A recent review of PD clinical trials performed during the last two decades found that study duration of phase 2 trials ranged between 1 and 2.5 years and duration of phase 3 trials ranged between 1.5 and 3 years [30]. Hence, it is important to determine, whether these objective markers are able to detect disease progression also during shorter follow-up periods.

In conclusion, patients with iRBD show marked progression of objectively measured intestinal dysfunction, sympathetic cardiac denervation, and dopaminergic nigrostriatal damage after 3 years of follow up. Our observation that both colonic transit time and colonic volume showed progression in the majority of iRBD patients over a 3-year period suggests that these safe techniques could have potential as adjunct biomarkers in future clinical trials of disease-modifying drugs. Furthermore, gastrointestinal dysfunction and sympathetic denervation seem to be mostly unrelated to dopaminergic damage. Future studies of larger patient samples are needed to verify our findings and assess whether these techniques are reliable during shorter follow-up intervals.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2022.07.005.

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