



Objective intestinal function in patients with idiopathic REM sleep behavior disorder

Karoline Knudsen^{a,*}, Tatyana D. Fedorova^a, Allan K. Hansen^a, Michael Sommerauer^{a,b}, Anne-Mette Haase^c, Kristina B. Svendsen^d, Marit Otto^d, Karen Østergaard^d, Klaus Krogh^c, Per Borghammer^a

^a Department of Nuclear Medicine and PET Centre, Aarhus University Hospital, Denmark

^b Department of Neurology, University Hospital Cologne, Cologne, Germany

^c Department of Hepatology and Gastroenterology, Aarhus University Hospital, Denmark

^d Department of Neurology, Aarhus University Hospital, Denmark

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ABSTRACT

Background: Parkinson's disease is characterized by pathological α -synuclein accumulation and cell death, which has been hypothesized to originate in peripheral nerve terminals and subsequently spread via autonomic nerves. Supporting this, most Parkinson's disease patients experience autonomic non-motor symptoms such as constipation, often years prior to diagnosis.

Objective: We aimed to study gastrointestinal transit time, colonic volume, and peristaltic movements in idiopathic REM Sleep Behavior Disorder patients, a prodromal marker of Parkinson's disease or Dementia with Lewy bodies.

Methods: Twenty-two patients were included and compared to previously published data from Parkinson's disease patients and controls. Gastrointestinal transit time, computed tomography-based volume estimation, and colonic motility were performed as markers of gastrointestinal function and autonomic involvement. Subjective constipation symptoms were evaluated with two different questionnaires.

Results: Gastrointestinal transit time was increased in 33% ($p = 0.039$) and colonic volume in 48% ($p = 0.0049$) of patients. Colonic transit time measured by the 3D-Transit system was increased in 70% ($p = 0.0326$) and the number of fast peristaltic colonic movements was reduced ($p = 0.015$). Mean small intestinal transit time was comparable to Parkinson's disease patients, although not significantly different compared to controls ($p = 0.18$). Subjective constipation symptoms were present in 18 or 41%, depending on type of questionnaire.

Conclusions: Total gastrointestinal transit time, colonic volume, and 3D-Transit colonic transit time were significantly increased compared to controls, although not to the extent seen in medicated Parkinson's patients. Limited correlation was seen between subjective constipation and objective markers. The findings support that marked GI dysfunction is present in the early prodromal PD phase.

1. Introduction

Parkinson's disease (PD) is a multi system disorder characterized by pathological α -synuclein (α -syn) accumulation and cell death of vulnerable neuron populations [1]. Braak and colleagues have suggested that α -syn pathology in some cases initiates in peripheral nerve

terminals and subsequently spreads to the central nervous system (CNS) via parasympathetic and enteric nerves [2–4]. Furthermore, the sympathetic pathways are also a potential spreading route [5,6]. In support of this view, most PD patients experience a range of autonomic non-motor symptoms such as constipation, often preceding the PD diagnosis by several years [4,7,8]. The field of enquiry into gastrointestinal (GI)

Abbreviations: PD, Parkinson's disease; α -syn, α -synuclein; CNS, central nervous system; GI, gastrointestinal; REM, rapid-eye-movement; iRBD, idiopathic REM sleep behavior disorder; DLB, dementia with Lewy bodies; MSA, multiple system atrophy; PSG, polysomnography; HC, healthy control; ROM, radio opaque marker; GITT, gastrointestinal transit time; ROI, region of interest; VOI, volume of interest; HU, Hounsfield unit; UPDRS, Unified Parkinson's disease Rating Scale; MoCA, Montreal Cognitive Assessment; NMSQuest, non-motor symptoms questionnaire; ANOVA, analysis of variance; CTT, colonic transit time; GTT, gastric transit time; SITT, small intestinal transit time

* Corresponding author. Department of Nuclear Medicine and PET Centre, Aarhus, Denmark.

E-mail address: karoknud@rm.dk (K. Knudsen).

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dysfunction in PD poses several problems. The majority of previous studies captured only the subjective symptomatology using questionnaires. However, subjective symptoms and objective markers of intestinal dysfunction correlate poorly in diagnosed PD patients [7], and the prevalence of objective dysfunction is considerably higher than prevalence of subjective symptoms [9,10]. Also, most studies investigated medicated PD patients, making it difficult to disentangle effects of medication from those of the neurodegenerative process [7]. Studies of GI dysfunction during the prodromal phase of PD are rare and relied mainly on questionnaires.

Idiopathic rapid-eye-movement (REM) sleep behavior disorder (iRBD) is a condition of dream enactment and lack of muscle atonia during the normally atonic REM sleep phase [11]. It has been demonstrated that the majority of iRBD patients in time will convert to PD, dementia with Lewy bodies (DLB), or in rare cases multiple system atrophy (MSA) [11,12]. Thus, iRBD is recognized as an early prodromal marker of PD or DLB, representing an opportunity to investigate GI dysfunction in the pre-motor phase of these synucleinopathies, and importantly, prior to inception of anti-parkinson medication. A few studies reported that the prevalence of subjective GI symptoms in iRBD cohorts equaled that of diagnosed PD groups [13,14], but to our knowledge no studies of objective intestinal dysfunction have been published. In this pilot-study, we aimed to investigate intestinal transit times, intestinal volumes, and colonic motility in polysomnography (PSG) verified iRBD patients with comparison to healthy controls and diagnosed PD patients.

2. Methods

2.1. Ethics statement

The study was approved by the Central Denmark Region Committee on Health Research Ethics (No. 1-10-72-160-16). All participants provided written informed consent.

2.2. Subjects

Twenty-two PSG confirmed iRBD patients aged 50–85 years were prospectively included as part of a previously published imaging study [15]. No selection of iRBD patients was conducted with respect to presence or degree of GI symptoms. Exclusion criteria were: PD or DLB diagnosis according to research criteria [16,17], previous or current cancer and/or major abdominal organ surgery, gastrointestinal disorders besides constipation, diabetes mellitus, psychiatric disease, substance abuse, heart, liver, or kidney failure, and use of cholinesterase inhibitors. Five patients were treated with laxatives prior to and during the study (Psyllium). Proton pump inhibitor intake in 2 iRBD subjects was discontinued > 3 days before examinations.

Data obtained in the iRBD cohort were compared to previously published data from mostly early stage PD patients and healthy control subjects (HC) acquired with identical methodologies [9,18]. Detailed demographic and clinical data from these reference groups are provided in Table 1.

2.3. Radio opaque markers

All participants underwent a 7-days radio opaque marker (ROM) protocol as previously described [9]. In short, one capsule containing 10 ROM was ingested each morning for 6 consecutive days. Total and segmental number of retained ROM were determined on an abdominal CT scan including intravenous contrast medium (Visipaque 270 mg/mL; 2 mL/kg) performed on day 7 and converted into gastrointestinal transit time (GITT) according to the following equation: $GITT = (\text{total ROM} + 5)/10$ [19].

2.4. Colonic volume

Total and segmental colonic volumes were determined as previously described [9]. In brief, using PMOD software (*PMOD Technologies, Zürich, Switzerland*), regions of interest (ROIs) outlining the colon were defined on each abdominal CT slice. ROIs were subsequently fused into 3D volumes of interest (VOIs) of the caecum, ascending, transverse, descending, rectosigmoid, and total colon. Absolute segmental volumes were defined by subtracting air in the colon at -300 Hounsfield CT unit (HU) threshold.

2.5. 3D-transit

The 3D-Transit ambulatory system methodology (*Motilis Medica SA, Lausanne, Switzerland*) was applied as described previously [18]. In short, a wireless electromagnetic capsule was ingested subsequent to a meal and monitored by a portable abdominal detector until capsule exit from the GI tract. Capsule position and GI contractions were subsequently determined by converting the electromagnetic field into space-time coordinates (position: x, y, z ; orientation angles: ϕ, θ). Segmental transit times as well as propagating colonic mass- and fast movements were defined as previously described [18].

During recording period, meals were restricted to 3 times a day, intake of alcohol, soft drinks, and coffee were prohibited, as were sports and hard physical labor. Furthermore, a diary was kept on defecation time, sleep, and daily activities.

2.6. Clinical assessment

Overnight video-polysomnography was performed as previously described on all participants to verify iRBD diagnosis [20]. Motor symptoms were scored using MDS Unified Parkinson's disease Rating Scale part III (MDS-UPDRS III). Olfactory function was evaluated with Sniffin' Sticks 16-item identification test (*Burghart, Wedel, Germany*) [21] and cognitive function by the Montreal Cognitive Assessment test (MoCA). Intestinal symptoms and presence of constipation were assessed by the ROME III functional constipation questionnaire [22]. General non-motor symptoms were evaluated by the non-motor symptoms questionnaire (NMSQuest) [23]. Details on constipation definitions according to ROME III and NMSQuest were provided previously [9].

2.7. Statistics

Statistical analyses were performed using Prism 6 (*GraphPad Software, La Jolla, USA*) and Stata 13 (*College Station, TX: StataCorp LP*). Normal distribution of data was tested by Q-Q plots and D'Agostino & Pearson omnibus normality test. For the majority of data types, we compared the iRBD group to HC and PD groups using chi-squared tests or unpaired t-tests or Mann-Whitney tests for parametric and non-parametric data, respectively. The applied test for each data type is stated in Table 1. For these data, no correction for multiple comparisons was applied, but exact p-values are listed and relevant data shown as scatter plots. Between-group differences of ROM and volumes in the five colonic segments were analyzed by two-way analysis of variance (ANOVA) with *post hoc* Sidak's multiple comparison correction. Time to first mass movement/fast movement in iRBD and HC was tested with Log-rank (Mantel-Cox) tests. Significance levels were defined as $p < 0.05$. Spearman Rank correlation was used to evaluate associations between objective markers and questionnaire items (ordinal data) without multiple comparison correction.

3. Results

Demographic and clinical data are summarized in Table 1.

No difference was seen in sex distribution, age, and BMI between

Table 1
Demographic, clinical, and study data in RBD, PD patients, and healthy controls (HC).

	RBD	HC	P-value	PD	P-value
Sex, male/female ^a	18/4	17/9	0.2018	20/12	0.1266
Age, years ^c	67.8 ± 8.5	65.4 ± 6.2	0.2753	64.7 ± 7.1	0.1507
BMI ^c	26.1 ± 3.6	26.9 ± 3.4	0.4530	26.4 ± 3.2	0.7627
Disease duration, years	–	–	–	4.4 ± 4	–
RBD symptom duration, years	6.3 ± 5.6	–	–	–	–
MDS-UPDRS (motor), off ^b	1 (0–5)	–	–	20 (6–35)	< 0.0001
Hoehn & Yahr stage I/II/III, off	–	–	–	2/24/4	–
Odor identification score ^b	6 (2–13)	12 (6–15)	< 0.0001	7 (1–14)	0.0920
ROME III					
Constipation value (total) ^b	4 (0–24)	0 (0–14)	0.0019	9 (0–45)	0.0203
Constipation value (9–15) ^b	3 (0–11)	0 (0–3)	0.0016	4 (0–26)	0.0819
Constipation ^a	41%	0%	0.0005	32%	0.5703
NMSQuest					
Total score ^b	6.5 (2–15)	1 (0–7)	< 0.0001	13 (2–20)	0.0422
Constipation ^a	18%	6%	0.3634	38%	0.1968
Radio opaque markers, total number* ^c	24 ± 16.1	14.6 ± 8.4	0.0390	32.8 ± 14	0.0590
Colonic transit time (days)*	2.9 ± 1.6	2.0 ± 0.8	0.0390	3.8 ± 1.4	0.0590
Colonic volume, cc total ^c	1029 ± 255	800 ± 270	0.0049	1153 ± 381	0.1946
3D-Transit time, min ^b					
Total**	2902 (532–8678)	1536 (580–3340)	0.0132	–	–
Stomach***	167 (9–339)	161 (77–304)	0.7608	165 (12–363)	0.6312
Small intestine***	382 (112–717)	295 (159–696)	0.1826	400 (199–802)	0.6859
Total colon***	2361 (161–8181)	1128 (205–2835)	0.0326	–	–

Data given as mean ± SD or median (range). P-value columns designate RBD vs. HC and RBD vs. PD comparisons, respectively. Evaluation of radio opaque markers and colonic volume was performed in 21 of 22 iRBD patients. 3D-Transit data was obtained in 21 iRBD patients, but in one case only small intestinal transit time could be determined. **n* = 24 PD and 16 HC. ***n* = 14 HC. ****n* = 22 PD and 15 HC. *****n* = 22 PD and 14 HC. ^aChi-square. ^bMann Whitney. ^cUnpaired *t*-test. Abbreviations: BMI = Body Mass Index. MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale. NMSQuest = Non-Motor Symptom Questionnaire.

iRBD and reference PD and HC groups. The prevalence and severity of hyposmia was comparable between the iRBD and PD. iRBD patients displayed significantly lower olfaction scores as well as increased rates of intestinal and non-motor symptoms compared to controls. The presence of subjective constipation in iRBD varied according to specific questionnaire criteria, but significantly more iRBD patients than controls were constipated using ROME III criteria.

iRBD patients showed cognitive MoCA scores in the normal range (median 27, range 23–30). The PD and HC groups were screened with the MMSE, and therefore a direct comparison could not be made. Nevertheless, both reference groups displayed intact cognitive performance.

3.1. Radio opaque markers

The iRBD group showed a significant increase in retained ROM and GITT (*p* = 0.039) compared to control subjects (Fig. 1A). The difference was most prominent in the rectosigmoid colonic segment (*p* = 0.0176) (Fig. 1B). No difference was seen between iRBD and PD patients in total ROM retention (*p* = 0.059), but a significantly higher number of ROMs was present in the transverse segment in PD patients (*p* = 0.0006). A cut-off of 23 ROMs was previously defined as optimal for separating PD patients and controls [9]. Using this threshold, only 7 of 21 (33%) iRBD patients showed delayed GITT (Fig. 1A).

3.2. Colonic volume

As previously reported, sex was the only factor associated with colonic volume differences [9]. Thus, sex-corrected volume data was used for analyses. Total colonic volume was significantly increased in iRBD patients compared to controls (*p* = 0.0049), but not in comparison to PD patients (*p* = 0.1946) (Fig. 1C). Segmental colonic volume showed a somewhat similar pattern in iRBD and PD patients, and a significant difference was seen in the transverse part in iRBD compared to HC (*p* = 0.0215) (Fig. 1D). A cut-off of 1024 cc was previously determined

as optimal for separating PD patients and controls [9]. Using this threshold, 10 of 21 (48%) iRBD patients showed increased colonic volume (Fig. 1C).

3.3. 3D-transit

Using the 3D-Transit system, iRBD patients showed significantly delayed colonic transit time (CTT) compared to control subjects (*p* = 0.0326) (Fig. 2A + C). A *post hoc* ROC analysis defined a CTT of 33 h as the optimal cut-off. By this criterion, 70% (14/20) of iRBD subjects and 7% of controls (1/14) had increased CTT (Fig. 2C). The iRBD group also displayed significantly prolonged total 3D-Transit time compared to controls (*p* = 0.0132). No significant differences were seen in gastric transit time (GTT) (*p* = 0.7608) and small intestinal transit time (SITT) (*p* = 0.1826) between iRBD and HC groups, although mean SITT in iRBD was similar to that of the PD group (Fig. 2A + B). Due to technical failure, CTT was only obtained in 14 control subjects. Full CTT was not obtained in the previously studied PD group, which prohibited iRBD vs. PD comparisons of full CTT.

Fig. 3 shows time to first mass- and fast movement in iRBD patients compared to controls. No group difference was seen in mass movements (Fig. 3B), but time to first fast movement was significantly increased in iRBD (*p* = 0.015) (Fig. 3C).

3.4. Correlations and questionnaires

The frequency of GI symptoms and general non-motor symptoms in iRBD were higher compared to HC but lower compared to PD (Table 1). The prevalence of subjective constipation in the iRBD group was 41% according to ROME III criteria and 18% according to NMSQuest criteria. Moreover, the two sets of diagnostic criteria defined separate subjects as being constipated (Supplementary Fig. 1).

No correlations were seen between NMSQuest total score and objective measures of GITT, total volume, and total colonic 3D-transit. Also, no correlations were seen between any of the objective measures

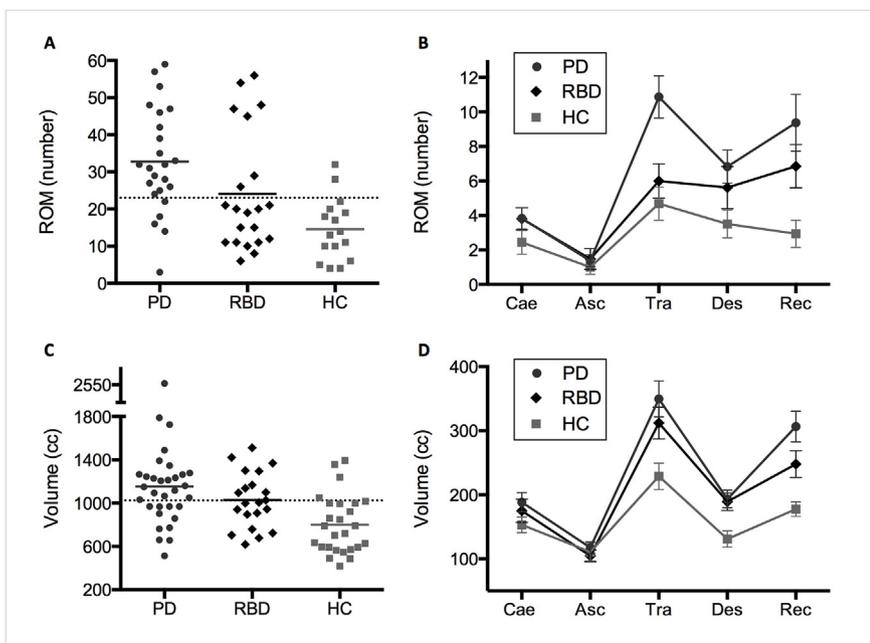


Fig. 1. A. Total number of retained radio opaque markers (ROM) in the colon (RBD vs. HC $p = 0.0390$). Solid lines indicate mean. Dashed line marks a cut-off of 23 ROM. B. Mean \pm SEM of retained ROM in separate colonic segments (Rec; RBD vs. HC $p = 0.0176$. Tra; RBD vs. PD $p = 0.0006$). C. Sex-corrected total segmented colonic volume (RBD vs. HC $p = 0.0049$). Solid lines indicate mean. Dashed line marks a cut-off of 1024 cc. D. Mean \pm SEM of sex-corrected segmented colonic volume in separate colonic segments (Tra; RBD vs. HC $p = 0.0215$). PD=Parkinson's disease patients, RBD = idiopathic REM sleep behavior disorder patients, HC = healthy control subjects, Cae = caecum, Asc = ascending, Tra = transverse, Des = descending, Rec = rectosigmoid.

and ROME III total scores. The ROME III 9–15 constipation-specific subset scores correlated significantly with total number of retained ROM ($p = 0.037$; $r = 0.459$) and colonic 3D-Transit ($p = 0.032$; $r = 0.481$) but not with total colonic volume. Overall, very limited concordance was seen between subjective constipation and objective markers of colonic dysfunction (Supplementary Fig. 1).

4. Discussion

The present study disclosed colonic dysfunction in a substantial fraction of iRBD subjects using three different objective measures. The overall pattern of dysfunction in both the small intestine and colon was similar to that seen in diagnosed medicated PD patients, though somewhat less pronounced.

Previous studies reported a similar load of subjective GI symptoms in iRBD and PD patients [13,14,24] and alterations in microbiome composition in both groups [25]. Also, in our recently published imaging data from the present iRBD patients, we detected marked dysfunction of both the parasympathetic and sympathetic nervous system at levels equivalent to diagnosed PD patients [15]. Thus, autonomic denervation probably contributes to the intestinal dysfunction revealed in the present study.

The novel 3D-Transit capsule method disclosed significantly increased CTT in the iRBD group. Interestingly, the 3D-Transit method

defined the majority of iRBD (70%) as having increased CTT, whereas the classical ROM methodology only defined 33% of iRBD as having increased GITT. This discrepancy suggests that the two measures are not interchangeable, but these findings need replication in larger cohorts. Time to first colonic fast movement was significantly increased in iRBD patients, and total number of fast movements significantly decreased in iRBD compared to controls. However, time to first colonic mass movement was normal in the iRBD group. The SITT was not significantly increased in iRBD compared to controls. This negative finding could, however, have been driven by the presence of three iRBD cases with extremely rapid SITT, whereas the remaining 17 iRBD cases as a group resembled the distribution seen in the PD comparator group (Fig. 2B). A larger study sample would most likely reveal that on average, SITT is also increased in iRBD. Overall, the present findings in iRBD mirror our previous results in diagnosed PD patients in that intestinal motility seems to be progressively dysfunctional from the stomach towards the colon [9,18]. Gastric transit time was normal in our iRBD patients, in agreement with a previous ^{13}C -octanoate breath test study in iRBD subjects, suggesting that gastric motility is not significantly altered in prodromal PD [26].

Our PD comparator group comprised early-to-moderate stage patients, most of whom were on dopamine replacement therapies. Thus, it is possible that the more pronounced intestinal dysfunction seen in these diagnosed PD patients was a consequence of combined disease

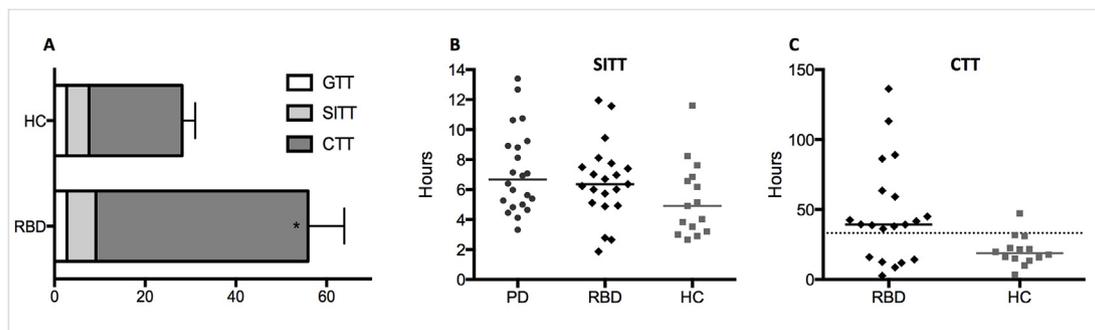


Fig. 2. A. Median 3D-Transit data in hours. * $P = 0.0326$. B. Small intestinal 3D transit time. C. Colonic 3D transit time. Dashed line marks a cut-off of 33 h. Solid lines indicate mean. GITT = gastric transit time, SITT = small intestinal transit time, CTT = colonic transit time. PD=Parkinson's disease patients, RBD = idiopathic REM sleep behavior disorder patients, HC = healthy control subjects.

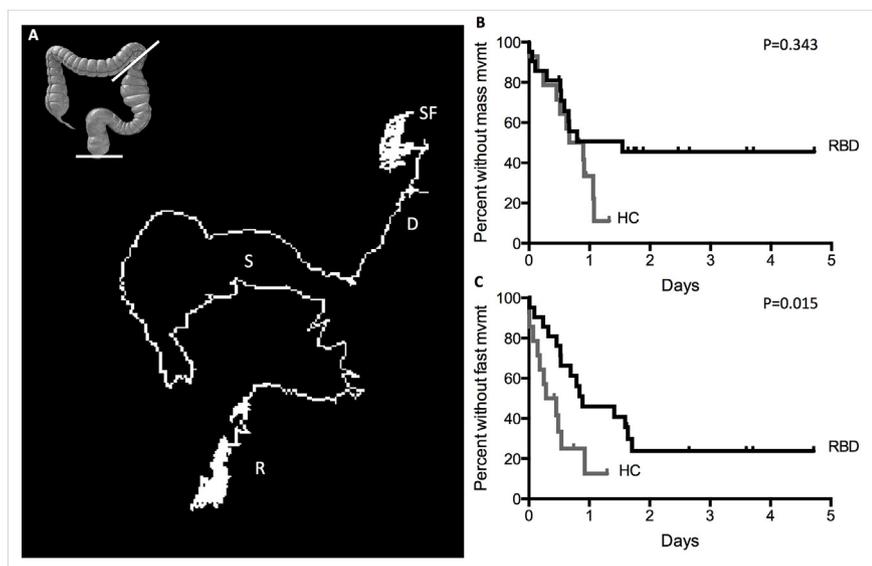


Fig. 3. 3D-Transit data. **A.** Mass movement in a HC subject with capsule passage from the splenic flexure (SF) to the rectum (R) through the descending (D) and sigmoid (S) colonic segments in < 2 min. Inset; colon anatomy. **B.** Time to first colonic mass movement in days. **C.** Time to first colonic fast movement in days. RBD = idiopathic REM sleep behavior disorder patients, HC = healthy control subjects.

involvement and medication effects, as it has been shown that dopaminergic treatment can promote constipation [27,28]. In support, we previously reported that levodopa-equivalent dose in PD patients correlated significantly with increased colonic volume but not with number of retained ROM [9].

Also, the PD comparator group was of unknown RBD-status. PD + RBD has been proposed to represent a distinct and more malignant phenotype comprising increased symptom load and more rapid disease progression compared to PD-RBD [16,24,29,30]. A recent study demonstrated that 64% of PD + RBD patients displayed pathological phosphorylated α -synuclein in the colon compared to only 13% of PD-RBD cases [31]. Thus, our results are only generalizable to RBD-positive prodromal PD patients. Future longitudinal studies might shed more light on the progression of GI dysfunction from prodromal to manifest stages of PD.

Subjective constipation symptoms were less pronounced in the present iRBD group compared to PD patients when applying NMSQuest criteria. This finding contrasts with previous studies using the NMSQuest criteria, which reported a constipation prevalence of approximately 50% in iRBD subjects [13,14,24]. Thus, it is possible that our iRBD cohort had less severely affected GI function compared to those in previous iRBD study groups of approximately comparable symptom duration. On the contrary, using ROME III constipation criteria, the prevalence was actually higher in the iRBD group compared to PD (41% vs. 32%), which taken together underlines the previously shown outcome differences according to the specific criterion applied [7,9]. It has also been reported that cultural and societal factors influence the prevalence of reported GI symptoms in various functional gastrointestinal disorders [32]. In addition, dietary factors such as amount of ingested fibers most likely affect the frequency of bowel movements, and therefore the prevalence of constipation, when bowel movement frequency is used as diagnostic criterion.

In a previous review of the PD constipation literature, we found a positive correlation between rates of subjective constipation in PD groups and the within-study HC groups [7]. In short, the prevalence of constipation in PD seems to be approximately 30% points above the within-study control group prevalence. In the previous iRBD studies, ~20% of controls and ~50% of iRBD patients were constipated [13,14,24]. Thus, considering that only 0%–6% of our controls were constipated, our finding of a 18%–41% constipation prevalence in iRBD seems to be in concordance with this “30% point rule”. Despite demographic group differences between the studies, the lower constipation rate in Danish iRBD patients could therefore partly be due to

dietary factors, and a lower constipation rate in the Danish background population.

It has been suggested that PD pathology in some cases initiate in the peripheral nervous system of the GI tract and olfactory bulb, subsequently spreading from neuron to neuron in a prion-like fashion [4,6,33]. In PD it has been proposed that genetic factors, age, cell stress conditions, gut microbiome, and inflammation are probable components of disease initiation and progression [25,33]. If the assumption of disease initiation in the gut is right in some cases, one would expect a more severe peripheral disease involvement years prior to time of diagnosis. Previously published imaging data of the present iRBD patients did in fact show a caudo-rostral gradient of neuronal pathology with the peripheral nervous system showing the most extensive damage, whereas the nigrostriatal dopamine innervation was relatively spared [15]. As the innervation of the GI tract decreases from the proximal to distal part, the functional consequence of neuronal death is expected to be more severe in the distal GI segments. The clear gradient of GI function seen in the 3D-Transit data with gradually more severe involvement from stomach to colon supports the hypothesis that intestinal neuronal innervation is affected very early on in the prodromal PD phase.

4.1. Limitations

The study has some limitations. First, sample sizes of iRBD and reference groups were modest and larger study groups would have improved the statistical power. Also, a few data points were missing in the iRBD group. Second, since RBD-negative and RBD-positive PD patients probably represent two distinct PD phenotypes, our results are only valid for the RBD-positive prodromal PD population. Third, five iRBD patients were treated with laxatives throughout the study, which could have affected colonic function. Thus, frequencies of constipation and colonic dysfunction may have been underestimated. Fourth, we used medicated PD patients as comparator group. Thus, the observed differences in colonic dysfunction between iRBD and PD could to some extent be explained by dopaminergic replacement therapy in the PD group. To establish the influence of dopaminergic agents on autonomic GI function, future studies of newly diagnosed PD patients before and after initiation of medical treatment are needed.

5. Conclusion

The present study showed that ROM gastrointestinal transit time

was increased in 33% and colonic volume pathologically increased in approximately half of iRBD cases. Colonic transit time was increased in 70% of iRBD patients when measured by the 3D-Transit capsule system, and a reduced number of fast peristaltic colonic movements was detected. Subjective constipation symptoms were present in 18 or 41% of iRBD cases depending on type of questionnaire applied. Total gastrointestinal transit time, colonic volume, and 3D-Transit colonic transit time were all significantly increased in the iRBD group compared to controls, although not to the extent seen in medicated PD patients. Our findings support that the GI tract is dysfunctional in the prodromal phase of PD, and that dopaminergic treatment, along with disease progression, may potentially further aggravate this dysfunction in diagnosed PD patients.

Declarations of interest

None.

Full financial disclosure (past 12 months)

Karoline Knudsen.

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Tatyana D Fedorova.

None.

Allan K Hansen.

None.

Michael Sommerauer.

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Anne-Mette Haase.

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Kristina B. Svendsen.

Stock Ownership in medically-related fields; *None.*

Intellectual Property Rights; *None.*

Consultancies; *None.*

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Other; *None.*

Marit Otto.

None.

Karen Østergaard.

Stock Ownership in medically-related fields; *None.*

Intellectual Property Rights; *None.*

Consultancies; *None.*

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Klaus Krogh.

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Per Borghammer.

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Author contributions

K Knudsen; Recruitment. Data acquisition, analysis, and interpretation. Drafting the article. Critical revision. Final approval.

T D Fedorova; Recruitment. Data acquisition, analysis, and interpretation. Critical revision. Final approval.

A K Hansen; Data acquisition. Critical revision. Final approval.

M Sommerauer; Data acquisition. Critical revision. Final approval.

AM Haase; Data analysis. Critical revision. Final approval.

K B Svendsen; Recruitment. Critical revision. Final approval.

M Otto; Recruitment. Critical revision. Final approval.

K Østergaard; Recruitment. Critical revision. Final approval.

K Krogh; Data analysis and interpretation. Critical revision. Final approval.

P Borghammer; Conception of study. Data acquisition, analysis, and interpretation. Critical revision. Final approval.

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Appendix A. Supplementary data

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