PRDOA 11 (2024) 100269

Contents lists available at ScienceDirect

Clinical Parkinsonism & Related Disorders

journal homepage: www.sciencedirect.com/journal/clinical-parkinsonism-and-related-disorders

Original Articles

Bowel movement frequency and difficult defecation using constipation assessment scale in patients with isolated REM sleep behavior disorder

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ARTICLE INFO

Keywords:
Bowel habits
Bowel movement frequency
Constipation assessment scale
Isolated REM sleep behavior disorder
Parkinson's disease
Dementia with Lewy bodies

ABSTRACT

Introduction: This study evaluated constipation, including reduced bowel movement frequency and difficult defecation, in patients with isolated rapid eye movement sleep behavior disorder (IRBD), which is prodromal Parkinson's disease (PD) or dementia with Lewy bodies (DLB) in middle-aged and older adults.
Methods: We used a validated Japanese version of the Constipation Assessment Scale (CAS-J) to evaluate bowel habits over 1 month in 117 men aged 50–86 years and 34 women aged 56–86 years with video-polysomnography-confirmed IRBD and 22 controls. Furthermore, we performed a longitudinal assessment of outcomes at follow-up visits.
Results: The CAS-J score was higher in the 22 IRBD patients than in 22 age- and gender-matched paired controls. In 151 IRBD patients, the CAS-J score was higher for women than for men. At baseline, the CAS-J score was similar between patients who developed PD and DLB, but the three IRBD patients who developed multiple system atrophy had a low CAS-J score. Those with constipation (CAS-J score ≥ 2) converted to PD or DLB in a significantly shorter time duration (i.e., time frame for phenoconversion) than those with CAS-J score < 2 (log-rank test, $p < 0.001$). When adjusted for age and gender, Cox hazards analysis revealed that the CAS-J score significantly predicted phenoconversion to PD or DLB (hazard ratio: 5.9, 95 % confidence interval: 1.8–19.1, $p = 0.003$).
Conclusions: Constipation, i.e., reduced bowel movement frequency and difficult defecation, was common in middle-aged and elderly patients with IRBD, and CAS-J score predicted phenoconversion to PD or DLB.

1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a REM parasomnia characterized by dream-enacting complex behaviors and REM sleep without atonia [1]. Longitudinal studies in isolated RBD (IRBD) patients revealed an increased risk of developing synucleinopathies, including Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) [2]. Most patients with PD describe autonomic symptoms at the time of diagnosis suggesting that these features may have potential sensitivity as clinical biomarkers of the premotor phase [3]. The recognition that damage to peripheral autonomic neurons is present in the early stages of PD has led to a search for specific abnormalities in autonomic function, such as constipation, urinary and sexual dysfunction, and reduced cardiac MIBG uptake [4], which could be predictive biomarkers or part of the parkinsonian clinical phenotype [5].

Constipation is a common non-motor symptom in PD or DLB, negatively impacting the quality of life of patients and serving as one of the earliest markers of PD development [6]. The Honolulu Heart Program provided strong evidence supporting the presence of constipation in preclinical PD. This study followed 6,790 men over a 24-year period and found that men with < 1 bowel movement per day have a 4.5-fold higher risk of PD compared to men with 2 bowel movements per day [7].

An important barrier to developing neuroprotective therapies for neurodegenerative diseases is that the onset of the PD/DLB pathology may be up to several decades before disease diagnosis [8]. Therefore,

Abbreviations: CAS-J, Japanese version of the Constipation Assessment Scale; IRBD, isolated REM sleep behavior disorder; PD, Parkinson's disease; DLB, dementia with Lewy bodies; MSA, multiple system atrophy.

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https://doi.org/10.1016/j.prdoa.2024.100269
Received 20 May 2024; Received in revised form 23 July 2024; Accepted 27 August 2024
Available online 31 August 2024

during the development of PD, constipation may help predict the risk of developing neurodegenerative diseases in IRBD patients before dopamine synthesis is reduced in dopaminergic nerve terminals [4]. Therefore, this study investigated the defecation frequency and difficult defecation using the Constipation Assessment Scale (CAS) [9] and longitudinally assessed the relationships between baseline evaluation and outcomes of neurodegenerative diseases.

2. Materials and methods

2.1. Participants

In total, 151 IRBD patients completed the CAS at baseline between May 2008 and May 2017. IRBD was diagnosed based on a history of dream-enacting behaviors and video-PSG demonstration of increased electromyographic activity during REM sleep associated with abnormal behaviors. RBD was defined according to the International Classification of Sleep Disorders [10]. All IRBD patients were followed systematically every 1–3 months by a neurologist (MM) with expertise in both sleep disorders and neurodegenerative diseases. At each visit, the neurologist performed a comprehensive neurological examination and obtained a detailed clinical history, including for cognitive and motor problems. If follow-up assessments revealed symptoms or signs of motor or cognitive impairment, the patients were referred for more detailed assessment. A full battery of neuropsychological tests was performed if cognitive impairment was suspected. The standard diagnostic criteria for PD [11], DLB [12], and MSA [13] were used. Clinical records were reviewed between March and July 2023 (the end of the current study) to assess the presence and type of neurodegenerative diseases identified during the follow-up period by the same neurologist (MM). If a new diagnosis of PD, DLB, or MSA was made, the date of the assessment was used as the date of condition onset. (Fig. 1).

We enrolled controls who had no significant medical history, such as diabetes mellitus, thyroid disease, or gastrointestinal tract diseases, at the time of complete medical checkup at the Dokkyo Medical University Saitama Medical Center Koshigaya Clinic.

The CAS [9] consists of eight constipation-related characteristics based on previous literature. Each characteristic is scored on a three-point rating scale (i.e., no problem, some problem, and severe problems), indicating scores 0, 1, and 2, respectively. The summed scores ranged from 0 for no constipation to 16 for most severe constipation. The completion time averaged about 2 min. In this study, we used the validated Japanese version of the CAS (CAS-J, Fukai et al., 1995) [14] to record the bowel movement frequency and difficult defecation. The clinician was blinded to the CAS-J score collected at a single point during baseline visits. Patients were categorized into non-constipation (CAS-J score 0 or 1) and constipation (CAS-J score $\geq$ 2) groups.

The study protocol was approved by our institutional ethics committee Dokkyo Medical University (approval no. R-2–22) and the Ethics Committee of Dokkyo Medical University Saitama Medical Center (approval no. 21060). Written consent was obtained from participants. However, because of the retrospective study design, some patients were unable to provide written consent and had the opportunity to opt out of the study at any time and seek further explanation.

2.2. Statistical analyses

Descriptive, demographic, and CAS-J data are presented as means with standard deviation or numbers with percentages, as appropriate. Comparisons between groups were performed using the χ^2 test or Mann-Whitney *U* Test, as appropriate. Neurological disease-free survival rates were estimated using Kaplan–Meier analysis and Cox-proportional hazards analysis. Disease-free survival rates were assessed from the date of CAS-J to the date of PD, DLB, or MSA diagnosis or to the last follow-up for censored observations.

All statistical analyses were performed using Prism software (version 10.3.0.0 for Mac; GraphPad Software, Inc., San Diego, CA, USA) and SPSS (version 29.0; IBM Corp., Armonk, NY, USA). Statistical significance was set at $p < 0.05$.

3. Results

Among the 22 age- and gender-matched paired patients with IRBD (disease duration: 8.7 ± 11.8 years), awareness of constipation ($p = 0.0019$) and frequency of laxative use ($p = 0.0093$) were significantly higher than those in healthy controls. With regard to the defecation frequency, IRBD patients were significantly less likely to defecate every day or more than twice a day ($p = 0.0452$) and more likely to defecate 3–6 times a week ($p = 0.1324$). The total CAS-J score was significantly higher in IRBD (median 4.0, interquartile range [IQR] = 2–6) compared to healthy controls (median 1.5, [IQR] = 1–2) ($p = 0.0001$). With regard to the individual items of CAS-J, compared to healthy individuals, 12 (54.5 %) IRBD patients had less frequent bowel movements ($p = 0.0006$), 13 (59.1 %) had rectal fullness or pressure ($p = 0.0040$), and 19

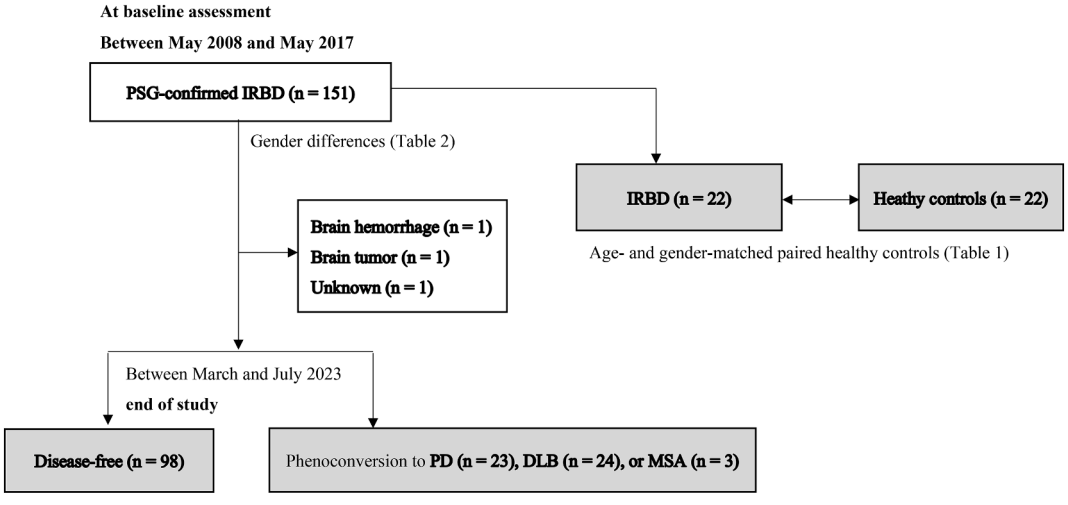

Fig. 1. Study flow chart. IRBD, isolated rapid eye movement sleep behavior disorder; PSG, polysomnography; PD, Parkinson's disease; DLB, dementia with Lewy bodies; MSA, multiple system atrophy.

(86.4 %) had low stool volume (p = 0.0005) (Table 1). The receiver operating characteristic curve analysis showed that the optimal CAS-J cutoff scores of 1.5 and 2.5 discriminated between IRBD patients and controls with sensitivity rates of 86.4 % and 50.0 % and specificity rates of 68.2 and 86.4 %, respectively. Compared to the control group, the IRBD group had a higher number of individuals in the constipation group (CAS-J score of 2 or more; 86.4 %) than in the non-constipation group (CAS-J score of 0 or 1; 13.6 %).

Among the 151 IRBD patients, constipation was perceived by 62.4 % of men and 76.5 % of women, whereas 52.9 % of women used laxatives compared to 32.5 % of men (p = 0.0428). The CAS-J score for IRBD was higher for women than for men (p = 0.0063). With regard to the individual items of CAS-J, women had significantly higher rates of feeling bloated or bloating (p = 0.0017) and diarrhea-like or watery stools (p = 0.00191) compared to men (Table 2). In the IRBD group, compared to men, women were more commonly included in the constipation group (CAS-J score of 2 or more; 91.2 %) than in the non-constipation group (CAS-J score of 0 or 1; 8.8 %).

Furthermore, 50 (33.1 %) of the 151 IRBD patients evaluated between March and July 2023 developed clinically defined PD (n = 23), DLB (n = 24), or MSA (n = 3) at 6.2 ± 4.0 years after baseline CAS-J assessment. Compared to IRBD patients who were still disease-free (3.7 ± 2.8) or developed PD (4.3 ± 2.9) or DLB (4.6 ± 2.4), the CAS-J score was lower in patients with MSA (0, 1, 1) (Supplemental Fig. 1). Patients with constipation, defined as CAS-J score ≥ 2, converted to PD or DLB in a significantly shorter time duration than those without constipation (log-rank test, p < 0.001; Fig. 2). When adjusted for age and gender, Cox hazards analysis showed that CAS-J significantly predicted phenoconversion to PD or DLB (hazard ratio [HR] = 5.9, 95 % confidence interval [CI] = 1.8–19.1, p = 0.003).

4. Discussion

In this study, patients with IRBD reported more frequent problems with defecation compared to age- and gender-matched paired controls. We quantified the bowel frequency and use of laxatives, as well as assessed the feeling of difficult defecation, using the CAS-J. Furthermore, > 60 % of men and women with IRBD experienced constipation. Men used laxatives less frequently than women. IRBD patients reported more frequent defecation difficulties than age- and gender-matched paired controls. The CAS evaluates the presence and severity of constipation. Chronic idiopathic constipation is one of the most common gastrointestinal disorders, with a global prevalence of 14 %. It is more common in women than in men, and its prevalence increases with age [15]. Our study revealed that constipation occurs more frequently in IRBD than in the general population.

Moreover, we compared the presence of constipation using CAS-J between IRBD patients and those who were disease-free or had developed PD or DLB. IRBD patients with a higher CAS-J score at baseline developed PD or DLB, whereas those with a lower CAS-J score developed MSA. The rate of progression to PD or DLB over time was lower in the group with a CAS-J score 0–1 compared to the group with a CAS-J score ≥ 2.

Previous studies have examined the association between constipation and subsequent PD risk [7]. Constipation is considered to be one of the primary early markers of PD [16] and DLB [17], but few studies have quantitatively assessed the defecation symptoms in

Table 1
Defecation symptoms and CAS-J for age- and sex-mached healthy controls and IRBD patients.

	IRBD	Controls	P value
Number of cases	22	22	N/A
Sex, M:F	18:4	18:4	N/A
Age, y	63.4 ± 6.7	63.4 ± 6.6	0.3145*
Awareness of constipation, n (%)	15 (68.2)	4 (18.2)	**0.0019**
Laxative use (more than 1–2 times a month), n (%)	9 (40.9)	1 (4.5)	**0.0093**
Bowel movement frequency			
Every day or more than one time each day, n (%)	12 (54.5)	19 (86.4)	**0.0452**
Three to six times each week, n (%)	7 (31.8)	2 (9.1)	0.1324
Two or less than two times each week, n (%)	3 (13.6)	1 (4.5)	0.6069
CAS-J			
Total score, mean ± standard deviation	4.3 ± 2.9	1.6 ± 1.1	**0.0001***
Total score, median [interquartile range]	4.0 [2–6]	1.5 [1–2]	
CAS 0–1, n (%)	3 (13.6)	11 (50.0)	**0.0217**
CAS 2 or more, n (%)	19 (86.4)	11 (50.0)	
CAS item			
1. Abnormal distension or bloating, n (%)	13 (59.1)	6 (27.3)	0.0666
2. Change in amount of gas passed rectally, n (%)	4 (18.2)	3 (13.6)	> 0.9999
3. Less frequent bowel movements, n (%)	12 (54.5)	1 (4.5)	**0.0006**
4. Oozing liquid stool, n (%)	14 (63.6)	8 (36.4)	0.1308
5. Rectal fullness or pressure, n (%)	13 (59.1)	3 (13.4)	**0.0040**
6. Rectal pain with bowel movement, n (%)	6 (27.3)	1 (4.5)	0.0946
7. Small volume of stool, n (%)	19 (86.4)	7 (31.8)	**0.0005**
8. Unable to pass stool, n (%)	4 (18.2)	7 (31.8)	0.4876

CAS-J, Japanese version of the Constipation Assessment Scale; IRBD, isolated REM sleep behavior disorder. p-value, Fisher's exact test p-value for the difference between the percentages of controls and IRBD patients. *, p-value, Mann-Whitney U Test. Bold values were statistically significant.

Table 2
Gender differences in defecation symptoms and CAS-J in IRBD patients.

	Total	Men	Women	P value
Number of cases	151	117 (77.5)	34 (22.5)	< **0.0001**
Age, y	67.7 ± 6.3	67.5 ± 6.3	68.6 ± 6.5	0.6769*
Awareness of constipation, n (%)	99 (65.6)	73 (62.4)	26 (76.5)	0.1538
Laxative use (more than 1–2 times a month), n (%)	56 (37.1)	38 (32.5)	18 (52.9)	**0.0428**
Bowel movement frequency				
Every day or more than one time each day, n (%)	77 (51.0)	59 (50.4)	8 (23.5)	**0.0060**
Three to six times each week, n (%)	54 (35.8)	46 (39.3)	18 (52.9)	0.1721
Two or less than two times each week, n (%)	20 (13.2)	12 (10.3)	8 (23.5)	0.0797
CAS-J				
Total score, mean ± standard deviation	3.9 ± 2.8	3.6 ± 2.7	5.1 ± 2.9	**0.0063***
Total score, median [interquartile range]	4.0 [2–6]	3.0 [1–5]	5.0 [2–7.25]	
CAS 0–1, n (%)	34 (22.5)	31 (26.5)	3 (8.8)	**0.0352**
CAS 2 or more, n (%)	117 (77.5)	86 (73.5)	31 (91.2)	
CAS item				
1. Abnormal distension or bloating, n (%)	70 (46.4)	46 (39.3)	24 (70.6)	**0.0017**
2. Change in amount of gas passed rectally, n (%)	35 (23.2)	24 (20.5)	11 (32.4)	0.1690
3. Less frequent bowel movements, n (%)	74 (49.3)	53 (45.3)	21 (61.8)	0.1190
4. Oozing liquid stool, n (%)	79 (52.3)	55 (47.0)	24 (70.6)	**0.0019**
5. Rectal fullness or pressure, n (%)	47 (31.1)	36 (30.8)	11 (32.4)	0.8268
6. Rectal pain with bowel movement, n (%)	48 (32.0)	34 (29.1)	14 (41.2)	0.2113
7. Small volume of stool, n (%)	116 (76.8)	88 (75.2)	28 (82.4)	0.4913
8. Unable to pass stool, n (%)	31 (20.7)	23 (19.7)	8 (23.5)	0.6338

CAS-J, Japanese version of the Constipation Assessment Scale; IRBD, isolated REM sleep behavior disorder. p-value, Fisher's exact test p-value for the difference between the men and women in IRBD patients. *, p-value, Mann-Whitney U Test for men vs. women. Bold values indicate significant difference.

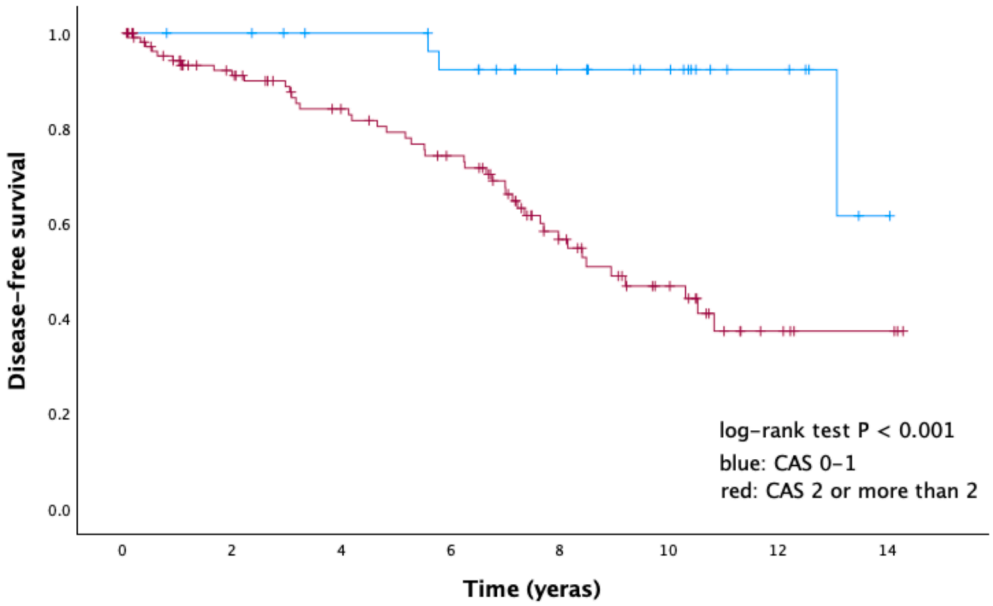

Fig. 2. Onset of PD or DLB in patients with isolated rapid eye movement sleep behavior disorder (Kaplan-Meier analysis). PD, Parkinson's disease; DLB, dementia with Lewy bodies.

individuals with IRBD [18,19]. In a multicenter IRBD study, Cox proportional hazards analysis adjusted for age, gender, and center significantly predicted constipation outcomes (HR=1.67) [19]. However, the definition of constipation varied among studies as they used different criteria, such as the Movement Disorders Society Revised Unified Parkinson's Disease Rating Scale [11], the Uniform MSA Rating Scale [20], the SCOPA-AUT [18], and the Rome Criteria [21]. In most studies, frequency and straining have been reported separately, when available. The prevalence of constipation varies with the definition used, which in turn depends on the questionnaire used [22]. CAS has been studied in adult cancer patients, pediatric patients, and pregnant women [9,23]. Our study focused on the feeling of difficult defecation, which is included in the definition of constipation in the CAS-J. We performed a comprehensive semiquantitative assessment of functional constipation in IRBD patients.

In vivo staging of IRBD using ^{11}C-donepezil positron emission tomography to assess cholinergic vagal innervation in the stomach demonstrated reduced colonic ^{11}C-donepezil uptake in IRBD patients compared to healthy controls [24]. The same group demonstrated that the colonic transit time examined using radio-opaque markers and colonic volume assessed on abdominal computed tomography scans showed worsening in most IRBD patients over a 3-year period [4]. Furthermore, a recent study demonstrated reduced amplitude of the gastric peristaltic wave in IRBD, a prodromal stage of PD. In fact, the stomach is already markedly involved in IRBD patients several years before the involvement of substantia nigra and the onset of manifest PD [25]. The association between IRBD and constipation is strongly related to accelerated progression of cognitive impairment and motor symptoms [26,27]. Furthermore, gender differences exist in neuropsychological test performances, with men having worse global cognition, speed-attention processing, verbal learning, and memory compared to women at early stages of PD. These findings suggest that men are more susceptible than women to the association between constipation and cognitive decline in patients with PD or IRBD [27]. In the current study, women with IRBD were more likely than men to experience abnormal bowel movements, highlighting the need to monitor the urge to defecate in men with IRBD. One possible mechanism for the aforementioned findings is that PD patients with marked gut dysbiosis may progress faster than those without gut dysbiosis [28]. The intestinal environment can have substantial effects on the activity of the central nervous system through the physiological contributions of the microbiota, regulation of the intestinal barrier function, and altered activity of peripheral neurons [29]. In IRBD patients, targeting the premotor intestinal stages of PD for therapeutic intervention may slow or halt disease progression to the central nervous system, which would significantly enhance the quality of life of IRBD patients. Therefore, it is essential to perform a comprehensive and accurate assessment of constipation in IRBD patients to facilitate therapeutic interventions.

Certain limitations of the present study should be acknowledged. First, the data were derived from a single center, and there was gender disparity in the IRBD patients. Second, although the diagnoses of PD and DLB were based on the standard clinical criteria, they lacked pathological confirmation. Finally, this study compared the disease-free group and disease group of IRBD patients but did not compare patients with age-matched healthy controls.

5. Conclusion

Our results emphasize the importance of evaluating the baseline CAS-J score in IRBD patients. These findings provide evidence for the usefulness of evaluating constipation using assessment questionnaires, a sensitive biomarker for the short-term risk of phenoconversion to PD or DLB in IRBD patients. Future studies should evaluate constipation combined with other known biomarkers of phenoconversion to optimize the short-term phenoconversion risk assessment for use with disease-modifying/neuroprotective therapies.

CRediT authorship contribution statement

Tomoyuki Miyamoto: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Itsuo Nakajima:** Supervision, Investigation, Data curation. **Takuo Arikawa:** Supervision, Investigation, Data curation. **Masayuki Miyamoto:** Writing – review & editing, Visualization, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2024.100269.

References

[1] C.H. Schenck, S.R. Bundlie, M.G. Ettinger, M.W. Mahowald, Chronic behavioral disorders of human REM sleep: a new category of parasomnia, Sleep 9 (2) (1986) 293–308.

[2] A. Galbiati, L. Verga, E. Giora, M. Zucconi, L. Ferini-Strambi, The risk of neurodegeneration in REM sleep behavior disorder: A systematic review and meta-analysis of longitudinal studies, Sleep Med. Rev. 43 (2019) 37–46.

[3] J.A. Palma, H. Kaufmann, Autonomic disorders predicting Parkinson's disease, Parkinsonism Relat. Disord. 20 Suppl 1(0 1):S94–8 (2014).

[4] T.D. Fedorova, K. Knudsen, K.B. Andersen, J. Horsager, C. Skjaerbaek, C.P. Beier, et al., Imaging progressive peripheral and central dysfunction in isolated REM sleep behaviour disorder after 3 years of follow-up, Parkinsonism Relat. Disord. 101 (2022) 99–104.

[5] S.M. Fereshtehnejad, Y. Zeighami, A. Dagher, R.B. Postuma, Clinical criteria for subtyping Parkinson's disease: biomarkers and longitudinal progression, Brain 140 (7) (2017) 1959–1976.

[6] B. Huang, S.W.H. Chau, Y. Liu, J.W.Y. Chan, J. Wang, S.L. Ma, et al., Gut microbiome dysbiosis across early Parkinson's disease, REM sleep behavior disorder and their first-degree relatives, Nat. Commun. 14 (1) (2023) 2501.

[7] R.D. Abbott, H. Petrovitch, L.R. White, K.H. Masaki, C.M. Tanner, J.D. Curb, et al., Frequency of bowel movements and the future risk of Parkinson's disease, Neurology 57 (3) (2001) 456–462.

[8] M.G. Cersosimo, E.E. Benarroch, Autonomic involvement in Parkinson's disease: pathology, pathophysiology, clinical features and possible peripheral biomarkers, J. Neurol. Sci. 313 (1–2) (2012) 57–63.

[9] SC McMillan, FA Williams, Validity and reilability of the Constipation Assessmen Scale, Cancer Nurs. 12 (1989) 183–188.

[10] American Academy of Sleep Medicine. International Classification of Sleep Disorders, 3rd ed, text revision., American Academy of Sleep Medicine, Darien, IL, 2023, pp. 301–310.

[11] R.B. Postuma, D. Berg, M. Stern, W. Poewe, C.W. Olanow, W. Oertel, et al., MDS clinical diagnostic criteria for Parkinson's disease, Mov. Disord. 30 (12) (2015) 1591–1601.

[12] I.G. McKeith, B.F. Boeve, D.W. Dickson, G. Halliday, J.P. Taylor, D. Weintraub, et al., Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium, Neurology 89 (1) (2017) 88–100.

[13] S. Gilman, G.K. Wenning, P.A. Low, D.J. Brooks, C.J. Mathias, J.Q. Trojanowski, et al., Second consensus statement on the diagnosis of multiple system atrophy, Neurology 71 (9) (2008) 670–676.

[14] K. Fukai, A. Sugita, M. Tanaka, A developmental study of the japanese version of the constipation assessment scale, The Jpn. J. Nursing Res. 28 (1995) 25–32.

[15] C.J. Black, A.C. Ford, Chronic idiopathic constipation in adults: epidemiology, pathophysiology, diagnosis and clinical management, Med. J. Aust. 209 (2) (2018) 86–91.

[16] R.D. Abbott, G.W. Ross, H. Petrovitch, C.M. Tanner, D.G. Davis, K.H. Masaki, et al., Bowel movement frequency in late-life and incidental Lewy bodies, Mov. Disord. 22 (11) (2007) 1581–1586.

[17] W. Hu, S. Liu, F. Wang, H. Zhu, X. Du, L. Ma, et al., Autonomic symptoms are predictive of dementia with Lewy bodies, Parkinsonism Relat. Disord. 95 (2022) 1–4.

[18] L. Ferini-Strambi, W. Oertel, Y. Dauvilliers, R.B. Postuma, S. Marelli, A. Iranzo, et al., Autonomic symptoms in idiopathic REM behavior disorder: a multicentre case-control study, J. Neurol. 261 (6) (2014) 1112–1118.

[19] R.B. Postuma, A. Iranzo, M. Hu, B. Hogl, B.F. Boeve, R. Manni, et al., Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study, Brain 142 (3) (2019) 744–759.

[20] G.K. Wenning, F. Tison, K. Seppi, C. Sampaio, A. Diem, F. Yekhlef, et al., Development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS), Mov. Disord. 19 (12) (2004) 1391–1402.

[21] F. Mearin, B.E. Lacy, L. Chang, W.D. Chey, A.J. Lembo, M. Simren, et al., Bowel Disorders, Gastroenterology (2016).

[22] K. Knudsen, K. Krogh, K. Ostergaard, P. Borghammer, Constipation in parkinson's disease: Subjective symptoms, objective markers, and new perspectives, Mov. Disord. 32 (1) (2017) 94–105.

[23] A. Dal Molin, S.C. McMillan, F. Zenerino, V. Rattone, S. Grubich, A. Guazzini, et al., Validity and reliability of the Italian Constipation Assessment Scale, Int. J. Palliat. Nurs. 18 (7) (2012) 321–325.

[24] K. Knudsen, T.D. Fedorova, A.K. Hansen, M. Sommerauer, M. Otto, K.B. Svendsen, et al., In-vivo staging of pathology in REM sleep behaviour disorder: a multimodality imaging case-control study, Lancet Neurol. 17 (7) (2018) 618–628.

[25] W.H. Oertel, E. Paule, T. Hasemann, E. Sittig, M. Belke, M.M. Unger, et al., Reduced Gastric Contraction in Rapid-Eye-Movement Sleep Behavior Disorder and De Novo Parkinson's Disease, Mov. Disord. 39 (1) (2024) 53–63.

[26] K.A. Woo, S. Kim, H. Nam, Y.K. Kim, B. Jeon, J.Y. Lee, Constipation is linked to accelerated cognitive and motor decline in isolated REM sleep behavior disorder, Parkinsonism Relat. Disord. 119 (2024) 105775.

[27] W.L. Kong, Y. Huang, E. Qian, M.J. Morris, Constipation and sleep behaviour disorder associate with processing speed and attention in males with Parkinson's disease over five years follow-up, Sci. Rep. 10 (1) (2020) 19014.

[28] H. Nishiwaki, M. Ito, T. Hamaguchi, T. Maeda, K. Kashihara, Y. Tsuboi, et al., Short chain fatty acids-producing and mucin-degrading intestinal bacteria predict the progression of early Parkinson's disease, NPJ Parkinsons Dis. 8 (1) (2022) 65.

[29] M.C. Houser, M.G. Tansey, The gut-brain axis: is intestinal inflammation a silent driver of Parkinson's disease pathogenesis? NPJ Parkinsons Dis. 3 (2017) 3.