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New insights in non-motor symptoms in Parkinson's disease

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New insights in non-motor symptoms in Parkinson's disease

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Leg restlessness and hyperparathyroidism in Parkinson's disease, a further clue to RLS pathogenesis?

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Background: Non-motor manifestations are the main features of Parkinson's disease (PD). These have been associated with vitamin D abnormalities, but the role of parathormone (PTH) is still obscure. Among the non-motor symptoms of PD, the pathogenesis of restless leg syndrome (RLS) is still debated, but it has been associated with the vitamin D/PTH axis in other disease models. Our study deepens the association between vitamin D and PTH with the prevalence of non-motor symptoms of PD and explores such a relationship in patients reporting leg restlessness.

Methods: Fifty patients with PD were extensively investigated with motor and non-motor scales. Data on serum levels of vitamin D, PTH, and related metabolites were obtained, and patients were stratified as having vitamin D deficiency or hyperparathyroidism according to standardized criteria.

Results: Overall, 80% of patients with PD exhibited low vitamin D levels, and hyperparathyroidism was diagnosed in 45%. The analysis of the non-motor symptoms profile using the non-motor symptom questionnaire (NMSQ) revealed 36% of leg restlessness, a main feature of RLS. This was significantly associated with worse motor symptoms, quality of sleep, and quality of life. Moreover, it was associated with hyperparathyroidism (OR: 3.48) and with PTH levels, independent of vitamin D, calcium/phosphate levels, and motor status.

Conclusion: Our results suggest a significant association between the vitamin D/PTH axis and leg restlessness in PD. PTH has a putative role in nociceptive modulation, and previous evidence on hyperparathyroidism has suggested a possible interrelation with RLS. Further investigations are necessary to add PTH to the non-dopaminergic non-motor landscape of PD.

KEYWORDS

sleep, vitamin D, restless legs, dopamine agonist, parathormone

Introduction

Parkinson's disease (PD) is characterized by motor and non-motor symptoms. The latter are the main determinants of quality of life and are known to cover several pathophysiological underpinnings of Parkinson's disease, being involved in the prodromal phase and in milestones of the progression through stages (1). In this regard, some of them including leg restlessness, poor quality of sleep, and behavioral disorders are of key importance. Not much is known about the underlying etiologies of such symptoms, and if serum biomarkers may correlate with

such manifestations. Patients with PD are also known to exhibit lower 25(OH)D levels than the general population. Indeed, there is growing evidence about the association between vitamin D and non-motor manifestations of PD–cognition, mood, autonomic functions, and falls (2). The presence of insufficient 25(OH)D levels is associated with insomnia, a lower quality of sleep, and a bad disease profile overall (3). Moreover, there are several studies on the role of parathormone (PTH), closely interconnected with vitamin D, in the pathogenesis of restless leg syndrome (RLS) in other disease models, such as end-stage renal disease (4, 5). The link between vitamin D, PTH, and PD patient's non-motor and sleep profiles, however, has not yet been investigated. Both molecules are strictly interconnected. PTH is produced by the parathyroid glands to maintain the right balance of calcium, phosphate, and vitamin D in the bloodstream. Parathyroid levels are controlled by a feedback loop of calcium levels, where low levels of calcium stimulate parathyroid hormone release (6). Hyperparathyroidism may be classified as primary, due to a disorder of the glands, or secondary, thus due to hypocalcemia, frequently secondary to low vitamin D levels (7). The aim of the present study is to investigate the relationship between the vitamin D—PTH axis and non-motor symptoms. Hence, we prospectively studied such associations in a well-structured sample of patients with PD.

Methods

Patients with PD aged 55–80 years were consecutively enrolled in the outpatient PD clinic of our institution in the winter season of 2020–2021 (21 December to 20 March). We excluded subjects with diseases that could affect bone and calcium metabolism, and administration of drugs affecting calcium concentrations other than peroral vitamin D supplements. All our patients were evaluated by an experienced rater to collect data on disease duration (years), modified Hoehn and Yahr scale (H&Y), Unified Parkinson's Disease Rating scale (UPDRS) part 1 to 4, Non-motor Symptom Questionnaire (NMSQ), Parkinson's Disease Quality of Life Questionnaire (PDQ-39), Montreal Cognitive Assessment (MoCA), and PD Sleep Scale (PDSS). Data on comorbidities, PD therapies, vitamin D supplementations, and dietary oral intake of calcium were also obtained. All the patients were on chronic treatment with levodopa and were tested on their ON-DOPA condition during the morning. Blood samples were collected during the same evaluation to obtain data on 25(OH)D, PTH, calcium, and phosphate levels. Creatinine, blood urea nitrogen (BUN), glomerular filtration rate (GFR), and albumin were also collected to provide corrections to the 25(OH)D and the calcium/phosphate metabolism. The presence of hyperparathyroidism was identified by the PTH cut-off value of >85 pg/ml, while deficient or insufficient 25(OH)D was identified by the cut-off values of <30 and <20 ng/ml, respectively (8). Patients with ongoing 25(OH)D supplementation were included to observe the effect of peroral therapies on the variables investigated. Total serum calcium and serum albumin were measured using automated methods. Serum phosphate and creatinine were also measured by automated techniques. 25(OH)D was measured by an immunochemiluminometric assay (Abbott Laboratories Diagnostics Division, Abbott Park, IL, 60064, USA). Intact PTH was measured by an immunochemiluminometric assay using the automatic analyzer Modular E170 (Roche Diagnostics, Indianapolis, Ind, USA) in the laboratory of our institution. Data were reported as median (QII–QIII) or frequencies (%). Inferential statistics were performed through the Wilcoxon test or the chi-square test according to the distribution. Correlations between variables were tested with Spearman's ρ and the degree of the association with logistic regression or generalized linear modeling. Statistics were performed through the JMP software (SAS, v16.0). The study was conducted according to the Declaration of Helsinki principles and all subjects signed informed consent. The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

TABLE 1 Serum PTH, vitamin D, and related metabolites in our PD cohort.

Variable [reference range]	Median (QI-QIII)
PTH [14–85 pg/ml]	83.35 (66.08–105.35)
25(OH)D [20–50 ng/ml]	21.7 (15.5–27.7)
Calcium [8.4–10.2 mg/dl]	9.2 (9.2–9.4)
Phosphate [2.3–4.7 mg/dl]	3.1 (2.8–3.43)
Calcium dietary intake (mgs per day)	716.5 (512.5–978.25)

PTH, parathormone.

Results

Clinical, demographic, and biological characteristics of the PD cohort

Our sample included 50 subjects, 17 (34%) were women. The median age was 69.5 (61.7–74) years, and the median disease duration was 6 (3–10) years. The UPDRS part 3, H&Y, and MoCA scores had median values of 20 (15–25), 2 (2–2.5), and 24 (22–26), respectively. The median sleep quality as reported by the PDSS was 94.5 (79.25–109.75). All subjects were on levodopa, with 15 (30%) also taking a dopamine agonist (DA) (total LEDD 600 mgs, 482.5–957.5). Serum levels of 25(OH)D, PTH, calcium, phosphate, and calcium dietary intake are reported in Table 1. Twenty-one (43%) and 15 (35%) patients showed deficient and insufficient 25(OH)D levels, respectively. Hyperparathyroidism was diagnosed in 21 subjects (45%). Twelve patients were on peroral vitamin D supplements (24%). Calcium and phosphate levels were within the normal range, as well as creatinine, BUN, and albumin. All subjects had a GFR >60 ml/min.

Correlations between vitamin D and PTH metabolism with non-motor symptoms and sleep

Patients reported a median of 10 (7–14) non-motor symptoms at NMSQ. There was no association between 25(OH)D, PTH, and sleep as assessed through the PDSS. Vitamin D was significantly lower in patients who gave a positive answer to the NMSQ questions about memory impairment ($p = 0.036$), while PTH levels were higher in patients with constipation ($p = 0.044$), trouble in having sex ($p = 0.021$), and leg restlessness ($p = 0.020$) (Supplementary Table 1). To further verify the clinical significance of such associations,

we analyzed the relationship between NMSQ question outcomes and the presence of 25(OH)D insufficiency or deficiency and hyperparathyroidism, according to the established criteria (see Methods section). The only significant association, maintained upon such stratification, was between the NMSQ question 26 ("presence over the last month of unpleasant sensations in legs at night or while resting, and a feeling that they needed to move") and hyperparathyroidism (64.7 vs. 34.5%, $p = 0.045$). Hence, the sample was consequently stratified accordingly in restless PD (rPD, $n = 18$, 36%) vs. non-restless PD (nrPD).

Characterization of patients with leg restlessness and correlations with the vitamin D/parathormone axis

The presence of leg restlessness was higher in the female sex; it was associated with higher UPDRS part 3 and PDQ-39 scores and with lower MoCA and PDSS scores (Table 2). Groups (nrPD vs. rPD) did not differ in their LEDD and DA therapy consumption. The rPD group was strongly associated with the PDQ-39 score (ρ 0.670; $p < 0.001$) and with the PDSS score (ρ −0.340; $p = 0.006$). The former association occurred in an independent fashion with respect to sleep quality in a multivariate model. Similarly, the relationship between rPD and quality of life was maintained after correcting for age, sex, and motor status (UPDRS part 3) in a multivariate generalized linear model (Supplementary Table 2). 25(OH)D, calcium, phosphate, dietary calcium, and vitamin D intake were equally distributed across groups. Similarly, creatinine, BUN, and albumin were similar across groups and were excluded for further analysis. As previously mentioned, serum PTH and the prevalence of hyperparathyroidism were higher in the rPD than in the nrPD group (Table 2; unitary odds ratio for PTH pg/ml is 1.02; odds ratio of having RLS in patients with hyperparathyroidism vs. patients without is 3.48).

By means of a generalized linear model, there was no effect of sex in the relationship between rPD and PTH ($p = 0.037$). A similar result was observed also after adding the age of the patients in the multivariate model. To investigate the association between PTH, 25(OH)D, calcium, phosphate levels, and calcium dietary intake with rPD, which was selected as a dependent variable, a further model was created. Such analysis confirmed the presence of an independent relationship between PTH levels and leg restlessness ($p = 0.021$), also after adding in the same model the UPDRS part III score as a covariate ($p = 0.041$) (Supplementary Table 3).

Finally, to check the effect of peroral 25(OH)D supplementation, we stratified the sample accordingly and observed that patients with rPD who did not receive 25(OH)D supplements had significantly higher PTH levels and lower PDSS values than nrPD (Table 3).

TABLE 2 Demographic data, disease features, vitamin D (25(OH)D), and PTH-related parameters distributed according to leg restlessness.

Variables	nrPD ($n = 32$)	rPD ($n = 18$)	p-value
Demographic and disease features			
Age (years)	69.5 (62.5–73)	70.5 (59.8–76.3)	0.675
Sex (F)	6 (18.8%)	11 (61.1%)	**0.004**
Disease duration (years)	5 (2–10)	7 (3–9.25)	0.905
Modified Hoehn and Yahr score	2 (2–2)	2.5 (1.875–3)	0.088
UPDRS part 3 total score	18 (13.5–21)	25 (19.5–33.25)	**0.010**
MoCA total score	25 (23–26)	23 (21.25–25.25)	**0.026**
LEDD (mgs)	562 (406.5–880)	800 (500–1,095)	0.901
Use of dopamine agonist	8 (25%)	7 (38.8%)	0.347
PDSS	103 (84.5–116.5)	82.5 (61.75–96.25)	**0.005**
PDQ-39	14.21 (7.9–14.2)	44 (32–56)	**<0.001**
Metabolic parameters			
25(OH)D (ng/ml)	22 (14.9–27.44)	20.95 (16.65–30.25)	0.386
25(OH)D deficiency	13 (42%)	8 (47%)	0.806
25(OH)D insufficiency	12 (38.7%)	5 (29.5%)	
Normal 25(OH)D	6 (19.3%)	4 (23.5%)	
PTH (pg/ml)	75.5 (58.6–99.7)	98.8 (69.45–116.65)	**0.020**
Hyperparathyroidism	10 (34.5%)	11 (64.7%)	**0.045**
Vitamin D supplementation	8 (25%)	4 (22%)	1.000
Calcium intake (mgs)	749 (518–979)	681 (496–846)	0.379

UPDRS, Unified Parkinson's Disease Rating Scale; MOCA, Montreal Cognitive Assessment; LEDD, levodopa equivalent daily dose; PDSS, Parkinson's disease sleep scale; PDQ-39, Parkinson's disease questionnaire-39. Statistical significance in bold.

Discussion

Vitamin D and its hormonal axis are involved in Parkinson's non-motor profile. This is further confirmed by the present study, which is in line with the available literature and with its heterogeneity (3). The latter is probably caused by differences in the demographic sample characteristics, in the outcome measures, and by the biological variability of the 25(OH)D and PTH metabolism over time, during seasons due to light exposure, but also age and sex (9). Our real-life study was conducted on a mild-to-moderate sample of patients with PD during the winter season when vitamin D levels are putative to be lower with a possible increase in PTH than in other periods of the year. Nevertheless, the high prevalence of hyperparathyroidism in PD (45% of our cohort) has never been systematically reported. Our study also documented that almost 80% of patients had impaired 25(OH)D levels, with 40% of them bearing insufficient levels (<10 ng/ml). In light of such data, it is not surprising that patients with PD exhibit high PTH levels. In a few anecdotal reports, authors described patients with concomitant parkinsonism and hyperparathyroidism (10, 11), questioning if the latter was an incidental finding or a causative condition; noteworthy surgical removal of the parathyroid glands improved symptoms.

TABLE 3 Prevalence of leg restlessness in patients with or without 25(OH)D supplementation.

25(OH)D un-supplemented	nrPD ($n = 22$)	rPD ($n = 13$)	p-value
PTH	75.7 (60–104)	98.8 (78.7–118)	**0.031**
25(OH)D	19.3 (14–23.6)	18.5 (16.6–30.2)	0.772
PDSS	106 (81.75–116.5)	87.5 (66–96.5)	**0.021**
25(OH)D supplemented	**nrPD ($n = 7$)**	**rPD ($n = 4$)**	**p-value**
PTH	75 (42–87.5)	84.5 (60–118)	0.780
25(OH)D	33.4 (27.8–43.7)	22.5 (16–30)	**0.018**
PDSS	93 (86.25–118)	71 (59.25–92.75)	0.174

PTH, parathormone; PDSS, Parkinson's disease sleep scale. Statistical significance in bold.

Despite the non-motor symptom screening with NMSQ identified various possible associations with 25(OH)D and PTH (i.e., memory performances, constipation, sexual function, and restless legs), only the link between PTH levels and restless legs maintained after selecting clinically relevant measures of interest (i.e., the presence of insufficiency or deficiency of vitamin D and hyperparathyroidism according to standardized criteria). In line with previous studies obtained with NMSQ (12), we found that 30–40% of patients with PD reported leg restlessness as "unpleasant sensations in legs at night or while resting, and a feeling that they needed to move." The latter was confirmed to be a strong determinant of sleep quality and quality of life, independent of motor status.

Leg restlessness is a frequent symptom in PD and the epidemiological link between PD, leg restlessness and RLS is complex, as the prevalence of RLS in PD shows diverging results ranging from 0 to 50% (13), with prospective studies identifying a more trustable prevalence of 10–20% (14). Such variability is mainly caused by the heterogeneity of methods used for RLS screening: from having the symptom of "irresistible desire to move the legs, particularly at night" used in the former data on prevalence (15), to the use of the IRLSSG diagnostic criteria (which have undergone two revisions since their first publication in 1995) in the latter (16). Of interest, in our series, patients presented with a median of 10 non-motor symptoms but only the presence of leg restlessness had a direct correlation with higher PTH values and prevalence of hyperparathyroidism.

In this regard, the association between PTH and RLS is not entirely new. High levels of PTH are associated with bad quality of sleep and RLS in patients affected by the end-stage renal disease (4), and even in this case, surgical removal of the parathyroid glands appears to improve symptoms of RLS, hypothesizing that an imbalance between calcium and phosphate levels could be the underlying etiology of the irresistible urge to move the legs (17). Some studies, however, reported no correlation between RLS and biochemical abnormalities including electrolyte levels in patients undergoing hemodialysis (18). In line with this, our study showed no signs of renal impairment or alteration in calcium and phosphate homeostasis. As a result, despite several studies addressing this phenomenon, the association between hyperparathyroidism and RLS is still poorly understood.

Hypothesis on the presence of RLS in patients with PD includes a progressive depletion of the dopaminergic system due to long disease duration or a consequence of long-term antiparkinsonian therapy (19). The sensation of leg motor restlessness (LMR), yet not fulfilling the diagnostic criteria of RLS, has been found to be present also in drug-naive patients with early Parkinson's disease. Such symptoms, however, did not have diurnal fluctuations, reflecting possible akathisia or other causes of restlessness (20). It has been postulated that LMR may be a prodrome of the future development of RLS (21). In our study, patients with PD were all on treatment, and despite the disease duration being similar between groups, patients with rPD had higher motor and lower cognitive scores at UPDRS part 3 and MoCA, respectively. However, the importance of the management of leg restlessness in our patients was supported by the prominent relationship between RLS and quality of life (i.e., PDQ-39), which occurs independently of any other sleep disturbances as evaluated by the PDSS.

The link between hyperparathyroidism and RLS in PD is possible and represents a new therapeutic chance. In our study, the relationship between PTH and leg restlessness appears to be independent of potential confounders—including motor status or age and sex which are known to be involved in PTH dynamics (19). The central nervous system exhibits the parathyroid hormone receptor 2, which is concentrated in the endocrine and limbic regions in the forebrain. Its endogenous ligand, TIP39, modulates several aspects of the stress response, in particular, the nociceptive processing (i.e., facilitating the nociceptive transmission at a supraspinal level), through what is called the neuroendocrine system (22). Accordingly, growing evidence supports the view of RLS as a derangement of sensorimotor interaction and of the gating of nociceptive information to the central nervous system (23) where high PTH levels might have an effect. PTH has been shown to modulate dopamine turnover in the rat *in vivo*, implicating a link between the concentration of two molecules, (24) and their possible interrelation in the pathophysiology of RLS. Furthermore, the two molecules both inhibit phosphate transport in cultured mouse proximal tubule cells, contributing to shared mechanisms in the feedback loop between calcium/phosphate/PTH (25). Elevated parathyroid hormone levels are also associated with poor sleep quality, and parathyroidectomy has been found to improve insomnia substantially (26). Vitamin D has negative feedback on PTH exertion and may therefore be a possible actor in the management of leg restlessness. To corroborate a possible exclusive association between PTH and RLS and in the absence of a more specific scale, it is worthy to report that in our cohort neither NMSQ question 10 ("unexplained pains") nor UPDRS II question 17 ("sensory complaints related to parkinsonism") reported a statistical association with PTH (data not shown). Our data, therefore, provide early possible evidence of an effect of 25(OH)D supplementation on PTH and RLS symptoms. The increase in vitamin D levels would play a role in calcium absorption and, consequently, in PTH reduction through a negative feedback loop (27).

The present study has the main limitation of relying on the NMSQ to identify the symptom of leg restlessness and not RLS ascertained through the IRLSSG criteria. The former has a good sensibility (~85%) but a lower specificity (15), owing probably to the fact that it does not account for relief induced by movement. Our sample might contain RLS mimics, such as polyneuropathy and akathisia. Signs or symptoms of such conditions were not reported

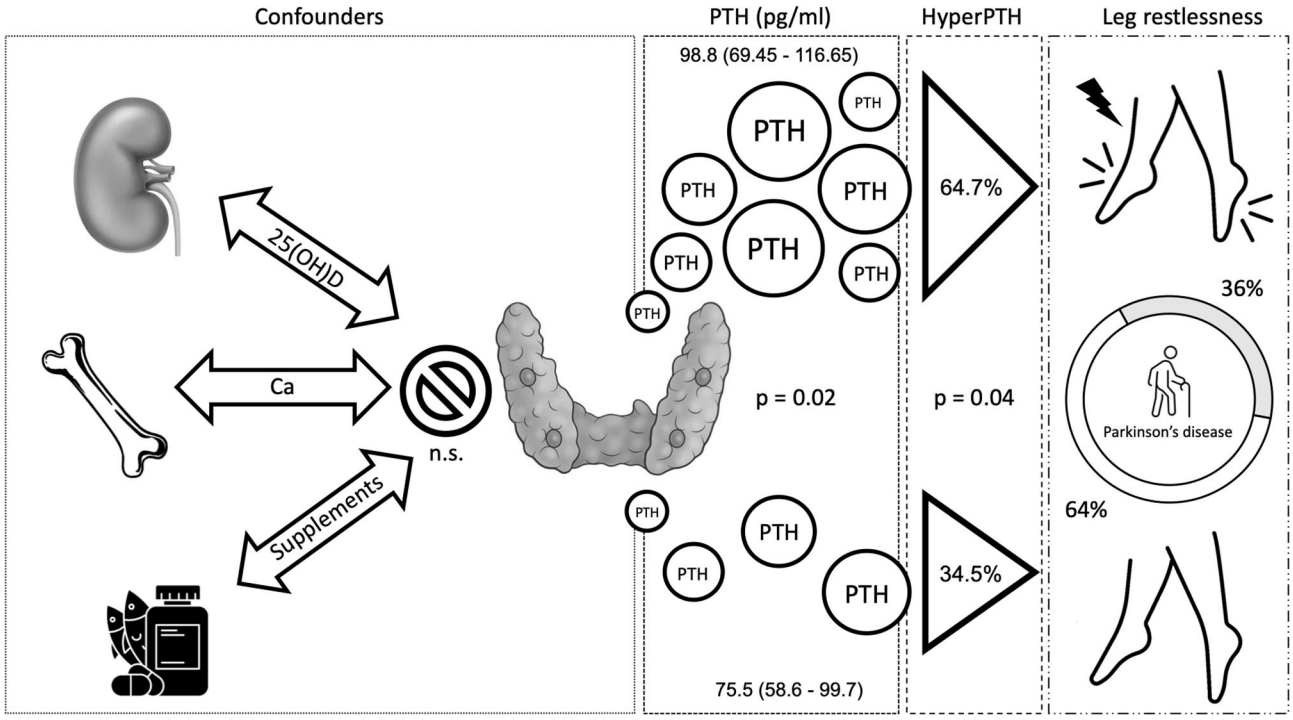

FIGURE 1
Hypothetical interrelation between hyperparathyroidism and leg restlessness.

in the clinical routine of our cohort, but given that the protocol was not designed to address such conditions, further studies are warranted to verify our hypothesis. In our opinion, however, our results deserve to be shared to allow replication studies with a more complete methodology (e.g., RLS criteria and rating scales, bone metabolism instrumental investigation, neurophysiological tests) on larger controlled samples. Moreover, the lack of consistency in the link between PTH and restless legs vs. PTH and pain questions at NMSQ or UPDRS II reinforces our hypothesis. Prospective longitudinal data would be of further help in characterizing the associations between PTH and PD. Despite our preliminary results being compatible with the presence of a possible effect of 25(OH)D supplementation on PTH and RLS symptoms, a study with a specific design is furtherly warranted. We may speculate, therefore, that in predisposed individuals, such as patients with PD, PTH may preferentially act as a neuromodulator able to enhance non-motor symptoms such as leg restlessness, probably through a non-dopaminergic pathway.

In conclusion, PTH, but not calcium, phosphate, or even vitamin D itself, is associated with the presence of RLS symptoms in PD, and such relationship is not significantly influenced by the patient's motor features (Figure 1). Leg restlessness may, indeed, be improved using vitamin D, allowing us to hypothesize future pathophysiologic and therapeutic scenarios for leg restlessness in patients with PD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Committee Campus Bio-Medico University, Rome. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MM: data collection, study design, first draft writing, and statistical analysis. VP: first draft writing. AM: data collection and study design. AP: study design. VD, GT, VP, AP, and AN: review and critique. All authors contributed to the article and approved the submitted version.

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Conflict of interest

MM, VP, AM, GT, AN, AP, and VD was employed by the company Fondazione Policlinico Universitario Campus Bio-Medico.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1113913/full#supplementary-material

References

1. Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. *Nat Rev Neurosci.* (2017) 18:435–50. doi: 10.1038/nrn.2017.62

2. Fullard ME, Duda JE. A review of the relationship between vitamin D and Parkinson disease symptoms. *Front Neurol.* (2020) 11:454. doi: 10.3389/fneur.2020.00454

3. Zhang HJ, Zhang JR, Mao CJ, Li K, Wang F, Chen J, et al. Relationship between 25-Hydroxyvitamin D, bone density, and Parkinson's disease symptoms. *Acta Neurol Scand.* (2019) 140:274–80. doi: 10.1111/ane.13141

4. Stefanidis I, Vainas A, Dardiotis E, Giannaki CD, Gourli P, Papadopoulou D, et al. Restless legs syndrome in hemodialysis patients: an epidemiologic survey in Greece. *Sleep Med.* (2013) 14:1381–6. doi: 10.1016/j.sleep.2013.05.022

5. Schneider R, Karakas E, Bartsch DK, Schlosser K. The influence of parathyroidectomy on restless legs syndrome in patients with renal hyperparathyroidism. *World J Surg.* (2013) 37:2866–71. doi: 10.1007/s00268-013-2185-4

6. Khan M, Jose A, Sharma S. Physiology, Parathyroid hormone. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing (2022). Available online at: https://www.ncbi.nlm.nih.gov/books/NBK499940/

7. Bilezikian JP, Bandeira L, Khan A, Cusano NE. Hyperparathyroidism. *Lancet.* (2018) 391:168–78. doi: 10.1016/S0140-6736(17)31430-7

8. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* (2011) 96:1911–30. doi: 10.1210/jc.2011-0385

9. Barichella M, Garrì F, Caronni S, Bolliri C, Zocchi L, Macchione MC, et al. Vitamin D status and Parkinson's disease. *Brain Sci.* (2022) 12:790. doi: 10.3390/brainsci12060790

10. Luján-Martínez D, Sánchez-Cifuentes Á, Peña-Ros E, Albarracín-Marín-Blázquez A, Candel-Arenas MF. Parkinsonismo como síntoma principal de hiperparatiroidismo: recuperación tras cirugía. *Cir Cir*. (2019) 86:10. doi: 10.24875/CIRU.M18000010

11. De Rosa A, Rinaldi C, Tucci T, Pappatà S, Rossi F, Morra VB, et al. Co-existence of primary hyperparathyroidism and Parkinson's disease in three patients: an incidental finding? *Parkinsonism Relat Disord.* (2011) 17:771–3. doi: 10.1016/j.parkreldis.2011.04.021

12. Ferini-Strambi L, Carli G, Casoni F, Galbiati A. Restless legs syndrome and Parkinson disease: a causal relationship between the two disorders? *Front Neurol.* (2018) 9:551. doi: 10.3389/fneur.2018.00551

13. Yang X, Liu B, Shen H, Li S, Zhao Q, An R, et al. Prevalence of restless legs syndrome in Parkinson's disease: a systematic review and meta-analysis of observational studies. *Sleep Med.* (2018) 43:40–6. doi: 10.1016/j.sleep.2017.11.1146

14. Bhalsing K, Suresh K, Muthane UB, Pal PK. Prevalence and profile of restless legs syndrome in Parkinson's disease and other neurodegenerative disorders: a case-control study. *Parkinsonism Relat Disord.* (2013) 19:426–30. doi: 10.1016/j.parkreldis.2012.12.005

15. Romenets SR, Wolfson C, Galatas C, Pelletier A, Altman R, Wadup L, et al. Validation of the non-motor symptoms questionnaire (NMS-Quest). *Parkinsonism Relat Disord.* (2012) 18:54–8. doi: 10.1016/j.parkreldis.2011.08.013

16. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated international restless legs syndrome study group (IRLSSG) consensus criteria-history, rationale, description, and significance. *Sleep Med.* (2014) 15:860–73. doi: 10.1016/j.sleep.2014.03.025

17. Ghanei Gheshlagh R, Farajzadeh M, Zarei M, Baghi V, Dalvand S, Sayehmiri K. The prevalence of restless legs syndrome in patients undergoing hemodialysis: a systematic review and meta-analysis study. *Basic Clin Neurosci.* (2017) 8:105–12. doi: 10.18869/nirp.bcn.8.2.105

18. Peeraully T, Tan EK. Linking restless legs syndrome with Parkinson's disease: clinical, imaging and genetic evidence. *Transl Neurodegener.* (2012) 1:6. doi: 10.1186/2047-9158-1-6

19. Haden ST, Brown EM, Hurwitz S, Scott J, El-Hajj Fuleihan G. The effects of age and gender on parathyroid hormone dynamics: age, gender, and PTH dynamics. *Clin Endocrinol (Oxf).* (2000) 52:329–38. doi: 10.1046/j.1365-2265.2000.00912.x

20. Gjerstad MD, Tysnes OB, Larsen JP. Increased risk of leg motor restlessness but not RLS in early Parkinson disease. *Neurology.* (2011) 77:1941–6. doi: 10.1212/WNL.0b013e31823a0cc8

21. Arnulf I, Morgan J. Not all that goes "bump in the night" is RLS: leg motor restlessness in PD. *Neurology.* (2011) 77:1936–7. doi: 10.1212/WNL.0b013e31823a0f0f

22. Dobolyi A, Dimitrov E, Palkovits M, Usdin TB. The neuroendocrine functions of the parathyroid hormone 2 receptor. *Front Endocrinol.* (2012) 3:121. doi: 10.3389/fendo.2012.00121

23. Antelmi E, Rocchi L, Latorre A, Belvisi D, Magrinelli F, Bhatia KP, et al. Restless legs syndrome: Known knowns and known unknowns. *Brain Sci.* (2022) 12:118. doi: 10.3390/brainsci12010118

24. Harvey S, Hayer S, Sloley BD. Parathyroid hormone-induced dopamine turnover in the rat medial basal hypothalamus. *Peptides.* (1993) 14:269–74. doi: 10.1016/0196-9781(93)90041-E

25. Isaac J, Berndt TJ, Chinnow SL, Tyce GM, Dousa TP, Knox FG. Dopamine enhances the phosphaturic response to parathyroid hormone in phosphate-deprived rats. *J Am Soc Nephrol.* (1992) 2:1423–9. doi: 10.1681/ASN.V291423

26. Chou FF, Lee CH, Chen JB, Huang SC, Lee CT. Sleep disturbances before and after parathyroidectomy for secondary hyperparathyroidism. *Surgery.* (2005) 137:426–30. doi: 10.1016/j.surg.2004.12.010

27. Rolighed L, Rejnmark L, Sikjaer T, Heickendorff L, Vestergaard P, Mosekilde L, et al. Vitamin D treatment in primary hyperparathyroidism: a randomized placebo controlled trial. *J Clin Endocrinol Metab.* (2014) 99:1072–80. doi: 10.1210/jc.2013-3978

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The Gut Dysmotility Questionnaire for Parkinson's disease: Insights into development and pretest studies

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Objective: A total of 48% of patients with Parkinson's disease (PD) present symptoms of gastrointestinal dysfunction, particularly constipation. Furthermore, gastrointestinal tract (GIT)-related non-motor symptoms (NMSs) appear at all stages of PD, can be prodromal by many years and have a relevant impact on the quality of life. There is a lack of GIT-focused validated tools specific to PD to assess their occurrence, progress, and response to treatment. The aim of this study was to develop and evaluate a novel, disease- and symptom-specific, self-completed questionnaire, titled Gut Dysmotility Questionnaire (GDQ), for screening and monitoring gastrointestinal dysmotility of the lower GIT in patients with PD.

Methods: In phase 1, a systematic literature review and multidisciplinary expert discussions were conducted. In phase 2, cognitive pretest studies comprising standard pretests, interviews, and evaluation questionnaires were performed in patients with PD ($n = 21$), age- and sex-matched healthy controls (HC) ($n = 30$), and neurologists ($n = 11$). Incorporating these results, a second round of cognitive pretests was performed investigating further patients with PD ($n = 10$), age- and sex-matched HC ($n = 10$), and neurologists ($n = 5$). The questionnaire was adapted resulting in the final GDQ, which underwent cross-cultural adaptation to the English language.

Results: We report significantly higher GDQ total scores and higher scores in five out of eight domains indicating a higher prevalence of gastrointestinal dysmotility in patients with PD than in HC ($p < 0.05$). Cognitive pretesting improved the preliminary GDQ so that the final GDQ was rated as relevant (100/100%), comprehensive (100/90%), easy to understand concerning questions and answer options (100/90%), and of appropriate length (80/100%) by neurologists and patients with PD, respectively. The GDQ demonstrated excellent internal consistency (Cronbach's alpha value of 0.94). Evidence for good construct validity

is given by moderate to high correlations of the GDQ total score and its domains by intercorrelations ($r_S = 0.67–0.91$; $p < 0.001$) and with validated general NMS measures as well as with specific items that assess gastrointestinal symptoms.

Interpretation: The GDQ is a novel, easy, and quick 18-item self-assessment questionnaire to screen for and monitor gastrointestinal dysmotility with a focus on constipation in patients with PD. It has shown high acceptance and efficacy as well as good construct validity in cognitive pretests.

KEYWORDS

bowel movement, constipation, gut, questionnaire, Parkinson's disease, cognitive pretest, non-motor symptoms

1. Introduction

Patients with Parkinson's disease (PwPD) present with motor and non-motor symptoms (NMSs). Although the clinical diagnosis of Parkinson's disease (PD) is primarily based on motor symptoms caused by dopamine deficiency (1–3), NMSs are increasingly relevant diagnostic criteria for PD (2, 4).

A broad spectrum of NMSs is already prevalent in the prodromal stage, several years before motor symptoms appear. NMSs are common in all PwPD and occur at all stages of the disease (1, 4–6). Several studies have shown that NMSs have a greater impact on health-related quality of life (HRQoL) in PwPD in comparison to motor symptoms (7). Therefore, evaluation, monitoring, and treatment of NMSs are crucial for a holistic approach to PwPD.

In particular, gastrointestinal dysfunctions are common, prominent, and troublesome NMSs, which can impair the absorption of oral anti-PD drugs and potentially affect HRQoL in PwPD (5, 8–13). Up to 48% of PwPD present gastrointestinal symptoms, particularly constipation (14). There are global NMS tools such as the Non-Motor Symptoms Questionnaire (NMSQuest) (12) and the NMSS (15) that ask about gastrointestinal symptoms next to other NMS but more in a sense if there is an involvement of the gastrointestinal tract (GIT) or not. Specific questionnaires such as the SCOPA-AUT (16) assess the whole GIT and autonomic symptoms, but there is still a lack of validated disease- and symptom-specific instruments to screen for and monitor gastrointestinal dysmotility of the lower GIT with a focus on constipation in PD nor are there validated instruments for other diseases that could be transferred and used in PwPD. This is an unmet need based on the following rationale: Constipation is an important symptom in the prodromal stage of PD and is associated with a higher risk of PD development (6, 8, 17, 18). Furthermore, in the majority of patients with PD, it is hypothesized that the pathophysiological process leading to clinically manifested PD starts in the gut (19–24). Indeed, pathological alpha-synuclein deposits could already be detected in the entire gastrointestinal tract 20 years before diagnosis (20, 21, 25).

Thus, there is a need for a questionnaire that can detect gut dysmotility, and the questionnaire should be applicable to screen people who are at risk of PD development. Furthermore, constipation is evident throughout the whole course of PD (15, 26), so that the assessment and monitoring of gastrointestinal motility and constipation are necessary for any patient with PD on a regular basis. In addition, treatment effects should be recognized when monitoring these symptoms as well as their effect on HRQoL. The need for such a questionnaire has already been expressed by the Movement Disorders Society (MDS) (27). In addition, the development of scales and questionnaires such as the NMSQuest (12) or the symptom-specific Parkinson's Disease Sleep Scale (28) has resulted in a better understanding of NMS and enhanced the diagnostic and treatment approaches in PD.

Therefore, we developed the Gut Dysmotility Questionnaire (GDQ) as a screening and monitoring tool for gastrointestinal dysmotility with a focus on constipation in international collaboration (29). A comprehensive cognitive pretest study was performed including PwPD, and healthy controls (HC) as well as neurologists. This resulted in the final GDQ as a disease- and symptom-specific, self-completed, short, and holistic questionnaire to screen for and monitor gastrointestinal dysmotility of the lower GIT in PwPD.

2. Materials and methods

2.1. Phase 1: Development of the preliminary GDQ

In phase 1, a systematic literature search was performed to identify questionnaires and to reveal relevant questions in relation to lower gastrointestinal tract symptoms. In the PubMed search, we used combinations of the key terms "Constipation AND Parkinson," "Bowel Movement AND Parkinson," and "Constipation AND Questionnaire," including all articles in English and German of any type up to October 2018. A selection of questions in English was developed and discussed in repetitive multidisciplinary expert group meetings. Hereby, the preliminary GDQ (pGDQ) was developed.

2.2. Phase 2: Standard and cognitive pretest study of the GDQ

The objective of this study was to perform standard and cognitive pretests on PwPD, HC, and neurologists using the German version of the pGDQ to verify its wording and effectiveness (30) as well as to further refine the questionnaire. Phase 2a covered the first standard and cognitive pretest. Hereafter, the GDQ was adapted and pretested again in phase 2b.

2.2.1. Study design and procedures

The standard and cognitive pretest study was performed as an open, prospective, single-center evaluation study at the Department of Neurology of the Technische Universität Dresden (TUD), Germany.

The cognitive pretests included structured interviews and evaluation questionnaires in the following three groups: patients with idiopathic PD, age and sex-matched HC, and neurologists specialized in movement disorders.

Patients with Parkinson's disease were consecutively recruited in the movement disorders-specialized out- and in-patient clinics of the Department of Neurology of TUD. The HC were mainly relatives and companions of the investigated PwPD. Ethical approval (EK 518122019) was granted by the ethics committee of TUD. All participants gave written informed consent before any study-related procedure was initiated.

In phase 2a, a standardized study protocol was performed in PwPD and HC with a collection of sociodemographic and disease-related data. In addition, validated PD-specific scales and questionnaires were used to obtain a clinical impression of motor and non-motor burden (Montreal Cognitive Assessment, Hoehn & Yahr stage, clinical impression of severity index for PD, Beck Depression Inventory), general medical health state (clinical global impression, patient global impression), and HRQoL (Parkinson's Disease Quality of Life Questionnaire eight, EQ-5D-5L). Furthermore, questionnaires assessing gastrointestinal symptoms (MDS-UPDRS part I question 1.11, SCOPA-AUT, NMSQuest), influencing factors, and habits such as smoking and caffeine consumption, and physical activity were recorded. The standard and cognitive pretests were interview-based on a specifically prepared interview guideline and protocol and conducted with all PwPD and HC (30). The PwPD and HC completed the pGDQ as well as the evaluation questionnaire themselves. While doing so, verbal and non-verbal reactions were observed by the study personnel. Following completion, each individual question of the pGDQ as well as any unusual verbal and non-verbal reactions observed during the completion of the pGDQ were discussed in a personal interview with the participants. Techniques of think-aloud, verbal probing, and a confidence rating were used (30). For the think-aloud method, the participant was asked to express his or her thoughts on each question before and during answering the question. Patients were encouraged to reflect on all possible thoughts on each question. In verbal probing, specific questions were asked about the answer types of the questionnaire. For confidence rating, participants were asked to indicate how correctly they answered each question. If uncertainties were stated, the participants were asked why they felt so. In addition, each data point of the interview protocols was quantitatively and qualitatively analyzed by the developers for further guidance. The participants themselves were also encouraged to make valuable and well-structured suggestions for the improvement of the pGDQ. The time taken to complete the questionnaire was recorded.

The study protocol for the neurologists was more concise and required demographic data and a level of expertise in the field of neurology. Each neurologist scored a total of four pGDQ questionnaires (two completed by PwPD and two by HC) using a provided scoring guide and further completed an evaluation questionnaire for cognitive pretesting.

The evaluation questionnaire of the pGDQ was the same in all three study groups. It contained simple yes and no answers with an additional free text option for remarks and was adopted from the literature (31). In addition, the neurologists evaluated the different domains and the scoring system of the pGDQ.

The pGDQ, the scoring guide, and the evaluation questionnaire were adapted to the results of phase 2a resulting in the prefinal GDQ (pfGDQ) which was retested in phase 2b investigating further PwPD and HC as well as neurologists who had already participated in phase 2a. The standardized study protocol of phase 2a was shortened and performed with the standard and cognitive pretests in all PwPD and HC. The PwPD and HC completed the pGDQ as well as the evaluation questionnaire themselves, followed by an interview as in phase 2a.

The study protocol for the neurologists was repeated, and each neurologist scored a total of four pGDQ questionnaires (two completed by PwPD and two by HC) using a provided scoring guide and completed an evaluation questionnaire for cognitive pretesting.

2.2.2. Inclusion and exclusion criteria

Healthcare professionals were included if certified as neurologists and study nurses, each with specific knowledge in movement disorders or geriatrics. Participants of the PD study group had to be diagnosed with idiopathic PD based on the clinical diagnostic criteria (2) and had to be at least 18 years old. HC had to be between 30 and 80 years old.

The exclusion criteria for the PD study group were any diagnosis of atypical or secondary PD, severe memory impairment, or any uncontrolled psychiatric illness such as psychosis. HC was excluded if they were diagnosed with severe memory impairment or any acute and uncontrolled neurological, psychiatric, or gastrointestinal concomitant diseases (e.g., psychosis and gastrointestinal infection).

2.2.3. Data analysis

Data analysis was performed using SPSS. Demographic and clinical characteristics of phase 2a and phase 2b were analyzed using non-parametric tests as the data were mostly not normally distributed.

For the evaluation of the preliminary and prefinal GDQ, the following parameters were analyzed: data quality (<10% missing data and more than 90% calculable scores), floor and ceiling effects

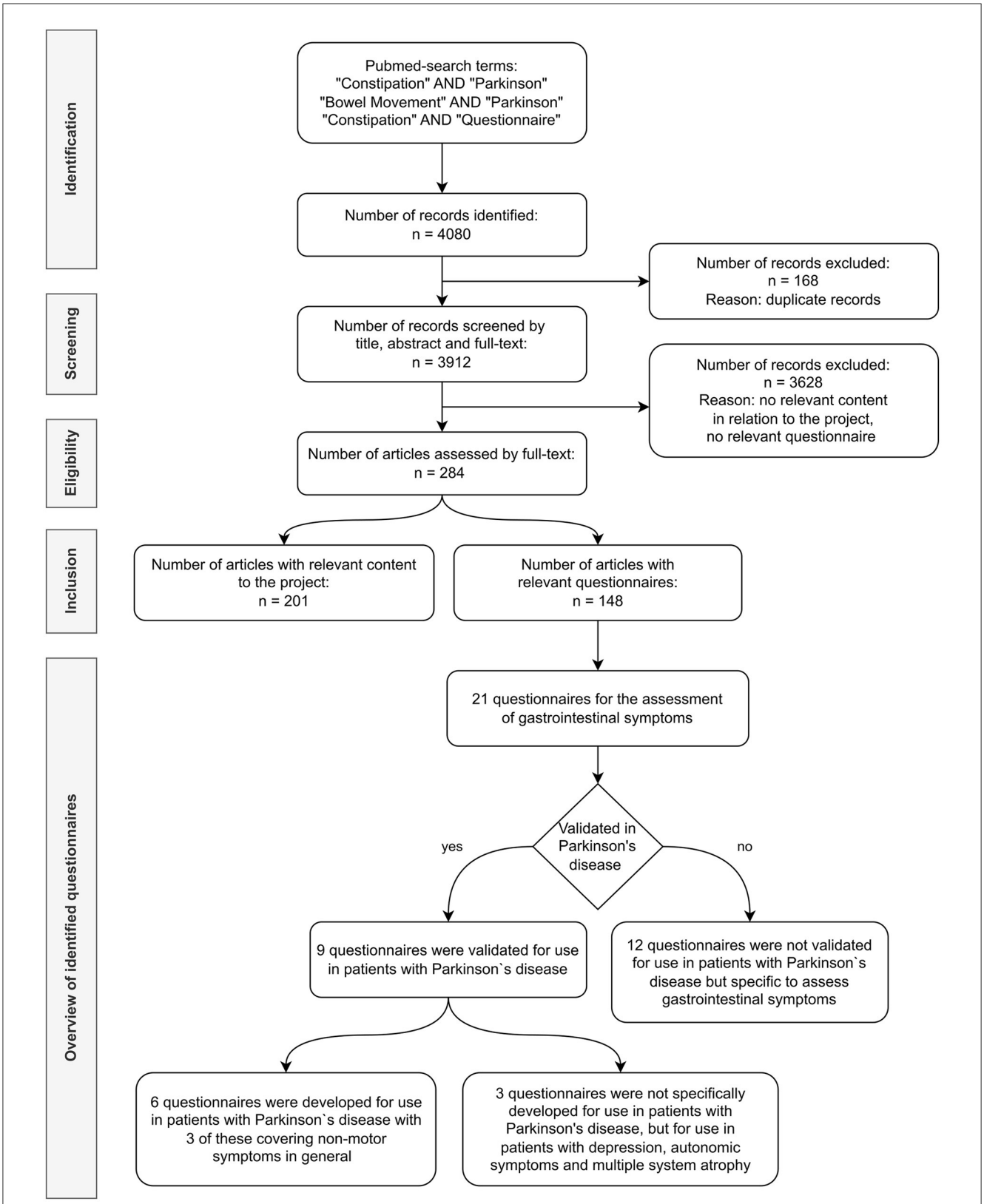

FIGURE 1
Flowchart summarizing the literature search.

below 15%, and skewness between −1 and +1. The reliability of both questionnaires was explored with Cronbach's alpha (>0.70), inter-item correlation (0.20–0.75), item homogeneity coefficient (>0.15), and corrected item-total correlation (≥0.30). Spearman's rank correlation coefficients were considered "weak" if the r_s-value was <0.3, "moderate" if 0.3–0.59, and "high" if >0.60 (32, 33).

Data from the standard pretests, cognitive pretests, and evaluation questionnaires were analyzed with qualitative and quantitative methods, including descriptive tests. The collected data were categorized and quantified using an adapted Classification Coding Scheme (CCS) (34). A *P*-value of <0.05 was considered to be statistically significant.

2.3. Cross-cultural adaptation of the GDQ

The cross-cultural adaptation of the GDQ followed international guidelines with translation from German to English language and vice versa (35). Detailed information will be published in another scientific article.

3. Results

3.1. Phase 1

Based on a systematic literature search (Figure 1) and identified questionnaires, a selection of questions in English was developed aiming to cover all relevant domains in relation to gastrointestinal dysmotility and PD. In repetitive multidisciplinary expert group meetings including internationally recognized movement disorders specialists ($N = 12$), gastrointestinal specialists ($N = 2$), and PD specialist nurses and study nurses ($N = 2$), the following points were discussed: relevant questions/content, design of questions and answer possibilities, meaningful domains to merge questions, the relevance of influencing factors and associated symptoms, and scoring system.

Phase 1 resulted in the pGDQ, which consisted of 16 questions with eight sub-questions, comprising 24 questions in total. The questions were assigned to eight different domains: frequency, duration, severity, consistency, assistance, pain, quality of life, and development (Table 2). Answers were mainly provided by a four-item unipolar response scale. In the domain of stool consistency, answers were assessed in a table with small drawings for visualization. The answer options in the domain development were designed as a visual analog scale, ranging from constipation "improving" over "stable" to "worsening." As a scoring method, a basic summation of all answers was chosen so that the total score of the pGDQ could range from 0 to 74 points with higher values implicating worse gastrointestinal dysmotility.

3.2. Phase 2

3.2.1. Phase 2a study: Cognitive pretests of the preliminary GDQ

3.2.1.1. Characteristics of the study sample

In phase 2a, 21 PwPD and 30 HC as well as 11 neurologists were included. Demographic, motor, and non-motor characteristics of PwPD and HC are summarized in Table 1.

The neurologists (63.6% female patients) had a mean (±SD) age of 37.2 ± 11.4 (ranging from 27.5 to 66.6) years and a mean duration of experience in neurology of 8.6 ± 10.0 (ranging from 0.8 to 35.0) years with 45.5% acting as a resident physician and 54.5% as a consultant or in a higher position. In the total group, the years of experience, particularly in PD, were 5.6 ± 9.8 (ranging from: 0.0 to 30.0).

The included PwPD and HC were age- and sex-matched, and cognitive assessments were within normal ranges so that the results of self-completed questionnaires and scales were considered to be reliable (Table 1). Regarding data quality, no relevant data from any of the study participants were missing.

Patients with Parkinson's disease showed a significantly higher impairment in comparison to HC in all PD-specific questionnaires and scales evaluating motor and non-motor symptoms as well as in the clinical global impression of health state. Furthermore, PwPD presented with a significantly worse HRQoL in contrast to HC (Table 1).

Significant differences in the confounders and co-morbidities recorded were found between PwPD and HC, with PwPD presenting more often with depression ($p < 0.01$), dysphagia ($p < 0.05$), and surgery on the gastrointestinal tract ($p < 0.01$), especially the small/large intestine ($p < 0.05$). There were also significant differences in the use of antidepressants ($p < 0.01$), antipsychotics ($p < 0.05$), painkillers ($p < 0.01$), laxatives ($p < 0.001$), and ulcer therapy ($p < 0.05$), which were taken more frequently by PwPD. In addition, PwPD exercised less ($p < 0.05$) but got physiotherapy more often ($p < 0.001$) compared to HC. All PwPD received PD-specific therapy, of which 76.2% of patients received combination therapy of at least two drugs. Approximately, 28.6% of PwPD had an advanced therapy with deep brain stimulation and at least one oral medication, and 14.3% of patients used a pump therapy and at least one oral medication. An overview of all PD therapies in the PwPD group is provided in Figure 2.

Patients with Parkinson's disease showed a significantly higher total score in the pGDQ compared to HC. Furthermore, in five out of eight domains of the pGDQ, PwPD scored significantly higher than HC (Table 2). This is in correspondence with the results of validated measures of constipation in PD such as NMSQuest question 5 (percentage "yes-answer" in PwPD 57.1% vs. in HC 0%, $p < 0.001$, MW U-test) and SCOPA-AUT question 5 (percentage with constipation in PwPD 50% vs. in HC 3.3%, $p < 0.01$, chi-square test). The pGDQ total score, PD duration ($r_s = 0.29$, $p > 0.05$), and LEDD ($r_s = 0.32$, $p > 0.05$) showed a weak positive correlation.

3.2.1.2. Acceptability

The GDQ total score showed a minor floor effect with 4.8% of PwPD having the lowest total score, but no ceiling effect. The pGDQ domains showed a moderate floor effect, ranging from 4.8% of PwPD reaching the lowest score in the domain severity up to 52.4% in the domain assistance and from 3.3% of HC reaching the lowest score in the domain development up to 100% in the domain frequency. None of the pGDQ domains showed a ceiling effect. Apart from the assistance domain (5.48) in the HC, moderate skewness was found for all domains and the total score in both groups.

3.2.1.3. Psychometric properties

Internal consistency was high for all items of the questionnaire (Cronbach's alpha value of 0.92), and for the domain pain (α =

TABLE 1 Demographic, motor, and non-motor characteristics of patients with Parkinson's disease (PD) and healthy controls of the phase 2a study.

	PD patients ($n = 21$)	Healthy controls ($n = 30$)	*P*-value
Age (years) (minimum-maximum)	65.52 ± 8.63 (49.00–80.00)	59.70 ± 14.02 (30.00–80.00)	0.168
Sex (m/f)	12/9	16/14	0.788
Education (years) (minimum-maximum)	10.81 ± 1.29 (8.00–13.00)	10.80 ± 1.69 (8.00–14.00)	0.984
Disease duration (years) (minimum-maximum)	9.67 ± 6.02 (2.00–21.00)	N/A	N/A
LEDD (mg/day) (minimum-maximum)	802.54 ± 469.57 (0.00–1730.38)	N/A	N/A
Hoehn and Yahr stage*	3 (2.0–3.0)	0 (0.0–0.0)	**<0.001**
CGI-S (minimum-maximum)	3.90 ± 0.70 (3.00–5.00)	1.93 ± 0.98 (1.00–4.00)	**<0.001**
NMSQ	11.22 ± 5.65	2.67 ± 2.47	**<0.001**
SCOPA-AUT Item 5[a]	0.90 ± 1.02	0.03 ± 0.18	**<0.001**
SCOPA-AUT Item 6[b]	1.20 ± 1.06	0.23 ± 0.43	**<0.001**
MoCA	27.00 ± 2.30	28.47 ± 1.53	**<0.05**
BDI	9.55 ± 9.47	1.70 ± 2.61	**<0.001**
PDQ-8	8.80 ± 5.19	N/A	N/A
EQ-5D-5L Index Value	0.76 ± 0.19	0.96 ± 0.06	**<0.001**
pGDQ (minimum-maximum)	18.05 ±12.40 (0.00–40.00)	6.10 ± 3.11 (2.00–12.00)	**<0.001**
Non-alcoholic drinks (ml/d) (minimum-maximum)	1411.90 ± 602.48 (500.00–2500.00)	1848.33 ± 666.63 (500.00–3750.00)	**<0.05**
Caffeinated drinks (ml/d) (minimum-maximum)	485.71 ± 222.57 (0.00–800.00)	478.33 ± 307.29 (0.00–1500.00)	**<0.05**
Alcoholic drinks (ml/d) (minimum-maximum)	100.68 ± 191.28 (0.00–750.00)	173.71 ± 331.85 (0.00–1500.00)	**<0.05**

Data are presented as mean ± SD or *median (25^{th}-75^{th} percentiles). Differences between groups were tested using the Mann–Whitney U-test or Pearson chi-square test were appropriate. PD, Parkinson's disease; LEDD, Levodopa Equivalent Daily Dose; CGI-S, Clinical Global Impression–Severity scale; NMSQ, Non-Motor Symptoms Questionnaire; SCOPA-AUT, Scales for Outcomes in PD–Autonomic; MoCA, Montreal Cognitive Assessment; BDI, Beck Depression Inventory; PDQ-8, Parkinson's Disease Questionnaire-8; pGDQ, preliminary Gut Dysmotility Questionnaire. [a]Item 5, "In the past month, have you had problems with constipation?" (0 = Never; 1 = Sometimes; 2 = Regularly; 3 = Often); [b]Item 6, "In the past month, did you have to strain hard to pass stools?" (0 = Never; 1 = Sometimes; 2 = Regularly; 3 = Often). The *p*-values are bold if they are significant (<0.05).

0.92), it was good for the domain frequency (α = 0.75) and adequate for all other domains (α = 0.46–0.68) in PwPD.

The intercorrelation and construct validity of the pGDQ are summarized in Table 3. In PwPD, all pGDQ domains, except development, showed a high-level positive correlation with the total score (r_s = 0.67–0.91; $p < 0.001$). The pGDQ domains showed a moderate- to high-level positive correlation with each other (r_s = 0.44–0.91, $p < 0.05$) apart from a weak positive correlation between the domain pain and frequency ($r_s = 0.30$, $p > 0.05$) and any correlation of the domain development. The total score of the pGDQ correlated positively on a high level with the NMSQ total score and Item five as well as Item seven of the NMSQ, which are specific to assess constipation. It is noteworthy that the pGDQ total score also correlated on a high level with the NMSQ Items 12 and 13, which relate to memory and mood. The SCOPA-AUT Item five, Item six, and the total score as well as the MDS-UPDRS Item 1.11 and the PDQ-8 total score correlated positively on a high level with the pGDQ total score (Table 3). The total score of the pGDQ also correlated positively on a moderate level with the Hoehn and Yahr stage, with the BDI, and on a weak level with the CGI-S (Table 3). The PDQ-8 total score correlated positively on a high level with the pGDQ QoL domain.

In HC, the total score of the pGDQ correlated positively with the NMSQ on a weak level ($r_s = 0.33$, $p < 0.05$). In addition, the QoL domain of the pGDQ correlated negatively on a weak level with the EQ-5D-5L score ($r_s = -0.43$, $p < 0.01$) (Table 3).

3.2.1.4. Evaluation of the pGDQ using the interview protocol and the evaluation questionnaire with corresponding adaptation

In total, 355 problems were identified in the interviews with PwPD and HC which were performed directly after the self-completion of the pGDQ. These problems were categorized into 24 CCS codes, which were assigned to the corresponding questions of the pGDQ (Table 4). In particular, question 16 with overall 27% entries, question 12 with 17.5%, question 2 with 7.3%, and question 8.1 with 6.5% entries were found to stand out. The highest-rated issues were the type of answer possibilities with "unclear respondent instruction" and "missing response categories" for questions 12 (stool consistency) and 16 (development of constipation during the past 3 months). In both questions, the answer options were differently designed compared to the four-item response scale of most other questions, which was well received. Therefore, in question 12, the type of answer option was changed from a table to individual questions with the four-item response scale. Moreover, the visual analog scale of question 16, which was just a line without any numeric values was adapted comprising boxes ranging from "constipation gets worse" (-5 points) to "no change in constipation" (0 points) to "constipation gets better" (5 points), and one further box has an alternative answer option of "no constipation." Hereby, also the scoring of the answer was improved as it had been prone to errors in the evaluation by neurologists with a relevant number of total scores

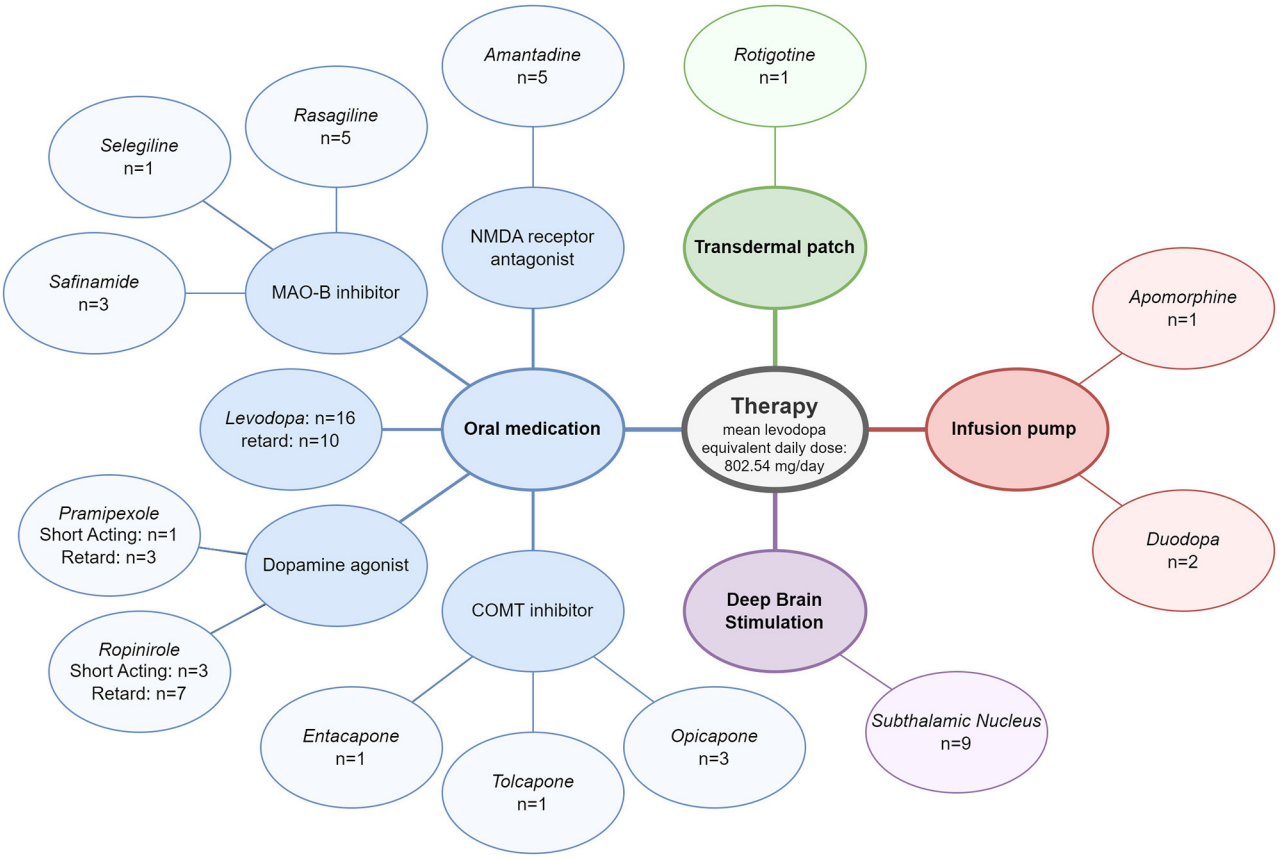

FIGURE 2
Therapy of patients with Parkinson's disease included in phase 2a.

being incorrectly calculated. In addition, question 16 was excluded to be counted toward the total score of the GDQ based on results of the intercorrelation and convergent validity but was retained in the questionnaire as it was found to be valuable by neurologists. Another often observed issue was "complex/awkward syntax" for questions 2 (duration of constipation in years) and 6 (incomplete evacuation). Therefore, the wording of question 2 was simplified. Question 6 was removed from the questionnaire due to the results of the evaluation questionnaire, which showed no meaningful difference between questions 5 and 6. Question 5 remained as it was better received and evaluated. "Complex/awkwardly detailed response definition" was a common issue for many questions. Questions 3 (straining during defecation), 4 (constriction in the anus during defecation), 5 (incomplete evacuation), 6 (incomplete evacuation), 8 (painful abdomen), 9 (rectal pain), 10 (laxative usage), 11 (manual aid for defecation), 12 (stool consistency), and 13 (fecal incontinence) had frequencies as response options with additional text in brackets to specify the terms, which was often found to be confusing or too detailed. In addition, PwPD and HC did not find the answer options to be exhaustive as rated in "missing response categories." There was a lack of options, e.g., in frequency-related response options, such as "rarely" between the provided choices "never" and "sometimes." Subsequently, all frequency response options were replaced with the four-item response scale "never," "rarely/sometimes," "often," and "mostly/always." The response options of question 15 (quality of life) were found to be too complex and were simplified. Questions 8.2 and 9.2 used severity response options with definitions in brackets, which were found to be too detailed and confusing. The answer options were simplified to "not applicable," "mild," "moderate," and "severe." Another point of criticism was the conditional omission of questions. This applied to the four questions with subcategories of frequency and severity: question 8 about painful pull in the stomach or unpleasant bloating, 9 about rectal pain, 10 about the use of laxatives, and 13 about stool incontinence. If the frequency "never" was chosen, the question about the severity should be skipped. This was confusing as well as it was not followed by some participants and therefore caused an incorrect scoring of the pGDQ. As a consequence, the subcategories of questions 8 and 9 were changed to two different questions, one asking for frequency and one for severity. Question 10 was reduced to one question, not asking about the efficacy of the use of laxatives anymore. Question 13 on fecal incontinence was removed from the questionnaire due to an additional low inter-item correlation in its domain, and it reduced the internal consistency of the questionnaire measurably.

The results of the evaluation questionnaires of PwPD, HC, and neurologists are presented in Table 5. Most study participants of the three groups found the pGDQ to be relevant and helpful to assess current gastrointestinal health state, comprehensive, simple, and clear to understand; to be having suitable, clear, and appropriate

TABLE 2 Total and domain scores and completion time of the preliminary GDQ of patients with Parkinson's disease and healthy controls of the phase 2a study.

pGDQ	PD patients ($n = 21$)	Healthy controls ($n = 30$)	*P*-value
Total score	18.05 ± 12.40 (0.00 to 40.00)	6.10 ± 3.11 (2.00 to 12.00)	**<0.001**
Domain-frequency	1.43 ± 1.40 (0.00 to 4.00)	0.00 ± 0.00 (0.00 to 0.00)	**<0.001**
Domain-duration	2.14 ± 1.46 (0.00 to 5.00)	0.27 ± 0.45 (0.00 to 1.00)	**<0.001**
Domain-severity	4.14 ± 2.67 (0.00 to 11.00)	1.27 ± 1.05 (0.00 to 4.00)	**<0.001**
Domain-consistency	4.24 ± 2.90 (0.00 to 9.00)	3.10 ± 1.45 (0.00 to 5.00)	0.096
Domain-assistance	1.24 ± 1.51 (0.00 to 5.00)	0.10 ± 0.55 (0.00 to 3.00)	**<0.001**
Domain-pain	3.48 ± 3.39 (0.00 to 10.00)	1.57 ± 1.48 (0.00 to 6.00)	0.056
Domain-HRQoL	1.67 ± 1.59 (0.00 to 5.00)	0.23 ± 0.57 (0.00 to 2.00)	**<0.001**
Domain-development	−0.35 ± 1.06 (-4.00 to 1.00)	−1.30 ± 2.11 (-5.00 to 0.00)	0.505
Completion time (min)	8.45 ± 5.28 (3.00 to 15.00)	5.90 ± 2.24 (2.00 to 5.00)	**<0.05**

Data are presented as mean ± SD (minimum–maximum). PD, Parkinson's Disease; pGDQ, preliminary Gut Dysmotility Questionnaire; HRQoL, Health-Related Quality of Life. The *p*-values are bold if they are significant (<0.05).

answers; and to be having a sensible order of the questions. About half of the study participants of each group found the pGDQ to be difficult to answer. This was in line with the results of the interview protocol as described above. Disagreement was found in the question if the pGDQ is too long with 54.5% of the neurologists evaluating the pGDQ as too long in contrast to PwPD (23.8 %) and HC (3.3 %) who are the once who completed the pGDQ. Due to the removal of questions and streamlining of the pGDQ by simplification as described above, we addressed this issue. Interestingly, 27.3% of the neurologists found the pGDQ strange or embarrassing whereas none of the HC and only 14.3 % of the PwPD declared this.

The evaluation questionnaires of the neurologists revealed that the scoring of the pGDQ was too complex, mainly due to the different types as well as the changing value of the response options (from low to high and high to low scores). As the response options were homogenized based on the feedback by the PwPD and HC in the interviews as shown earlier, the scoring got simplified. In addition, all response options were scored from left to right with increasing scores.

Based on these results of the phase 2a study, the preliminary GDQ was adapted to the pfGDQ, which was tested in a phase 2b study. The pfGDQ consisted of only 18 instead of 24 questions and did not contain any sub-questions. The questions were still assigned to the same eight domains as in the pGDQ (Table 2). All answers were provided on a four-item response scale, which was equalized wherever possible. Only the answer option of the domain development remained as a visual analog scale in an adapted version as described above.

3.2.2. Phase 2b study: Cognitive pretests of the prefinal GDQ

In phase 2b, the adapted pGDQ, titled pfGDQ, was cognitively pretested in a smaller sample size to evaluate the changes and to create the final GDQ. A total of 10 PwPD, 10 HC, and five neurologists were investigated.

Demographic, motor, and non-motor characteristics of PwPD and HC are summarized in Table 6.

The five neurologists (60% men), which also participated in phase 2a, were selected based on their answers of the evaluation questionnaire from phase 2a. Particular concern was given to those who were critical and who had negative comments. Their mean (±SD) age was 43.9 ± 14.7 (ranging from: 29.7 to 67.7) years, and their mean duration of general experience in neurology was 14.4 ± 5.6 (ranging from 3.0 to 35.0) years with 11.8 ± 5.5 years of experience particularly in PD.

Patients with Parkinson's disease and HC were matched for age and sex, and the cognitive scores were within normal ranges, so that the results of the self-completed questionnaires and scales were regarded as reliable (Table 6). Regarding data quality, one pfGDQ from a PwPD was incomplete and could not be used for full statistical analysis (missing 5%).

Patients with Parkinson's disease showed a significantly higher total score of the pfGDQ compared to HC. In addition, PwPD scored significantly higher in five out of the eight domains of the pfGDQ compared to HC (Table 6). The mean completion time of the pfGDQ was significantly longer for PwPD than for HC but shorter compared to the completion time of the pGDQ (in PwPD 1.05 and in HC 2.52 min less).

3.2.2.1. Acceptability

The pfGDQ total score showed no floor and no ceiling effect. The pfGDQ domains showed a moderate floor effect, ranging from 10% of PwPD reaching the lowest score in the domain consistency up to 40% in the domain assistance and from 20% of HC reaching the lowest score in the domain severity, pain and development up to 100% in the domain frequency, assistance, and development. A low ceiling effect was detected with 10% of PwPD reaching the highest score in the domain severity and development. A moderate skewness was found for all domains and the total score in both groups.

TABLE 3 Intercorrelation and construct validity of pGDQ domains in patients with Parkinson's disease.

	pGDQ-total score	pGDQ-frequency	pGDQ-duration	pGDQ-severity	pGDQ-consistency	pGDQ-assistance	pGDQ-pain	pGDQ-HRQoL	pGDQ-development
pGDQ-frequency	0.79***								
pGDQ-duration	0.81***	0.70***							
pGDQ-severity	0.88***	0.72***	0.66**						
pGDQ-consistency	0.84***	0.55**	0.57**	0.61**					
pGDQ-assistance	0.79***	0.64**	0.82***	0.66**	0.53**				
pGDQ-pain	0.67***	0.30	0.50*	0.58**	0.68***	0.44*			
pGDQ-HRQoL	0.91***	0.63**	0.79***	0.81***	0.66**	0.84***	0.64**		
pGDQ-development	−0.05	−0.04	−0.24	−0.09	−0.08	−0.06	0.04	0.07	
Hoehn and Yahr stage	0.56**	0.60**	0.61**	0.44*	0.48*	0.46*	0.22	0.41*	0.32
CGI-S	0.37*	0.67***	0.58**	0.31	0.20	0.34	0.18	0.33	−0.02
NMSQ-item 5[a]	0.80***	0.84***	0.77***	0.66**	0.61**	0.76***	0.32	0.74***	0.07
NMSQ-item 7[b]	0.76***	0.77***	0.72***	0.71***	0.58**	0.65**	0.54*	0.66**	−0.14
NMSQ-item 12[c]	0.70**	0.47*	0.71**	0.71**	0.48*	0.53*	0.47*	0.70**	−0.15
NMSQ-item 13[d]	0.71***	0.75***	0.60**	0.58**	0.66**	0.45*	0.65**	0.52*	−0.19
NMSQ-total score	0.85***	0.64**	0.81***	0.84***	0.71***	0.64**	0.62**	0.74***	−0.15
SCOPA-AUT-item 5[e]	0.62**	0.71***	0.73***	0.45*	0.48*	0.65**	0.26	0.56**	0.03
SCOPA-AUT-item 6[f]	0.77***	0.76***	0.79***	0.66**	0.55**	0.70***	0.46*	0.72***	0.05
SCOPA-AUT-total score	0.75***	0.80***	0.78***	0.64**	0.63**	0.63**	0.43	0.65**	−0.03
MDS-UPDRS -item 1.11[g]	0.72***	0.49*	0.71***	0.58**	0.58**	0.75***	0.61**	0.69**	−0.16
PDQ-8-total score	0.83***	0.77***	0.77***	0.77***	0.64**	0.65**	0.59**	0.80***	−0.01
BDI-total score	0.57**	0.60**	0.62**	0.54**	0.50*	0.33	0.36	0.45*	−0.07

Spearman's rank correlation coefficients. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. BDI, Beck Depression Inventory; CGI-S, Clinical Global Impression–Severity scale; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale, NMSQ, Non-Motor Symptoms Questionnaire; PDQ-Q, Parkinson's Disease Questionnaire; pGDQ, preliminary Gut Dysmotility Questionnaire; HRQoL, Health-Related Quality of Life; SCOPA-AUT, Scales for Outcomes in PD–Autonomic. [a]Item 5, "Have you experienced any of the following in the last month? Constipation (<3 bowel movements a week) or having to strain to pass a stool (feces)" (0 = No; 1 = Yes); [b]Item 7, "Have you experienced any of the following in the last month? Feeling that your bowel emptying is incomplete after having been to the toilet" (0 = No; 1 = Yes); [c]Item 12, "Have you experienced any of the following in the last month? Problems remembering things that have happened recently or forgetting to do things" (0 = No; 1 = Yes); [d]Item 13, "Have you experienced any of the following in the last month? Loss of interest in what is happening around you or doing things" (0 = No; 1 = Yes); [e]Item 5, "In the past month, have you had problems with constipation?" (0 = Never; 1 = Sometimes; 2 = Regularly; 3 = Often); [f]Item 6, "In the past month, did you have to strain hard to pass stools?" (0 = Never; 1 = Sometimes; 2 = Regularly; 3 = Often); [g]Item 1.11, "Over the past week have you had constipation troubles that cause you difficulty moving your bowels?" (0 = Normal; 1 = Slight; 2 = Mild; 3 = Moderate; 4 = Severe).

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TABLE 4 Problem labels for the classification coding scheme codes of each question of the pGDQ compiled by the interview protocols of patients with Parkinson's disease and healthy controls for the phase 2a study.

	Question number of the preliminary Gut Dysmotility Questionnaire [frequency (*N*), occurrence per question in %]																																		Total (frequency, overall in %)	
	1		2		3		4		5		6		7		8.1		8.2		9.1		9.2		10.1		10.2		11		12		13.1		13.2		14		15		16			
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Complex estimation, difficult mental calculation required	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	2	3.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.0%	3	0.8%
Complex topic	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.6%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.3%
Complex/awkward syntax	0	0.0%	12	46.2%	0	0.0%	0	0.0%	0	0.0%	7	43.8%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	3	23.1%	0	0.0%	22	6.2%
Complex/awkwardly detailed response definition	1	12.5%	0	0.0%	9	50.0%	6	33.3%	5	35.7%	2	12.5%	0	0.0%	5	21.7%	1	25.0%	6	50.0%	0	0.0%	2	33.3%	1	12.5%	3	50.0%	6	9.7%	2	40.0%	0	0.0%	0	0.0%	1	7.7%	2	2.1%	52	14.6%
Erroneous assumption	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	33.3%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.6%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	2	2.1%	4	1.1%
High detail required or information unavailable	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	33.3%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	5	8.1%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	6	1.7%
Layout or formatting	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	7	11.3%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	6	6.3%	13	3.7%
Long recall or reference period	3	37.5%	5	19.2%	0	0.0%	0	0.0%	1	7.1%	2	12.5%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.6%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	12	3.4%
Missing response categories	0	0.0%	1	3.8%	5	27.8%	2	11.1%	2	14.3%	0	0.0%	0	0.0%	4	17.4%	0	0.0%	1	8.3%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.6%	0	0.0%	0	0.0%	1	33.3%	0	0.0%	30	31.3%	47	13.2%
Non-verbal reaction (re-reading, skeptical or thoughtful)	2	25.0%	1	3.8%	0	0.0%	0	0.0%	2	14.3%	1	6.3%	0	0.0%	1	4.3%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	12.5%	0	0.0%	4	6.5%	0	0.0%	0	0.0%	0	0.0%	2	15.4%	9	9.4%	23	6.5%
Other answer type preferred	1	12.5%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	5	8.1%	0	0.0%	0	0.0%	0	0.0%	1	7.7%	2	2.1%	9	2.5%
Overlapping categories	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.6%	0	0.0%	0	0.0%	1	33.3%	0	0.0%	0	0.0%	2	0.6%
Potentially sensitive or desirability bias	0	0.0%	0	0.0%	1	5.6%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	8	34.8%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	16.7%	1	1.6%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	11	3.1%
Question not applicable to some respondents	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	32	33.3%	32	9.0%
Question order	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	2	2.1%	2	0.6%
Question too long	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	4	30.8%	0	0.0%	4	1.1%
Several questions	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.6%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.3%
Topic carried over from earlier question	0	0.0%	0	0.0%	0	0.0%	1	5.6%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	2	15.4%	0	0.0%	3	0.8%
Uncertain or failure to skip	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	5	83.3%	0	0.0%	6	75.0%	0	0.0%	0	0.0%	0	0.0%	2	25.0%	0	0.0%	0	0.0%	0	0.0%	13	3.7%
Unclear respondent instruction	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	25	40.3%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	7	7.3%	32	9.0%
Undefined term	0	0.0%	2	7.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	33.3%	0	0.0%	1	25.0%	0	0.0%	1	16.7%	0	0.0%	0	0.0%	1	16.7%	0	0.0%	1	20.0%	1	12.5%	0	0.0%	0	0.0%	0	0.0%	8	2.3%
Undefined/vague term	1	12.5%	1	3.8%	0	0.0%	8	44.4%	3	21.4%	0	0.0%	0	0.0%	3	13.0%	1	25.0%	5	41.7%	0	0.0%	4	66.7%	0	0.0%	1	16.7%	0	0.0%	1	20.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	28	7.9%
Vague term	0	0.0%	1	3.8%	1	5.6%	1	5.6%	0	0.0%	1	6.3%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	5	62.5%	0	0.0%	0	0.0%	0	0.0%	9	2.5%
Vague/unclear question	0	0.0%	3	11.5%	2	11.1%	0	0.0%	1	7.1%	3	18.8%	0	0.0%	2	8.7%	1	25.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.6%	1	20.0%	0	0.0%	1	33.3%	0	0.0%	3	3.1%	18	5.1%
Total (frequency, occurrence overall in %)	8	2.3%	26	7.3%	18	5.1%	18	5.1%	14	3.9%	16	4.5%	3	0.8%	23	6.5%	4	1.1%	12	3.4%	6	1.7%	6	1.7%	8	2.3%	6	1.7%	62	17.5%	5	1.4%	8	2.3%	3	0.8%	13	3.7%	96	27.0%	355	100.0%

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TABLE 5 Results of the evaluation questionnaire for neurologists and patients with Parkinson's disease of the phase 2a and 2b study.

Questions of the evaluation questionnaire	Answer options	Neurologists				PD patients			
		Phase 2a ($n = 11$)		Phase 2b ($n = 5$)		Phase 2a ($n = 21$)		Phase 2b ($n = 10$)	
		N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Do you consider the questionnaire relevant?	Yes	11	100.0	5	100.0	19	90.5	10	100.0
	No	0	0.0	0	0.0	2	9.5	0	0.0
Does the questionnaire help you to assess the current health status related to gastrointestinal symptoms of your PD patients?	Yes	11	100.0	5	100.0	16	76.2	9	90.0
	No	0	0.0	0	0.0	5	23.8	1	10.0
Do you find the questionnaire sufficiently comprehensive?	Yes	11	100.0	5	100.0	17	81.0	9	90.0
	No	0	0.0	0	0.0	4	19.0	0	0.0
Do you think the questionnaire is too long?	Yes	6	54.5	1	20.0	5	23.8	0	0.0
	No	5	45.5	4	80.0	16	76.2	10	100.0
Do you find the questions simple and clear to understand?	Yes	8	72.7	5	100.0	13	61.9	9	90.0
	No	3	27.3	0	0.0	8	38.1	1	10.0
Do you find questions strange / embarrassing?	Yes	3	27.3	N/A		3	14.3	0	0.0
	No	8	72.7	N/A		18	85.7	10	100.0
Do you find certain questions difficult to answer?	Yes	5	45.5	N/A		11	52.4	1	10.0
	No	6	54.5	N/A		10	47.6	9	90.0
Do you find the answer options suitable, clear and appropriate?	Yes	9	81.8	5	100.0	15	71.4	9	90.0
	No	2	18.2	0	0.0	6	28.6	0	0.0
Do you find the order of the questions sensible?	Yes	10	90.9	5	100.0	21	100	9	90.0
	No	1	9.1	0	0.0	0	0.0	0	0.0
Do you have any comments or general suggestions for improving the questionnaire?	Yes	6	54.5	N/A		5	23.8	3	30.0
	No	5	45.5	N/A		16	76.2	7	70.0
Do you find the instructions for conducting and evaluating the questionnaire suitable?	Yes	N/A		5	100.0	N/A		N/A	
	No	N/A		0		N/A		N/A	
Does the questionnaire help you in screening healthy controls for gastrointestinal symptoms?	Yes	10	90.9	5	100.0	N/A		N/A	
	No	1	9.1	0	0.0	N/A		N/A	
Do you find the evaluation of the questionnaire suitable?	Yes	6	54.5	5	100.0	N/A		N/A	
	No	5	45.5	0	0.0	N/A		N/A	
Do you find the assignment of the individual questions to the 8 different domains correct and sensible?	Yes	8	72.7	5	100.0	N/A		N/A	
	No	3	27.3	0	0.0	N/A		N/A	

PD, Parkinson's disease.

3.2.2.2. Psychometric properties

Internal consistency was high for all items of the pfGDQ (Cronbach's alpha value of 0.94). Further analyses were not performed as results of phase 2a were satisfying and the sample size of phase 2b was too small to result in any relevant new findings.

3.2.2.3. Evaluation of the pfGDQ by the evaluation questionnaire with corresponding adaptation

The results of the evaluation questionnaires of the pfGDQ as assessed by PwPD, HC, and neurologists are summarized in Table 5. The majority of the three groups found the pfGDQ easy to understand, not too long, comprehensive, and relevant. There were no major points of criticism in the evaluation questionnaires of all three groups. The simplified scoring of the pfGDQ was an improvement as evaluated by the neurologists and reflected in zero errors in the calculation of the pfGDQ scores by the neurologists. Therefore, only minor adjustments to the pfGDQ were necessary. A grammatical error in the answer options of question 2 (duration) was criticized and corrected. Questions 14 and 15 (consistency) contained a description of consistency in parentheses, which was criticized as being too restrictive. To mitigate this, "for example" was added. Question 18 (development) also contained definition text in parentheses, which was removed.

TABLE 6 Demographic, motor, and non-motor characteristics and prefinal GDQ score characteristics of patients with Parkinson's disease and healthy controls of the phase 2b study.

	PD patients ($n = 10$)	Healthy controls ($n = 10$)	*P* value
Age (years) (minimum-maximum)	67.80 ± 9.51 (47.00 to 82.00)	64.41 ± 14.30 (32.00 to 80.00)	0.631
Sex (m/f)	4/6	5/5	0.653
Disease duration (years) (minimum-maximum)	9.03 ± 5.80 (1.67 to 19.68)	N/A	N/A
Hoehn and Yahr stage*	2 (2.0 to 3.0)	0 (0.0 to 0.0)	**<0.001**
MoCA (minimum-maximum)	27.17 ± 2.79 (22.00 to 30.00)	N/A	N/A
pfGDQ total score (minimum-maximum)	17.10 ± 9.92 (1.00 to 32.00)	6.40 ± 4.20 (1.00 to 13.00)	**<0.05**
pfGDQ-frequency (minimum-maximum)	0.70 ± 0.48 (0.00 to 1.00)	0.00 ± 0.00 (0.00 to 0.00)	**<0.01**
pfGDQ-duration (minimum-maximum)	1.40 ± 1.07 (0.00 to 3.00)	0.20 ± 0.42 (0.00 to 1.00)	**<0.05**
pfGDQ-severity (minimum-maximum)	4.40 ± 2.84 (1.00 to 9.00)	1.50 ± 1.08 (0.00 to 3.00)	**<0.05**
pfGDQ-consistency (minimum-maximum)	3.70 ± 2.36 (0.00 to 8.00)	1.80 ± 1.69 (0.00 to 4.00)	0.054
pfGDQ-assistance (minimum-maximum)	1.00 ± 1.15 (0.00 to 3.00)	0.00 ± 0.00 (0.00 to 0.00)	**<0.01**
pfGDQ-pain (minimum-maximum)	4.10 ± 3.00 (0.00 to 8.00)	2.20 ± 1.69 (0.00 to 6.00)	0.135
pfGDQ-HRQoL (minimum-maximum)	1.80 ± 1.62 (0.00 to 4.00)	0.70 ± 1.06 (0.00 to 3.00)	0.278
pfGDQ-development (minimum-maximum)	−1.00 ± 3.16 (-5.00 to 5.00)	0.00 ± 0.00 (0.00 to 0.00)	**<0.05**
pfGDQ-completion time (min)	7.40 ± 3.84	3.38 ± 0.98	**<0.05**

Data are presented as mean ± SD or *median (25^{th}-75^{th} percentiles). Differences between groups were tested using the Mann–Whitney U-test or Pearson chi-square where appropriate. PD, Parkinson's disease; pfGDQ, prefinal Gut Dysmotility Questionnaire; MoCA, Montreal Cognitive Assessment; HRQoL, Quality of Life. The *p*-values are bold if they are significant (<0.05).

The phase 2b study resulted in the adaptation of the pfGDQ to the final GDQ. The final GDQ is a self-completed questionnaire consisting of 18 multiple-choice questions and takes approximately 4 min to complete (Figure 3, print version of the GDQ in Supplementary Figure 1). It covers eight domains (Table 7). The total score of the final GDQ results from the sum of the questions 1 to 17; each scored from 0 to 3 points from left to right in the respective answer options (Figure 4). The total score of the final GDQ accounts from 0 to a maximum of 51 points with higher scores indicating more disturbed gastrointestinal motility and, in particular, constipation. Question 18 is used to monitor the development of constipation and is not included in the total score. If there is a worsening of constipation, the score is increasingly negative, and if constipation improves, the score is increasingly positive with a maximum of 5 points, respectively; no change is rated as zero.

4. Discussion

We describe the development and cognitive pretesting and provide clinimetric attributes of the novel self-completed Gut Dysmotility Questionnaire (GDQ) as a quick and comprehensive tool to screen for and monitor gastrointestinal dysmotility of the lower GIT with a focus on constipation in PwPD.

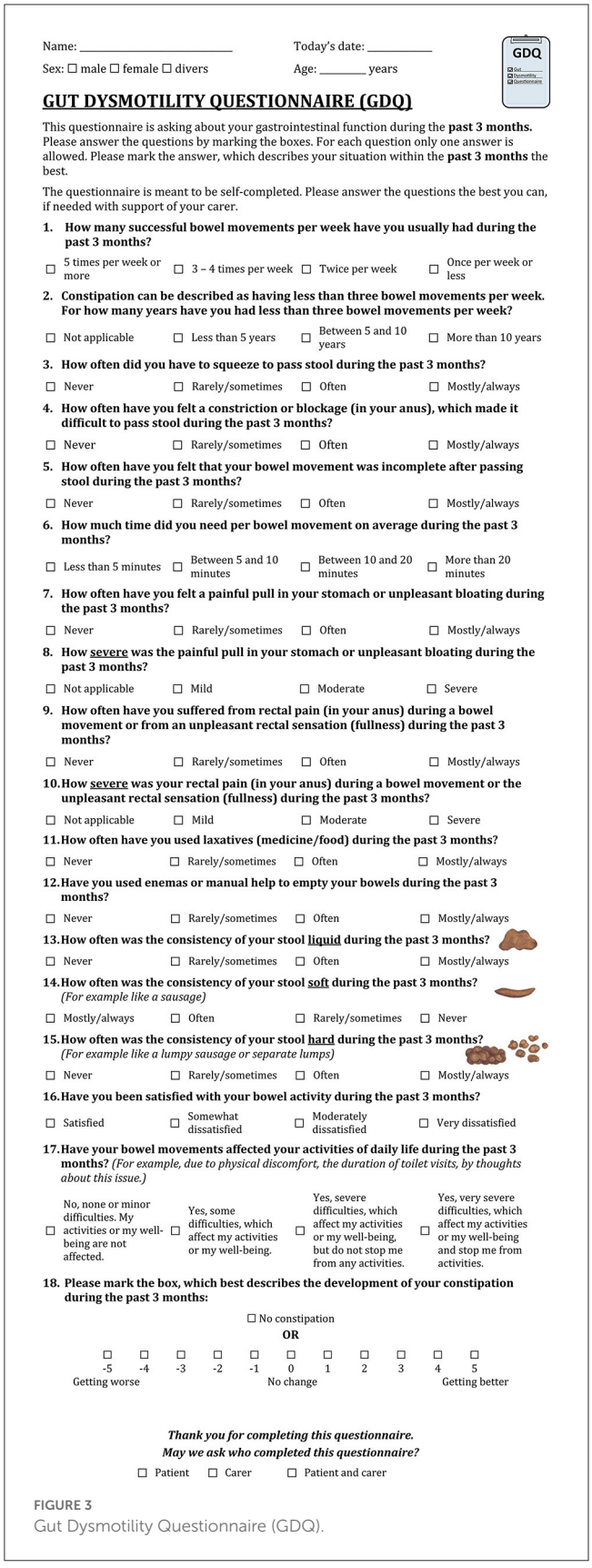
In phase 1, we revealed a lack of symptom-specific (gastrointestinal motility) and disease-specific (PD) validated instruments by a systematic literature review. Instruments such as the NMSQuest (12) and the NMSS (15) that are validated for use in patients with PD, assess several NMS including a domain-entitled gastrointestinal tract with eight and three questions, respectively, asking for dribbling of saliva, dysphagia, and constipation. These instruments aim to assess if there is an involvement of the gastrointestinal tract or not. In contrast, the SCOPA-AUT (16) obtains more detailed information about the whole GIT and autonomic symptoms. In addition, there is the GIDS-PD, which has also been newly developed and validated in PD to assess gastrointestinal dysfunction including the entire GIT (36). However, there is no questionnaire, which focuses on the lower GIT and covers symptoms of dysmotility and constipation.

The second issue we revealed in phase 1 was a wide range of diverse definitions of constipation as also identified in previous studies (37). Therefore, we applied the Rome IV criteria, the gold standard for gastroenterologists, in defining criteria for assessing gastrointestinal disorders as well as for diagnosing constipation (38).

Moreover, the period to be covered by the questionnaire was challenging to define. It should not exceed the recall period but also be unaffected by short-term influencing factors such as the consumption of specific food or infections. The final consensus was 3 months, also taking into account international expert consortia and the Rome IV criteria (38).

Potential questions and associated domains were identified in the literature review, then compiled, and discussed in repetitive national and international expert consortia involving different disciplines. The technique of questioning, the wording, and the type of response options were also discussed. We decided to use four-item response options in the form of multiple-choice answers for all questions, except for the domain consistency and development, for which we used a table and a visual analog scale, respectively.

Phase 1 resulted in the preliminary GDQ. A limitation of phase 1 was that not all critiques could be included in the



Name: _____ Today's date: _____

Sex: ☐ male ☐ female ☐ divers Age: _____ years

GDQ

GUT DYSMOTILITY QUESTIONNAIRE (GDQ)

This questionnaire is asking about your gastrointestinal function during the **past 3 months.** Please answer the questions by marking the boxes. For each question only one answer is allowed. Please mark the answer, which describes your situation within the **past 3 months** the best.

The questionnaire is meant to be self-completed. Please answer the questions the best you can, if needed with support of your carer.

1. How many successful bowel movements per week have you usually had during the past 3 months?

☐ 5 times per week or more ☐ 3 – 4 times per week ☐ Twice per week ☐ Once per week or less

2. Constipation can be described as having less than three bowel movements per week. For how many years have you had less than three bowel movements per week?

☐ Not applicable ☐ Less than 5 years ☐ Between 5 and 10 years ☐ More than 10 years

3. How often did you have to squeeze to pass stool during the past 3 months?

☐ Never ☐ Rarely/sometimes ☐ Often ☐ Mostly/always

4. How often have you felt a constriction or blockage (in your anus), which made it difficult to pass stool during the past 3 months?

☐ Never ☐ Rarely/sometimes ☐ Often ☐ Mostly/always

5. How often have you felt that your bowel movement was incomplete after passing stool during the past 3 months?

☐ Never ☐ Rarely/sometimes ☐ Often ☐ Mostly/always

6. How much time did you need per bowel movement on average during the past 3 months?

☐ Less than 5 minutes ☐ Between 5 and 10 minutes ☐ Between 10 and 20 minutes ☐ More than 20 minutes

7. How often have you felt a painful pull in your stomach or unpleasant bloating during the past 3 months?

☐ Never ☐ Rarely/sometimes ☐ Often ☐ Mostly/always

8. How severe was the painful pull in your stomach or unpleasant bloating during the past 3 months?

☐ Not applicable ☐ Mild ☐ Moderate ☐ Severe

9. How often have you suffered from rectal pain (in your anus) during a bowel movement or from an unpleasant rectal sensation (fullness) during the past 3 months?

☐ Never ☐ Rarely/sometimes ☐ Often ☐ Mostly/always

10. How severe was your rectal pain (in your anus) during a bowel movement or the unpleasant rectal sensation (fullness) during the past 3 months?

☐ Not applicable ☐ Mild ☐ Moderate ☐ Severe

11. How often have you used laxatives (medicine/food) during the past 3 months?

☐ Never ☐ Rarely/sometimes ☐ Often ☐ Mostly/always

12. Have you used enemas or manual help to empty your bowels during the past 3 months?

☐ Never ☐ Rarely/sometimes ☐ Often ☐ Mostly/always

13. How often was the consistency of your stool liquid during the past 3 months?

☐ Never ☐ Rarely/sometimes ☐ Often ☐ Mostly/always

14. How often was the consistency of your stool soft during the past 3 months? *(For example like a sausage)*

☐ Mostly/always ☐ Often ☐ Rarely/sometimes ☐ Never

15. How often was the consistency of your stool hard during the past 3 months? *(For example like a lumpy sausage or separate lumps)*

☐ Never ☐ Rarely/sometimes ☐ Often ☐ Mostly/always

16. Have you been satisfied with your bowel activity during the past 3 months?

☐ Satisfied ☐ Somewhat dissatisfied ☐ Moderately dissatisfied ☐ Very dissatisfied

17. Have your bowel movements affected your activities of daily life during the past 3 months? *(For example, due to physical discomfort, the duration of toilet visits, by thoughts about this issue.)*

☐ No, none or minor difficulties. My activities or my well-being are not affected. ☐ Yes, some difficulties, which affect my activities or my well-being. ☐ Yes, severe difficulties, which affect my activities or my well-being, but do not stop me from any activities. ☐ Yes, very severe difficulties, which affect my activities or my well-being and stop me from activities.

18. Please mark the box, which best describes the development of your constipation during the past 3 months:

☐ No constipation

OR

☐ -5 ☐ -4 ☐ -3 ☐ -2 ☐ -1 ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Getting worse — No change — Getting better

Thank you for completing this questionnaire.

May we ask who completed this questionnaire?

☐ Patient ☐ Carer ☐ Patient and carer

FIGURE 3
Gut Dysmotility Questionnaire (GDQ).

preliminary questionnaire as these would have been inappropriate for everyday clinical use (e.g., free text answers), would have greatly lengthened the questionnaire (e.g., assessment of co-morbidities and influencing factors on the GIT such as habits and medical therapy), or was believed to have arisen from a feeling of shame about some questions.

TABLE 7 Domains of the final GDQ with corresponding questions.

GDQ Domain	Question number
Frequency	1
Duration	2, 6
Severity	3, 4, 5
Pain	7, 8, 9, 10
Assistance	11, 12
Consistency	13, 14, 15
Quality of life	16, 17
Development	18

The gold standard for developing qualitative questionnaires is cognitive pretests, which we conducted in phase 2 (30). The cognitive pretest of the pGDQ combined quantitative and qualitative methods including interviews and evaluation questionnaires as this has been proven to be useful and effective for a new questionnaire. Based on similar studies on testing questionnaires and referring to cost-benefit considerations in the published literature, an average of 20 people per cognitive pretest is recommended due to the high volume of collected data per individual (30). A statistical case number estimation is not possible when performing cognitive pretests. We included 21 PwPD and 30 age- and sex-matched HC in phase 2a. The cognitive pretests led to changes in the selection of questions, the technique of questioning and their structure, the kind and structure of answer options, as well as the wording. Significantly more and precise criticisms were collected in the oral interviews, especially with the method of thinking aloud, than in the evaluation questionnaires (355 vs. 72). This was accounted by a greater willingness of participants to declare criticisms orally in a conversation than in written form. In addition, in PwPD, writing can be restricted by motor symptoms. This is an important finding and shows the necessity of guided interviews in scale development even though this means a considerably higher time commitment. In our experience, interviews could last more than 3 h, particularly with advanced PwPD. In contrast, the evaluation questionnaires of PwPD and HC provided valuable feedback about the improvements after adjusting the questionnaire to the results of phase 2a.

A major criticism was expressed by PwPD and HC in relation to questions, which included sub-questions and the need to skip questions dependent on the previous answer. Furthermore, including a variety of response options such as multiple-choice, scales, and tables proved to be impractical, error-prone, and demotivating for the participants. In particular, question 12 about stool consistency, which was designed as a table, was split into individual multiple-choice questions to achieve a more continuous method of collection. Question 16 about the development of constipation, which was recorded as a scale, was adapted with clear boxes to tick including numeric values and an additional option

Gut Dysmotility Questionnaire (GDQ)

Instructions for administration and evaluation

The GDQ is a quick tool for screening and monitoring of gastrointestinal symptoms in Parkinson's disease.

This questionnaire shall be completed by the patient which takes about 5 to 10 minutes. The total score of the GDQ is derived from the questions 1 to 17 by addition of the single scores and ranges from 0 to a maximum of 51 points. High scores indicate worse gastrointestinal motility and especially constipation. Question 18 serves to monitor the development of constipation and is not included in the total score.

The following 8 domains are covered:

- *Frequency: Question 1*
- *Duration: Question 2, 6*
- *Severity: Question 3, 4, 5*
- *Pain: Question 7, 8, 9, 10*
- *Assistance: Question 11, 12*
- *Consistency: Question 13, 14, 15*
- *Satisfaction/quality of life: Question 16, 17*
- *Development: Question 18*

Evaluation of the individual questions:

The questions 1 to 17 are always scored in the correspondent answer options from left to right in ascending order from 0 to 3 points.

1. How many successful bowel movements per week have you usually had during the past 3 months?

☐ 5 times per week or more	☐ 3 – 4 times per week	☐ Twice per week	☐ Once per week or less
= 0 Points	**= 1 Point**	**= 2 Points**	**= 3 Points**

The question 18 is not included in the total score, but serves to check the development of constipation.

18. Please mark the box, which best describes the development of your constipation during the past 3 months:

☐ No constipation

OR

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
-5	-4	-3	-2	-1	0	1	2	3	4	5

Getting worse — No change — Getting better

FIGURE 4
Instructions for administration and evaluation of the Gut Dysmotility Questionnaire (GDQ).

to record, i.e., "no constipation." It was also removed from the overall rating and is designed to stand alone for the evaluation of the development of constipation intended to serve as a progress indicator for the neurologists in addition to the total score. By equalization of the design of questions as well as answer options to a 4-point multiple-choice response, ranging from no symptoms

(0 points) to the worst symptoms (3 points) with the zero-point answer always being the first answer option, we could minimize confusion, and it helped to streamline the answering process as confirmed by PwPD and HC in phase 2b. Hereby, the calculation of the total score of the questionnaire improved. In phase 2a, we revealed a relevant number of total scores that were incorrectly calculated, whereas in phase 2b, all total scores were correct. This can also be referred to the scoring guide which was greatly simplified and proved to be quick to learn, easy to implement, and less prone to errors. The streamlining of the questionnaire is also objectively reflected in the required median completion time, which was reduced from 6 to 4 min. In addition, PwPD, HC, and neurologists reported improvements in the evaluation questionnaires of phase 2b in comparison to 2a in relation to relevance, comprehensiveness, length, and comprehensibility of questions and answers of the pfGDQ in comparison to the pGDQ. Sudman and Bradburn (39) said, "Even after years of experience, no expert can write a perfect questionnaire."

The data quality of phase 2 was very satisfactory with all included participants being fully computable. Reliable responses of the self-completed questionnaires were secured by regular results in the cognitive assessment. The study group of PwPD can be evaluated as a representative group for PD as PwPD throughout all disease stages from newly diagnosed drug-naive PwPD to advanced PwPD with disease durations up to 21 years, and high LEDD were investigated (Tables 1, 4, 6). Furthermore, PwPD showed on average an intermediate motor burden based on the H&Y stage and were evaluated as moderately ill in the CGI-S (Table 1). PwPD presented with more NMS and worse HRQoL in comparison to HC as expected (12, 40). Gastrointestinal dysmotility and constipation were also significantly more common in PwPD than in HC. This was found in the established validated questionnaires and scales as well as in the pGDQ (Tables 1, 2, 4). All pGDQ domains except the domain development showed a high association with the pGDQ total score as well as the pGDQ total score with the NMSQuest total score as a measure of general NMS burden and the SCOPA-AUT total score as a measure of gastrointestinal and autonomic symptoms (Table 3). Furthermore, the pGDQ total score and its domains were tested against corresponding individual questions of these validated instruments (Table 3). We found significant correlations primarily on a moderate and high level. These findings provide good construct validity of the pGDQ. We also used the PDQ-8, a validated measure of HRQoL in PD, as a further measure for convergent validity. The similar content of the pGDQ domains with the independent corresponding measures explains the high correlations but also reflects that these symptoms can be assessed in a simpler and brief way, which is relevant for routine assessments in clinics. Constipation is a known symptom of depression, independent of PD, so that a significant correlation of the pGDQ and the BDI in PwPD and HC on a lower level was expected (41). This was indeed the case with a correlation on a moderate level further supporting the discriminant validity of the pGDQ. Furthermore, the observed strong correlation between memory and constipation has also been discussed in the literature (42).

In the pGDQ and pfGDQ, a high-floor effect was found for some questions and domains. This was expected since not every participant exhibited all the characteristics of gut dysmotility so that this high-floor effect was particularly pronounced in the control group. However, the number of study participants is relatively small for this kind of analysis, so that in the validation study with a larger sample size, it has to be clarified whether these reflect sample characteristics or scale properties. There was no relevant ceiling effect. For a phase 2 study, these findings indicate a suitable acceptability of the questionnaire.

In the clinimetric statistics of the pGDQ questions containing sub-questions, the domains that included these questions (mainly the domain pain) as well as the domain consistency and development with different types of response options stood out negatively. This was supported by the results of the interviews and evaluation questionnaires. Subsequently, main adjustments were performed in relation to these questions and domains.

The pGDQ and the pfGDQ demonstrated excellent internal consistency (Cronbach's alpha value up to 0.92 and 0.94).

Limitations of the phase 2 studies were mainly related to the performance of specific analyses such as the evaluation of floor/ceiling effects as discussed above, the evaluation of temporal reliability by a retest, and the definition of cutoff scores to discriminate between participants with and without constipation. This is linked to the small number of participants in cognitive pretest studies in comparison to validation studies. However, the number of participants in this cognitive pretest study was higher for PwPD and HC than recommended (30).

Phase 2 resulted in the final GDQ that enquires in 18 questions with detailed information about gastrointestinal dysmotility with a focus on constipation during the past 3 months and covers eight domains including the effect of bowel movements on HRQoL and the development of constipation (Figure 3; Table 7). The GDQ showed both high acceptance and effectiveness in assessing gastrointestinal dysmotility in PwPD and HC as well as sufficient reliability and construct validity. The self-completed GDQ can be used as a comprehensive, simple, and quick instrument for screening and monitoring gastrointestinal dysmotility in PwPD and HC. Furthermore, the length of time required for completion by the patients as well as evaluation by the physicians is a few minutes so that the GDQ can easily be integrated into clinical practice (Figure 4). How valuable the GDQ is for measuring changes in gastrointestinal dysmotility after treatment or in the course of PD needs to be assessed in further studies. Even though we performed an intensive cognitive pretesting to create the GDQ, an international validation study with a higher number of PwPD and HC including a retest to investigate temporal reliability is planned.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Technische Universität Dresden, Dresden, Germany.

The patients/participants provided their written informed consent to participate in this study.

Author contributions

VR and LK conceptualized the project, had a major role in the study execution of phase 1 and 2, analyzed data, and wrote the manuscript. LB analyzed data. KRC, RS, JH, SB, ZK, VL, BF, HR, AR, and RU had a major role in the study execution of phase 1. RU, AF, BF, and HR had a major role in the study execution of phase 2. BF, HR, AR, and AS performed the cross-cultural adaptation. All authors critically revised the manuscript for intellectual content and approved the final draft.

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Conflict of interest

RU has received a grant from the Stiftung Hochschulmedizin (medical university foundation) Dresden outside the present study. He was or is an investigator in pharmaceutical studies sponsored by Amylyx, Bial, Ferrer, Orion Pharma, and UCB outside the present study. AR has received salary support from the National Institute of Health Research (NIHR) Clinical Research Network (CRN) South London, Guy's Hospital, Great Maze Pond, London SE1 9RT, UK and the International Parkinson and Movement Disorder Society (MDS), 555 East Wells Street, Suite 1100, Milwaukee, WI 53202-3823 USA outside the present study. VL reports honoraria for sponsored symposium from UCB, Bial, Invisio, Profile, AbbVie, and Britannia Pharmaceuticals, outside the submitted work. AS has received funding from the Deutsche Forschungsgemeinschaft (German Research Association) and the Helmholtz-Association outside the present study. He has received honoraria for presentations/advisory boards/consultations from Global Kinetics Corporation (manufacturer of the PKG®), Desitin, Lobsor Pharmaceuticals, STADA, Bial, RG Gesellschaft, Zambon, NovoNordisk and AbbVie outside the present study. He has received royalties from Kohlhammer Verlag and Elsevier Press. He serves as an editorial board member of Stem Cells International. HR was acting on Advisory Boards, gave lectures and received research grants from Abbott, Abbvie, Bayer Health Care, Bial, Boehringer/Ingelheim, Brittania, Cephalon, Desitin, Eisai, GSK, Lundbeck, Medtronic, Merck-Serono, Novartis, Orion, Pfizer, TEVA, UCB Pharma, Valeant, and Zambon. BF reports no funding related to the conduct of this study. Outside of the submitted work, he reports grants from the German Research Foundation (DFG) and speaker honoraria from AbbVie, Stadapharm, Desitin, Zambon and Bial. LK reports habilitation funding for women from the Medical Faculty of the Technical University (TU) Dresden, Germany. Further, the development of the GDQ was supported by the university of excellence of TU Dresden, funded by the excellence strategy of the federal and state governments (Str1911_038) without any influence on the scientific content.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1149604/full#supplementary-material

References

1. Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. *Nat Rev Neurosci.* (2017) 18:435–50. doi: 10.1038/nrn.2017.62

2. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord.* (2015) 30:1591–601. doi: 10.1002/mds.26424

3. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol.* (2006) 5:525–35. doi: 10.1016/S1474-4422(06)70471-9

4. Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, et al. MDS research criteria for prodromal Parkinson's disease. *Mov Disord.* (2015) 30:1600–11. doi: 10.1002/mds.26431

5. Leta V, Raeder V, Ray Chaudhuri K. "Chapter Two - General approach to patients with autonomic dysfunction in Parkinson's disease,." In: Falup-Pecurariu C, editor. *Autonomic Dysfunction in Parkinson's Disease*. International Review of Movement Disorders. Academic Press (2021). p. 19–39. doi: 10.1016/bs.irmvd.2021.08.007

6. Schrag A, Horsfall L, Walters K, Noyce A, Petersen I. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. *Lancet Neurol.* (2015) 14:57–64. doi: 10.1016/S1474-4422(14)70287-X

7. Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol.* (2006) 5:235–45. doi: 10.1016/S1474-4422(06)70373-8

8. Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. *Curr Treat Options Neurol.* (2018) 20:54. doi: 10.1007/s11940-018-0539-9

9. Woitalla D, Kassubek J, Timmermann L, Lauterbach T, Berkels R, Grieger F, et al. Reduction of gastrointestinal symptoms in Parkinson's disease afteraswitch from oral therapy to rotigotine transdermal patch: anon-interventional prospective multicenter trial. *Park Relat Disord.* (2015) 21:199–204. doi: 10.1016/j.parkreldis.2014.11.024

10. Heetun ZS, Quigley EMM. Gastroparesis and Parkinson's disease: a systematic review. *Parkinsonism Relat Disord.* (2012) 18:433–40. doi: 10.1016/j.parkreldis.2011.12.004

11. Politis M, Wu K, Molloy S, Bain PG, Chaudhuri KR, Piccini P. Parkinson's disease symptoms: the patient's perspective. *Mov Disord.* (2010) 25:1646–51. doi: 10.1002/mds.23135

12. Chaudhuri KR, Martinez-Martin P, Schapira AHV, Stocchi F, Sethi K, Odin P, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. *Mov Disord.* (2006) 21:916–23. doi: 10.1002/mds.20844

13. Poewe W, Antonini A, Zijlmans JC, Burkhard PR, Vingerhoets F. Levodopa in the treatment of Parkinson's disease: an old drug still going strong. *Clin Interv Aging.* (2010) 5:229–38. doi: 10.2147/CIA.S6456

14. Rodriguez-Blazquez C, Schrag A, Rizos A, Chaudhuri KR, Martinez-Martin P, Weintraub D. Symptoms and non-motor fluctuations in Parkinson's disease using the MDS-NMS. *Mov Disord Clin Pract.* (2021) 8:231–9. doi: 10.1002/mdc3.13122

15. Chaudhuri KR, Martinez-Martin P, Brown RG, Sethi K, Stocchi F, Odin P, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study. *Mov Disord.* (2007) 22:1901–11. doi: 10.1002/mds.21596

16. Visser M, Marinus J, Stiggelbout AM, van Hilten JJ. Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT. *Mov Disord.* (2004) 19:1306–12. doi: 10.1002/mds.20153

17. Abbott RD, Ross GW, Petrovitch H, Tanner CM, Davis DG, Masaki KH, et al. Bowel movement frequency in late-life and incidental lewy bodies. *Mov Disord.* (2007) 22:1581–6. doi: 10.1002/mds.21560

18. Abbott RD, Petrovitch H, White LR, Masaki KH, Tanner CM, Curb JD, et al. Frequency of bowel movements and the future risk of Parkinson's disease. *Neurology.* (2001) 57:456–62. doi: 10.1212/WNL.57.3.456

19. Klingelhoefer L, Reichmann H. Pathogenesis of Parkinson disease - the gut-brain axis and environmental factors. *Nat Rev Neurol.* (2015) 11:625–36. doi: 10.1038/nrneurol.2015.197

20. Beach TG, Adler CH, Sue LI, Vedders L, Lue LF, White CL, et al. Multi-organ distribution of phosphorylated α-synuclein histopathology in subjects with lewy body disorders. *Acta Neuropathol.* (2010) 119:689–702. doi: 10.1007/s00401-010-0664-3

21. Stokholm MG, Danielsen EH, Hamilton-Dutoit SJ, Borghammer P. Pathological α-synuclein in gastrointestinal tissues from prodromal Parkinson disease patients. *Ann Neurol.* (2016) 79:940–9. doi: 10.1002/ana.24648

22. Braak H, Rüb U, Gai WP, Del Tredici K. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. *J Neural Transm.* (2003) 110:517–36. doi: 10.1007/s00702-002-0808-2

23. Horsager J, Andersen KB, Knudsen K, Skjærbæk C, Fedorova TD, Okkels N, et al. Brain-first versus body-first Parkinson's disease: a multimodal imaging case-control study. *Brain.* (2020) 143:3077–88. doi: 10.1093/brain/awaa238

24. Pan-Montojo F, Schwarz M, Winkler C, Arnhold M, O'Sullivan GA, Pal A, et al. Environmental toxins trigger PD-like progression via increased alpha-synuclein release from enteric neurons in mice. *Sci Rep.* (2012) 2:898. doi: 10.1038/srep00898

25. Gelpi E, Navarro-Otano J, Tolosa E, Gaig C, Compta Y, Rey MJ, et al. Multiple organ involvement by alpha-synuclein pathology in lewy body disorders. *Mov Disord.* (2014) 29:1010–8. doi: 10.1002/mds.25776

26. Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, et al. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disord.* (2009) 24:1641–9. doi: 10.1002/mds.22643

27. Evatt ML, Chaudhuri KR, Chou KL, Cubo E, Hinson V, Kompoliti K, et al. Dysautonomia rating scales in Parkinson's disease: sialorrhea, dysphagia, and constipation-Critique and recommendations by movement disorders task force on rating scales for Parkinson's disease. *Mov Disord.* (2009) 24:635–46. doi: 10.1002/mds.22260

28. Chaudhuri KR, Pal S, DiMarco A, Whately-Smith C, Bridgman K, Mathew R, et al. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* (2002) 73:629–35. doi: 10.1136/jnnp.73.6.629

29. Räder V, Chaudhuri KR, Batzu L, Leta V, Reichmann H, Falkenburger B, et al. Abstract No 1275. 24th International Virtual Congress of Parkinson's Disease and Movement Disorders. *Mov Disord.* (2020) 35:(Suppl. S1) S581.

30. Lenzner T, Neuert C, Otto W. *GESIS Survey Guidelines Kognitives Pretesting* (2015)

31. Martinez-Martin P, Schrag A, Weintraub D, Rizos A, Rodriguez-Blazquez C, Chaudhuri KR. Pilot study of the international parkinson and movement disorder society-sponsored non-motor rating scale (MDS-NMS). *Mov Disord Clin Pract.* (2019) 6:227–34. doi: 10.1002/mdc3.12728

32. Fisk JD, Brown MG, Sketris IS, Metz LM, Murray TJ, Stadnyk KJ, et al. A comparison of health utility measures for the evaluation of multiple sclerosis treatments. *J Neurol Neurosurg Psychiatry.* (2005) 76:58–63. doi: 10.1136/jnnp.2003.017897

33. Nunnally JC, Bernstein IH. *Psychometric Theory : Nunnally and Bernstein, 3rd edition*. New York, NY: McGraw-Hill (2008).

34. Willis GB. *Questionnaire Pretesting. SAGE Handb Surv Methodol.* (2016). p. 359–81. doi: 10.4135/9781473957893.n24

35. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. *Spine.* (2000) 25:3186–91. doi: 10.1097/00007632-200012150-00014

36. Camacho M, Greenland JC, Williams-Gray CH. The gastrointestinal dysfunction scale for Parkinson's disease. *Mov Disord.* (2021) 36:2358–66. doi: 10.1002/mds.28675

37. Knudsen K, Krogh K, Østergaard K, Borghammer P. Constipation in parkinson's disease: subjective symptoms, objective markers, and new perspectives. *Mov Disord.* (2017) 32:94–105. doi: 10.1002/mds.26866

38. Drossman DA, Hasler WL. Rome IV - Functional GI disorders: disorders of gut-brain interaction. *Gastroenterology.* (2016) 150:1257–61. doi: 10.1053/j.gastro.2016.03.035

39. Sudman S, Bradburn NM. *Asking Questions. A Practical Guide to Questionnaire Design*. San Francisco, CA: Jossey-Bass (1982).

40. Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. *Mov Disord.* (2011) 26:399–406. doi: 10.1002/mds.23462

41. Chang T-Y, Chen Y-H, Chang M-H, Lin C-H. Is there a close association of depression with either constipation or dysosmia in Parkinson's disease? *Sci Rep.* (2020) 10:15476. doi: 10.1038/s41598-020-72381-0

42. Leta V, Urso D, Batzu L, Weintraub D, Titova N, Aarsland D, et al. Constipation is associated with development of cognitive impairment in de novo Parkinson's disease: a longitudinal analysis of two international cohorts. *J Parkinsons Dis.* (2021) 11:1209–19. doi: 10.3233/JPD-212570

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The longitudinal progression of autonomic dysfunction in Parkinson's disease: A 7-year study

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Background: Autonomic dysfunction, including gastrointestinal, cardiovascular, and urinary dysfunction, is often present in early Parkinson's Disease (PD). However, the knowledge of the longitudinal progression of these symptoms, and the connection between different autonomic domains, is limited. Furthermore, the relationship between the presence of autonomic symptoms in early-stage PD and olfactory dysfunction, a possible marker of central nervous system involvement, has not been fully investigated.

Objectives: We aimed to investigate the occurrence and progression of autonomic dysfunction in recently diagnosed (< 2 years) untreated PD patients and determine any coexistence of symptoms in individual patients. We also investigated the relationship between autonomic symptoms, olfactory dysfunction, and motor impairment.

Methods: Data were obtained from the Parkinson's Progression Markers Initiative (PPMI) database. Autonomic dysfunction was measured using the Scales for Outcomes in Parkinson's Disease (SCOPA-AUT). Symptom frequency and mean scores over 7 years were determined. The simultaneous occurrence of different autonomic symptoms was also examined. Finally, the relationships between SCOPA-AUT scores, olfactory dysfunction, and motor impairment were investigated using the University of Pennsylvania Smell Identification Test (UPSIT) and the Movement Disorder Society—Unified Parkinson's Disease Rating Scale (MDS-UPDRS), respectively.

Results: Follow-up data were available for 7 years for 171 PD patients and for 5 years for 136 HCs. Mean SCOPA-AUT score increased significantly from baseline to the 7-year follow-up for each autonomic domain, except for female sexual dysfunction. Most patients reported three or more autonomic symptoms. Common clusters of symptoms were composed of combinations of gastrointestinal, urinary, thermoregulatory, and sexual dysfunction. At baseline, greater SCOPA-AUT total score was associated with lower UPSIT scores ($r = -0.209$, $p = 0.006$) and with greater total MDS-UDPRS III score ($r = 0.218$, $p = 0.004$).

Conclusions: Autonomic dysfunction, often with coexistence of autonomic manifestations, is common in early PD and progressively worsens over the first

7 years of disease, suggesting that these symptoms should be addressed with appropriate treatments early in the disease. The association between greater autonomic dysfunction and greater olfactory impairment, coupled with the association with more severe motor scores at baseline, indicates that patients who show more severe autonomic dysfunction could also have more severe involvement of the central nervous system at the time of diagnosis.

KEYWORDS

autonomic dysfunction, SCOPA-AUT, PPMI (Parkinson's progression markers initiative), olfactory dysfunction, Parkinson's disease

Introduction

Autonomic dysfunction is common in Parkinson's disease (PD) and poses a significant impact on patients' quality of life (1). It is increasingly recognized that autonomic symptoms, manifesting as gastrointestinal, urinary, cardiovascular, thermoregulatory, and pupillomotor dysfunction, can be present in the early stages of PD. A previous study by Stanković and colleagues found that 71% of early PD patients, classified as Hoehn and Yahr (H&Y) stage I, reported having autonomic symptoms (2). Autonomic dysfunction may also be a prodromal manifestation of PD, with early autonomic features predicting a faster rate of PD progression (3–5). Furthermore, pathological studies have shown the presence of alpha-synuclein deposition within the nuclei of autonomic plexi, which has been found to correlate with accelerated cell death in the autonomic nervous system (6, 7). However, the knowledge of how autonomic dysfunction progresses and the degree to which different autonomic symptoms cluster together, is limited (2).

Olfactory dysfunction is also a defining PD feature, and is often a prodromal manifestation (8, 9). Approximately 10% of subjects with idiopathic loss of smell receive a diagnosis of PD within 10 years (10). Olfactory dysfunction is associated with male sex and non-motor manifestations such as apathy (11) and cognitive dysfunction (12). However, the relationship between olfactory and autonomic dysfunction is unclear, and its investigation may be worthwhile in light of the proposed "brain-first" and "body-first" models of disease progression. Indeed, this hypothesis proposes two main routes of PD pathological progression, one following an ascending route originating from peripheral organs, e.g., the gut, and one following a descending route originating from the olfactory-amygdala complex (13, 14).

Therefore, in this study we investigated: (i) the longitudinal progression and coexistence of autonomic symptoms in early PD over a period of seven years and compared it to a cohort of healthy controls; (ii) the presence of olfactory dysfunction; (iii) the association between autonomic dysfunction, olfactory impairment, and motor manifestations in early PD (13).

Methods

Study population

PD patients and healthy controls (HC) were retrieved from the Parkinson's Progression Markers Initiative (PPMI) database. PPMI is an ongoing, multicentre clinical study investigating the longitudinal progression of PD. The study includes treatment-naïve PD subjects, with a disease duration of 2 years or less. Loss of dopaminergic neurons in the nigrostriatal tracts is confirmed in all subjects using dopamine transporter - single photon emission computed tomography (DaT-SPECT). HCs were all ≥30 years old and had no first-degree family members diagnosed with PD. HC diagnosed with PD at any time-point over the course of the study were excluded from analysis. A complete list of inclusion and exclusion criteria for the study can be found in the PPMI study protocol (https://www.ppmi-info.org/sites/default/files/docs/archives/Amendment-12.pdf). All participating PPMI sites received approval from an ethical standards committee prior to study initiation and written informed consent for research was obtained from all participants in the study.

Data for the analyses in this paper were accessed on the 2nd September 2022.

PD and HC subjects with seven years of follow-up data available were identified from the database. Participants who had missing data throughout the observation period were excluded from the analysis.

We identified 171 PD participants with complete datasets for 7-year analysis. In the HC group, 196 participants with baseline SCOPA-AUT data were available. Only a small number of participants had available data at year 7 ($n = 23$) or year 6 ($n = 101$), whereas 136 had available data for 5 years of follow-up. Therefore, we included only 5 years of follow-up data in the analysis of the HC population.

Clinical assessment and demographics

Autonomic dysfunction was evaluated using the self-completed SCOPA-AUT questionnaire (15), assessing the following six autonomic domains, using their corresponding subscales: gastrointestinal (questions 1–7), urinary (questions 8–13), cardiovascular (questions 14–16), thermoregulatory (questions 17–18 and 20–21), pupillomotor (question 19) and sexual (questions 22–23 for males, and 24–25 for females). Total scores were calculated from the sum of all responses from questions 1–23 for male participants, and 1–21 and 24–25 for female participants. Each item score ranges from 0 to 3, based on the occurrence of specific autonomic symptoms; 0 (never), 1 (sometimes), 2 (regularly), and 3 (often).

To assess the frequency of autonomic symptoms, the percentage of subjects reporting a score > 0 for each item,

representing individuals experiencing autonomic symptoms sometimes, regularly, and often, was calculated at each follow-up. The percentage of subjects reporting symptoms in a single autonomic domain (e.g., cardiovascular domain, questions 14–16) was determined by identifying subjects with a total domain score > 0.

The coexistence of autonomic symptoms in two or more domains was determined by analyzing the percentage of subjects reporting symptoms (SCOPA-AUT domain score > 0) in multiple domains. The percentage of subjects scoring above zero in one, two, three, four, five and all six autonomic domains, was determined. The data was also analyzed to assess whether there was any clustering of autonomic symptoms across PD participants. A cluster was defined by ≥ 10 individuals reporting a specific combination of symptoms.

Olfactory dysfunction was assessed with the University of Pennsylvania Smell Identification Test (UPSIT), and motor impairment with the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Published normative UPSIT scores were used to define normosmia, hyposmia, and anosmia (16).

Statistical analysis

Baseline demographics and general clinical characteristics of PD patients and HCs were compared using the Chi-square test for categorical variables (e.g., gender) and Mann-Whitney test for continuous variables. To investigate the progression and differences between PD and HC in SCOPA-AUT total scores and sub-scores (gastrointestinal, urinary, cardiovascular, pupillomotor, thermoregulatory, male/female sexual dysfunction), two-way repeated measures ANOVA models were implemented for each dependent variable, and a grouping variable (HC or PD) was used as a factor. For each dependent variable, the Greenhouse-Geisser corrected overall model (group*assessment) was considered to evaluate the significance of the model. Univariate tests and Bonferroni-corrected pairwise comparisons based on estimated marginal means (EMMs) were used to test differences between PD and HC scores at each assessment. Multivariate tests and Bonferroni-corrected pairwise comparisons based on EMMs were used to test scores' differences between assessments in each group. Since data from year 5 to year 7 was present for PD participants only, one-way repeated measures ANOVA models were carried out to investigate the progression of SCOPA total score and sub-scores in such timeframe. To investigate statistical differences in the proportions of PD and HC reporting symptoms at baseline and each annual follow-up, Chi-square tests with Bonferroni p-value correction for multiple comparisons were used. To investigate the relationship between UPSIT, SCOPA-AUT and MDS-UPDRS III scores, Pearson correlation was carried out in PD subjects at baseline.

Statistical analysis was performed using SPSS Version 28 (IBM SPSS). Statistical significance level for hypothesis testing was set at $p < 0.05$, two-sided.

Results

Baseline demographics and clinical characteristics

Gender proportions ($\chi 2 = 2.823$, $p = 0.093$) and age ($U = 11705.5$, $p = 0.920$) were not significantly different between PD and HC (Table 1). At baseline, PD patients had a significantly higher mean SCOPA-AUT total score and sub-scores for gastrointestinal, urinary, cardiovascular, and male sexual domains compared to HCs (all Bonferroni-corrected $p_s < 0.01$, from the repeated measures ANOVAs comparing baseline scores; Figure 1). Mean scores within the pupillomotor, thermoregulatory, and female-specific sexual domains, however, were not significantly different between patients and HCs at baseline.

Longitudinal progression of autonomic symptoms over 7 years

In PD, there was a significant increase in mean total SCOPA-AUT score from baseline to 5 years (baseline: EMM [SE]: 9.00 [0.37]; 5 years: EMM [SE] 14.74 [0.65]; $F = 25.050$, $p < 0.001$) and from 5 to 7 years (7 years: EMM [SE] 17.13 [0.74]; $F = 9.294$, $p < 0.001$). No significant increase was shown in HC (baseline: EMM [SE]: 5.81 [0.41]; 5 years: EMM [SE] 7.27 [0.73]; $F = 1.667$, $p = 0.142$). Figure 1 shows SCOPA-AUT total and sub-domain scores in PD and HC over the first 5 years after baseline.

In PD patients, SCOPA-AUT sub-scores significantly increased from baseline to the 5th year of follow-up in the gastrointestinal ($F = 25.329$, $p < 0.001$), urinary ($F = 7.837$, $p < 0.001$), cardiovascular ($F = 7.540$, $p < 0.001$), pupillomotor ($F = 4.553$, $p < 0.001$), thermoregulatory ($F=5.232$, $p < 0.001$), and male sexual dysfunction ($F = 7.924$, $p < 0.001$) domains. No change in the female sexual dysfunction domain score was found ($F = 0.856$, $p = 0.511$). No significant changes were found in sub-domains in HC.

At the 5 years follow up, SCOPA-AUT total score and all domains sub-scores, except female dysfunction, were significantly higher in PD compared to HC (all Bonferroni-corrected $ps<0.05$; Figure 1). Thermoregulatory and pupillomotor dysfunction sub-scores, which were not different between PD and HC at baseline, became significantly different at first-year follow-up, and this difference remained significant thereafter (all Bonferroni-corrected $p_s \leq 0.001$).

Symptom frequencies

Urinary dysfunction was the most frequently reported symptom at baseline and during follow up for both patients and controls (Table 2). In controls, the most frequently reported urinary symptoms were increased frequency (69.9%) and nocturia (81.6%). The second-most common symptom domain in PD was gastrointestinal dysfunction. The comparison between groups showed that the percentage of PD subjects reporting gastrointestinal and cardiovascular symptoms were significantly greater than controls ($p < 0.0001$) at every time-point. Higher

TABLE 1 Baseline clinical and demographic features of Parkinson's Disease (PD) and healthy participants (HC).

	Baseline information of PD subjects $N = 171$	Baseline information of HCs $N = 136$	p-value
Gender Number, Female/male (%)	51/120 (29.8/70.2)	53/83 (39.0/61.0)	0.093[a]
Age, years, mean (SD)	60.55 (9.81)	60.22 (11.27)	0.920[b]
Disease duration at enrolment, months, mean (SD)	6.62 (6.63)	-	-
Reported symptoms duration at enrolment, months, mean (SD)	49.28 (20.27)	-	-
MDS-UPDRS part III, mean (SD)	19.37 (8.56)	-	-
Hoehn and Yahr, median (range)	1 (1–3)	-	-
SCOPA-AUT scores			
Gastrointestinal	1.88 (± 1.95)	0.68 (± 0.98)	**< 0.001**[c]
Urinary	4.16 (± 2.75)	3.07 (± 2.28)	**< 0.001**[c]
Cardiovascular	0.41 (± 0.67)	0.15 (± 0.39)	**< 0.001**[c]
Pupillomotor	0.40 (± 0.68)	0.29 (± 0.53)	0.102[c]
Thermoregulatory	1.06 (± 1.24)	0.93 (± 1.15)	0.366[c]
Sexual - male	0.74 (± 1.01)	0.36 (± 0.94)	**0.007**[c]
Sexual - female	0.35 (± 1.35)	0.32 (± 0.81)	0.787[c]
TOTAL	9.00 (± 5.42)	5.80 (± 3.81)	< 0.001[c]

([a]) chi-square test; ([b]) Mann-Whitney U test; ([c]) pairwise comparisons from repeated measures ANOVA models, Bonferroni-corrected p-values; MDS-UPDRS, Movement Disorders Society—Unified Parkinson's Disease Rating Scale; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease-Autonomic Dysfunction; SD, Standard Deviation.

frequencies of symptoms were also identified in the PD group compared to the HC group, in the pupillomotor, thermoregulatory, and sexual domains, but these were not consistent over time. No differences were identified between the two groups in urinary dysfunction and female sexual dysfunction frequencies.

Coexistence of autonomic symptoms

In the PD group, 2% reported no autonomic symptoms at baseline. Six percent of patients reported autonomic symptoms in one domain, 21% in two, 22% in three, 28% in four, 17% in five and 4% in all six domains (Figure 2). At 5-year follow-up, 1% of patients reported no autonomic symptoms, with 3% reporting autonomic symptoms in one domain, 11% reporting symptoms in two domains, 19% in three domains, 29% in four domains, 24% in five domains and 13% in all six domains. Finally, at seven years, all patients reported symptoms in at least one autonomic domain, with 1% experiencing symptoms in one domain only, 11% in two, 14% in three, 26% in four, 37% in five and 11% in all six.

At baseline, eight clusters (i.e., ≥ 10 PD participants reporting a specific combination of symptoms) with common combinations of symptoms were identified: six of them contained gastrointestinal and urinary symptoms among others, while two of them included urinary symptoms only and urinary and sexual symptoms together. Interestingly, at 5 and 7 years, five clusters were overlapping with baseline (Figure 3). Ten clusters of symptoms were present at five years and nine at 7 years, and all of them included the gastrointestinal and urinary domains. Furthermore, at 5 and 7 years' follow up, a cluster of participants with symptoms in all domains was present.

Association between autonomic, olfactory, and motor function

At baseline, 14 PD participants were normosmic, 95 hyposmic and 62 anosmic according to UPSIT normative scores. No differences were found between participants with a normal vs. abnormal score, or between hyposmic vs. anosmic participants, in baseline SCOPA-AUT total score, MDS-UPDRS part III total score and bradykinesia, rigidity and tremor sub-scores (Mann-Whitney U test, all $p_s > 0.05$).

Participants with baseline SCOPA-AUT total scores in the upper half of the scores' distribution (baseline SCOPA-AUT score median = 8) had significantly higher baseline MDS-UPDRS III total score compared to those in the lower half (median [interquartile range]: 22 [9] vs. 16.5 [9]; $U = 2598.5$, $p = 0.002$). Conversely, no significant differences were present in bradykinesia, rigidity, or tremor sub-scores between participants with SCOPA-AUT scores in the upper half of the distribution compared to those in the lower half.

There was a significant inverse association between UPSIT and SCOPA-AUT total scores in PD ($r = -0.209$, $p = 0.006$,

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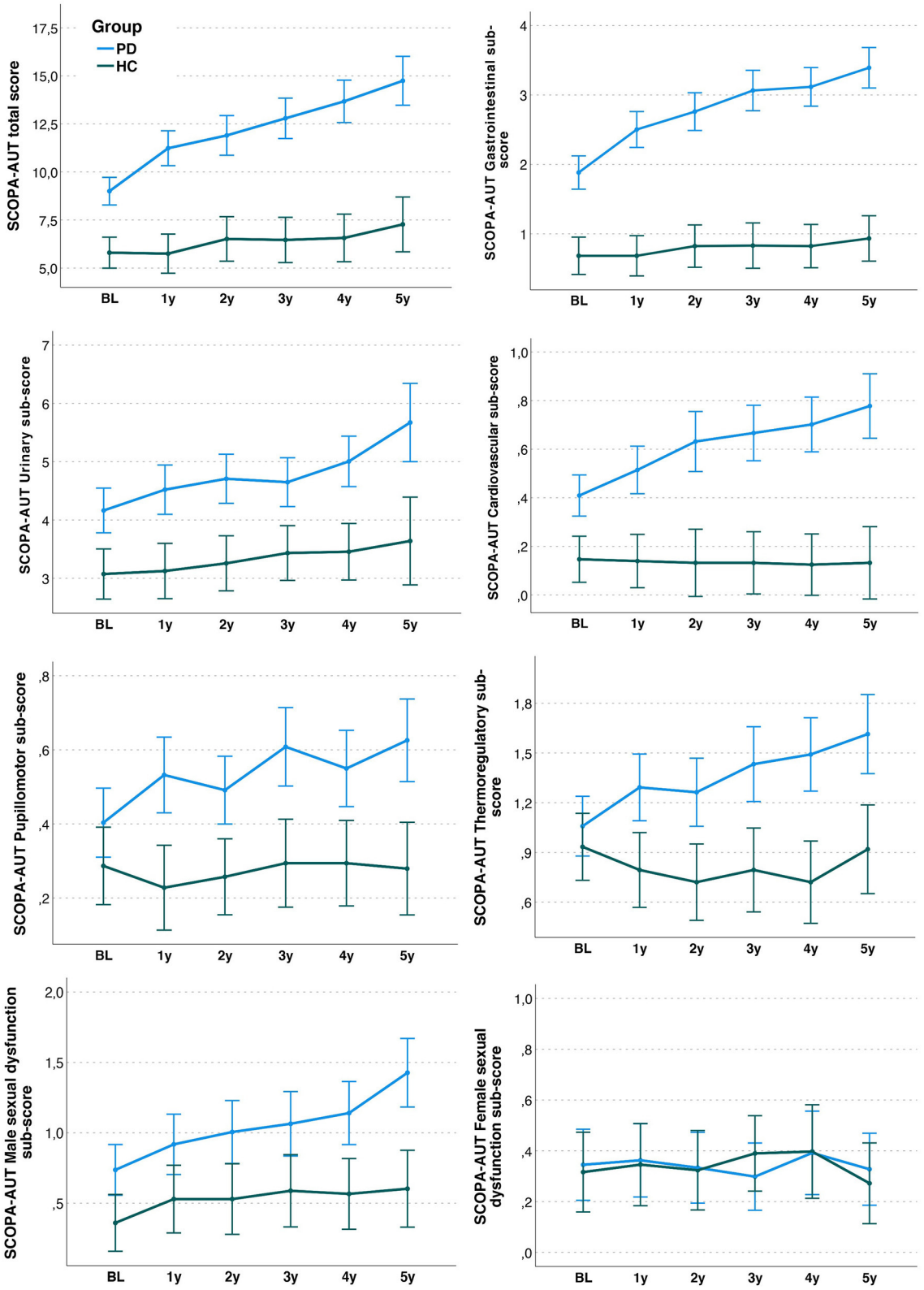

FIGURE 1
SCOPA-AUT total and sub-domain scores in Parkinson's disease (PD) and Healthy Controls (HC) over the first 5 years after baseline. Scores depicted in the panels are based on estimated marginal means (and 95% confidence intervals) from repeated-measures ANOVA models.

TABLE 2 Symptom frequencies from baseline to year 5 in HC, and to year 7 in PD.

Number and percentage of subjects reporting symptoms in each domain									
Time-point	Baseline			Year-1			Year-2		
SCOPA-AUT domain	PD	HC	*p*	PD	HC	*p*	PD	HC	*p*
Gastrointestinal	121 (71%)	56 (41%)	**<0.0001**	142 (83%)	56 (41%)	**<0.0001**	147 (86%)	57 (42%)	**<0.0001**
Urinary	165 (96%)	125 (92%)	0.081	163 (95%)	125 (92%)	0.218	165 (96%)	126 (93%)	0.132
Cardiovascular	55 (32%)	18 (13%)	**<0.0001**	61 (36%)	18 (13%)	**<0.0001**	66 (39%)	14 (10%)	**<0.0001**
Pupillomotor	54 (32%)	35 (26%)	0.262	67 (39%)	26 (19%)	**<0.0001**	69 (40%)	32 (24%)	0.002
Thermoregulatory	99 (58%)	73 (54%)	0.459	105 (61%)	60 (44%)	0.003	102 (60%)	59 (43%)	0.005
Sexual	79 (46%)	45 (33%)	0.020	86 (50%)	54 (40%)	0.064	88 (51%)	47 (34%)	0.003
Male ($N = 120$; 83)	53 (44%)	22 (27%)	0.017	60 (50%)	31 (37%)	0.107	64 (53%)	27 (33%)	0.003
Female ($N = 51$; 53)	26 (51%)	22 (42%)	0.333	26 (51%)	22 (42%)	0.333	24 (47%)	20 (38%)	0.336
Time-point	Year-3			Year-4			Year-5		
SCOPA-AUT domain	PD	HC		PD	HC		PD	HC	
Gastrointestinal	151 (88%)	61 (45%)	**<0.0001**	152 (89%)	63 (46%)	**<0.0001**	155 (91%)	66 (49%)	**<0.0001**
Urinary	163 (95%)	129 (95%)	0.850	164 (96%)	125 (92%)	0.139	164 (96%)	130 (96%)	0.891
Cardiovascular	74 (43%)	16 (12%)	**<0.0001**	77 (45%)	15 (11%)	**<0.0001**	77 (45%)	15 (11%)	**<0.0001**
Pupillomotor	78 (46%)	34 (25%)	**<0.0001**	70 (41%)	35 (26%)	0.005	74 (43%)	32 (24%)	**<0.0001**
Thermoregulatory	109 (64%)	60 (44%)	**0.001**	107 (63%)	59 (43%)	**0.001**	105 (61%)	70 (51%)	0.081
Sexual	90 (53%)	59 (43%)	0.107	99 (58%)	54 (40%)	0.002	104 (61%)	55 (40%)	**<0.0001**
Male ($N = 120$;83)	67 (56%)	33 (40%)	0.037	73 (61%)	32 (39%)	0.003	82 (68%)	36 (43%)	**<0.0001**
Female ($N = 51$;53)	23 (45%)	25 (47%)	0.832	26 (45%)	21 (40%)	0.245	22 (43%)	19 (36%)	0.447
Time-point	Year-6			Year-7					
SCOPA-AUT domain	PD	HC	*p*	PD	HC	*p*			
Gastrointestinal	158 (92%)	-	-	163 (95%)	-	-			
Urinary	166 (97%)	-	-	165 (96%)	-	-			
Cardiovascular	84 (49%)	-	-	85 (50%)	-	-			
Pupillomotor	82 (48%)	-	-	81 (47%)	-	-			
Thermoregulatory	112 (65%)	-	-	125 (73%)	-	-			
Sexual	98 (57%)	-	-	98 (57%)	-	-			
Male ($N = 120$;83)	77 (64%)	-	-	74 (62%)	-	-			
Female ($N = 51$;53)	21 (41%)	-	-	21 (41%)	-	-			

Values represent the number of subjects with a score in each domain >0, with the percentage in parentheses based on the total number of subjects (171 PD; 136 HC). The total score for the sexual domain is divided further into specific scores for male and female, in which the percentage is based on the total number of male and female PD and HC subjects, appropriately. *P*-values comparing PD and HC cohorts are derived from Chi-square tests with Bonferroni correction for multiple comparisons (corrected *p*-value threshold = 0.001).

Figure 4) and HC subjects ($r = -0.267$, $p = 0.002$) at baseline. In PD, a significant direct association was also present between baseline MDS-UDPRS III score and SCOPA-AUT score ($r = 0.218$, $p = 0.004$).

Discussion

Our study investigated the longitudinal progression of autonomic symptoms in a large, well characterized cohort of de novo PD patients over a period of seven years and followed the coexistence of autonomic symptoms over time to examine multi-domain clustering patterns. The association between autonomic, olfactory, and motor symptoms was also explored.

Baseline demographics and clinical features

When comparing SCOPA-AUT scores between groups at baseline, we identified a significantly higher mean score in the gastrointestinal, urinary, cardiovascular, and sexual domains in PD patients compared to controls. However, while reported male sexual dysfunction symptoms were significantly greater in patients compared to controls, no significant difference was identified in

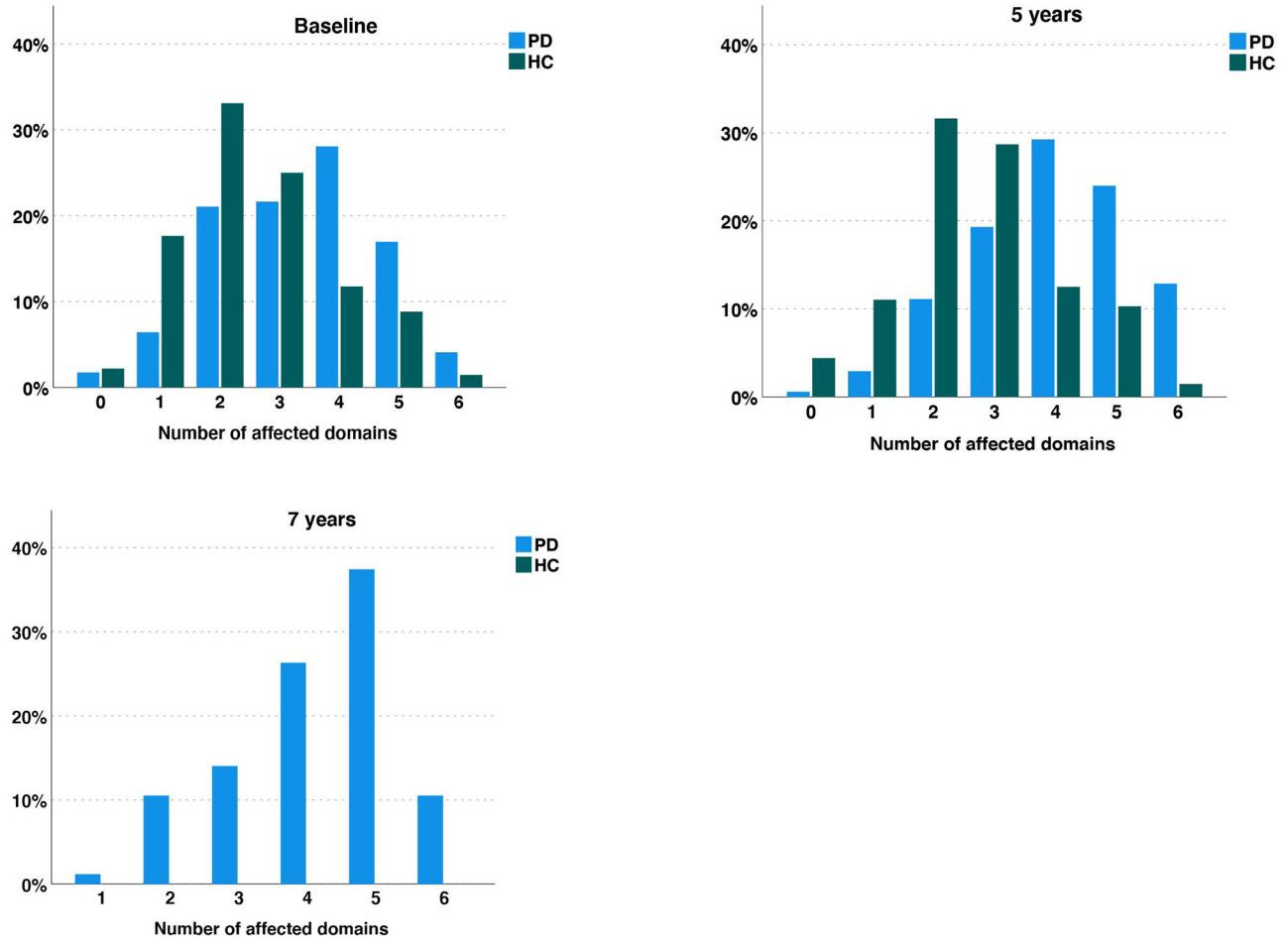

FIGURE 2
Diagram representing the percentage of Parkinson's disease (PD) patients and Healthy Controls (HC) reporting none, one, two, three, four five or all six autonomic symptoms over 5 years for both cohorts, and an additional 2 years in the PD group. Each column represents the percentage of participants in each group (PD or HC) with the indicated number of symptoms.

female sexual dysfunction. Although under investigated, female sexual dysfunction has been reported in PD (17, 18). We believe our finding may be related to different factors, such as the early stage of the PD cohort that was studied and the fact that the SCOPA-AUT questionnaire, which contains only two specific questions for female sexual dysfunction, may be unable to identify differences with controls.

Conversely, no significant differences in mean scores were found between cohorts for thermoregulatory or pupillomotor domains. Taken together with a previous study (2), these results would suggest that pupillomotor dysfunction and possibly thermoregulatory dysfunction are mild and/or uncommon in the early stages of PD.

Longitudinal assessment of autonomic symptoms over 7 years

Our study also investigated the longitudinal progression of autonomic dysfunction over a period of 7 years. To our knowledge this is the longest follow-up of autonomic dysfunction in a large cohort of early PD patients. Another strength of this study is that a complete dataset was available for PD subjects for 7 years, with no missing assessments, providing a realistic account of autonomic dysfunction in these patients over time.

We observed a significant increase in mean SCOPA-AUT score over time. This finding was consistent for all domains, excluding female sexual symptoms, which did not significantly increase over the observation period.

No significant increases in SCOPA-AUT total or sub-domains scores were shown in HC over the 5 years in which these subjects were observed.

One previous study with shorter follow-up (3 years) on 107 PD patients found increasing severity in urinary, gastrointestinal, cardiovascular domains, and sexual dysfunction. However, sexual dysfunction was not reported separately for males and females. Also, pupillomotor and thermoregulatory scores did not change over time (2). It should be noted that in that study the frequency of individual autonomic symptoms at baseline and the changes over time are smaller compared to the ones observed in our study. This may be due to factors related to the cohort that was assessed,

consisting of participants with milder PD (H&Y stage I). Indeed, compared to the patients included in the current analysis from the PPMI cohort, their baseline mean MDS-UPDRS was 3.4 points lower and mean SCOPA-AUT total score 5.3 points lower.

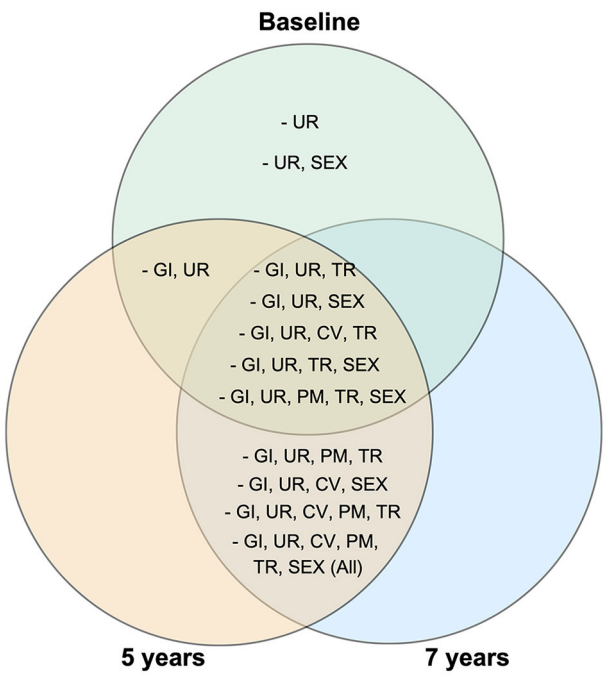

FIGURE 3
Venn diagram showing specific combinations of autonomic symptoms present in at least 10 Parkinson's disease participants at baseline, 5 years and 7 years follow ups. GI, gastrointestinal; UR, urinary; CV, cardiovascular; TR, thermoregulatory; PM, pupillomotor; SEX, sexual domain.

Overall, our findings of worsening autonomic symptoms over time reinforce previous conclusions that autonomic dysfunction is associated with increasing PD severity and duration (2, 19–21) Furthermore, we add a detailed longitudinal analysis in all autonomic sub-domains over a long period of time, with a comparison between PD and HC over 5 years, and an additional follow up to a total of 7 years for PD.

Frequency of individual autonomic symptoms over the 7-year period

Urinary dysfunction was the most reported autonomic symptom in individuals with PD at every time-point, affecting 95–97% of patients over the 7-year period. Interestingly, 92–96% of HCs also reported symptoms within the urinary domain, suggesting that urinary symptoms are also common in healthy controls (22). However, mean SCOPA-AUT scores in the urinary domain at baseline were significantly higher in PD than controls, indicating greater dysfunction in PD. In a previous large study of mid-stage PD patients (mean disease duration 10.5 years), greater scores in the urinary domain were found as well, compared to controls (23). Together with our findings, this suggests that urinary dysfunction may be present at the earliest stages of PD and worsens with disease progression.

Gastrointestinal dysfunction was the second most reported complaint among PD patients, with 71% experiencing symptoms at baseline, 91% at the 5-year follow-up, and 95% at 7 years. Within the gastrointestinal domain, constipation was found to be the most common symptom, followed by excessive drooling. Only 41–49% HCs reported these symptoms over the whole 5-year period. Our findings are in keeping with existing knowledge that PD patients frequently report gastrointestinal dysfunction both prior to the

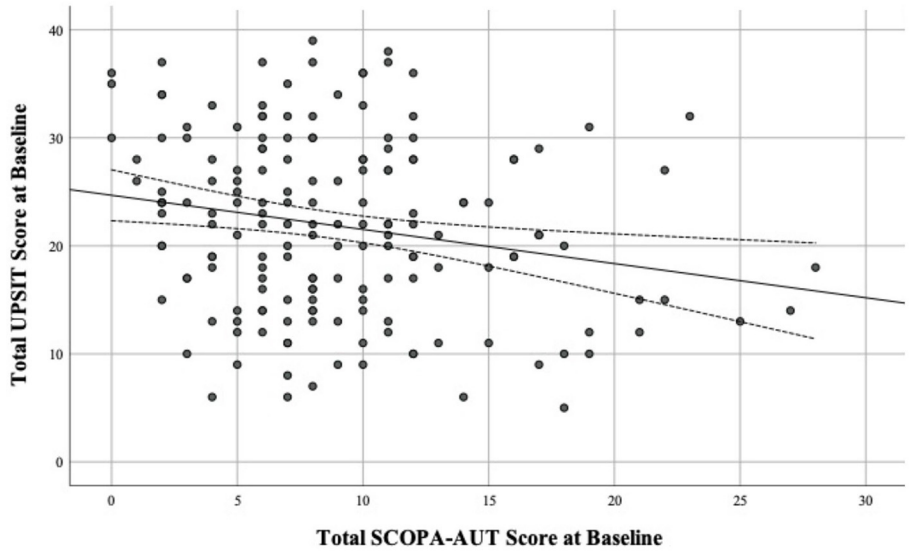

FIGURE 4
Scatter plot of total UPSIT score by total SCOPA-AUT score at Baseline in Parkinson's disease (PD), using Pearson correlation with 95% confidence intervals.

onset of motor symptoms and in early disease (23, 24). Of note there was a 24% increase in patients reporting gastrointestinal symptoms over the 7-year period, indicating that gastrointestinal dysfunction becomes more common with PD progression. A previous study conducted in a PD cohort with variable disease durations (mean 3.6 years and standard deviation 4.26) showed that greater right caudate dopaminergic deficit may be associated with greater gastrointestinal dysfunction (25).

Symptoms of cardiovascular dysfunction were reported by less than half of the PD patients at each assessment. However, at all assessments, the percentage of PD patients with these symptoms was significantly higher than the control population, suggesting a direct role of the neurodegenerative process in the occurrence of these symptoms.

Despite being one of the most common complaints at each assessment, the frequency of sexual dysfunction in males and females were not different between PD and controls until the 5-year follow-up assessment, when less than half (43%) of the male control population experienced sexual dysfunction compared to 62% of male PD patients. It is known that sexual symptoms, including erectile dysfunction, are commonly experienced by male PD patients (17), which occur in conjunction with other autonomic symptoms. Furthermore, reduced testosterone levels have also been shown in PD and this may contribute to such symptoms (26). It should also be acknowledged that scores of male sexual dysfunction were higher in PD than controls; therefore, although PD and HC showed similar frequencies, the severity was greater in PD.

Previous studies have identified sexual issues in females with PD, such as vaginal tightness and loss of libido (17, 18). The finding of more prominent sexual dysfunction in males than females with PD had also been reported in a previous small study of 34 patients with PD (27).

A previous study concluded that constipation, a drop in systolic blood pressure, and erectile dysfunction could identify PD 5 years before the diagnosis of the disease with a high sensitivity (4). Accordingly, at baseline (within 2 years of diagnosis) we identified that the largest difference in symptom frequencies between PD and HC subjects was in the gastrointestinal, cardiovascular, and male-specific sexual domains.

Coexistence of autonomic symptoms in individual PD patients

We observed that the coexistence of autonomic symptoms in individual PD patients is very common, even in the first 2 years of disease, suggesting multi-organ involvement, which requires attention and appropriate management from the early stages of the disease. At baseline, only a minority of PD patients reported no autonomic dysfunction (3%) or a single symptom in any of the SCOPA-AUT domains (6%). Conversely, most of them (71%) reported symptoms in more than two domains and 4% reported problems in all six domains.

The percentage of patients experiencing multiple autonomic symptoms further increased over the 7-year follow-up, with all participants reporting at least one autonomic symptom at the last follow-up, and the percentage of patients reporting all six symptoms almost tripled to 11%.

The percentage of PD patients reporting five symptoms also increased from 17% to 37%, while the percentage of patients reporting autonomic symptoms in one or two domains dropped from 6% to 1% and from 21% to 11%, respectively.

Conversely, we did not observe a notable change in the proportions of HCs experiencing symptoms in multiple autonomic domains over the course of the 5-year follow-up period.

These findings further detail the progression of multiple autonomic symptoms from the early stages of PD (6) and extend the findings reported by Stanković and colleagues who also identified multi-domain dysfunction progressing over 3 years (2).

In our study, urinary symptoms were present in every PD cluster at baseline, 5 and 7 years, predominantly appearing with gastrointestinal, thermoregulatory, and sexual symptoms, suggesting these symptoms occur together in PD. Although to a lesser extent, cardiovascular and pupillomotor symptoms also appeared in conjunction with these symptoms. The clustering of these symptoms may be due to differential anatomical involvement of the peripheral autonomic nervous system, the dominant system innervating the organ (e.g., sympathetic or parasympathetic), and the residual innervation and function of the organ (28).

Although clustering of symptoms was also present in controls, the majority reported two or three symptoms, and only 1% experienced all six. It is probable that healthy controls will experience some autonomic symptoms due to, e.g., the normal process of ageing. It should also be acknowledged that our method of evaluating autonomic symptoms clustering does not consider severity and mean scores, which have been shown to be higher in the PD cohort (6).

Association between autonomic and olfactory function in PD

At baseline, greater autonomic dysfunction was associated with both greater olfactory impairment and more severe motor scores. No differences were found in terms of motor manifestations between participants with and without olfactory dysfunction.

These findings may be indicative of a "clustering" of worse manifestations, i.e., patients with a more aggressive phenotype, as indicated in recent studies that have shown the possibility of subdividing PD populations in benign, intermediate and malignant subtypes (29, 30).

Furthermore, these findings should also be discussed in light of the hypothesis that the pathological PD process may progress in a bottom-up (body-first) or top-down (brain-first) fashion (8). Indeed, one could expect that PD patients with a "body-first" phenotype and predominant autonomic manifestations may have less olfactory impairment, and patients with a "brain-first" phenotype may have olfactory impairment and less autonomic dysfunction. However, in a "body-first" phenotype with autonomic symptoms, by the time motor symptoms arise, the pathological process may have already spread to cause olfactory dysfunction. Based on the available pathological evidence, it has been proposed that "body-first patients" might have a higher burden of cerebral Lewy body pathology (including in the olfactory bulbs) by the time PD becomes manifest, and this may, in turn, be associated with a higher degree of olfactory impairment (14). Conversely,

in "brain-first patients" the involvement of the olfactory bulb may be more frequently unilateral, resulting in smaller olfactory impairment. In this context, the association between greater autonomic dysfunction and greater olfactory impairment may be driven by PD patients with a greater spread of pathology throughout the brain, a process that possibly started in the peripheral nervous system.

Finally, it may be hypothesized that the association between autonomic and olfactory dysfunction may be related to aging. Indeed, this same inverse correlation was also identified in the HC group. However, it should be noted that 65% of controls had normal olfactory function and overall low SCOPA-AUT scores, while PD participants were mostly hyposmic or anosmic and had significantly higher SCOPA-AUT scores than HC.

Limitations

Several limitations should be acknowledged. Due to the lack of HCs with data at 6 and 7 years, we were unable to compare HCs and PD at the last two follow ups. We were also unable to control for PD medications, which may have effects on autonomic function. Similarly, concomitant conditions such as diabetes may also have influenced these symptoms, therefore further research may consider a full medical history of individual subjects to further improve the analysis, as well as uncover any associations with other pathologies.

We selected participants who had complete data over the entire follow up. This may have excluded more severe participants that were less able to attend the frequent PPMI visit schedule. Therefore, when interpreting the results of this study, it should be considered that the cohort might include a greater proportion of milder PD patients.

Our study focused on autonomic dysfunction. Other clinical and imaging data was not systematically included in the analysis. Further evaluation looking for other clinical and paraclinical associations of autonomic dysfunction may prove a useful avenue of future research.

It must also be acknowledged that the SCOPA-AUT does not include a threshold for allowing the clinical determination of dysautonomia in PD. In this study, the ability to determine whether scores reflect severe or mild dysfunction would have allowed a more apt analysis of autonomic function decline in PD. Furthermore, the subjective nature of the SCOPA-AUT opens the potential for underestimation or overestimation of autonomic symptoms, which could limit the significance of our results. Objective measures of autonomic dysfunction, alongside subjective SCOPA-AUT scores, would allow a more accurate analysis of autonomic function.

Conclusions

Overall, our study provides novel insights into the progression of autonomic dysfunction in the first 7 years of idiopathic PD. A progressive increase in multi-domain dysfunction was identified over time. We also found that multiple autonomic symptoms in different organ domains cluster together in PD. Future studies investigating the progression of SCOPA-AUT score and multi-domain prevalence in PD in the later stages could lead to better understanding as to whether less frequently reported autonomic symptoms (e.g., cardiovascular and pupillomotor dysfunction) become more prevalent over time. Finally, at baseline higher autonomic dysfunction scores were associated with lower olfactory function scores, a finding that should be further investigated in future studies, considering the top-down and bottom-up models of PD pathology progression.

Author's note

Members of Parkinson's Progression Markers Initiative (PPMI) are listed in the Supplementary material.

Data availability statement

The data analysed in this study was obtained from the Parkinson's Progression Markers Initiative (PPMI) database (https://www.ppmi-info.org). Data used in the preparation of this article is available from the corresponding author upon request.

Author contributions

CS: conception and design, acquisition of data, analysis, and interpretation write-up. JP: conception and design, analysis, and interpretation review. DL, KA, and SS: critical revision of article. VF and DG: critical revision of article and data collection. NP: critical revision of article and conception and design. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1155669/full#supplementary-material

References

1. Tomic S, Rajkovaca I, Pekic V, Salha T, Misevic S. Impact of autonomic dysfunctions on the quality of life in Parkinson's disease patients. *Acta Neurol Belg.* (2017) 117:207–11. doi: 10.1007/s13760-016-0739-6

2. Stanković I, Petrović I, Pekmezović T, Marković V, Stojković T, Dragašević-Mišković N, et al. Longitudinal assessment of autonomic dysfunction in early Parkinson's disease. *Parkinsonism Relat Disord.* (2019) 66:74–9. doi: 10.1016/j.parkreldis.2019.07.008

3. De Pablo-Fernandez E, Tur C, Revesz T, Lees AJ, Holton JL, Warner TT. Association of autonomic dysfunction with disease progression and survival in Parkinson's disease. *JAMA Neurol.* (2017) 74:970–6. doi: 10.1001/jamaneurol.2017.1125

4. Postuma RB, Gagnon JF, Pelletier A, Montplaisir J. Prodromal autonomic symptoms and signs in Parkinson's disease and dementia with Lewy bodies. *Movement Disorders.* (2013) 28:597–604. doi: 10.1002/mds.25445

5. Schrag A, Bohlken J, Dammertz L, Teipel S, Hermann W, Akmatov MK, et al. Widening the spectrum of risk factors, comorbidities, and prodromal features of Parkinson disease. *JAMA Neurol.* (2023) 80:161. doi: 10.1001/jamaneurol.2022.3902

6. Minguez-Castellanos A, Chamorro CE, Escamilla-Sevilla F, Ortega-Moreno A, Rebollo AC, Gomez-Rio M. et al. Do α-synuclein aggregates in autonomic plexuses predate Lewy body disorders? A cohort study. *Neurology.* (2007) 68:2012–8. doi: 10.1212/01.wnl.0000264429.59379.d9

7. Amino T, Orimo S, Itoh Y, Takahashi A, Uchihara T, Mizusawa H. Profound cardiac sympathetic denervation occurs in Parkinson disease. *Brain Pathology.* (2005) 15:29–34. doi: 10.1111/j.1750-3639.2005.tb00097.x

8. Doty RL. Olfactory dysfunction in Parkinson disease. *Nat Rev Neurol.* (201) 8:329–39. doi: 10.1038/nrneurol.2012.80

9. Cecchini MP, Mantovani E, Federico A, Zanini A, Ottaviani S, Masala C, et al. Olfaction in patients with Parkinson's disease: a new threshold test analysis through turning points trajectories. *J Neural Transm.* (2021) 128:1641. doi: 10.1007/s00702-021-02387-z

10. Haehner A, Masala C, Walter S, Reichmann H, Hummel T. Incidence of Parkinson's disease in a large patient cohort with idiopathic smell and taste loss. *J Neurol.* (2019) 266:339–45. doi: 10.1007/s00415-018-9135-x

11. Solla P, Masala C, Liscia A, Piras R, Ercoli T, Fadda L, et al. Sex-related differences in olfactory function and evaluation of possible confounding factors among patients with Parkinson's disease. *J Neurol.* (2020) 267:57–63. doi: 10.1007/s00415-019-09551-2

12. Solla P, Masala C, Ercoli T, Frau C, Bagella C, Pinna I, et al. Olfactory impairment correlates with executive functions disorders and other specific cognitive dysfunctions in Parkinson's disease. *Biology.* (2023) 12:112. doi: 10.3390/biology12010112

13. Horsager J, Andersen KB, Knudsen K, Skjærbæk C, Fedorova TD, Okkels N, et al. Brain-first versus body-first Parkinson's disease: a multimodal imaging case-control study. *Brain.* (2020) 143:3077–88. doi: 10.1093/brain/awaa238

14. Borghammer P, Just MK, Horsager J, Skjærbæk C, Raunio A, Kok EH, et al. A postmortem study suggests a revision of the dual-hit hypothesis of Parkinson's disease. *NPJ Parkinsons Dis.* (2022) 8:1–11. doi: 10.1038/s41531-022-00436-2

15. Visser M, Marinus J, Stiggelbout AM, Van Hilten JJ. Assessment of autonomic dysfunction in Parkinson's disease: The SCOPA-AUT. *Movement Disorders.* (2004) 19:1306–12. doi: 10.1002/mds.20153

16. Doty RL. The *Smell Identification Test: Administration Manual.* Sensonics, Incorporated (1995).

17. Meco G, Rubino A, Caravona N, Valente M. Sexual dysfunction in Parkinson's disease. *Parkinsonism Relat Disord.* (2008) 14:451–6. doi: 10.1016/j.parkreldis.2007.10.008

18. Welsh M, Hung L, Waters CH. Sexuality in women with Parkinson's disease. *Mov Disord.* (1997) 12:923–7. doi: 10.1002/mds.870120614

19. Simuni T, Caspell-Garcia C, Coffey CS, Weintraub D, Mollenhauer B, Lasch S, et al. Baseline prevalence and longitudinal evolution of non-motor symptoms in early Parkinson's disease: the PPMI cohort. *J Neurol Neurosurg Psychiatry.* (2018) 89:78–88. doi: 10.1136/jnnp-2017-316213

20. Bostantjopoulou S, Katsarou Z, Danglis I, Karakasis H, Milioni D, Falup-Pecurariu C. Self-reported autonomic symptoms in Parkinson's disease: properties of the SCOPA-AUT scale. *Hippokratia.* (2016) 20:115–20.

21. Wang L, Cheng W, Rolls ET Dai F, Gong W, Du J, et al. Association of specific biotypes in patients with Parkinson's disease and disease progression. *Neurology.* (2020) 95:E1445–60. doi: 10.1212/WNL.0000000000010498

22. Yang X, Chen H, Zheng Y, Qu S, Wang H, Yi F. Disease burden and long-term trends of urinary tract infections: a worldwide report. *Front Public Health.* (2022) 10:10. doi: 10.3389/fpubh.2022.888205

23. Verbaan D, Marinus J, Visser M, Van Rooden SM, Stiggelbout AM, Van Hilten JJ. Patient-reported autonomic symptoms in Parkinson's disease. *Neurology.* (2007) 69:333–41. doi: 10.1212/01.wnl.0000266593.50534.e8

24. Sung HY, Park JW, Kim JS. The frequency and severity of gastrointestinal symptoms in patients with early Parkinson's disease. *J Mov Disord.* (2014) 7:7–12. doi: 10.14802/jmd.14002

25. van Deursen DN, van den Heuvel OA, Booij J, Berendse HW, Vriend C. Autonomic failure in Parkinson's disease is associated with striatal dopamine deficiencies. *J Neurol.* (2020) 267:1922–30. doi: 10.1007/s00415-020-09785-5

26. Okun MS, DeLong MR, Hanfelt J, Gearing M, Levey A. Plasma testosterone levels in Alzheimer and Parkinson diseases. *Neurology.* (2004) 62:411–3. doi: 10.1212/01.WNL.0000106840.72938.84

27. Brown RG, Jahanshahi M, Quinn N, Marsden CD. Sexual function in patients with Parkinson's disease and their partners. *J Neurol Neurosurg Psychiatry.* (1990) 53:480–6. doi: 10.1136/jnnp.53.6.480

28. Siegel A, Sapru HN. Essential Neuroscience. 4th ed. LWW. Wolters Kluwer Health. (2018). 648 p. Available online at: https://www.lww.co.uk/9781496382405/essential-neuroscience/

29. De Pablo-Fernández E, Lees AJ, Holton JL, Warner TT. Prognosis and neuropathologic correlation of clinical subtypes of Parkinson's disease. *JAMA Neurol.* (2019) 76:470–9. doi: 10.1001/jamaneurol.2018.4377

30. Fereshtehnejad SM, Zeighami Y, Dagher A, Postuma RB. Clinical criteria for subtyping Parkinson's disease: biomarkers and longitudinal progression. *Brain.* (2017) 140:1959–76. doi: 10.1093/brain/awx118

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Impact of non-motor fluctuations on QOL in patients with Parkinson's disease

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Introduction: Long-term levodopa treatment in patients with Parkinson's disease (PwPD) often causes motor fluctuations, which are known to affect their quality of life (QOL). These motor fluctuations may be accompanied by fluctuations in non-motor symptoms. There is no consensus on how non-motor fluctuations affect QOL.

Methods: This was a single-center, retrospective study and included 375 patients with Parkinson's disease (PwPD) who visited the neurology outpatient department of Fukuoka University Hospital between July 2015 and June 2018. All patients were evaluated for age, sex, disease duration, body weight, and motor symptoms by the Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III, depression scale by the Zung self-rating depression scale, apathy scale, and cognitive function by the Japanese version of The Montreal Cognitive Assessment. A nine-item wearing-off questionnaire (WOQ-9) was used to assess the motor and non-motor fluctuations. QOL in PwPD was investigated using the eight-item Parkinson's Disease Questionnaire (PDQ-8).

Results: In total, 375 PwPD were enrolled and classified into three groups according to the presence or absence of motor and non-motor fluctuations. The first group included 98 (26.1%) patients with non-motor fluctuations (NFL group), the second group included 128 (34.1%) patients who presented with only motor fluctuations (MFL group), and the third group included 149 (39.7%) patients without fluctuations in motor or non-motor symptoms (NoFL group). Among them, the PDQ-8 SUM and SI were significantly higher in the NFL group than in the other groups ($p<0.005$), implying that the NFL group had the poorest QOL among groups. Next, multivariable analysis showed that even one non-motor fluctuation was an independent factor that worsened QOL ($p<0.001$).

Conclusion: This study showed that PwPD with non-motor fluctuation had a lower QOL than those with no or only motor fluctuation. Moreover, the data showed that PDQ-8 scores were significantly reduced even with only one non-motor fluctuation.

KEYWORDS

Parkinson's disease, wearing-off phenomenon, motor fluctuation, non-motor fluctuation, wearing-off questionnaire (WOQ-9), Parkinson's disease questionnaire-8 (PDQ-8)

Introduction

Parkinson's disease (PD) is characterized by motor symptoms such as tremor, rigidity, and bradykinesia, and a variety of non-motor symptoms such as cognitive impairment, neuropsychiatric symptoms, gastrointestinal symptoms, autonomic dysfunction, pain, and fatigue (1). Advances in diagnosis and treatment for PD have progressed due to the development of recent diagnostic criteria, dopaminergic treatment, and device-aided therapy, and the average life expectancy of patients with Parkinson's disease (PwPD) has significantly increased (2–4).

As a result, many patients are living with the disease for a longer period of time, and under these circumstances, it is desirable to improve their quality of life (QOL) during that period. Although levodopa remains the most effective therapeutic agent for symptomatic treatment of PD (5, 6), patients often experience motor fluctuations after long-term treatment with levodopa that affect their QOL (7). PwPD with motor fluctuations may also experience fluctuations in their non-motor symptoms (8). Non-motor symptoms are expected to have a greater potential for affecting QOL than motor symptoms in PwPD (9–11). However, there are few studies to date that address how non-motor fluctuations affect patients' QOL, compared to motor fluctuations. There is no established assessment of non-motor fluctuations except the newly developed MDS-NMS Non-Motor Fluctuations subscale (12). Here, we used the nine-item wearing-off questionnaire (WOQ-9) to evaluate motor and non-motor fluctuations. WOQ-9, which consists of five questions relating to motor symptoms and four questions relating to nonmotor symptoms, was developed as a screening tool for wearing-off, and previous studies propose its efficacy for the early detection of wearing-off (13–15). This study aimed to investigate the impact of non-motor fluctuations for QOL in PwPD using WOQ-9.

Materials and methods

Protocol approval

This study was approved by the institutional ethics committee at the Department of Neurology, Fukuoka University Hospital (U20-04-001). Oral, informed consent was obtained from each patient before enrolment and participation in the study.

Patients and study design

This was a single center, cross sectional, retrospective study of 375 consecutive PwPD. Movement Disorder Society Clinical Diagnostic Criteria for PD (16) were used to diagnose PD, and those patients that met the diagnostic criteria for definite or probable PD were included. All patients enrolled in this study between July 2015 and June 2018 at the Department of Neurology, Fukuoka University Hospital in Japan. All patients were evaluated for age, sex, disease duration, body weight, presence of wearing off, dyskinesia, REM sleep behavior disorder, and visual hallucinations; this information was extracted from each patient's medical record. Disease severity was defined according to the Hoehn & Yahr stage, and motor symptoms were evaluated using the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III (17). Cognitive function was assessed with the Japanese version of the Montreal Cognitive Assessment (MOCA-J) (18, 19). Mood disorders were evaluated by the Zung self-rating depression scale (SDS) (20). The evaluation of motor and non-motor fluctuations was performed using WOQ-9, then all patients were classified into three groups according to the results of WOQ-9 as follows: patients with non-motor fluctuations (NFL group), those with only motor fluctuations (MFL group), and those with no fluctuation (NoFL group). Exclusion criteria included dementia, severe psychiatric symptoms, and those not willing to take part in this study. Each patient's QOL was evaluated by the Parkinson's Disease Questionnaire-8 (PDQ-8). PDQ-8 is a questionnaire which is a short-form version of the 39-item Parkinson's Disease Questionnaire (PDQ-39) (21), and the total score (PDQ-8 SUM) and summary index (PDQ-8 SI) were calculated. Then, we studied the correlation between non-motor fluctuations and QOL.

Statistics

All basic data were expressed as mean ± SD or *n* (%). These data were compared using ANOVA for continuous variables or using chi-square test for categorical variables. This study involved three sets of analyses: In the first, we compared the PDQ-8 SUM/PDQ-8 SI among each of three groups according to the results of WOQ-9 mentioned above. We performed the analysis using analysis of covariance (ANCOVA) with Tukey's *post-hoc* test, including age, sex, disease duration, MDS-UPDRS part III score, and hallucination as covariates. In the second set of analyses, we assessed associations between the PDQ-8 SUM/PDQ-8 SI and the numbers of motor/non-motor fluctuations in WOQ-9. Additionally, we assessed whether the sum of the numbers of motor/non-motor symptoms had a statistical trend for the PDQ-8 scores by regarding the sum of the numbers as a numerous variable. We performed these analyses using ANCOVA including age, sex, disease duration, and MDS-UPDRS part III score as covariates. In the third set of analyses, we compared the PDQ-8 SUM/PDQ-8 SI among each of four groups divided by disease duration as follows: patients with <2 years duration (DU1 group), those with >2 and < 5 years duration (DU2 group), those with >5 and <10 years duration (DU3 group), and patients with >10 years duration (DU4 group). We performed the analysis using ANCOVA, including age, sex, and MDS-UPDRS part III score as covariates. In the fourth set of analyses, we compared with the item of the non-motor fluctuation among each of motor subtypes of the patients and analyzed the relationship between them by chi-square test. Statistical significance was set at $p < 0.05$. All analyses were conducted using IBM SPSS v.26 and SAS software v.9.4.

Results

A total of 375 PwPD participated in this study. The first group included 98 (26.1%) patients with non-motor fluctuations (NFL group), the second group included 128 (34.1%) patients who presented with only motor fluctuations (MFL group), and the third group included 149 (39.7%) patients without fluctuations in motor or non-motor symptoms (NoFL group). The demographics and clinical

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TABLE 1 Demographics and clinical characteristics.

	Total (*n*=375)	NFL (*n*=98, M+NF=93, NF=5)	MFL (*n*=128)	NoFL (*n*=149)	Value of *p*
Sex, male, *n* (%)	140 (37.3%)	33 (33.7%)	33 (25.8%)	74 (49.7%)	< 0.001
Age, year (SD)	69.8 (10.6)	67.7 (11.0)	68.8 (11.8)	72.0 (8.8)	0.004
Age at onset, year (SD)	62.1 (11.8)	58.9 (12.1)	60.9 (12.0)	65.1 (10.8)	< 0.001
Disease duration, year (SD)	7.8 (6.4)	8.9 (4.7)	8.1 (5.9)	6.9 (7.5)	0.041
RBD, *n* (%)	177 (47.8%)	58 (59.8%)	55 (44.0%)	64 (43.2%)	0.022
Hallucinations, *n* (%)	97 (26.0%)	36 (36.7%)	26 (20.6%)	35 (23.5%)	0.019
H&Y	2.8 (1.8)	2.8 (0.8)	2.7 (0.9)	2.9 (2.7)	0.733
MDS-UPDRS part III	30.4 (14.7)	31.7 (15.5)	30.0 (15.8)	30.0 (12.9)	0.645
Motor fluctuation number (SD)	1.2 (1.3)	2.3 (1.2)	1.8 (0.9)	0	< 0.001
Non-motor fluctuation number (SD)	0.5 (0.9)	1.7 (0.8)	0	0	< 0.001
MMSE (SD)	26.9 (3.3)	26.7 (3.6)	27.5 (3.2)	26.8 (3.2)	0.092
MoCA (SD)	22.7 (3.4)	22.4 (5.7)	23.4 (4.8)	22.2 (4.3)	0.123
PDQ-8 SI (SD)	21.7 (19.3)	29.7 (20.1)	20.6 (20.6)	17.4 (15.1)	< 0.001
PDQ-8 SUM (SD)	6.9 (6.2)	9.5 (6.7)	6.6 (6.6)	5.6 (4.8)	< 0.001
SDS (SD)	43.0 (10.3)	46.7 (9.7)	42.2 (10.0)	41.2 (10.3)	0.001

NFL, Patients with non-motor fluctuations; MFL, Patients with only motor fluctuations; NoFL, Patients with no fluctuations; M + NF, Patients with non-motor fluctuations and motor fluctuations; PD, Parkinson disease; RBD, REM sleep behavior disorder; H&Y, Hoehn & Yahr scale; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; MoCA, The Montreal Cognitive Assessment; PDQ-8 SI, The Parkinson's Disease Questionnaire-8 summary index; PDQ-8 SUM, The Parkinson's Disease Questionnaire-8 sum score; WOQ-9, 9-item Wearing-off Questionnaire; SDS: self-rating depression scale.

TABLE 2 Multivariable analysis of the association between PDQ-8 SUM/PDQ-8 SI and the three groups according to the results of WOQ-9.

	NFL vs. MFL	NFL vs. NoFL	MFL vs. NoFL
PDQ-8 SI	NFL MFL	NFL NoFL	MFL NoFL
Mean (95% CI)	28.1(24.5–31.6), 20.3 (17.2–23.4)	28.1(24.5–31.6), 18.7 (15.9–21.6)	20.3 (17.2–23.4), 18.7 (15.9–21.6)
Difference	7.8 (3.2–12.4)	9.3 (4.7–14.0)	1.6 (−2.7–5.8)
p value	0.003	<0.001	0.751
PDQ-8 SUM	NFL MFL	NFL NoFL	MFL NoFL
Mean (95% CI)	9.0 (7.8–10.1), 6.5 (5.5–7.5)	9.0 (7.8–10.1), 6.0 (5.1–6.9)	6.5 (5.5–7.5), 6.0 (5.1–6.9)
Difference	2.5 (1.0–4.0)	3.0 (1.5–4.5)	0.5 (−0.9–1.9)
p value	0.003	<0.001	0.752

NFL, Patients with non-motor fluctuations; MFL, Patients with only motor fluctuations; NoFL, Patients with no fluctuations; PDQ-8 SI, The Parkinson's Disease Questionnaire-8 summary index; PDQ-8 SUM, The Parkinson's Disease Questionnaire-8 sum score; WOQ-9, 9-item Wearing-off Questionnaire; CI, confidence interval. For multivariable analysis, mean differences, 95% confidence intervals, and value of *p*s were estimated using ANCOVA with Tukey's *post hoc* test, including age, sex, disease duration, MDS-UPDRS part III score, and hallucination as covariates.

characteristics among the three groups are presented in Table 1. The age, and age at PD onset of the NoFL group were significantly higher than those of the other two groups. The disease duration of the NoFL group was shorter than those of the other two groups ($p = 0.038$). The higher scores of PDQ-8 corresponded to lower scores of QOL (Table 1).

In the first analysis, the scores of PDQ-8 SUM and PDQ-8 SI in the NFL group were significantly higher than those in the other two groups even after adjusting for covariates (NFL group vs. MFL group regarding PDQ-8 SUM: differences, 2.5, 95% CI 1.0–4.0, value of *p*, 0.003; NFL group vs. NoFL group regarding PDQ-8 SUM: differences, 3.0, 95% CI, 1.5–4.5, value of $p < 0.001$; NFL group vs. MFL group regarding PDQ-8 SI: differences, 7.8, 95% CI, 3.2–12.4, value of *p*, 0.003; NFL group vs. NoFL group regarding PDQ-8 SI: differences 9.3, 95% CI, 4.7–14.0, value of $p < 0.001$; Table 2).

In the second analysis, there were linear associations between the scores of PDQ-8 SUM/PDQ-8 SI and the numbers of motor/non-motor fluctuations. The value of *p* trend for the associations between motor numbers and PDQ-8 SUM, motor numbers and PDQ-8 SI, non-motor numbers and PDQ-8 SUM, and non-motor numbers and PDQ-8 SI were 0.003, 0.003, <0.001, and < 0.001, respectively. Furthermore, the value of *p* trend for the associations between the total number of motor and non-motor fluctuations and PDQ-8 SUM and between the total number of motor and non-motor fluctuations and PDQ-8 SI were <0.001 and <0.001, respectively (Table 3; Figure 1).

TABLE 3 Relationship between the scores of PDQ-8 SUM/PDQ-8 SI and the number of motor fluctuations; relationship between the scores of PDQ-8 SUM/ PDQ-8 SI and the number of non-motor fluctuations.

	The numbers of motor fluctuation						*p* for trend
	0	1	2	3	4	5	
N	154	77	79	40	20	5	
PDQ-8 SI Mean (SD)	17.7 (15.2)	22.6 (21.5)	23.6 (21.0)	26.5 (22.7)	27.7 (20.1)	37.5 (16.1)	0.003
PDQ-8 SUM Mean (SD)	5.7 (4.9)	7.2 (6.9)	7.6 (6.7)	8.5 (7.3)	8.9 (6.4)	12.0 (5.2)	0.003
	The numbers of non-motor fluctuation						*p* for trend
	0	1	2	3	4		
N	277	51	26	19	2		
PDQ-8 SI Mean (SD)	18.9 (17.9)	27.9 (20.6)	25.1 (20.4)	39.8 (21.2)	39.1 (2.2)		<0.001
PDQ-8 SUM Mean (SD)	6.0 (5.7)	8.9 (6.6)	8.0 (6.5)	12.7 (6.8)	12.5 (0.7)		<0.001

PDQ-8 SI, The Parkinson's Disease Questionnaire-8 summary index; PDQ-8 SUM, The Parkinson's Disease Questionnaire-8 sum score; WOQ-9, 9-item Wearing-off Questionnaire.

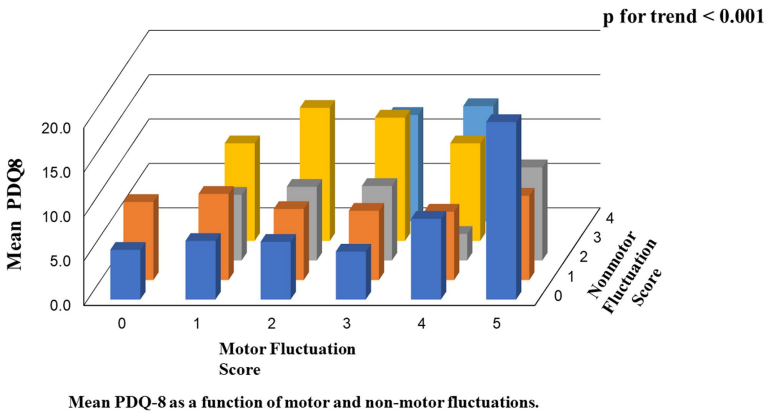

FIGURE 1
Motor and nonmotor fluctuations.

Among the items in WOQ-9, pain is the most weighted fluctuated symptom related to QOL, followed by anxiety. In addition, a multivariable analysis was performed to examine the association between combination of WOQ-9 items on non-motor fluctuation and QOL, but no combination was found to be correlated ($p = 0.157$).

In the third analysis, all of the 375 PwPD were classified by disease duration into the following four groups. We used ANCOVA including age, sex, and MDS-UPDRS part III score as covariates. The first group which contained 60 (16.0%) patients was classified as a DU1. The second group had 53 (14.1%) patients was labeled DU2. The third group labeled as DU3 had 145 (38.7%) patients. Then, the fourth group, DU4, had 117 (31.2%) patients. We studied the relationships between disease duration and fluctuations in PwPD (Figure 2). The proportion of PwPD with motor and non-motor fluctuations increased when the PD disease duration increased ($p < 0.05$).

In the fourth analysis, two out of the 375 PwPD were excluded due to lack of motor subtype data, then the total of 373 PwPD was classified by motor subtypes into the three groups: tremor-dominant, postural instability and gait difficulty, and mixed. The non-motor fluctuations of mood changes, pain, cloudy/thinking, and anxiety/panic among the three groups were analyzed by chi-square test. We obtained a clear relationship between the non-motor fluctuation of cloudy/thinking and motor subtypes ($p < 0.05$), while others have no relationship with motor subtypes (Table 4). PwPD with the motor subtype of postural instability and gait difficulty have a clear correlation with the non-motor fluctuation of cloudy/thinking.

Discussion

This single-center, retrospective study conducted in Japan showed that non-motor fluctuations were an independent risk factor for reducing patients' QOL. Prevalence of non-motor fluctuations were found in 26.1% of the participants, and increased with severity of PD. These results were slightly lower overall than the frequency of NMF in the MDS-NMS study of 9.1% for <2 years of disease duration, 54.3% for 2–5 years, 63.6% for 5–10 years, and 71.0% for ≥10 years, with an average of 49.2% (22). It is known that factors such as older age, disease duration, reduced activity of daily living, severity of motor symptoms, and long off-time reduce the QOL score of PwPD (23). Using a score that quantified non-motor symptoms, it has been reported that non-motor symptoms are more important than motor symptoms for QOL in PwPD (11). To date, no studies have evaluated the relationship between non-motor fluctuations and QOL in

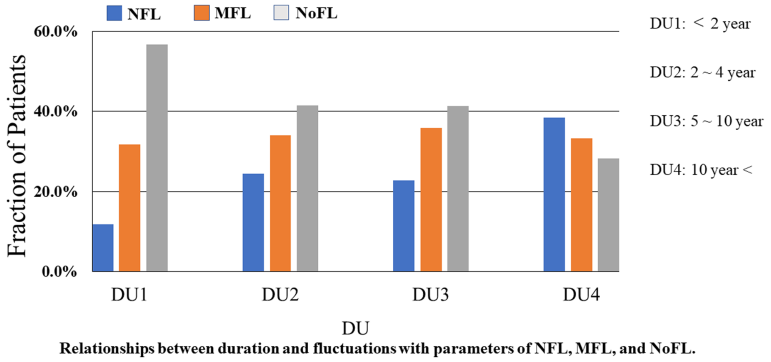

FIGURE 2
Relationship between duration and fluctuations.

TABLE 4 Mood changes between PwPD with the three motor subtypes according to the results of WOQ-9; pain/aching between PwPD with the three motor subtypes according to the results of WOQ-9; cloudy/thinking between PwPD with the three motor subtypes according to the results of WOQ-9; and anxiety/Panic between PwPD with the three motor subtypes according to the results of WOQ-9.

		Motor subtypes			*p* value
WOQ-9		Tremor-dominant	Postural instability and gait difficulty	Mixed	
Mood changes	Yes	22 (5.9)	26 (7.0)	4 (1.1)	0.181
	None	180 (48.3)	122 (32.7)	19 (5.1)	
Pain/Aching	Yes	18 (4.8)	18 (4.8)	2 (0.5)	0.593
	None	184 (49.3)	130 (34.9)	22 (5.9)	
Cloudy/Thinking	Yes	17 (4.6)	30 (8.0)	2 (0.5)	0.004
	None	185 (49.6)	118 (31.6)	21 (5.6)	
Anxiety/Panic	Yes	11 (2.9)	14 (3.8)	4 (1.1)	0.079
	None	191 (51.2)	134 (35.9)	19 (5.1)	

WOQ-9, 9-item Wearing-off Questionnaire. In the four present analyses, *p* values were estimated using chi-square tests. Statistical significance was defined as value of $p < 0.05$. All data are presented as *n* (%).

comparison with motor fluctuations. In this study, PDQ-8 scores such as SUM and SI in the NFL group were higher than scores for MFL and NoFL ($p < 0.001$), implying that the NFL group had the poorest QOL among groups. WOQ-9 is a simple tool that can be easily used in daily clinical practice for research, as opposed to a complicated questionnaire. It was shown that non-motor fluctuations obtained in this assessment directly affected QOL, making it a target for more aggressive therapeutic intervention. Generally, non-motor fluctuations appear after the presence of motor fluctuations, however, in this study there were a few cases in which only non-motor fluctuations were seen, without the motor fluctuations shown in the previous study (10). In addition, it was observed that non-motor fluctuations could appear even at an early stage; alternately, there were many patients who continued with only motor fluctuations for a long time. Thus, it can be considered that the group with the earliest occurrence of non-motor fluctuations formed a subtype with poor QOL such as a subtype with severe motor and non-motor dysfunction/malignancy.

This study has some limitations. This was a single center, cross-sectional study, therefore the number of patients was limited. However, reliability of the data was confirmed because diagnosis and clinical evaluation was performed by specialists of movement disorders. Patients were consecutive without selection, and they were involved from an early stage to a progressive one. Second, the study did not include patients with severe dementia or more advanced stages. Third, the study did not include detailed information on medications other than LED. Medication content may affect the prevalence of non-motor fluctuations, and further investigation considering the type of antiparkinsonian medications is necessary. Fourth, evaluation of non-motor fluctuations by MDS-NMS, which has recently been validated as a new qualitative test, was not performed in this study. In addition, the reason for the lower non-motor fluctuation prevalence compared to the MDS-NMS Non-Motor Fluctuations subscale (12) in this study may have been due to the lower sensitivity of non-motor fluctuations as a result of using WOQ-9 rather than MDS-NMS. However, the usefulness of WOQ-9 lies in its simplicity, which makes it suitable for use during routine clinical practice. We here investigated how combinations within the four non-motor items of WOQ-9 correlated with QOL, but owing to the small number of patients in each group, we were unable to obtain significant differences. Since it seems important to ascertain which combinations of non-motor symptom items are most relevant to quality of life, future large-scale studies should be conducted to clarify this point. Further research is also needed to analyze the risk factors for non-motor fluctuations, which could not be examined here.

In conclusion, this is the first report to assess the prevalence of non-motor fluctuations using a simplified WOQ-9 in

PwPD. Furthermore, it was shown that the non-motor fluctuations affected QOL independently of motor fluctuations. Non-motor fluctuations should therefore be accurately evaluated in PwPD.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional ethics committee at the Department of Neurology, Fukuoka University Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

AK: methodology, statistical analysis, investigation, and writing—original draft. MK: statistical analysis. KK and TM: review and editing. YT: conceptualization, formal analysis, and supervision. All authors contributed to the article and approved the final version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. *J Neurochem*. (2016) 139:318–24. doi: 10.1111/jnc.13691

2. Wanneveich M, Moisan F, Jacqmin-Gadda H, Elbaz A, Joly P. Projections of prevalence, lifetime risk, and life expectancy of Parkinson's disease (2010-2030) in France. *Mov Disord*. (2018) 33:1449–55. doi: 10.1002/mds.27447

3. Rajput AH, Uitti RJ, Rajput AH, Offord KP. Timely levodopa (LD) administration prolongs survival in Parkinson's disease. *Parkinsonism Relat Disord*. (1997) 3:159–65. doi: 10.1016/s1353-8020(97)00030-8

4. Scigliano G, Musicco M, Soliveri P, Piccolo I, Girotti F, Giovannini P, et al. Mortality associated with early and late levodopa therapy initiation in Parkinson's disease. *Neurology*. (1990) 40:265–9. doi: 10.1212/wnl.40.2.265

5. Fox SH, Katzenschlager R, Lim SY, Barton B, de Bie RMA, Seppi K, et al. Movement Disorder Society evidence-based medicine committee. International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord*. (2018) 33:1248–66. doi: 10.1002/mds.27372

6. Cilia R, Akpalu A, Sarfo FS, Cham M, Amboni M, Cereda E, et al. The modern pre-levodopa era of Parkinson's disease: insights into motor complications from sub-Saharan Africa. *Brain*. (2014) 137:2731–42. doi: 10.1093/brain/awu195

7. Obeso JA, Grandas F, Vaamonde J, Luquin MR, Artieda J, Lera G, et al. Motor complications associated with chronic levodopa therapy in Parkinson's disease. *Neurology*. (1989) 39:11–9.

8. Witjas T, Kaphan E, Azulay JP, Blin O, Ceccaldi M, Pouget J, et al. Nonmotor fluctuations in Parkinson's disease: frequent and disabling. *Neurology*. (2002) 59:408–13. doi: 10.1212/wnl.59.3.408

9. Pfeiffer RF. Non-motor symptoms in Parkinson's disease. *Parkinsonism Relat Disord*. (2016) 22:S119–22. doi: 10.1016/j.parkreldis.2015.09.004

10. Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol*. (2006) 5:235–45. doi: 10.1016/S1474-4422(06)70373-8

11. Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KRNMSS Validation Group. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. *Mov Disord*. (2011) 26:399–406. doi: 10.1002/mds.23462

12. Rodriguez-Blazquez C, Schrag A, Rizos A, Chaudhuri KR, Martinez-Martin P, Weintraub D. Prevalence of non-motor symptoms and non-motor fluctuations in Parkinson's disease using the MDS-NMS. *Mov Disord Clin Pract*. (2021) 8:231–9. doi: 10.1002/mdc3.13122

13. Stacy MA, Murphy JM, Greeley DR, Stewart RM, Murck H, Meng X, et al. The sensitivity and specificity of the 9-item wearing-off questionnaire. *Parkinsonism Relat Disord*. (2008) 14:205–12. doi: 10.1016/j.parkreldis.2007.07.013

14. Fukae J, Higuchi MA, Yanamoto S, Fukuhara K, Tsugawa J, Ouma S, et al. Utility of the Japanese version of the 9-item wearing-off questionnaire. *Clin Neurol Neurosurg*. (2015) 134:110–5. doi: 10.1016/j.clineuro.2015.04.021

15. Stacy M, Bowron A, Guttman M, Hauser R, Hughes K, Larsen JP, et al. Identification of motor and nonmotor wearing-off in Parkinson's disease: comparison of a patient questionnaire versus a clinician assessment. *Mov Disord*. (2005) 20:726–33. doi: 10.1002/mds.20383

16. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. (2015) 30:1591–601. doi: 10.1002/mds.26424

17. Kashihara K, Kondo T, Mizuno Y, Kikuchi S, Kuno S, Hasegawa K, et al. Official Japanese version of the International Parkinson and Movement Disorder Society-unified Parkinson's disease rating scale: validation against the original English version. *Mov Disord Clin Pract*. (2014) 1:200–12. doi: 10.1002/mdc3.12058

18. Nasreddine ZS, Phillips NA, Bedirian V, Bédirian V, Charbonneau S, Whitehead V, et al. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. (2005) 53:695–9. doi: 10.1111/j.1532-5415.2005.53221.x

19. Fujiwara Y, Suzuki H, Yasunaga M, Sugiyama M, Ijuin M, Sakuma N, et al. Brief screening tool for mild cognitive impairment in older Japanese: validation of the Japanese version of the Montreal cognitive assessment. *Geriatr Gerontol Int*. (2010) 10:225–32. doi: 10.1111/j.1447-0594.2010.00585.x

20. Zung WW. A self-rating depression scale. *Arch Gen Psychiatry*. (1965) 12:63–70. doi: 10.1001/archpsyc.1965.01720310065008

21. Peto V, Jenkinson C, Fitzpatrick R. PDQ-39: a review of the development, validation and application of a Parkinson's disease quality of life questionnaire and its associated measures. *J Neurol*. (1998) 245:S10–4. doi: 10.1007/pl00007730

22. van Wamelen DJ, Rota S, Schrag A, Rizos A, Martinez-Martin P, Weintraub D, et al. Characterization of non-motor fluctuations using the movement disorder society non-motor rating scale. *Mov Disord Clin Pract*. (2022) 9:932–40. doi: 10.1002/mdc3.13520

23. Zhao N, Yang Y, Zhang L, Zhang Q, Balbuena L, Ungvari GS, et al. Quality of life in Parkinson's disease: a systematic review and meta-analysis of comparative studies. *CNS Neurosci Ther*. (2021) 27:270–9. doi: 10.1111/cns.13549

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Long-term effects of intrajejunal levodopa infusion on sleep in people with advanced Parkinson's disease

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Background: Sleep disturbances are commonly encountered in people with advanced Parkinson's disease (PD). In these stages, levodopa–carbidopa intestinal gel (LCIG) is recommended for improving motor symptoms, some non-motor dysfunctions, and quality of life in these patients. This study aimed to assess the effects of LCIG on sleep in PD in a longitudinal study.

Study design: An open-label observational study in patients with advanced PD undergoing LCIG treatment was carried out.

Measures and outcomes: In total, 10 consecutive advanced people with PD were evaluated at the baseline and after 6 months and 1 year, respectively, of LCIG infusion. Sleep parameters were assessed with several validated scales. We assessed the evolution of sleep parameters under LCIG infusion over time and the effects on sleep quality.

Results: Significant improvement following LCIG was observed in PSQI total score ($p = 0.007$), SCOPA-SLEEP total score ($p = 0.008$), SCOPA-NS subscale ($p = 0.007$), and AIS total score ($p = 0.001$) at 6 months and 1 year, compared to the baseline. The PSQI total score at 6 months correlated significantly with the Parkinson's Disease Sleep Scale, version 2 (PDSS-2) "disturbed sleep" item at 6 months ($p = 0.28$; $R = 0.688$), while the PSQI total score at 12 months significantly correlated with the PDSS-2 total score at 1 year ($p = 0.025$, $R = 0.697$) and with the AIS total score at 1 year ($p = 0.015$, $R = 0.739$).

Conclusion: LCIG infusion demonstrated beneficial effects on sleep parameters and sleep quality, which were constant over time for up to 12 months.

KEYWORDS

intrajejunal levodopa infusion, sleep, insomnia, advanced Parkinson's disease, longitudinal

1. Introduction

Sleep disorders are common in people with Parkinson's disease (PwPD) (1). A broad spectrum of sleep complaints has been identified in these patients: insomnia, fragmented sleep, daytime sleepiness, restless legs syndrome (RLS), nocturia, and REM sleep behavior disorder (RBD) (1). Previous studies have suggested that the prevalence of sleep disturbances is higher as the disease advances (2, 3); moreover, sleep complaints are among the top five most bothersome symptoms in people with advanced PD (4) and are associated with a reduced quality of life, which is more evident as the disease progress (5).

As the co-occurrence of sleep disturbances in people with PD might have several causes, being related to complex motor complications in some of the cases, a personalized approach is advisable for the thorough assessment of sleep complaints in order to establish a comprehensive management plan (6). The diagnosis and treatment of symptoms during nighttime were reported by patients as an unmet need. More focus on the management of these symptoms with a 24-h complex approach is advised (7).

Traditional treatment in PD aims to control motor symptoms. The most commonly used oral products, levodopa/benserazide and levodopa/carbidopa, offer control of the motor features, until the onset of motor fluctuations, with no effect on disease progression (8). Levodopa–carbidopa intestinal gel (LCIG) infusion with an average duration of 15–16 h/day represents an effective treatment of complex motor symptoms in people with advanced PD (9, 10). Previous studies reported an improvement in certain non-motor symptoms, including beneficial consequences on sleep and general quality of life (11–13). These studies assessed globally the non-motor symptoms. Few studies have assessed the efficacy of LCIG over time specifically on sleep disturbances.

The objectives of this open-label observational study were to assess the effectiveness of LCIG infusion on sleep disturbances in PwPD at 6 months and 1 year after the initiation of this treatment.

2. Materials and methods

2.1. Patients and study design

Consecutive people with advanced PD who started LCIG infusion were recruited from the Department of Neurology, County Clinical Hospital of Braşov, Romania. The inclusion criteria were as follows: (i) diagnosis of PD according to the MDS clinical diagnosis criteria of PD (14); (ii) advanced stage of the disease, in treatment with LCIG (15); (iii) no dementia or severe cognitive impairment (Mini-Mental State Examination test $>$ 24); and (iv) patients who were willing to voluntarily participate in the study (by signing the informed consent). The exclusion criteria were as follows: (i) secondary parkinsonism; (ii) advanced PD patients with indications for other device-aided therapies; (iii) severe cognitive impairment; and (iv) comorbidities known to impair sleep and quality of sleep (such as stroke, chronic pulmonary, renal, or hepatic disorders).

Patients underwent clinical assessment at the baseline (prior to LCIG treatment), and after 6 and 12 months of LCIG treatment, respectively. The evaluation of the patients was performed in "ON" states.

2.2. Clinical assessment

Information regarding age, gender, age at PD onset, duration of disease, Hoehn & Yahr (H&Y) stage during ON and OFF stages, previous medication for sleep disorders, and levodopa equivalent daily dose (LEDD) were collected. Patients were assessed at all three time points with validated scales for cognition evaluation (Mini-Mental State Examination—MMSE) and for sleep examination, which are described below. All patients included in the present study signed informed consent forms. The study was approved by the Ethics Committee of the University Transilvania of Braşov (1.11/01/2019).

2.3. Questionnaires

We used questionnaires and scales validated for PwPD. The Parkinson's Disease Sleep Scale, version 2 (PDSS-2) is a comprehensive evaluation scale of the various sleep impairments commonly identified in PD (16). For all 15 questions included in the questionnaire, the patient chooses an appropriate response from zero (never) to four (very frequent). The highest score of 60 represents maximal nocturnal disturbance, while a cutoff score of 15 was proposed to identify "bad" sleepers (16). In total, three derived PDSS-2 subscales could be identified (16), with a maximum score of 20 each: "disturbed sleep": items 1–3, 8, and 14; "motor problems at night": items 4–6, 12, and 13; "PD symptoms at night": items 7, 9–11, and 15. Nocturia was assessed using item 8 of the PDSS-2.

The Scale for Outcomes in Parkinson's Disease-Sleep (SCOPA-SLEEP) (17) was designed specifically for evaluating sleep characteristics in the PD population. The subscale assessing the night symptoms (SCOPA-NS) consists of five items offering a grading possibility from 0 ("not at all") to 3 ("a lot"), with a cutoff score of 7 indicating nighttime impairments (17, 18). Similarly, sleep symptoms during the daytime were evaluated through six items within the SCOPA-Daytime Symptoms subscale (SCOPA-DS), with a cutoff score of five, suggestive of the presence of disturbances (17). One additional item, which does not count for the total score, explores the overall sleep quality, varying from "very well" to "very bad" (17).

The Pittsburgh Sleep Quality Index (PSQI) (19) is a frequently used generic scale containing 19 questions for the assessment of the quality of sleep. A score of $\geq$5 was proposed to identify "bad" sleepers (19, 20).

The Athens Insomnia Scale (AIS) is a self-administered questionnaire designed for assessing the severity of insomnia. It consists of eight questions related to various aspects of insomnia, with a maximum score of 24 points indicating severe disturbances (21). A score higher than 6 is suggestive of patients with insomnia (22). We used the following criteria for grading the severity of insomnia, as proposed by Okajma et al.: absent (0–5), mild (6–9), moderate (10–15), and severe (16–24) (23).

The Epworth Sleepiness Scale (ESS) (24) was used to evaluate daily sleepiness. The patients' scores evaluated were from zero (never) to three (always), showing the probability of falling asleep in different eight daily situations. Scores higher than 10 were considered suggestive of EDS (25).

2.4. Data analysis

Data were analyzed using the SPSS software package for Windows, release 23.0. Descriptive data were used in order to evaluate the patients' clinical characteristics at the baseline. The Wilcoxon signed-rank test is used if the differences between pairs

of data are non-normally distributed, while the Friedman test can compare more than two groups. Therefore, the Wilcoxon signed-rank test was applied for comparisons of test score values before and after the initiation of LCIG. The Friedman test was used to compare the mean ranks before and after 6 and 12 months after LCIG. We applied Bonferroni's correction in case of multiple comparisons using Microsoft Excel.

Spearman's rank correlation coefficients were employed for associations. All *p*-values reported were two-tailed. A probability *p*-value of <0.05 was considered to be statistically significant.

3. Results

A total of 10 PD patients were enrolled in this longitudinal research. In the study, three patients were female subjects. The mean age ± standard deviation (SD) at inclusion was 69.8 ± 8.4 years, the mean age ± SD of disease onset was 62.8 ± 9.3 years and that of PD duration was 7 ± 2.74 years. The mean infusion duration ± SD was 15 ± 0.87 h/day. None of our patients was treated for 24 h/day. LEDD increased slightly from 1261 ± 334 mg at the baseline to 1373 ± 373 mg ($p = 0.008$) at 12 months after LCIG. None of the patients received other oral dopaminergic treatment following LCIG initiation. MAO inhibitors were withdrawn in all patients, and four patients received clonazepam for treatment of probable RBD symptoms at the baseline and during the entire follow-up period, and another patient received lorazepam for treatment of insomnia at the baseline and had reduced the dose at 12 months after LCIG implementation. The mean value of the Hoehn and Yahr stage in ON state ± SD was 3.6 ± 0.51 at the baseline, 2.9 ± 0.31 at 6 months, and 3 ± 0.47 at 12 months follow-up. Significant improvement following LCIG was observed at 6 and 12 months in the PSQI total score ($p = 0.007$), SCOPA-SLEEP total score ($p = 0.008$), SCOPA-NS subscale ($p = 0.007$), and AIS total score ($p = 0.001$; Table 1). No significant differences were observed between the ESS score ($p = 0.27$) and SCOPA-DS ($p = 0.37$) at 6 and 12 months following LCIG.

Regarding sleep quality, as evaluated with PSQI, three subdomains showed significant improvement following LCIG at 6 and 12 months (Table 2): component 1, *subjective sleep quality* ($p = 0.004$), Component 2, *sleep latency* ($p = 0.012$), and component 4, *sleep efficiency* ($p = 0.003$).

Total sleep time, which was self-estimated by the patients, has increased from 5.9 ± 1.19 h before the initiation of LCIG treatment to 7 ± 0.66 h at 6 months after LCIG initiation and to 7.2 ± 0.63 h at 12 months of treatment ($p = 0.001$). As expected, the PDSS-2 total score significantly improved over time (0.006). All three subdomains of the PDSS-2 for "disturbed sleep," "motor problems at night," and "PD symptoms at night" showed improvement following LCIG infusion (Table 3). Specifically, the items "poor sleep quality," "difficulties to fall asleep," "difficulties to stay asleep," "tiredness in the morning," "painful postures in the morning," "tremor when waking," "uncomfortable and immobility," and "painful arms or legs" demonstrated a statistically significant change from the baseline (Figure 1). There was a trend toward an improvement in symptoms related to nocturia, distressing dreams, and muscular cramps and a trend toward worsening of hallucinations; however, these trends did not reach statistical significance.

With regard to SCOPA-SLEEP total and SCOPA-NS subscores, results showed a quite remarkable improvement in sleep quality. Mean SCOPA-SLEEP total was 15.9 ± 5.91 at the baseline, with an improvement after 6 months (10.1 ± 2.51), respectively after 12 months (5.91 ± 2.21; $p = 0.008$; Table 1). The evolution of the overall item ("C1—Overall, how well you slept at night during the past month?") in SCOPA-SLEEP is presented in Table 4. A trend of improvement in subjective quality of sleep was noted in most of the patients after LCIG therapy at 6 and 12 months.

Regarding the quality of sleep and other sleep parameters, Spearman rank correlation analyses were performed. The PSQI total score at 6 months correlated significantly with PDSS2 "disturbed sleep" item at 6 months ($p = 0.28$; $R = 0.688$); moreover, there was a significant correlation between the PSQI total score at 12 months and the PDSS-2 total score at 12 months ($p = 0.025$, $R = 0.697$) and between PSQI total score at 12 months and AIS total score at 12 months ($p = 0.015$, $R = 0.739$). Significant differences were also found for the baseline measurement vs. 12 months reevaluation, after Bonferroni correction, except for Component 4: Sleep efficiency (p 0.003 vs. 0.039) of PDSS2.

4. Discussion

This study evaluated the effect of LCIG treatment in advanced PD at 6 and 12 months. Sleep complaints have been reported by more than half of PD patients, being known to significantly affect the quality of life in these patients (26). Therefore, it is essential for clinicians to establish a comprehensive therapeutical plan that should be effective for both motor and non-motor characteristics. Sleep disorders were commonly reported in our study group. In total, four patients were previously diagnosed with probable RBD and were treated with clonazepam, one patient was treated with lorazepam for persistent insomnia, while the other patients had no treatment for their sleep disorders.

Several explanations for the development of sleep disturbances in advanced PD have been proposed. Due to fluctuations in the motor symptoms and the association of painful cramps, akinesia, and dystonia during night, sleep might also be disturbed (27). Neurodegeneration of the regions involved in sleep regulation and low concentrations of dopaminergic medications during night might be involved in the occurrence of sleep complaints in advanced PD (28). Moreover, early morning off periods, which can be identified in almost 60% of PwPD with dopaminergic treatment, might also cause several disturbances during nighttime, given the number of non-motor symptoms that can be associated—the urgency of urination, anxiety, pain, and limb paresthesia (29).

The main finding of our research was a significant improvement in sleep parameters and quality of sleep at 6 and 12 months after LCIG initiation. Total scores of the PDSS-2, SCOPA-SLEEP and SCOPA-SLEEP NS subscale, AIS, and PSQI showed significant reductions compared to the baseline. Overall sleep disturbances persisted at 12-month follow-up but with reduced intensity.

TABLE 1 Assessment of people with Parkinson's disease at LCIG infusion initiation (baseline) and after 6 and 12 months of LCIG infusion.

		Baseline	6 months	12 months	*p*-value*	*p*-value**
MMSE	Mean	28.9	29.10	28.90	0.568	0.999
	SD	1.52	1.28	0.99		
PSQI total	Mean	10.10	6.9	6.2	**0.007**	**0.004**
	SD	3.24	2.13	2.04		
SCOPA—SLEEP	Mean	15.9	10.1	9.7	**0.008**	**0.006**
	SD	5.91	2.51	2.21		
SCOPA—NS	Mean	10.5	5.5	5.4	**0.007**	**0.000**
	SD	3.62	0.7	0.699		
SCOPA—DS	Mean	5.4	4.6	4.3	0.37	0.369
	SD	2.98	2.31	2.31		
AIS	Mean	17.1	7.4	13.7	**0.001**	**0.0001**
	SD	5.83	1.83	3.46		
ESS	Mean	10.9	9.2	8.9	0.27	0.387
	SD	5.52	4.56	4.53		

*Friedman test; Significant results are indicated in bold. Values are expressed as average (standard deviation). **Bonferroni adjusted $p < 0.016$ for baseline measurement vs. 12 months. AIS, Athens Insomnia Scale; ESS, Epworth Sleepiness Scale; MMSE, Mini-Mental State Examination; PSQI, Pittsburgh Sleep Quality Index; SCOPA—NS, Scale for Outcomes in Parkinson's Disease (Sleep)—Night Symptoms; SCOPA—DS, Scale for Outcomes in Parkinson's Disease (Sleep)—Day Symptoms.

TABLE 2 PSQI test scores and its subdomains in the people with Parkinson's disease, at the baseline and after 6 and 12 months of LCIG infusion.

	Baseline	6 months	12 months	*p*-value*	*p*-value**
Component 1: subjective sleep quality	2.1 (0.73)	1.1 (0.31)	1.1 (0.31)	**0.004**	**0.001**
Component 2: sleep latency	2.6 (0.69)	1.9 (0.56)	1.7 (0.48)	**0.012**	**0.003**
Component 3: sleep duration	1 (1.05)	0.8 (0.42)	0.7 (0.48)	0.687	0.424
Component 4: sleep efficiency	1.3 (1.05)	0.4 (0.96)	0.3 (0.94)	**0.003**	0.039
Component 5: sleep disturbance	1.4 (0.51)	1.2 (0.42)	1.1 (0.31)	0.097	0.134
Component 6: sleep medication	0.8 (1.31)	0.5 (1.08)	0.4 (0.96)	0.156	0.448
Component 7: daytime dysfunction	0.9 (0.56)	1 (0)	0.9 (0.31)	0.717	1.000

*Friedman test; significant results are indicated in bold. Values are expressed as average (standard deviation). **Bonferroni adjusted $p < 0.016$ for baseline measurement vs. 12 months. PSQI, Pittsburgh Sleep Quality Index.

Insomnia, one of the most frequently declared sleep problems in PD patients, was demonstrated to be less severe with LCIG therapy (most of the subjects reported moderate insomnia at the baseline and mild insomnia at the two follow-up visits, as recorded with the total AIS score). The items from the PDSS-2 concerning insomnia ("difficulty falling asleep" and "difficulty staying asleep") showed significant changes from the baseline, suggesting improvements in this domain. Poor sleep quality, tiredness in the morning, as well as other symptoms related to motor problems or PD symptoms at nighttime (painful postures in the morning, tremor, immobility and discomfort, and limb pain) presented a significant improvement with continuous dopamine delivery, as evaluated with PDSS-2. On the contrary, for item 7 of the PDSS-2 ("distressing hallucinations"), it was noticed a slight worsening at 12 months compared to that of the baseline and 6 months, and item 15 ("snoring") was constant during the entire follow-up period. Daytime sleepiness (as evaluated with ESS and SCOPA-DS) did not show statistically significant improvement during the follow-up period. This result might be explained either by the small sample size or by increased LEDD administration.

To the best of our knowledge, few studies have characterized the evolution of sleep parameters over time as a primary outcome in patients treated with LCIG infusion.

Our conclusions are in line with the results of other studies, which revealed that an appropriate dopaminergic supply during nighttime can be effective on sleep complaints. However, most of the previous questionnaire-based studies have assessed the effectiveness of LCIG infusion using multidomain scales such as the Non-Motor Symptoms Questionnaire (NMSQ) or Non-Motor Symptoms Scale (NMSS), which contain only some items related to sleep complaints. In our study, we used several validated scales to examine more specifically insomnia, sleep fragmentation, EDS, and the consequences of sleep disturbances on quality of life.

TABLE 3 PDSS-2 in the people with Parkinson's disease at the baseline and after 6 and 12 months of LCIG infusion.

	Baseline	6 months	12 months	*p*-value*	*p*-value**
Total sleep time (hours)	5.9 (1.19)	7.00 (0.66)	7.2 (0.63)	**0.001**	**0.007**
PDSS-2 total score	27.9 (13.08)	17.18 (6.99)	17.18 (7.6)	**0.006**	**0.003**
Disturbed sleep					
Item 1 reduced sleep quality	2.5 (0.84)	1.2 (0.42)	1.2 (0.42)	**0.004**	**0.004**
Item 2 difficulties to fall asleep	3.4 (1.07)	1.6 (0.51)	1.5 (0.52)	**0.003**	**0.000**
Item 3 difficulties to stay asleep	2.7 (1.05)	1.7 (0.48)	1.6 (0.51)	**0.013**	**0.008**
Item 8 passing urine during night	2.4 (1.17)	2.3 (1.15)	2.2 (1.13)	0.223	0.7
Item 14 tiredness in the morning	2.9 (1.19)	1.7 (0.67)	1.7 (0.67)	**0.016**	**0.012**
Motor problems at night					
Item 4 restlessness of limbs	1.5 (1.08)	0.7 (0.82)	0.9 (0.73)	0.074	0.164
Item 5 urge to move the limbs	1.5 (1.08)	0.6 (0.84)	0.8 (0.78)	0.074	0.115
Item 6 distressing dreams	1.7 (0.94)	1.4 (0.96)	1.3 (0.82)	0.156	0.327
Item 12 painful postures in the morning	2.3 (1.25)	1.2 (0.42)	1.4 (0.51)	**0.028**	0.049
Item 13 tremor when waking	1.6 (1.5)	1.2 (1.13)	1.4 (1.2)	**0.05**	0.751
PD symptoms at night					
Item 7 hallucinations	0.1 (0.31)	0.1 (0.31)	0.2 (0.63)	0.368	0.66
Item 9 uncomfortable and immobility	3.3 (1.05)	1.2 (0.42)	1.6 (0.51)	**0.001**	**0.000**
Item 10 painful arms or legs	2.2 (1.03)	1.3 (0.48)	1.4 (0.51)	**0.013**	0.041
Item 11 muscle cramps in limbs	2.1 (1.1)	2.2 (2.78)	1.2 (0.63)	0.065	0.037
Item 15 snoring	0.5 (0.07)	0.5 (0.07)	0.5 (0.07)	-	-

*Friedman test; Significant results are indicated in bold. Values are expressed as average (standard deviation). **Bonferroni adjusted $p < 0.016$ for baseline measurement vs. 12 months. PD, Parkinson's disease; PDSS-2, Parkinson's Disease Sleep Scale version 2.

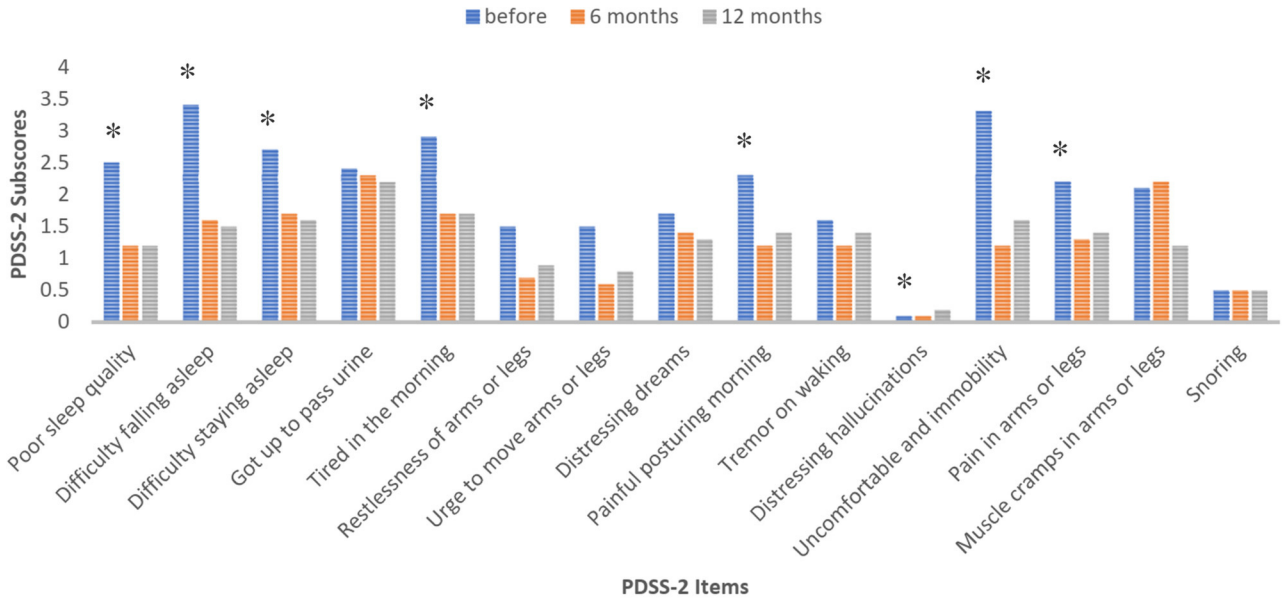

FIGURE 1
Evolution of the subscores (mean values) in the PDSS-2 at the baseline, 6 and 12 months follow-up. Values with asterisk (*) were statistically significant ($p < 0.05$), Friedman test.

TABLE 4 Evolution of overall item (C1—"Overall, how well you slept at night during the past month?") in SCOPA-SLEEP. Scores are shown in percentages.

Overall, how well you slept at night during the past month?	Baseline (%)	6 months follow up (%)	12 months follow up (%)
Very well	0	0	0
Well	0	50	40
Rather well	20	30	50
Not well but not badly	10	20	0
Rather badly	30	0	10
Badly	30	0	0
Very badly	10	0	0

SCOPA-SLEEP, Scale for Outcomes in Parkinson's Disease.

One of the first studies that demonstrated the benefits of LCIG on sleep was conducted by Honig et al. and included 22 PD patients who were followed up for 6 months (30). Significant improvements were observed in nine domains of the NMSS, including the sleep/fatigue domain (30).

Buongiorno et al. observed a significant decrease in insomnia at 3 months following the initiation of LCIG infusion, using a semi-structured interview (31).

One multicentric study analyzing the GLORIA registry included 258 PD patients in treatment with LCIG infusion, over a period of 24 months (12). The sleep domain was assessed with the NMSS, and at the last follow-up visit, a significant reduction in the sleep/fatigue domain score was recorded, compared to the baseline. The improvement in sleep quality was consistent with the alleviation of motor symptoms (12). Similar results were obtained by Chaudhuri et al. (13) from the GLORIA database. Among other non-motor symptoms, the sleep/fatigue domain assessed with the NMSS showed significant improvement compared to the baseline and also a significant association between the NMSS sleep scores and the improvement in the quality of life was observed (13).

The results at 1-year follow-up in the DUOGLOBE study showed an improvement in sleep complaints, as evaluated with the total PDSS-2 score. Improvements were also noticed in daytime sleepiness (ESS total score) (32); our results were in line with this even though in our study the positive effect on daytime symptoms measured with ESS and SCOPA-DS did not reach statistical significance.

Sleep parameters were assessed using PDSS-2 in two other previous studies (33, 34), with a significant improvement in LCIG therapy over time. Zibetti et al. (33) have also noticed that daytime sleepiness improved after 2–4 months of LCIG treatment in 12 patients.

On the contrary, De Fabregues et al. demonstrated that sleep quality was still poor in patients undergoing LCIG infusion, but it did not get worsened by the end of the follow-up period (35).

A better quality of sleep was observed in the study group. PSQI total scores decreased progressively at 6 and 12 months. Moreover, most of the patients included in our study evaluated a shorter sleep latency and better sleep efficiency (calculated as estimated total hours asleep/total hours in bed). Subjective improvement in sleep quality was correlated at 6 months with the alleviation of disturbed symptoms at night (difficulty initiating and maintaining sleep, nocturia, and tiredness in the morning) and at 12 months with an overall improvement in sleep complaints and reduced insomnia symptoms.

The effectiveness of LCIG infusion on sleep parameters and quality of sleep may be explained by a more stable concentration of levodopa obtained with the constant substance administration even though the infusion was stopped during nighttime. There are data suggesting that daytime LCIG may significantly improve sleep quality, as assessed using the PDSS scale and Parkinson's disease questionnaire PDQ-8 (27). The improvement of motor symptoms which appears to be steadier following continuous drug administration than oral therapies can be reflected on sleep patterns and might contribute to subjective improvements of complaints related to sleep.

We are aware that the present study has several limitations. The main limitation of this study is the lack of a control group. This was a questionnaire-based study, and the sleep disturbances identified in our patients were not assessed by objective methods, such as polysomnography. Several parameters, such as total sleep time, were self-estimated by the patients (anamnestic and not measured by polysomnography). We did not include the opinion or the evaluation of caregivers concerning the sleep quality of the patients. Furthermore, this is an unblinded open-label study. Considering the small sample size of our study, larger trial studies addressing specifically the effect of LCIG on sleep may be conducted. The power of the study is low; thus, some no significant differences in our study can become significant in a larger group. Several sleep disturbances, such as RLS, sleep apnea, or RBD were not evaluated specifically.

In conclusion, our findings suggest that sustained, long-term improvements in sleep parameters and sleep quality were obtained in patients undergoing LCIG infusion. In busy clinical practice, when complex objective assessments such as actigraphy or polysomnography are time-consuming and/or expensive to use, scales and questionnaires might be useful to monitor the effectiveness of medication on sleep. One may consider using the PDSS-2 to follow up on sleep disturbances under LCIG infusion as it assesses various aspects of sleep, is brief, and is easy to administer. Sleep disturbances have an important impact on quality of life, along with other motor and non-motor features associated with advanced PD. In these complex cases, the concept of personalized medicine should be applied. Our data support the observation that proper management of the motor symptoms with continuous levodopa delivery may also confer better sleep and a better quality of life for this category of PD patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the University Transilvania of Braşov (1.11/01/2019). The patients/participants provided their written informed consent to participate in this study.

Author contributions

ŞD, CF-P, and LI worked on conception and design of the study, and data collection, and analysis and interpretation of data. ŞD was drafting the article. LI, DŢ, and CF-P revised the article for important intellectual content. ŞD, LI, DŢ, and CF-P gave final approval of the version to be submitted. All authors contributed to the article and approved the submitted version.

Conflict of interest

CF-P received royalties from Elsevier and Springer Verlag, honoraria from Abbvie and International Parkinson's Disease and Movement Disorders Society, outside of the present work. DŢ received honoraria from Pfizer, Boehringer Ingelheim, Bayer, Novartis, and Astra Zeneca outside of the present work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer AF is currently editing a Research Topic with CF-P.

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References

1. Falup-Pecurariu C, Diaconu S. Sleep dysfunction in Parkinson's disease. *Int Rev Neurobiol*. (2017) 133:719–42. doi: 10.1016/bs.irn.2017.05.033

2. Sringean J, Stefani A, Marini K, Bergmann M, Werkmann M, Holzknecht E, et al. Rapid eye movement sleep behavior disorder and rapid eye movement sleep without atonia are more frequent in advanced versus early Parkinson's disease. *Sleep*. (2021) 44:zsab067. doi: 10.1093/sleep/zsab067

3. He G, Liu CF, Ye Q, Liu Z, Jin M, Shang H, et al. Prevalence and profile of nocturnal disturbances in chinese patients with advanced-stage Parkinson's disease: a cross-sectional epidemiology study. *BMC Neurol*. (2021) 21:194. doi: 10.1186/s12883-021-02217-5

4. Politis M, Wu K, Molloy S, G Bain P, Chaudhuri KR, Piccini P. Parkinson's disease symptoms: the patient's perspective. *Mov Disord*. (2010) 25:1646–51. doi: 10.1002/mds.23135

5. Liguori C, De Franco V, Cerroni R, Spanetta M, Mercuri NB, Stefani A, et al. Sleep problems affect quality of life in parkinson's disease along disease progression. *Sleep Med*. (2021) 81:307–11. doi: 10.1016/j.sleep.2021.02.036

6. Diaconu S, Falup-Pecurariu C. Personalized assessment of insomnia and sleep quality in patients with Parkinson's disease. *J Pers Med*. (2022) 12:322. doi: 10.3390/jpm12020322

7. Zhang H, Meng F, Li X, Ning Y, Cai M. Social listening - revealing Parkinson's disease over day and night. *BMC Neurol*. (2021) 21:2. doi: 10.1186/s12883-020-02024-4

8. Chen S, Le W. Neuroprotective therapy in Parkinson's disease. *Am J Ther*. (2006) 13:445–57. doi: 10.1097/01.mjt.0000174353.28012.a7

9. Antonini A, Odin P, Pahwa R, Aldred J, Alobaidi A, Jalundhwala YJ, et al. The long-term impact of levodopa/carbidopa intestinal gel on 'off'-time in patients with advanced Parkinson's disease: a systematic review. *Adv Ther*. (2021) 38:2854–90. doi: 10.1007/s12325-021-01747-1

10. Prakash N, Simuni T. Infusion therapies for Parkinson's disease. *Curr Neurol Neurosci Rep*. (2020) 20:44. doi: 10.1007/s11910-020-01062-2

11. Antonini A, Abbruzzese G, Berardelli A, Modugno N, Stroppa I, Tamma F, et al. The tandem investigation: efficacy and tolerability of levodopa-carbidopa intestinal gel in (LCIG) advanced Parkinson's disease patients. *J Neural Transm*. (2020) 127:881–91. doi: 10.1007/s00702-020-02175-1

12. Antonini A, Poewe W, Chaudhuri KR, Jech R, Pickut B, Pirtošek Z, et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's: final results of the Gloria registry. *Parkinson Relat Disord*. (2017) 45:13–20. doi: 10.1016/j.parkreldis.2017.09.018

13. Ray Chaudhuri K, Antonini A, Robieson WZ, Sanchez-Soliño O, Bergmann L, Poewe W. Burden of non-motor symptoms in Parkinson's disease patients predicts improvement in quality of life during treatment with levodopa-carbidopa intestinal gel. *Eur J Neurol*. (2019) 26:581.e43. doi: 10.1111/ene.13847

14. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. (2015) 30:1591–601. doi: 10.1002/mds.26424

15. Antonini A, Stoessl AJ, Kleinman LS, Skalicky AM, Marshall TS, Sail KR, et al. Developing consensus among movement disorder specialists on clinical indicators for identification and management of advanced Parkinson's disease: a multi-country Delphi-panel approach. *Curr Med Res Opin*. (2018) 34:2063–73. doi: 10.1080/03007995.2018.1502165

16. Trenkwalder C, Kohnen R, Högl B, Metta V, Sixel-Döring F, Frauscher B, et al. Parkinson's disease sleep scale–validation of the revised version PDSS-2. *Mov Disord*. (2011) 26:644–52. doi: 10.1002/mds.23476

17. Marinus J, Visser M, van Hilten JJ, Lammers GJ, Stiggelbout AM. Assessment of sleep and sleepiness in Parkinson disease. *Sleep*. (2003) 26:1049–54. doi: 10.1093/sleep/26.8.1049

18. Martinez-Martin P, Visser M, Rodriguez-Blazquez C, Marinus J, Chaudhuri KR, van Hilten JJ. Scopa-Sleep and PDSS: two scales for assessment of sleep disorder in Parkinson's disease. *Mov Disord*. (2008) 23:1681–8. doi: 10.1002/mds.22110

19. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res*. (1989) 28:193–213. doi: 10.1016/0165-1781(89)90047-4

20. Backhaus J, Junghanns K, Broocks A, Riemann D, Hohagen F. Test-retest reliability and validity of the pittsburgh sleep quality index in primary insomnia. *J Psychosom Res*. (2002) 53:737–40. doi: 10.1016/s0022-3999(02)00330-6

21. Soldatos CR, Dikeos DG, Paparrigopoulos TJ. Athens insomnia scale: validation of an instrument based on ICD-10 criteria. *J Psychosom Res*. (2000) 48:555–60. doi: 10.1016/s0022-3999(00)00095-7

22. Soldatos CR, Dikeos DG, Paparrigopoulos TJ. The diagnostic validity of the Athens insomnia scale. *J Psychosom Res*. (2003) 55:263–7. doi: 10.1016/s0022-3999(02)00604-9

23. Okajima I, Miyamoto T, Ubara A, Omichi C, Matsuda A, Sumi Y, et al. Evaluation of severity levels of the Athens insomnia scale based on the criterion of insomnia severity index. *Int J Environ Res Public Health*. (2020) 17:8789. doi: 10.3390/ijerph17238789

24. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. (1991) 14:540–5. doi: 10.1093/sleep/14.6.540

25. Johns MW. Sleepiness in different situations measured by the Epworth sleepiness scale. *Sleep*. (1994) 17:703–10. doi: 10.1093/sleep/17.8.703

26. Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, et al. The Priamo study: a multicenter assessment of nonmotor symptoms and

their impact on quality of life in Parkinson's disease. *Mov Disord*. (2009) 24:1641–9. doi: 10.1002/mds.22643

27. Stocchi F, Stirpe P. The relevance of dopaminergic level in nocturnal disability in Parkinson's disease: implications of continuous dopaminergic stimulation at night to treat the symptoms. *J Neural Transm*. (2014) 121(Suppl 1):S79–83. doi: 10.1007/s00702-014-1259-2

28. Abbott SM, Videnovic A. Chronic sleep disturbance and neural injury: links to neurodegenerative disease. *Nat Sci Sleep*. (2016) 8:55–61. doi: 10.2147/nss.S78947

29. Rizos A, Martinez-Martin P, Odin P, Antonini A, Kessel B, Kozul TK, et al. Characterizing motor and non-motor aspects of early-morning off periods in Parkinson's disease: an international multicenter study. *Parkinson Relat Disord*. (2014) 20:1231–5. doi: 10.1016/j.parkreldis.2014.09.013

30. Honig H, Antonini A, Martinez-Martin P, Forgacs I, Faye GC, Fox T, et al. Intrajejunal levodopa infusion in Parkinson's disease: a pilot multicenter study of effects on nonmotor symptoms and quality of life. *Mov Disord*. (2009) 24:1468–74. doi: 10.1002/mds.22596

31. Buongiorno M, Antonelli F, Cámara A, Puente V, de Fabregues-Nebot O, Hernandez-Vara J, et al. Long-term response to continuous duodenal infusion of levodopa/carbidopa gel in patients with advanced Parkinson disease: the Barcelona registry. *Parkinson Relat Disord*. (2015) 21:871–6. doi: 10.1016/j.parkreldis.2015.05.014

32. Standaert DG, Aldred J, Anca-Herschkovitsch M, Bourgeois P, Cubo E, Davis TL, et al. Duoglobe: one-year outcomes in a real-world study of levodopa carbidopa intestinal gel for Parkinson's disease. *Mov Disord Clin Pract*. (2021) 8:1061–74. doi: 10.1002/mdc3.13239

33. Zibetti M, Rizzone M, Merola A, Angrisano S, Rizzi L, Montanaro E, et al. Sleep improvement with levodopa/carbidopa intestinal gel infusion in Parkinson disease. *Acta Neurol Scand*. (2013) 127:e28–32. doi: 10.1111/ane.12075

34. Lopiano L, Modugno N, Marano P, Sensi M, Meco G, Solla P, et al. Motor and non-motor outcomes in patients with advanced Parkinson's disease treated with levodopa/carbidopa intestinal gel: final results of the greenfield observational study. *J Neurol*. (2019) 266:2164–76. doi: 10.1007/s00415-019-09337-6

35. De Fabregues O, Ferré A, Romero O, Quintana M, Álvarez-Sabin J. Sleep quality and levodopa intestinal gel infusion in Parkinson's disease: a pilot study. *Parkinsons Dis*. (2018) 2018:8691495. doi: 10.1155/2018/8691495

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Evaluation of perception threshold and pain in patients with Parkinson's disease using PainVision®

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Introduction: Pain is one of the most frequent non-motor symptoms occurring in patients with Parkinson's disease (PD). Traditionally, the Visual Analog Pain Scale (VAS), Numerical Rating Scale (NRS), and Wong-Baker Faces Pain Rating Scale (FRS) have been used for clinical pain assessment, but these assessments are subjective at best. In contrast, PainVision® is a perceptual/pain analyzer that can quantitatively evaluate pain as "pain intensity" based on "current perception threshold" and "pain equivalent current." We evaluated the current perception threshold in all PD patients and pain intensity in PD patients with pain using PainVision®.

Methods: We recruited 48 patients with PD (PwPD) with pain and 52 PwPD without pain. For patients with pain, we measured current perception threshold, pain equivalent current, and pain intensity using PainVision®, in addition to evaluation by VAS, NRS, and FRS. For patients without pain, only current perception threshold was measured.

Results: There was no correlation with either VAS or FRS, whereas only weak correlation was identified for NRS (γ = −0.376) with pain intensity. Current perception threshold was positively correlated with duration of the disease (γ = 0.347) and the Hoehn and Yahr stage (γ = 0.259). As a quantitative evaluation of pain, pain intensity by PainVision® does not correlate with conventional subjective pain assessments.

Discussion: This new quantitative evaluation method of pain may be suitable as an evaluation tool for future intervention research. Current perception threshold in PwPD was related to the duration and severity of the disease and may be involved in peripheral neuropathy associated with PD.

KEYWORDS

Parkinson's disease, pain, PainVision®, perception threshold, pain intensity

1. Introduction

Pain is one of the most salient non-motor symptoms that afflicts patients with Parkinson's disease (PwPD), and its frequency varies from 40 to 85%, depending on the report (1–3). Pain can occur at any stage of the disease, from early PD to advanced stages, and some pain is known to precede motor symptoms (4). As the disease progresses, the frequency of pain complications increases due to a variety of factors, including pain associated with motor fluctuation, dyskinesia, dystonia, and postural abnormalities. As it is a subjective sensation, pain has traditionally been considered difficult to quantify. The Visual Analog Pain Scale (VAS) is the most used, conventional pain assessment tool (5) because of its simplicity and ease of use. However, concern has been raised for its use as it is a subjective assessment tool that relies on patient reporting,

and these results can easily be swayed by personal experience and psychological factors. In response to this challenge, Shimazu et al. (6) developed an objective method of pain evaluation called PainVision®, which is a perceptual/pain analyzer that quantitatively evaluates pain as "pain intensity" based on "current perception threshold" and "pain equivalent current." PainVision® has contributed to a more objective evaluation of pain regardless of the disease; however, to our knowledge, there are no reports of pain in PD that have been assessed using PainVision®. Thus, we closely examined pain in PwPD by quantifying PD pain with PainVision® in addition to using conventional tools of pain assessment.

2. Materials and methods

This study was conducted as a single-center, cross-sectional study. We assessed 111 sequential PwPD (57 patients with pain and 54 patients without pain), who received treatment at the Department of Neurology, Fukuoka University Hospital from October 2020 to March 2022. Patients with a definite cause of pain other than PD, such as pain due to arthritis or malignancy, were excluded. All patients were examined by a movement disorder specialist and clinically diagnosed with established PD or probable PD according to the International Parkinson and Movement Disorder Society (MDS) diagnostic criteria (7). Eligible patients were over 20 years old, who understood the purpose and methods of the study, and gave written consent. Exclusion criteria were as follows: (1) patients who could not give consent; (2) patients with severe dementia or psychiatric symptoms that could interfere with the assessment; and (3) patients with electronic devices such as pacemakers or implantable cardioverter defibrillators in their bodies. This study was approved by the Ethical Review Board of Fukuoka University (U20-08-009). Demographic and background information such as age, sex, age at disease onset, duration of disease, wearing off phenomenon, dyskinesia, and hallucinations were extracted from the patient medical records. Levodopa-equivalent daily dose (LEDD) was calculated from the medications according to the standard assessments (8). Motor symptoms were evaluated by a movement disorder specialist using the Hoehn and Yahr (HY) stage (9) and the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III (10). Cognitive function was assessed with the Japanese version of the Montreal Cognitive Assessment (MoCA) (11, 12) and the Mini Mental State Examination (MMSE). The permission of using MoCA was obtained. Depression was assessed using Zung's Self-Rating Depression Scale (SDS) (13). The 9-symptom Wearing-off Questionnaire (WOQ-9) (14, 15) was used to evaluate the phenomenon of wearing off. In this study, patients were considered to have "wearing off" if they had two or more symptoms positive on the WOQ-9 item and if they improved with dopaminergic therapy. Patients' quality of life was assessed using the PDQ-8 (16), and their total score (PDQ-8 SUM) and summary index (PDQ-8 SI) were calculated (17). Patients' clinical subtypes were classified into tremor dominant (TD) subtype, postural instability/gait difficulty (PIGD) subtype, and indeterminate type based on TD scores and PIGD scores of the MDS-UPDRS (18). Pain in PD was qualitatively assessed using the King's Parkinson's Disease Pain Scale (KPPS) (19). The types of pain were classified as follows: 1, Musculoskeletal pain; 2, Chronic pain; 3, Fluctuation-related pain; 4, Nocturnal pain; 5, Oro-facial pain; 6, Discoloration, edema/swelling; and 7, Radicular pain (19). Pain was assessed using the VAS (5), Numerical Rating Scale (NRS) (20), and Wong-Baker Faces Pain Rating Scale (FRS) (21). In addition, we assessed current perception threshold, pain equivalent current, and pain intensity using PainVision®. For patients without pain, only current perception thresholds were assessed. We performed these evaluations during a patient's on state.

2.1. Scales

- KPPS: This is a scale for evaluating pain specific to PD patients. The KPPS classifies pain into seven domains. In response to the 14 questions, an evaluator will quantify and describe the severity and frequency of the symptom. The score for each item is obtained by multiplying the severity (0–3) by the frequency (0–4). The maximum score is 144, with higher scores indicating more pain (19).
- VAS: This is a scale for evaluating pain numerically. Participants can indicate the degree of pain by marking on a 100 mm line segment ranging from 0 mm of "no pain" to 100 mm of "greatest pain imaginable" (5).
- NRS: This is a scale for evaluating pain numerically. This scale is a 11, 21, or 101 point scale where the end points are the extremes of no pain and the worst pain. Participants point to their current level of pain in numerical terms. The NRS can be graphically or verbally delivered (20). In this study, the NRS was graphically delivered ranging from 0 of "no pain" to 10 of "greatest pain imaginable."
- FRS: This is a scale for evaluating pain according to a person's facial expressions. The illustrations of faces are lined up ranging from happy face to crying face. Patients are asked to select an illustration of a facial expression that is similar to their own feelings (21). In this study, we used the scale which shows a series of faces ranging from 0 of "no hurt" to 10 of "hurts worst."

2.2. PainVision®

PainVision® (PS-2100; Nipro Co., Osaka, Japan) is a medical device that can quantify and objectively evaluate degrees of pain. The degree of pain is replaced by a different sensation of current stimulation, which is measured as a current value. This test inflicts low levels of pain because it stimulates a portion of the Aβ and Aδ fibers in the sensory nerves, and less of the C fibers. A disposable electrode EL-BAND is attached to the medial forearm opposite to the dominant hand, and current is applied to the electrode to measure "current perception threshold" and "pain equivalent current" (Figure 1). To measure the current perception threshold, a weak current with a basic cycle of 50 HZ is applied to the electrode and gradually increased. The current perception threshold is measured by pressing a hand switch when the participant feels some stimulus at the electrode. The pain equivalent current is measured by further increasing the current stimulation and the pressing of a hand switch when the participant feels that the degree of pain and the electrode stimulation are equal or greater than the current stimulation. The current perception threshold

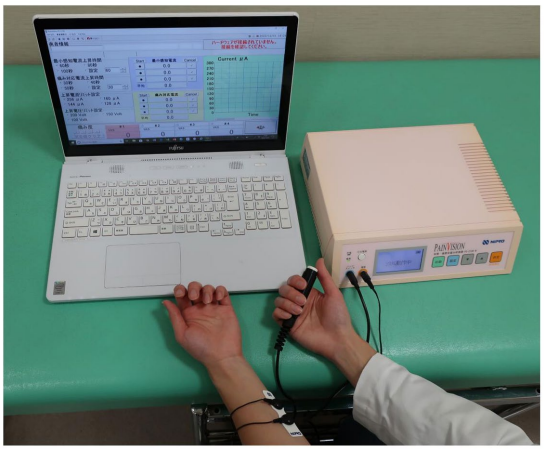

FIGURE 1
A disposable electrode is attached to the medial forearm, and current is applied to the electrode. The participant presses hand switch to measure "current perception threshold" and "pain equivalent current."

and the pain equivalent current are each measured three times, and the average value is extracted. Although there were no rules regarding measurement error, the current perception threshold was defined as a value that fell within ±1% of the mean value and the pain equivalent current as a value that fell within ±20% of the mean value in the three measurements. The mean values of the current perception threshold and the pain equivalent current were used to measure the pain intensity = (pain equivalent current − current perception threshold) × 100/current perception threshold (6).

2.3. Statistics

Age, age at onset, duration of disease, LEDD, HY stage, UPDRS part III, SDS, MMSE, MoCA, PDQ8-SUM, PDQ-8-SI, and current perception threshold were analyzed by Mann–Whitney U test between PwPD with pain and without pain. Sex, subtype (TD, PIGD, Indeterminate type), wearing off phenomenon, dyskinesia, and hallucinations between the two groups were analyzed by chi-square test. Correlation coefficients between pain intensity and duration of disease, VAS, NRS, and FRS were analyzed using Pearson's correlation coefficient. The correlations between current perception threshold and age of onset, duration of disease, LEDD, HY stage, and UPDRS Part III were analyzed using partial correlation coefficients after controlling for age. All value of $ps < 0.05$ were considered statistically significant. Data were analyzed by SPSS v.26 (SPSS Inc., Chicago, IL, United States).

3. Results

Eleven patients (nine with pain and two without pain) were excluded because seven of these patients had large measurement errors in current perception thresholds or pain equivalent current as measured by PainVision®, and four other patients had a definite cause of pain other than PD. Table 1 shows the clinical characteristics of the patients and comparison between PwPD with pain and without pain. The participants were 48 patients with pain and 52 patients without pain. There were 45 males and 55 females, mean age 68.0 ± 10.53 y, mean disease duration 7.95 ± 5.12 y, mean HY stage 2.57 ± 0.85, and mean UPDRS Part III 25.53 ± 12.36. Compared to PwPD without pain, PwPD with pain showed significantly longer disease duration ($p = 0.038$), higher LEDD ($p = 0.001$), higher HY stage ($p = 0.015$), more PIGD subtypes ($p = 0.004$), and higher dyskinesia complications ($p = 0.045$). Table 2 shows details of the background of patients' with pain. The mean duration of pain was 7.46 ± 8.91 y, and the use of analgesics was 39.6%. The majority of patients (75%) had musculoskeletal pain, and 37.5% had two or more types of pain. Table 3 shows correlation analysis of pain intensity and other factors. Correlation between VAS and FRS was non-significant and weak correlation was identified for NRS ($\gamma = -0.376$) with "pain intensity" evaluated by PainVision® (Figure 2). Table 4 shows correlation

TABLE 1 Baseline clinical characteristics of Parkinson's disease patients with pain and those without pain.

	Total (n=100)	No pain (n=52)	Pain (n=48)	Value of p
Sex, male (n)	45 (45%)	26 (50%)	19 (39.6%)	0.296
Age (years)	68.0 ± 10.53	68.85 ± 10.71	67.08 ± 10.35	0.472
Age at onset (years)	59.93 ± 10.86	61.79 ± 11.28	57.92 ± 10.12	0.74
Duration (years)	7.95 ± 5.12	6.87 ± 4.44	9.13 ± 5.57	0.038
LEDD (mg)	567.7 ± 354.57	454.29 ± 273.99	690.57 ± 392.06	0.001
HY stage	2.57 ± 0.85	2.37 ± 0.81	2.79 ± 0.85	0.015
UPDRS part III	25.53 ± 12.36	25.35 ± 14.35	25.73 ± 9.92	0.567
TD subtype	37 (37%)	28 (53.8%)	9 (18.8%)	<0.001
PIGD subtype	56 (56%)	22 (42.3%)	34 (70.8%)	0.004
Indeterminate type	6 (6%)	2 (3.8%)	4 (8.3%)	0.301
SDS	42.81 ± 9.25	41.62 ± 8.58	44.1 ± 9.85	0.198
MMSE	28.2 ± 3.36	28.37 ± 4.07	28.02 ± 2.39	0.613
MoCA	24.1 ± 4.69	24.08 ± 4.62	24.15 ± 4.8	0.895
Wearing off (n)	47 (47%)	22 (42.3%)	25 (52.1%)	0.328
Dyskinesia (n)	30 (30%)	11 (21.2%)	19 (39.6%)	0.045
Hallucination (n)	24 (24%)	11 (21.2%)	13 (27.1%)	0.488
PDQ-8 SI	19.62 ± 15.23	17.36 ± 13.41	22.07 ± 16.79	0.162
PDQ-8 SUM	6.28 ± 4.87	5.56 ± 4.29	7.06 ± 5.37	0.175
CPT	11.39 ± 4.92	10.41 ± 3.67	12.44 ± 5.84	0.092

All data are presented as mean ± standard deviation or n (%). LEDD, Levodopa equivalent daily dose; HY, Hoehn and Yahr; UPDRS, Unified Parkinson's Disease Rating Scale; TD, tremor dominant; PIGD, postural instability/gait difficulty; SDS, Self-Rating Depression Scale; MMSE, Mini-Mental State Examination; MoCA, The Montreal Cognitive Assessment; PDQ-8 SI, The Parkinson's Disease Questionnaire-8 Summary Index; PDQ-8 SUM, The Parkinson's Disease Questionnaire-8 Sum Score; CPT, current perception threshold.

analysis between VAS and other factors. Strong positive correlations were found between VAS and NRS ($\gamma = 0.758$) and FRS ($\gamma = 0.658$). Table 5 shows partial correlation coefficient between current perception threshold and other variables after controlling for age. There was a weak negative correlation between current perception threshold and age at onset ($\gamma = -0.308$), and weak positive correlations with duration of disease ($\gamma = 0.347$) and HY stage ($\gamma = -0.259$; Figure 3). No correlation was found between current perception threshold and pain intensity.

4. Discussion

Taking a different approach from traditional pain assessment tools, PainVision® provides a quantitative assessment of sensory thresholds and existing pain regardless of disease. It quantifies pain as "pain intensity" based on "current perception threshold" and "pain equivalent current." Objective pain assessment became possible by quantifying the degree of pain as "pain intensity." In this study, we measured "pain intensity" by using PainVision® in PwPD with pain and found no significant correlation with conventional subjective assessments of pain such as VAS and FRS; furthermore, there was only a weak positive correlation ($\gamma = 0.376$) with NRS.

Because the VAS is a subjective assessment based on past personal experience of pain, it varies widely among individuals (22). By contrast, "pain intensity" by PainVision® is an objective evaluation tool because it is less susceptible to psychological factors (23, 24). Most PwPD experience neuropsychiatric symptoms such as depression, anxiety, sleep disturbances, psychiatric symptoms, and behavioral and cognitive changes (25). In fact, it has been reported that 35% of PD patients have clinically significant depressive symptoms (26). The VAS assessment of pain may fail to capture the accurate level of pain in PwPD, especially when they are psychologically influenced. Although scales of subjective pain assessment such as VAS, are still important for evaluating patients' pain, objective assessment by PainVision® should also be incorporated at the same time as it can provide important background information that can impact the outcome of therapeutic intervention. Perceived pain is a mixture of subjectivity and objectivity, and patients' subjective assessments of pain are thought to be affected by their current mental status. However, PainVision® may be more objectively weighted.

Another advantage of PainVision® is its ease of use; PainVision® can be performed in a short period of time, is minimally invasive to the patient, and has a simple examination procedure. Even PwPD, many of whom are elderly, can operate it simply by pressing a hand switch after detecting the current and the current corresponding to the pain. This study was the first to use PainVision® for PD pain assessment, and we experienced no technical difficulties. This device has been used to assess persistent chronic pain, such as low back pain (27), chemotherapy-induced peripheral neuropathy (28), and pain in herpes zoster (24). Furthermore, it has been used in studies of treatment-related pain, such as evaluating the postoperative pain from single-site laparoscopic colectomy (29) and evaluating the effect of plexus brachialis block on postoperative pain after arthroscopic rotator cuff repair (30). Correlations between "pain intensity" by PainVision® and VAS have been reported in evaluations of various types of chronic pain (31), venous chemotherapy-induced vascular pain (32), and chemotherapy-induced peripheral neuropathy (33). On the other hand, contrary to the results of our study, some studies have shown no correlation between "pain intensity" and VAS (24, 34). In a study that assessed low back pain using the VAS, the McGill Pain Questionnaire (MPQ), and PainVision®, the values measured by PainVision® showed consistent results even after repeated calculations and good correlation with MPQ, but no

TABLE 2 Pain evaluations in Parkinson's disease patients with pain (n=48).

Duration of pain (years)	7.46 ± 8.91
Use of analgesics	19 (39.6%)
Pain assessment by various scales	
VAS (mm)	38.31 ± 20.17
NRS	4.19 ± 1.83
FRS	4.58 ± 1.75
Pain assessment by Pain Vision®	
CPT (uA)	12.44 ± 5.84
PEC (uA)	32.76 ± 24.16
Pain intensity	180.9 ± 191.18
KPPS domains	
Musculoskeletal pain	36 (75%)
Chronic pain	10 (20.8%)
Fluctuation-related pain	13 (27.1%)
Nocturnal pain	2 (4.2%)
Oro-facial pain	0 (0%)
Discoloration, edema/swelling	3 (6.3%)
Radicular pain	6 (12.5%)
Patients with more than one type of pain	18 (37.5%)

All data are presented as mean (standard deviation) or n (%). VAS, Visual Analog Scale; NRS, Numerical Rating Scale; FRS, Wong-Baker Faces Pain Rating Scale; CPT, current perception threshold; PEC, pain equivalent current.

TABLE 3 Pearson product–moment correlation coefficient between pain intensity and other variables.

Pain intensity vs.	Duration	HY stage	UPDRS Part III	SDS	VAS	NRS	FRS
γ	−0.196	−0.277	−0.177	−0.136	0.152	0.376	0.281
Value of p	0.182	0.057	0.228	0.358	0.303	0.008	0.053

HY, Hoehn and Yahr; UPDRS, Unified Parkinson's Disease Rating Scale; SDS, Self-Rating Depression Scale; VAS, Visual Analog Scale; NRS, Numerical Rating Scale; FRS, Wong-Baker Faces Pain Rating Scale.

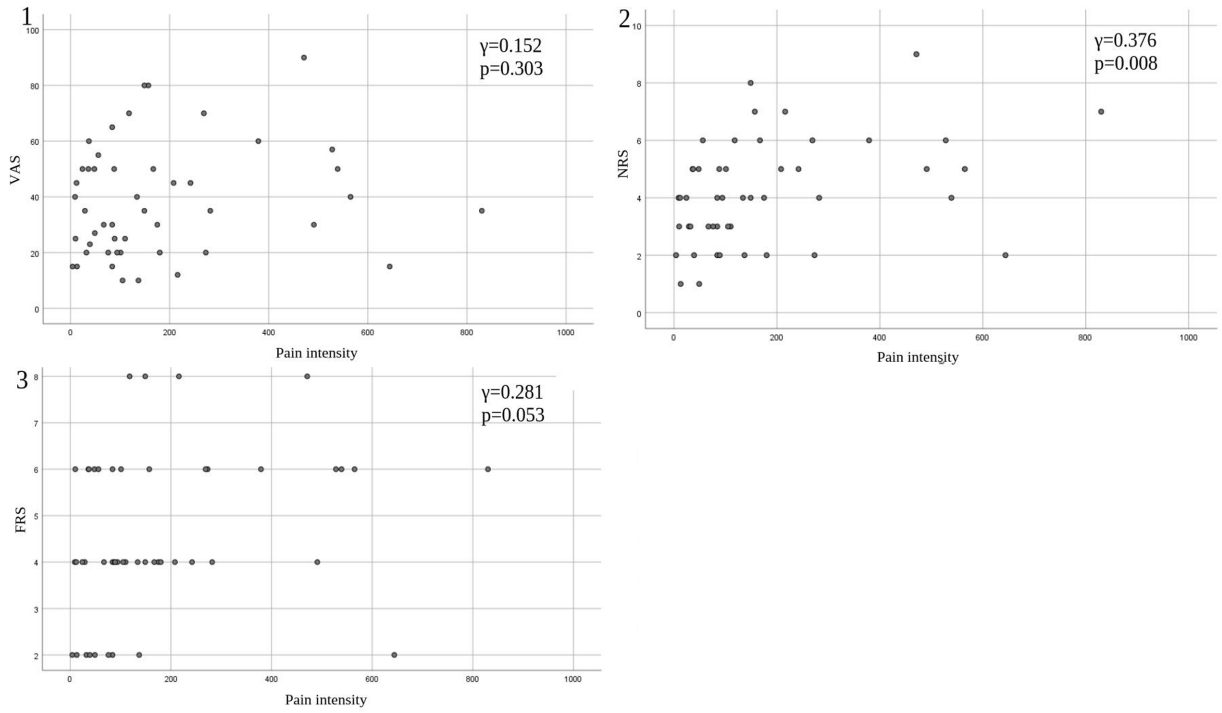

FIGURE 2
Correlation between pain intensity and conventional tools of pain assessment. (1) Pain intensity versus VAS. (2) Pain intensity versus NRS. (3) Pain intensity versus FRS. VAS, Visual Analog Scale; NRS, Numerical Rating Scale; FRS, Wong-Baker Faces Pain Rating Scale.

TABLE 4 Pearson product–moment correlation coefficient between visual analog scale and other variables.

VAS vs.	Duration	HY stage	UPDRS Part III	SDS	NRS	FRS
γ	0.225	0.245	0.225	−0.078	0.758	0.658
Value of *p*	0.125	0.093	0.124	0.599	<0.001	<0.001

HY, Hoehn and Yahr; UPDRS, Unified Parkinson's Disease Rating Scale; SDS, Self-Rating Depression Scale; VAS, Visual Analog Scale; NRS, Numerical Rating Scale; FRS, Wong-Baker Faces Pain Rating Scale.

correlation with VAS (34). It is interesting to note that the correlation between PainVision® and subjective pain assessment varies based on the disease.

In this study, partial correlation coefficient after controlling for age showed that current perception threshold had a negative correlation with age at onset, and a positive correlation with duration of disease and HY stage. Current perception thresholds in normal participants are higher in men than in women and increase with age (35). Elevated current perception thresholds are suggestive of sensory neuropathy. Sato et al. (36) and Hiramatsu et al. (37) report that current perception thresholds in diabetic patients are higher than in non-diabetic patients and are useful for detecting minor neuropathy without obvious neurological findings. Goda et al. (38) report that the current perception threshold of hemodialysis patients is higher than that of healthy participants. This study also suggests that the presence of minor peripheral neuropathy in PD may be detectable. The cause of peripheral neuropathy in PD is known to be associated with abnormalities in vitamin B12, methylmalonic acid, and fasting homocysteine, so the metabolic effects of long-term exposure to levodopa may cause peripheral neuropathy (39, 40). It is also reported that small fiber density is decreased in PD and that there is α-synuclein deposition in peripheral nerves on skin biopsy (41). PwPD with peripheral neuropathy are associated with suffering from non-motor symptoms such as cognitive decline, axial motor symptoms, and autonomic symptoms (42), suggesting that peripheral neuropathy develops with PD progression.

In this study, we compared PD patients with and without pain. The group with pain had significantly longer disease duration, higher LEDD, higher HY stage, more PIGD subtype, and a higher rate of dyskinesia complications as background factors. Previous studies report an association between pain in PD and duration of disease (43, 44) and that higher HY stage or higher disease severity is associated with pain severity (45, 46), which is consistent with the results of this study. Regarding dyskinesia and pain, a functional magnetic resonance imaging study showed that dyskinetic PwPD experience increased pain sensitivity and centrally sensitized nociceptive pathways (47). It is speculated that altered pain sensitivity may increase the frequency of pain complications in patients with dyskinesia. Regarding PD subtypes and pain, there is a report that pain is associated with the PIGD subtype because it involves more advanced dopaminergic striatal denervation, and dopamine deficiency causes hyperalgesia (48).

TABLE 5 Partial correlation coefficient between current perception threshold and other variables after controlling for age.

CPT vs.	Age at onset	Duration	LEDD	HY stage	UPDRS Part III	Pain intensity
γ	−0.308	0.347	0.171	0.259	0.152	−0.135
Value of p	<0.002	<0.001	0.090	0.010	0.133	0.367

CPT, current perception threshold; LEDD, levodopa equivalent daily dose; HY, Hoehn and Yahr; UPDRS, Unified Parkinson's Disease Rating Scale.

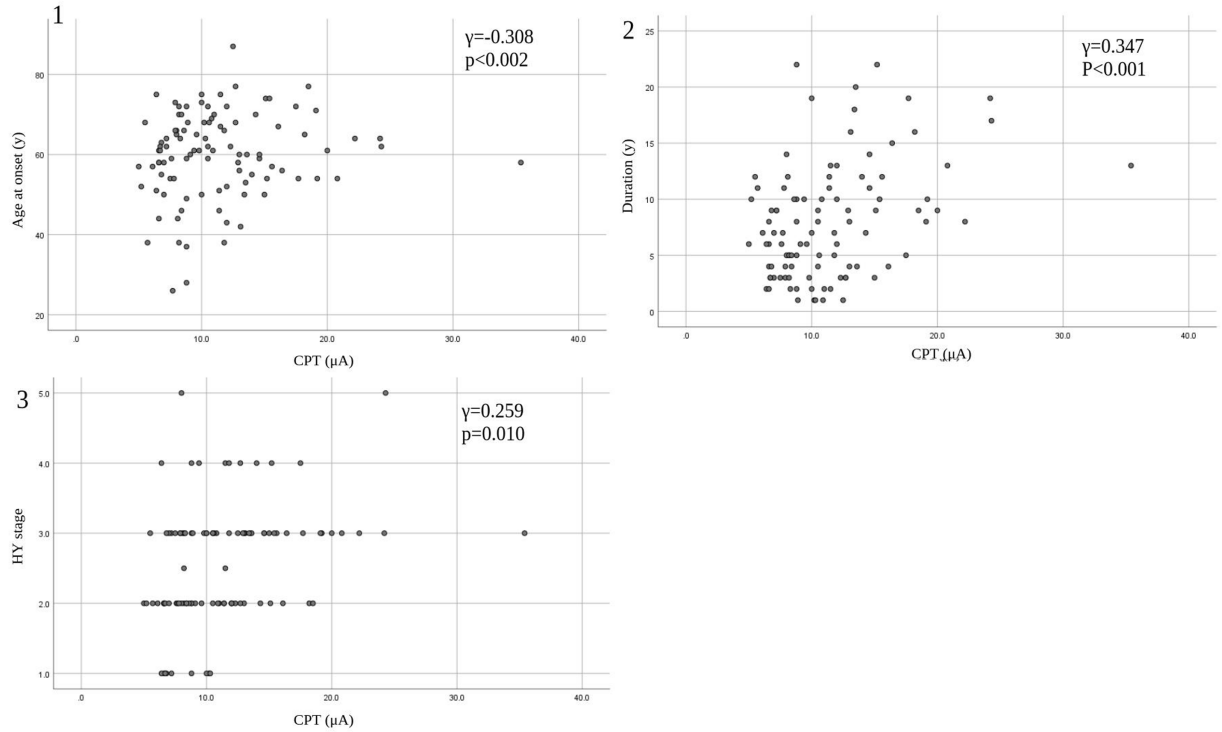

FIGURE 3
Correlation between CPT and patients' characteristics. (1) CPT versus age at onset. (2) CPT versus duration. (3) CPT versus HY stage. CPT, current perception threshold; HY, Hoehn and Yahr.

The first limitation of this study is that it was a single-center, small-scale study. More patients need to be evaluated with PainVision®. Second, the degree of pain was not compared to other assessment methods such as the McGill Pain Questionnaire. Third, though pain in PD is heterogeneous and classified into seven classifications of the KPPS, individual analysis of pain was not performed in this study. Most previous reports of Pain Vision® show that it can measure the degree of nociceptive or neuropathic pain. However, pain in PD has a wide variety of causes, including a lowered pain threshold to nociceptive stimuli and activation of ascending pain pathways (49), and reduced descending pain inhibition (50), which lead to difficult aspects in the interpretation of measurements. Therefore, the type of pain that is most useful for evaluation by PainVision® should be considered in the future.

Despite the above mentioned limitations, we believe PainVision®, which enables objective evaluation that is less susceptible to psychological influences, is a useful tool for the evaluation of pain in PwPD. However, as pain in PD is complex, further study is warranted.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Review Board of Fukuoka University (U20-08-009). The patients/participants provided their written informed consent to participate in this study.

Author contributions

KK: methodology, statistical analysis, investigation, and writing – original draft. TM and SF: review and editing. YT: conceptualization, formal analysis, and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Wasner G, Deuschl G. Pains in Parkinson disease--many syndromes under one umbrella. *Nat Rev Neurol*. (2012) 8:284–94. doi: 10.1038/nrneurol.2012.54

2. Broen MP, Braaksma MM, Patijn J, Weber WE. Prevalence of pain in Parkinson's disease: a systematic review using the modified QUADAS tool. *Mov Disord*. (2012) 27:480–4. doi: 10.1002/mds.24054

3. Ford B. Pain in Parkinson's disease. *Mov Disord*. (2010) 25:S98–S103. doi: 10.1002/mds.22716

4. Tseng MT, Lin CH. Pain in early-stage Parkinson's disease: implications from clinical features to pathophysiology mechanisms. *J Formos Med Assoc*. (2017) 116:571–81. doi: 10.1016/j.jfma.2017.04.024

5. DeLoach LJ, Higgins MS, Caplan AB, Stiff JL. The visual analog scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale. *Anesth Analg*. (1998) 86:102–6. doi: 10.1097/00000539-199801000-00020

6. Shimazu H, Seno S, Kato S, Kobayashi H, Akimoto M. Development of a quantitative measurement method for the magnitude of pain using painless electrical stimulation and its evaluation using experimental pain. *Trans Jpn Soc Med Biol Eng*. (2005) 43:117–23. doi: 10.11239/jsmbe.43.117

7. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. (2015) 30:1591–601. doi: 10.1002/mds.26424

8. Schade S, Mollenhauer B, Trenkwalder C. Levodopa equivalent dose conversion factors: an updated proposal including opicapone and safinamide. *Mov Disord Clin Pract*. (2020) 7:343–5. doi: 10.1002/mdc3.12921

9. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology*. (1967) 17:427–42. doi: 10.1212/wnl.17.5.427

10. Kashihara K, Kondo T, Mizuno Y, Kikuchi S, Kuno S, Hasegawa K, et al. Official Japanese version of the Movement Disorder Society-unified Parkinson's disease rating scale: validation against the original English version. *Mov Disord Clin Pract*. (2014) 1:200–12. doi: 10.1002/mdc3.12058

11. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. (2005) 53:695–9. doi: 10.1111/j.1532-5415.2005.53221.x

12. Fujiwara Y, Suzuki H, Yasunaga M, Sugiyama M, Ijuin M, Sakuma N, et al. Brief screening tool for mild cognitive impairment in older Japanese: validation of the Japanese version of the montreal cognitive assessment. *Geriatr Gerontol Int*. (2010) 10:225–32. doi: 10.1111/j.1447-0594.2010.00585.x

13. Zung WW. A self-rating depression scale. *Arch Gen Psychiatry*. (1965) 12:63–70. doi: 10.1001/archpsyc.1965.01720310065008

14. Stacy MA, Murphy JM, Greeley DR, Stewart RM, Murck H, Meng X, et al. The sensitivity and specificity of the 9-item wearing-off questionnaire. *Parkinsonism Relat Disord*. (2008) 14:205–12. doi: 10.1016/j.parkreldis.2007.07.013

15. Kondo T, Takahashi K. Translation and linguistic validation of the Japanese version of the wearing-off questionnaires (WOQ-19 and WOQ-9). *Brain Nerve*. (2011) 63:1285–92.

16. Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well-being for individuals with Parkinson's disease. *Qual Life Res*. (1995) 4:241–8. doi: 10.1007/BF02260863

17. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman R. The PDQ-8: development and validation of a short-form Parkinson's disease questionnaire. *Psychol Health*. (1997) 12:805–14. doi: 10.1080/08870449708406741

18. Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK, Tilley BC. How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. *Mov Disord*. (2013) 28:668–70. doi: 10.1002/mds.25383

19. Chaudhuri KR, Rizos A, Trenkwalder C, Rascol O, Pal S, Martino D, et al. King's Parkinson's disease pain scale, the first scale for pain in PD: an international validation. *Mov Disord*. (2015) 30:1623–31. doi: 10.1002/mds.26270

20. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *J Clin Nurs*. (2005) 14:798–804. doi: 10.1111/j.1365-2702.2005.01121.x

21. Wong DL, Baker CM. Pain in children: comparison of assessment scales. *Pediatr Nurs*. (1988) 14:9–17.

22. McCormack HM, Horne DJ, Sheather S. Clinical applications of visual analogue scales: a critical review. *Psychol Med*. (1988) 18:1007–19. doi: 10.1017/s0033291700009934

23. Kato J. Pain vision. *Masui*. (2011) 60:1059–63.

24. Maekawa N, Morimoto M, Morimoto M, Uchida T, Umeda T, Koga Y. Can we revaluate pain with PainVision, a device for quantitative analysis of perception and pain? A feasibility study of pain in herpes zoster patients. *J Jpn Soc Clin Anesth*. (2009) 29:824–8. doi: 10.2199/jjsca.29.824

25. Aarsland D, Marsh L, Schrag A. Neuropsychiatric symptoms in Parkinson's disease. *Mov Disord*. (2009) 24:2175–86. doi: 10.1002/mds.22589

26. Reijnders JS, Ehrt U, Weber WE, Aarsland D, Leentjens AF. A systematic review of prevalence studies of depression in Parkinson's disease. *Mov Disord*. (2008) 23:183–9. doi: 10.1002/mds.21803

27. Ohtori S, Kawaguchi H, Takebayashi T, Orita S, Inoue G, Yamauchi K, et al. PainVision apparatus is effective for assessing low back pain. *Asian Spine J*. (2014) 8:793–8. doi: 10.4184/asj.2014.8.6.793

28. Saito M, Odajima S, Yokomizo R, Tabata J, Iida Y, Ueda K, et al. A simple method of quantifying chemotherapy-induced peripheral neuropathy using PainVision PS-2100®. *Asia Pac J Clin Oncol*. (2020) 16:80–5. doi: 10.1111/ajco.13293

29. Hiraki M, Takemasa I, Uemura M, Haraguchi N, Nishimura J, Hata T, et al. Evaluation of invasiveness in single-site laparoscopic colectomy, using "the PainVision™ system" for quantitative analysis of pain sensation. *Surg Endosc*. (2014) 28:3216–23. doi: 10.1007/s00464-014-3594-7

30. Mifune Y, Inui A, Nagura I, Sakata R, Muto T, Harada Y, et al. Application of pain quantitative analysis device for assessment of postoperative pain after arthroscopic rotator cuff repair. *Open Orthop J*. (2015) 9:89–93. doi: 10.2174/1874325001509010089

31. Arita H. Objective measurement of pain by pain vision. *J Jpn Soc Pain Clinicians*. (2008) 15:144–9.

32. Matsuoka T, Yoshida Y, Aisu N, Yamada T, Mogi A, Komono A, et al. Evaluation of vascular pain in patients with colorectal cancer receiving peripheral venous chemotherapy with or without oxaliplatin. *Sci Rep*. (2019) 9:1819. doi: 10.1038/s41598-018-37966-w

33. Yoshida Y, Satoh A, Yamada T, Aisu N, Matsuoka T, Koganemaru T, et al. The relationship between evaluation methods for chemotherapy-induced peripheral neuropathy. *Sci Rep*. (2019) 9:20361. doi: 10.1038/s41598-019-56969-9

34. Kim J, Lee KS, Kong SW, Kim T, Kim MJ, Park SB, et al. Correlations between electrically quantified pain degree, subjectively assessed visual analogue scale, and the McGill pain questionnaire: a pilot study. *Ann Rehabil Med*. (2014) 38:665–72. doi: 10.5535/arm.2014.38.5.665

35. Seno S, Kato S, Kobayashi H, Watanabe A, Shimazu H. Evaluation of sex and age differences in the perception threshold of body surface against electrical stimulation—measurement of perception threshold to determine the possibility of diabetic neuropathy diagnoses—. *Trans Jpn Soc Med BiolEng*. (2011) 49:163–9.

36. Sato A. Setting a reference value of current perception threshold by Painvision. *Diabetes*. (2007) 50:S291.

37. Hiramatsu K, Yamashita H, Shigematsu O, Komazu M, Yamauchi K, Hashizume K. Quantitative measurement system of current perception threshold in diabetes. *Diabetes*. (2007) 50:S233.

38. Gohda T, Oka H, Gotoh H, Sato M, Tanimoto M, Io H, et al. Analysis of current perception threshold(CPT)using PainVision®PS-2100 in hemodialysis patients. *J Jpn Soc Dial Ther*. (2009) 42:77–83. doi: 10.4009/jsdt.42.77

39. Zis P, Grünewald RA, Chaudhuri RK, Hadjivassiliou M. Peripheral neuropathy in idiopathic Parkinson's disease: a systematic review. *J Neurol Sci*. (2017) 378:204–9. doi: 10.1016/j.jns.2017.05.023

40. Ceravolo R, Cossu G, Bandettini di Poggio M, Santoro L, Barone P, Zibetti M, et al. Neuropathy and levodopa in Parkinson's disease: evidence from a multicenter study. *Mov Disord*. (2013) 28:1391–7. doi: 10.1002/mds.25585

41. Giannoccaro MP, Donadio V, Incensi A, Pizza F, Cason E, Di Stasi V, et al. Skin biopsy and I-123 MIBG scintigraphy findings in idiopathic Parkinson's disease and parkinsonism: a comparative study. *Mov Disord*. (2015) 30:986–9. doi: 10.1002/mds.26189

42. Merola A, Rosso M, Romagnolo A, Comi C, Fasano A, Zibetti M, et al. Peripheral neuropathy as marker of severe Parkinson's disease phenotype. *Mov Disord*. (2017) 32:1256–8. doi: 10.1002/mds.27025

43. Camacho-Conde JA, Campos-Arillo VM. The phenomenology of pain in Parkinson's disease. *Korean J Pain*. (2020) 33:90–6. doi: 10.3344/kjp.2020.33.1.90

44. Tinazzi M, Del Vesco C, Fincati E, Ottaviani S, Smania N, Moretto G, et al. Pain and motor complications in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. (2006) 77:822–5. doi: 10.1136/jnnp.2005.079053

45. Agrawal AK, Anand KS, Juneja A, Kumar P, Saluja A, Dhamija RK. Predictors of pain severity and its impact on quality of life in patients with Parkinson's disease. *Neurol India*. (2021) 69:979–83. doi: 10.4103/0028-3886.325323

46. Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, et al. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disord*. (2009) 24:1641–9. doi: 10.1002/mds.22643

47. Sung S, Farrell M, Vijiaratnam N, Evans AH. Pain and dyskinesia in Parkinson's disease may share common pathophysiological mechanisms - an fMRI study. *J Neurol Sci*. (2020) 416:116905. doi: 10.1016/j.jns.2020.116905

48. Ren J, Hua P, Pan C, Li Y, Zhang L, Zhang W, et al. Non-motor symptoms of the postural instability and gait difficulty subtype in de novo Parkinson's disease patients: a cross-sectional study in a single center. *Neuropsychiatr Dis Treat*. (2020) 16:2605–12. doi: 10.2147/NDT.S280960

49. Brefel-Courbon C, Payoux P, Thalamas C, Ory F, Quelven I, Chollet F, et al. Effect of levodopa on pain threshold in Parkinson's disease: a clinical and positron emission tomography study. *Mov Disord*. (2005) 20:1557–63. doi: 10.1002/mds.20629

50. Mylius V, Engau I, Teepker M, Stiasny-Kolster K, Schepelmann K, Oertel WH, et al. Pain sensitivity and descending inhibition of pain in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. (2009) 80:24–8. doi: 10.1136/jnnp.2008.145995

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The role of the microbiota-gut-brain axis and intestinal microbiome dysregulation in Parkinson's disease

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Parkinson's disease (PD) is a complex progressive neurodegenerative disease associated with aging. Its main pathological feature is the degeneration and loss of dopaminergic neurons related to the misfolding and aggregation of α-synuclein. The pathogenesis of PD has not yet been fully elucidated, and its occurrence and development process are closely related to the microbiota-gut-brain axis. Dysregulation of intestinal microbiota may promote the damage of the intestinal epithelial barrier, intestinal inflammation, and the upward diffusion of phosphorylated α-synuclein from the enteric nervous system (ENS) to the brain in susceptible individuals and further lead to gastrointestinal dysfunction, neuroinflammation, and neurodegeneration of the central nervous system (CNS) through the disordered microbiota-gut-brain axis. The present review aimed to summarize recent advancements in studies focusing on the role of the microbiota-gut-brain axis in the pathogenesis of PD, especially the mechanism of intestinal microbiome dysregulation, intestinal inflammation, and gastrointestinal dysfunction in PD. Maintaining or restoring homeostasis in the gut microenvironment by targeting the gut microbiome may provide future direction for the development of new biomarkers for early diagnosis of PD and therapeutic strategies to slow disease progression.

KEYWORDS

Parkinson's disease, microbiota-gut-brain axis, intestinal microbiome dysregulation, inflammation, gastrointestinal dysfunction

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease associated with aging (1), and its prodromal stage may be longer than 20 years. The prodromal stage is characterized by specific non-motor symptoms, including rapid eye movement sleep behavior disorder (RBD), autonomic nerve dysfunction, and cognitive disorders (1, 2). The main pathological feature of PD is the progressive loss of dopaminergic neuron (DN), which is related to the misfolding and aggregation of α-synuclein (1–3). However, α-synuclein could be detected in both central nervous system (CNS) and enteric nervous system (ENS). Studies on animal models of PD indicate that abnormal α-synuclein may spread to the CNS in a prion-like manner through the vagus (4, 5). In the pathogenesis and development of PD, the intestinal

microbiome affects the close two-way communication between the gastrointestinal tract and the brain, which is called the microbiota-gut-brain axis (Figure 1). PD patients have significant intestinal microbiome disorders and metabolite changes, which may promote the damage of the intestinal epithelial barrier, intestinal inflammation, and abnormal phosphorylation of α-synuclein to spread upward from the ENS to the brain in individuals with genetic susceptibility and further lead to gastrointestinal dysfunction, neuroinflammation, and neurodegeneration of CNS through the disordered microbiota-gut-brain axis (6, 7). Currently, no treatment can cure or effectively prevent the progression of PD. Although dopamine replacement therapy helps to improve the initial motor symptoms, it cannot inhibit dopaminergic neurodegeneration and is associated with motor complications (8, 9). Meanwhile, oral administration of levodopa and other PD-related drugs requires the optimal gastrointestinal function to determine the ideal drug metabolism. However, gastrointestinal dysfunction and intestinal microbiome disorders in PD patients will interfere with the absorption and utilization of drugs (10–15), while some therapeutic agents (such as dopamine agonists) may directly affect the gut microbiome and aggravate gastrointestinal dysfunction (16–18). Therefore, there is an urgent need to better determine the pathobiological mechanism of the highly complex bidirectional association of the microbiota-gut-brain axis in PD. Hence, in this review, we aimed to summarize recent advancements in studies focusing on the role of the microbiota-gut-brain axis in the pathogenesis of PD, especially the potential mechanism of intestinal microbiome dysregulation, intestinal inflammation, and gastrointestinal dysfunction in PD. In order to reveal new insights into the etiology and pathophysiology of PD, a new strategy is provided for the early diagnosis and treatment of PD from the perspective of the intestinal tract by targeting the gut microbiome.

2. The body-first and brain-first PD

Since Braak et al. discovered that pathological α-synuclein aggregated in the ENS may spread retrogradely to the brain through the vagus (19), a series of studies have shown that there is an important two-way interaction between the gut and the brain (20, 21). PD is assumed to exist in two subtypes: The brain-first PD, in which α-synuclein pathology spreads from the CNS affects the autonomic nervous system, and body-first PD, in which α-synuclein pathology originates from the intestinal or peripheral autonomic nervous system and then spreads to the CNS through vagus and sympathetic connections (22, 23). Compared to normal subjects, α-synuclein was found in the stomach and vagus of PD subjects (24). Human epidemiological data showed that complete truncal vagotomy

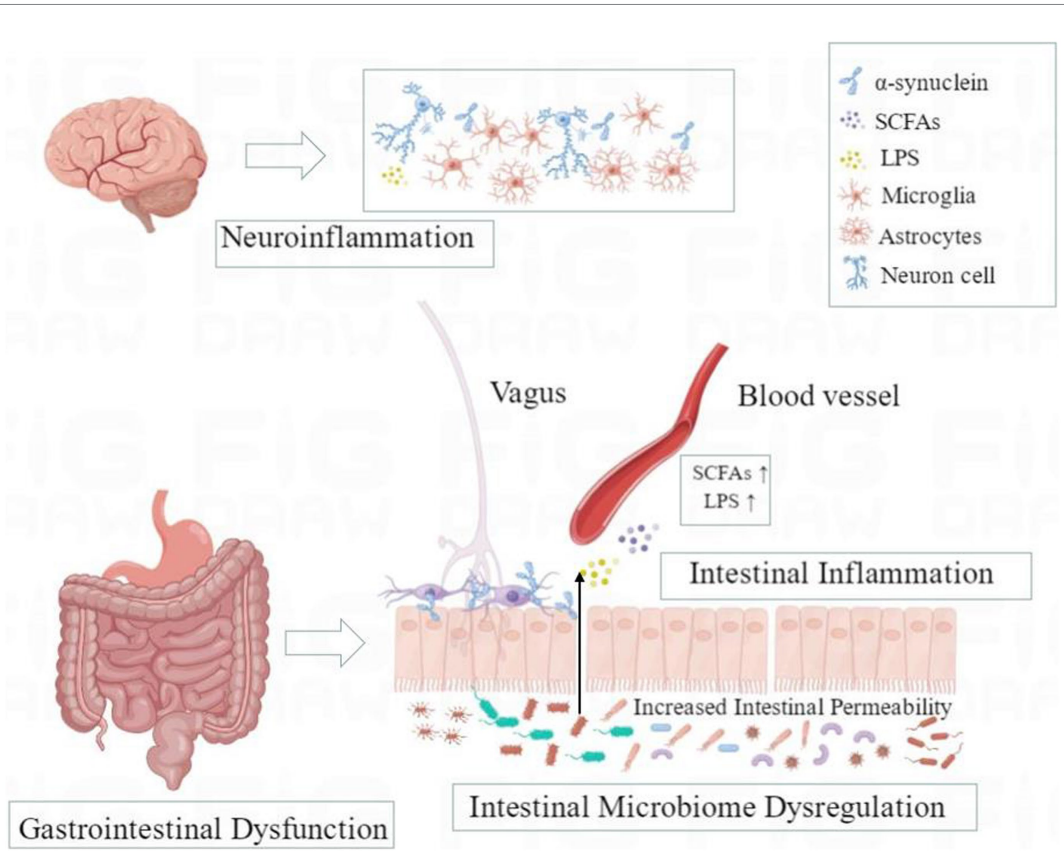

FIGURE 1
A schematic overview of microbiota-gut-brain axis in Parkinson's disease. Dysregulation of intestinal microbiota may promote the damage of the intestinal epithelial barrier, intestinal inflammation, and the upward diffusion of phosphorylated α-synuclein from the enteric nervous system (ENS) to the brain through the vagus nerve in susceptible individuals and further lead to gastrointestinal dysfunction, neuroinflammation, and neurodegeneration of the central nervous system (CNS) through the disordered microbiota-gut-brain axis.

could reduce the risk of secondary PD and delay the age of PD onset (25), indicating that α-synuclein is not only deposited in the substantia nigra but also in the gastrointestinal tract and the vagus. Animal studies have shown that α-synuclein aggregates can spread from the gastrointestinal tract to the brain through the autonomic nervous system. By injecting pathological α-synuclein into the duodenum and the pyloric muscle layer of mice (26) or the duodenal wall of rats (20), initial retrograde multi-synaptic propagation of pathological α-synuclein along with the loss of DN, motor and non-motor symptoms. However, trunk vagotomy and loss of α-synuclein could prevent the transmission of α-synuclein from the gut to the brain and the associated neurodegeneration and behavioral defects (26). Arotcarena et al. found that in non-human primate models, enteral injection or striatal injection of α-synuclein from PD patients can induce striatal injury and pathological manifestations of the ENS (21).

RBD is the strongest prodromal marker of PD, and clinical and imaging evidence suggests that RBD can be used as a clinical marker to distinguish body-first PD (RBD positive) from brain-first PD (RBD negative) (27, 28). The PET tracer 11C-Donepezil was used clinically to evaluate parasympathetic enteric innervation, and it was found that patients with RBD had reduced uptake of 11C-donepezil in the colon and small intestine (29), indicating that the body-first PD patients showed autonomic nerve innervation loss in the prodromal stage. This was verified in 37 newly diagnosed PD patients, using a multi-modal imaging case–control PET study which found that the 11C-donepezil intake of the colon in body-first type was significantly lower than that in the brain-first type (30). Cardiac 123I-MIBG imaging can effectively assess whether sympathetic dysfunction is present, and the study found that 92% of RBD patients show pathological 123I-MIBG imaging (27), and body-first PD patients show significantly a lower cardiac 123I-MIBG signal due to sympathetic dysfunction (30). The above imaging evidence supports the existence of brain-first and body-first subtypes of PD. In addition, colonic dysfunction can be quantified objectively by total colonic volume and colonic transit time (CTT). Studies have found that compared with healthy control groups, PD patients usually have significantly prolonged CTT and larger total colon volume (30, 31), among which total colon volume and CTT increase more significantly in patients with body-first PD (27).

Both clinical studies and animal model evidence (19–32) indicate that the dysfunctional autonomic nervous system (such as vagus) may be the pathway of pathological transmission of α-synuclein in PD between ENS and CNS, which is consistent with the body-first and brain-first hypothesis mechanism of PD.

3. Microbiota–gut–brain axis and intestinal microbiome dysregulation in PD

The gut microbiota is the densest microbiome in the human body, composed of bacteria, viruses, protozoa, fungi, etc., and communicates bidirectional with the brain through the microbiota gut–brain axis, thus significantly affecting the intestinal barrier function, inflammatory response, and nervous system function of the host (33, 34). The structure and function of the intestinal microbiome are constantly undergoing dynamic changes, which will be significantly affected by genetic factors and environmental factors (infection, medication, food, etc.), and the abnormal quantity or quality is called intestinal microbiota disorder (35). The dysregulation of intestinal microbiome in PD patients leads to increased exposure to various pro-inflammatory and neurotoxic microorganisms, and the changes in the entire intestinal microbiome are shown as a decreased level of short-chain fatty acids (SCFAs) and increased lipopolysaccharide (LPS) (36–38). In addition, intestinal microbiota can produce functional amyloid protein, namely, microbial amyloid protein, which can not only promote intestinal and systemic inflammation but also accelerate the aggregation of α-synuclein in the intestinal nerve plexus and spreads to the CNS through a transsynaptic cell-to-cell transmission (39). The above mechanisms may cause neuronal damage or promote susceptibility to neuronal damage, thus affecting the occurrence and development of PD (40).

3.1. Changes of major intestinal microbiota in PD and their correlation with clinical characteristics

The composition and function of intestinal microbiota are closely related to clinical characteristics of PD, including clinical symptoms, disease progression, and severity (41, 42). The high-throughput sequencing studies found that intestinal microbiome changes in PD patients persisted in follow-up sampling 2 years later (43), and the most significant changes were the decrease of the bacterial group producing SCFAs (with anti-inflammatory effects) and the increase of the bacterial group producing LPS (with pro-inflammatory properties) (44). With the development of PD, the abundance of *Faecalibacterium*, Roseburia, Prevotella, Lachnospiraceae family and their key member Butyrivibrio decrease significantly, while the abundance of Megasphaera, Akkermansia, and Verrucomicrobia as well as Lactobacillaceae continued to increase in PD patients (45–47). Among them, Roseburia decomposed carbohydrates to produce SCFAs, which can protect the gut from pathogens. The decreased abundance of Roseburia affects the host's ability to repair epithelial cells and regulate inflammation and is associated with the deterioration of cognitive function. Prevotella decomposes proteins and carbohydrates to produce SCFAs, the abundance of which is negatively correlated with disease severity. Its abundance is significantly decreased in rapidly progressing PD patients and is associated with the deterioration of cognitive function (48). Butyrivibrio abundance decline is correlated with poor motor function and motor complications (49). The accumulation of Akkermansia promotes intestinal mucous barrier damage and intestinal inflammation, leading to abnormal aggregation of α-synuclein in the intestine, and eventually leads to higher endotoxemia and systemic inflammation to promote the progress of neuropathology (46). Increased abundance of Megasphaera is associated with poor motor and cognitive function (50). At the same time, changes in the composition of intestinal microbiota can affect neurodegeneration through inflammatory response, the abundance of Bacteroides is correlated with the level of plasma TNF-α and the severity of motor symptoms (51). In addition, reduced abundance of the major producers of butyrate (including the genera Roseburia, Romboutsia, and Prevotella) was associated not only with worsening cognitive function but also with the severity of depressive symptoms in PD patients (52) (Table 1).

At present, there is heterogeneity in the results of studies on the changes in intestinal microbiota in PD, which may be due to

TABLE 1 Summary of altered intestinal microbiota in PD and their correlation with clinical symptoms.

Bacteria	Abundance	Function	Motor Symptom	Non-motor Symptom	References
Roseburia	↓	Produce SCFAs	-	Be associated with the deterioration of cognitive function; Be associated with depressive symptom	Mao et al. (48); Xie et al. (52)
Prevotella	↓	Produce SCFAs	-	Be associated with the deterioration of cognitive function; Be associated with depressive symptom	Mao et al. (48); Xie et al. (52)
Butyrivibrio	↓	Produce butyrate	Be correlated with poor motor function and motor complication	-	Toh et al. (49)
Romboutsia	↓	Produce butyrate	-	Be associated with worsening cognitive function and depressive symptom	Xie et al. (52)
Akkermansia	↑	Degrade intestinal mucin	-	Promote gastrointestinal dysfunction	Nishiwaki et al. (46); Cirstea et al. (121)
Megasphaera	↑	-	Be associated with poor motor function	Be associated with poor cognitive function	Vascellari et al. (50)
Bacteroides	↑	-	Be correlated with severity of motor symptom	-	Lin et al. (51)

↓ refers to decreased abundance and ↑ refers to increased abundance.

differences in research methods, disease status, and population as well as confounding factors (49). In order to elucidate the significance of changes in gut microbiome in PD and assess its potential as biomarkers for risk, diagnosis, treatment, and prognosis of PD, future large-scale clinical studies could employ a cross-comparative multi-omics approach combined with clear patient criteria (including geographic regions, ethnicity, disease stage, and detailed phenotypes and genotyping) to provide a comprehensive understanding of how the gut microbiome and its metabolites interact with the host and influence the cause, symptoms, and progression of PD. At the same time, more rigorous experimental design and more advanced detection methods are needed to deeply analyze the dynamic evolution process of intestinal microbiota in PD patients and animal models.

3.2. Changes in metabolites derived from gut microbiome

Microbial metabolites can not only reflect the composition and function of intestinal microbiota but also are closely related to the progression of PD. Abnormal microbial metabolites are correlated with the pathology of α-synuclein and the activation of microglia cells, which can promote the neurodegeneration and movement disorders of PD animal models (53). Among them, SCFAs are the main metabolite of dietary fiber fermentation by intestinal microflora (including acetic acid, propionic acid, and butyric acid.), which plays a key role in maintaining the integrity of the colon epithelium, regulating immune response and intestinal permeability, as well as affecting brain function (54). The case–control study confirmed that the fecal microbiome and metabolome composition of PD patients were significantly different from that of the control group, and the fecal SCFAs level and the bacteria-producing level were both decreased, but the plasma SCFAs level increased (55, 56), which is associated with impairment of the gut–blood barrier and may be aggravated by constipation (57). Metagenomic functional analysis confirmed differences in microbiome metabolism related to SCFAs precursor metabolism in PD patients (48). Microbial metabolite levels related to the relative abundance of the proinflammatory intestinal microbes, in PD patients, and the abundance of proinflammatory microorganisms such as Clostridiales bacterium and Ruminococcus sp. is significantly correlated with the decrease of SCFAs level in feces and the increase of SCFAs level in plasma, especially propionic acid (58). SCFAs levels in feces and plasma of PD patients are not only correlated to specific changes in intestinal microbiome but also closely related to the clinical severity of PD (59). Specifically, poor cognitive function of PD patients was significantly correlated with low SCFAs level in feces (55), high butyric acid, and valerate level in plasma (58). The poorer the motor function, the lower the fecal SCFAs level, and the higher the plasma propionic acid concentration (58), and the poor postural instability–gait disorder score is associated with a low butyric acid level (55). Meanwhile, elevated microbial metabolites in the plasma of PD patients include indole derivatives, secondary bile acids, and hippuric acid (HA), which act as signaling molecules that can cross the blood–brain barrier to regulate inflammatory response and metabolic homeostasis. Among them, the plasma HA level is correlated with PD disease status (60). The elevated plasma levels of Trimethylamine N-oxide derived from gut microbes through dietary components, including L-carnitine and choline, are associated with disease severity and progression of PD (61) (Table 2). In addition, preclinical studies have found changes in intestinal microbiota and metabolites in various animal models of PD, and restoring healthy intestinal microbiota can effectively improve the damage of dopamine neurons in animal models of PD. MPTP-induced mouse models with a reduced abundance of Faecalicatena was accompanied by decreased expression of propionic acid and striatal Tyrosine hydroxylase (TH)

TABLE 2 Changes of microbial metabolites and their effects on PD.

Microbial metabolites	Function	Plasma level	Effect on PD	References
Short-chain fatty acids (SCFAs)	Maintain the integrity of the colon epithelium; Regulate immune response and intestinal permeability; Affect brain function	↑	Be related to abundance of proinflammatory intestinal microbes; Be related to poor cognitive function; Be related to poor motor function	Tan et al. (55); Nuzum et al. (56); Chen et al. (58); Wallen et al. (59);
Hippuric acid	Regulate the brain's inflammatory response and metabolic homeostasis	↑	Be correlated with PD disease status	Chen et al. (60)
Trimethylamine N-oxide	Promote α-synuclein aggregations and neuroinflammation	↑	Be associated with disease severity and motor symptom progression	Chen et al. (61)

↓ refers to decreased plasma level and ↑ refers to increased plasma level.

(62). A fasting-simulated diet increases favorable gut microbiome and SCFAs in PD mice, thereby increasing brain-derived neurotrophic factor (BDNF) levels and reducing neuroinflammation (63). Osteocalcin can improve the dyskinesia and DN loss of PD mice by increasing Bacteroidetes and the level of propionic acid (64).

The clinical correlation between intestinal microbes with their metabolites and PD further supports intestinal microbes as new biomarkers for early diagnosis of PD and potential targets for treatment. Moreover, changes in intestinal microbiota composition affect fecal metabolomics characteristics. Therefore, fecal metabolomics can be used to better understand the association between intestinal microbiota and clinical features (including clinical phenotype, disease status, and progression) in PD patients.

4. Genetic and environmental factors contribute to the microbiota-gut-brain axis disturbance

The interaction between genetic susceptibility and environmental factors jointly promotes the occurrence and development of PD (65). Studies have shown that >85% of PD cases occur in a sporadic manner, and familial PD can be attributed to disease-causing gene mutations associated with PARK sites, including Parkin, PINK1, and LRRK2. Epidemiological data indicated that less than 50% of LRRK2 mutation carriers eventually develop PD (66), suggesting that environmental factors other than genetic mutations are needed to trigger PD. Neuropathological studies have shown that α-synuclein can spread from ENS to central DA, and age is the key factor for the spread of α-synuclein. Inoculation of α-synuclein into the gastrointestinal tract of elderly rats, α-synuclein transmits along enteric nerve (67) or sympathetic and parasympathetic nerves (68) to the brain. Mitochondria are key participants in inducing, promoting, or aggravating the pathogenesis of PD (69). Mitochondrial damage is involved in the inflammatory cascade (70, 71). Intestinal microbial disorders in PD patients may lead to the progressive loss of DN through mitochondrial dysfunction (72, 73).

The gastrointestinal tract is an important place of contact with the environment, and environmental risk factors related to PD, including infection, environmental pollutants, and pressure, can affect the intestinal microbiome, which is the trigger for the occurrence and development of PD in genetically susceptible hosts (74). A prospective cohort study involving 228,485 individuals aged 50 and above found that gastrointestinal infection was associated with an increased risk of PD, and the destruction of the gastrointestinal mucosa by bacterial and viral pathogens could trigger the aggregation of α-synuclein in intestinal neurons and initiate its retrograde transport to CNS (75). Repeated infection of intestinal *Citrobacter rodentium* can damage DN in PINK1$^{-/-}$ mice and lead to motor deficiency (76). Further studies have revealed changes in intestinal microbiota over time, including the increased abundance of Enterobacteriaceae and Verrucomicrobia (77). The above studies have shown that differences in intestinal microflora caused by gastrointestinal infection can trigger PD. After long-term administration of rotenone, α-synuclein accumulation was observed in the CNS and intestine of mice (78), and the development of motor dysfunction depend on the presence of intestinal microbiota, compared with sterile mice, the changes in intestinal microbiota composition in conventionally fed mice were the same as those in human PD patients, including increased Lactobacillaceae, and decreased Lachnospiraceae (79). Chronic stress causes hypothalamic–pituitary–adrenal dysfunction in PD mice, leading to intestinal barrier dysfunction and decreased anti-inflammatory bacteria Lactobacillus abundance (80). The ingestion of trichloroethylene in elderly rats induces reduced abundance of Blautia that produced SCFAs (81).

The above research results indicated that the diversity and stability of intestinal microbiota decrease with age can lead to an increased genetic susceptibility to PD-related neurodegeneration, and environmental factors are more likely to trigger the pathophysiological process of PD microbe-gut-brain axis disorder.

5. Intestinal microbiome dysregulation and intestinal inflammation

The dysbiosis of intestinal microbiota can lead to intestinal inflammation, which can initiate the accumulation of misfolded α-synuclein in ENS in the early stage, and activate microglia and astrocytes through the microbiota-gut-brain axis upward pathway, thus triggering and/or promoting CNS inflammation and neurodegeneration. The above mechanism can have a synergistic effect with genetic and environmental factors to jointly trigger and promote the occurrence and development of PD (82, 83). Rota et al. found that in α-synuclein transgenic mice, significant symptoms of gastrointestinal dysfunction (such as constipation) precede CNS neurodegeneration (84). Further studies showed that the aggregation of α-synuclein in the colon of early PD mouse could trigger intestinal

inflammation and induce impairment of the intestinal barrier, accompanied by reduced production of SCFAs such as butyric acid and propionic acid (85). Through the double-hit PD model, it was found that intestinal inflammation and microbial dysbiosis could promote mucosal barrier leakage, enhance intestinal inflammation in mice, and accompany DN loss (86, 87).

As producers of Toll-like sensors (TLRs) ligands, the dysregulation of intestinal microbiota causes damage to intestinal epithelial cells through the activation of TLRs, then triggered the downstream TLR4 signaling pathway, thus promoting the inflammatory response in the gut and brain of PD patients (88). Intestinal inflammation, neuroinflammation, intestinal dysfunction, and neurodegeneration were significantly reduced in PD rodent models with TLR4 knockout (89, 90). Some variants of the TLR4 genes are considered to be risk factors of inflammatory bowel disease (IBD) and PD (91). Intestinal inflammation, a hallmark of IBD, plays an important role in the occurrence and development of PD. Clinical studies have indicated that clear genetic and pathophysiological links between IBD and PD (92, 93), and IBD may moderately increase PD risk (94). Both IBD and PD have intestinal inflammation, intestinal barrier dysfunction, and intestinal microbiome dysbiosis (95). Dysregulation of intestinal microbiome is closely associated with chronic intestinal inflammation in IBD, IBD patients and PD patients had the same intestinal microbiome characteristics, showing pro-inflammatory microbiota profiles, with a lower microbial α-diversity，and the abnormal expression of α-synuclein has been found in both intestines and ENS of IBD patients (96, 97). Similar to the PD, the abundance of bacteria-producing SCFAs like Lachnospiraceae, Roseburia, Faecalibacterium, Ruminococcus and Blautia in patients with IBD decreased significantly (98), gut microbiota dysbiosis promotes the onset of IBD. Meanwhile, multiple cohort studies (99–102) and two systematic reviews and meta-analysis (103, 104) have found that irritable bowel syndrome (IBS) is associated with a higher hazard of PD. IBS is a functional bowel disorder characterized by recurrent abdominal pain and changes in bowel habits (105, 106). It has been found that intestinal inflammation, increased intestinal permeability and changes in intestinal microbiome are involved in the pathogenesis of IBS, which was similar to that of PD (107). A nested case–control study with 1.7 million participants suggested that IBS is associated with a higher risk of PD and support the importance of the microbiota-gut-brain axis in PD etiology (108). The above studies indicate that intestinal microbiome dysregulation promotes intestinal inflammation, which plays an important role in the pathogenesis of PD.

6. Intestinal microbiome dysregulation and gastrointestinal dysfunction

Clinical and neuropathological evidence shows that the neurodegeneration of PD is accompanied by gastrointestinal dysfunction (109–112). A retrospective study involving 1.5 million participants showed that the earliest estimated time of onset of PD prodromal gastrointestinal dysfunction occurred decades before motor symptoms (109). Heinzel et al. conducted a study on 666 elderly people and found that intestinal microbiota composition was related to PD precursor markers, and its changes would lead to changes in clinical symptoms (110).

6.1. Constipation

Constipation is the most common PD-related gastrointestinal dysfunction, which is considered as reliable evidence of autonomic nervous disorder in the PD prodromal stage (113). The severity of constipation can predict the progress of motor symptoms and cognitive impairment in PD patients and seriously affect their quality of life (114). Lubomski et al. found that PD patients were three times more likely to be constipated than healthy subjects (78.6 vs. 28.4%); age, stage, depression, anxiety, and autonomic dysfunction all increased the risk of constipation in PD patients (115); and the significantly reduced physical activity in PD patients was correlated with the severity of constipation (116). With the progression of the disease, the incidence of constipation in PD patients increases, and more than 80% of PD patients (including newly diagnosed PD patients) show prolonged CTT (117). At the same time, chronic constipation leads to slower gastrointestinal emptying, which can delay PD drug absorption (impaired pharmacodynamics) and thus lead to deterioration of motor function (118, 119). Clinical studies have proved that intestinal microbial dysregulation is related to gastrointestinal dysfunction in PD patients. According to the 16SrRNA gene sequence data of 324 participants, the effect of constipation on PD is as high as 76.56% mediated by intestinal microbial changes (120), and intestinal microflora dysbiosis plays an important role in PD-related constipation mainly through the reduction of SCFAs producing bacteria. Constipated PD patients show unique intestinal microbiota characteristics, namely, decreased butyrate synthesis, increased production of harmful amino acid metabolites, including an increase in Akkermansia and Bifidobacterium while a decrease in Faecalibacterium and Lachnospiraceae. Akkermansia was positively correlated with chronic constipation and stool hardness, while Faecalibacterium and bacteria-producing butyrate are negatively correlated with stool hardness and constipation (121). The above studies indicated that intestinal microbiota composition and metabolic changes in PD patients are closely related to intestinal function, and supplementation of probiotics containing SCFAs producing bacteria or drugs promoting the growth of SCFAs-producing bacteria which may have a potential application prospect in the prevention and treatment of PD-related constipation.

6.2. Small intestinal bacterial overgrowth (SIBO)

SIBO refers to a large amount of colonization of the small intestine by bacteria present in the colon (122). A meta-analysis involving 973 participants showed an increased prevalence of SIBO in PD patients (33–52%) and a strong association with motor complications (123). SIBO-positive patients exhibit increased intestinal permeability, bacterial translocation, promoting microglial cell activation and abnormal accumulation of α-synuclein in intestinal neurons, as well as affecting levodopa bioavailability due to peripheral inflammation or partial metabolism of levodopa. Van et al. found that PD patients with SIBO positive had a higher relative abundance of bacterial tyrosine decarboxylase in the proximal small intestine (the site of levodopa absorption), which reduces the level of levodopa *in situ* (10). Among the bacteria species identified so far, *Enterococcus faecalis* rich in tyrosine

decarboxylase can fully metabolize levodopa peripheral (11). Meanwhile, PD treatment drugs may be an important confounder of intestinal microbiome changes, and dopamine agonists can cause SIBO in healthy rats, including an increase in Lactobacillus, and affect L-dopa bioavailability (17). The above studies have shown a negative correlation between bacteria with tyrosine decarboxylase activity and the level of levodopa in the systemic circulation, and PD-related drugs essentially have significant effects on disease-related complications, including promoting gastrointestinal dysfunction, SIBO, and altering intestinal microbiome composition (18). Therefore, specific bacterial species in the small intestine such as *Enterococcus faecalis*, Lactobacillus species, and tyrosine decarboxylase activity levels can be used as biomarkers to monitor the efficacy of levodopa. Future studies need to consider the effects of PD therapeutics and SIBO eradication on gastrointestinal motor function and microbiome composition.

6.3. *Helicobacter pylori* (HP) infection

HP infection has been found to be associated with the pathophysiology and increased risk of PD (124). Colonization of HP in the gastrointestinal tract leads to the destruction of the blood–brain barrier, neuroinflammation, and degradation of DN through direct neurotoxic effects (neurotoxic factors directly damage cells), local effects (chronic mucosal inflammation damages the gastrointestinal barrier), and systemic immune responses (increased secretion of pro-inflammatory cytokines). Meanwhile, HP induces the reduction of gastric acid that leads to dysregulation of the gut microbiome, contributing to the development of SIBO, as previously described, which worsens the motor function of PD (125). The retrospective cohort study found that compared with the control group ($n = 9{,}105$), the HP infection group ($n = 9{,}105$) had a significantly higher risk of PD (126). Another case–control study found that HP-positive patients had worse motor function (127). A meta-analysis of 13 studies showed that HP infection was associated with more severe motor symptoms and worse drug response in PD patients (12). Another meta-analysis of 10 studies found that the eradication of HP could improve motor retardation and myotonia in PD patients as well as improve the therapeutic outcome of levodopa (13). Clinical observation suggested that duodenal inflammation induced by HP infection is accompanied by mucosal damage, which leads to poor drug response and motion fluctuation in PD patients through impaired levodopa bioavailability (14). The above studies emphasize that HP infection is involved in the pathophysiological process of PD, which can not only worsen the severity of the disease but also negatively affect the drug response of patients. HP eradication may improve its bioavailability by reducing HP-dependent levodopa consumption, thus improving motor control (15). Considering the high clinical prevalence of HP infection, it may be reasonable to screen people with a high risk of PD for HP. Meanwhile, for PD patients with poor symptom control, HP eradication may enhance the effect of levodopa, but whether HP eradication affects the natural process or progression of PD remains to be verified by further large-scale longitudinal studies and randomized controlled trials.

The prodromal stage is a window of opportunity for better understanding the pathogenesis of PD and early detection of the disease. Gastrointestinal dysfunction is the most important non-motor symptoms in PD patients (128). Currently, the management and treatment of PD-related gastrointestinal dysfunction are limited (129). Studies have shown that not only levodopa and other therapeutic drugs can directly affect the microbiome but also the intestinal microbiome can interfere with the absorption and utilization of drugs. Therefore, it is crucial to identify and treat PD-related gastrointestinal dysfunction, and further studies are needed on the potential interactions between intestinal microbiota and therapeutic drugs used, so as to improve the bioavailability of drugs such as levodopa and provide a basis for the development of new complementary therapeutic strategies for PD at the intestinal level.

7. PD therapy: disease remission strategies based on regulation of the gut microbiome

Considering the role of the microbiota-gut-brain axis in the occurrence and progression of PD, disease mitigation strategies based on intestinal microbiome regulation deserve further research, especially in the prevention and treatment of gastrointestinal dysfunction and motor symptoms in PD. At present, preclinical and clinical studies mainly focus on reducing the clinical symptoms of PD or delaying the progression of the disease through probiotics, prebiotics, and diet adjustment (130).

7.1. Food and diet pattern

Diet and nutrition are the main factors affecting the balance of intestinal microbiota (131). Epidemiological reports showed that the regulation of intestinal microbiota through food and diet pattern can not only reduce the risk of PD (132) but also improve the symptoms and quality of life of PD patients (133, 134). There is a strong correlation between the age of PD onset and dietary habits, with adherence to the Mediterranean diet that can reduce the probability of precursor PD in the elderly (135). Adherence to the MIND diet is closely associated with delayed onset of PD in women, with the longest delay of 17.4 years, and adherence to the Greek Mediterranean diet is associated with delayed onset of PD in men, with a difference of up to 8.4 years (136). A negative association between Mediterranean diet adherence and PD was observed in a cohort of more than 47,000 Swedish women (137). Evidence from a systematic review involving 52 studies suggests that following a Mediterranean diet can reduce the onset and clinical progression of PD (138). Specific dietary patterns can regulate intestinal inflammation and influence the risk of PD (139). Western diet rich in refined carbohydrates and animal saturated fats, may have a harmful effect on the microbiota-gut-brain axis, which can lead to intestinal microbiome dysbiosis and increase bacteria containing a large amount of LPS, thus affecting intestinal barrier function and leading to endotoxemia, systemic inflammation, and mitochondrial dysfunction (140), which is associated with increased risk and deterioration of PD. Rich in flavonoids, polyunsaturated fatty acids, and plant fiber, the Mediterranean diet has a positive effect on the gut microbiome, which can increase SCFAs-producing bacteria and induce GLP-1 and BDNF release, reduce intestinal inflammation, and prevent neurodegeneration, thereby reducing the risk of PD (141). A case–control study with 54 PD patients showed that a

TABLE 3 Summary of the role of food and diet pattern in PD.

Food or Diet Pattern	Effect on PD	References
Mediterranean diet	Reduce the risk of PD	Maraki et al. (135); Yin et al. (137); Bianchi et al. (138); Bianchi et al. (141)
MIND diet	Delay the onset of PD in women	Metcalfe-Roach et al. (136)
Greek Mediterranean diet	Delay the onset of PD in men	Metcalfe-Roach et al. (136)
Western diet	Increase risk and deterioration of PD	Terenzi et al. (139); Jackson et al. (140);
Vegetarian diet	Improve clinical motor symptoms of PD	Hegelmaier et al. (142)
Containing α-synuclein in the diet	Be involved in the pathogenesis of PD through autoimmunity.	Vojdani et al. (143); Vojdani et al. (144); Lerner et al. (145)

vegetarian diet including a high proportion of anti-inflammatory acting short-fatty acids (SCFA) can improve the pro-inflammatory intestinal microbiome in PD patients, with a significant clinical improvement as quantified by UPDRS III (142). In addition, α-synuclein in food, which share cross-reaction epitopes with human α-synuclein and have molecular similarity with brain antigens were involved in synaptic nucleoprotein lesions in the pathogenesis of PD through autoimmunity (143, 144), including forming immune complexes with antibodies to cross the blood–brain barrier and also reaching the blood–brain barrier from ENS (145). Therefore, elimination of foods containing α-synuclein in the diet may help to prevent or delay the occurrence and development of PD (Table 3).

The food and diet pattern may affect the microbiota-gut-brain axis by altering the composition of the microbiome, thereby improving the progression of PD. In future, it is necessary to further determine the potential beneficial effects of various dietary patterns in inhibiting amyloid accumulation and oxidative stress in ENS and better understand the effects of diet and intestinal microbial disorders on PD, including disease progression, autonomic dysfunction, and cognitive function. At the same time, the long-term nature of food and diet pattern needs to be considered, as well as the duration, dose, and combination of interventions for different dietary patterns.

7.2. Probiotics

Probiotics are live microorganisms that are beneficial to the health of the host when given in appropriate amounts, and preclinical and clinical studies have shown that probiotics regulate gut microbiota (improving intestinal barrier integrity, reducing overgrowth of potentially pathogenic bacteria in the gut, and inhibiting bacterial translocation), maintain immune homeostasis (regulating the immune system of the gastrointestinal mucosa), protect DN (inhibiting glial cell activation, increasing BDNF and SCFAs, and reducing LPS), and improve the overall PD behavioral phenotype (146). Intake of probiotics can not only improve constipation-related non-motor symptoms in PD patients but also alleviate motor dysfunction (147, 148). Multiple randomized controlled clinical trials have shown that the ingestion of probiotics (with multiple strains of probiotics alone (149, 150) or in combination with probiotic fibers (151)) can improve gastrointestinal symptoms in PD patients by modulating the microbiota-gut-brain axis, including reducing abdominal pain, bloating, and constipation symptoms, and improving stool hardness, bowel frequency, and bowel habits in PD patients with constipation (152). Therefore, probiotics relieve constipation by regulating intestinal microbiota, which has a good clinical application value (153). In addition, taking probiotics for 12 weeks can reduce MDS-UPDRS scores and improve insulin resistance in PD patients (154). At the same time, preclinical studies have found that probiotics can alleviate movement disorders in PD animal models and exert neuroprotective effects on DN. Long-term administration of probiotics can not only improve gastrointestinal symptoms and UPDRS scores of MitoPark PD mice but also inhibit the progressive degeneration of DN in the nigra (155). Goya et al. found that the probiotic *Bacillus subtilis* PXN21 could affect the release of intestinal microbial metabolites in *Caenorhabditis elegans*, thereby inhibiting and reversing the aggregation of α-synuclein and removing formed synuclein lesions (156). Intestinal microbiota can also affect the progression of PD by regulating intestinal endocrine through GLP-1, relieve oxidative stress and inflammatory response, and inhibit TH neuron apoptosis through activating its receptor GLP-1R (157). Ingestion of probiotics can reduce the intestinal pathogen Enterobacteriaceae in MPTP-induced PD mice (158), reverse the dysbiosis of intestinal microbiome (increased abundance of Alistipes) (159), and increase TH-positive neurons by increasing GLP-1.

Considering the high variability of the inherent intestinal microbiota from PD patients and exogenous probiotics, a further longitudinal study is needed on the influence of exogenous probiotics on the intestinal microenvironment of PD patients before and after intervention under optimal control conditions and to verify the long-term efficacy, safety, and mechanism of its treatment of PD. Meanwhile, accurate development of personalized treatment plans requires the determination of the most appropriate probiotics for PD treatment based on the specific intestinal microbiota profile of a single PD patient.

8. Conclusion

In summary, the preclinical and clinical research evidence discussed in this review supports the important role of bidirectional microbiota-gut-brain pathways and intestinal microbiome dysregulation in the initiation and progression of PD. In the condition of intestinal microbiota dysbiosis, the pro-inflammatory microenvironment may induce α-synuclein deposited in ENS to spread to the CNS in the form of transsynaptic cell transmission and further causes gastrointestinal dysfunction, neuroinflammation, and neurodegeneration through the disordered microbiota-gut-brain axis. The relationship between intestinal microbiota disorder and PD is far more complex than the one-way causal relationship. Elucidating the pathophysiological role of the microbiota-gut-brain axis in PD

can not only further reveal the early pathogenesis of PD and predict the progression of neurodegeneration, phenotypic transformation, and prognosis but also intestinal microbiome-oriented treatment strategies to maintain or restore the homeostasis of the intestinal microenvironment may alter the disease course of PD through the microbiota-gut-brain axis, which will provide future direction for the development of new biomarkers for early diagnosis and therapeutic targets to slow the progression of PD. This can be applied clinically to design more effective personalized or subtype-specific, patient-centered treatment and prevention strategies.

Author contributions

QL, L-bM, and Q-yY contributed to conception of the review. QL and L-bM wrote the first draft of the manuscript. L-jC, XS, LT, QZ, J-lY, XL, and YZ wrote sections of the manuscript. Q-yY was involved in critically revising the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Bloem BR, Okun MS, Klein C. Parkinson's disease. *Lancet*. (2021) 397:2284–303. doi: 10.1016/S0140-6736(21)00218-X

2. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. *JAMA*. (2020) 323:548–60. doi: 10.1001/jama.2019.22360

3. Tolosa E, Garrido A, Scholz SW, Poewe W. Challenges in the diagnosis of Parkinson's disease. *Lancet Neurol*. (2021) 20:385–97. doi: 10.1016/S1474-4422(21)00030-2

4. Breen DP, Halliday GM, Lang AE. Gut-brain axis and the spread of α-synuclein pathology: vagal highway or dead end? *Mov Disord*. (2019) 34:307–16. doi: 10.1002/mds.27556

5. Tan AH, Lim SY, Lang AE. The microbiome-gut-brain axis in Parkinson disease - from basic research to the clinic. *Nat Rev Neurol*. (2022) 18:476–95. doi: 10.1038/s41582-022-00681-2

6. Lubomski M, Tan AH, Lim SY, Holmes AJ, Davis RL, Sue CM. Parkinson's disease and the gastrointestinal microbiome. *J Neurol*. (2020) 267:2507–23. doi: 10.1007/s00415-019-09320-1

7. Pellegrini C, Antonioli L, Calderone V, Colucci R, Fornai M, Blandizzi C. Microbiota-gut-brain axis in health and disease: is NLRP3 inflammasome at the crossroads of microbiota-gut-brain communications? *Prog Neurobiol*. (2020) 191:101806. doi: 10.1016/j.pneurobio.2020.101806

8. Chen Z, Li G, Liu J. Autonomic dysfunction in Parkinson's disease: implications for pathophysiology, diagnosis, and treatment. *Neurobiol Dis*. (2020) 134:104700. doi: 10.1016/j.nbd.2019.104700

9. Gonzalez-Latapi P, Bhowmick SS, Saranza G, Fox SH. Non-dopaminergic treatments for motor control in Parkinson's disease: an update. *CNS Drugs*. (2020) 34:1025–44. doi: 10.1007/s40263-020-00754-0

10. van Kessel SP, Frye AK, El-Gendy AO, Castejon M, Keshavarzian A, van Dijk G, et al. Gut bacterial tyrosine decarboxylases restrict levels of levodopa in the treatment of Parkinson's disease. *Nat Commun*. (2019) 10:310. doi: 10.1038/s41467-019-08294-y

11. Maini Rekdal V, Bess EN, Bisanz JE, Turnbaugh PJ, Balskus EP. Discovery and inhibition of an interspecies gut bacterial pathway for levodopa metabolism. *Science*. (2019) 364:eaau6323. doi: 10.1126/science.aau6323

12. Zhong R, Chen Q, Zhang X, Li M, Lin W. *Helicobacter pylori* infection is associated with a poor response to levodopa in patients with Parkinson's disease: a systematic review and meta-analysis. *J Neurol*. (2022) 269:703–11. doi: 10.1007/s00415-021-10473-1

13. Bai F, Li X. Association of *Helicobacter pylori* treatment with parkinsonism and related disorders: a systematic review and meta-analysis. *Life Sci*. (2021) 281:119767. doi: 10.1016/j.lfs.2021.119767

14. Baj J, Forma A, Flieger W, Morawska I, Michalski A, Buszewicz G, et al. *Helicobacter pylori* infection and extragastric diseases-a focus on the central nervous system. *Cells*. (2021) 10:2191. doi: 10.3390/cells10092191

15. Nyholm D, Hellström PM. Effects of *Helicobacter pylori* on levodopa pharmacokinetics. *J Parkinsons Dis*. (2021) 11:61–9. doi: 10.3233/JPD-202298

16. Pfeiffer RF, Isaacson SH, Pahwa R. Clinical implications of gastric complications on levodopa treatment in Parkinson's disease. *Parkinsonism Relat Disord*. (2020) 76:63–71. doi: 10.1016/j.parkreldis.2020.05.001

17. van Kessel SP, Bullock A, van Dijk G, El Aidy S. Parkinson's Disease medication alters small intestinal motility and microbiota composition in healthy rats. *mSystems*. (2022) 7:e0119121. doi: 10.1128/msystems.01191-21

18. Dănău A, Dumitrescu L, Lefter A, Tulbă D, Popescu BO. Small intestinal bacterial overgrowth as potential therapeutic target in Parkinson's disease. *Int J Mol Sci*. (2021) 22:11663. doi: 10.3390/ijms222111663

19. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging*. (2003) 24:197–211. doi: 10.1016/S0197-4580(02)00065-9

20. van den Berge N, Ferreira N, Gram H, Mikkelsen TW, Alstrup AKO, Casadei N, et al. Evidence for bidirectional and trans-synaptic parasympathetic and sympathetic propagation of alpha-synuclein in rats. *Acta Neuropathol*. (2019) 138:535–50. doi: 10.1007/s00401-019-02040-w

21. Arotcarena ML, Dovero S, Prigent A, Bourdenx M, Camus S, Porras G, et al. Bidirectional gut-to-brain and brain-to-gut propagation of synucleinopathy in non-human primates. *Brain*. (2020) 143:1462–75. doi: 10.1093/brain/awaa096

22. Berg D, Borghammer P, Fereshtehnejad SM, Heinzel S, Horsager J, Schaeffer E, et al. Prodromal Parkinson disease subtypes - key to understanding heterogeneity. *Nat Rev Neurol*. (2021) 17:349–61. doi: 10.1038/s41582-021-00486-9

23. Borghammer P, Horsager J, Andersen K, Van Den Berge N, Raunio A, Murayama S, et al. Neuropathological evidence of body-first vs. brain-first Lewy body disease. *Neurobiol Dis*. (2021) 161:105557. doi: 10.1016/j.nbd.2021.105557

24. Beach TG, Adler CH, Sue LI, Shill HA, Driver-Dunckley E, Mehta SH, et al. Vagus and stomach synucleinopathy in Parkinson's disease, incidental Lewy body disease, and normal elderly subjects: evidence against the "body-first" hypothesis. *J Parkinsons Dis*. (2021) 11:1833–43. doi: 10.3233/JPD-212733

25. Svensson E, Horváth-Puhó E, Thomsen RW, Djurhuus JC, Pedersen L, Borghammer P, et al. Vagotomy and subsequent risk of Parkinson's disease. *Ann Neurol*. (2015) 78:522–9. doi: 10.1002/ana.24448

26. Kim S, Kwon SH, Kam TI, Panicker N, Karuppagounder SS, Lee S, et al. Transneuronal propagation of pathologic α-synuclein from the gut to the brain models Parkinson's disease. *Neuron*. (2019) 103:627–641.e7. doi: 10.1016/j.neuron.2019.05.035

27. Horsager J, Knudsen K, Sommerauer M. Clinical and imaging evidence of brain-first and body-first Parkinson's disease. *Neurobiol Dis*. (2022) 164:105626. doi: 10.1016/j.nbd.2022.105626

28. Horsager J, Knudsen K, Borghammer P. Radionuclide imaging of the gut-brain axis in Parkinson disease. *J Nucl Med*. (2021) 62:1504–5. doi: 10.2967/jnumed.121.262300

29. Knudsen K, Fedorova TD, Hansen AK, Sommerauer M, Otto M, Svendsen KB, et al. In-vivo staging of pathology in REM sleep behaviour disorder: a multimodality imaging case-control study. *Lancet Neurol*. (2018) 17:618–28. doi: 10.1016/S1474-4422(18)30162-5

30. Horsager J, Andersen KB, Knudsen K, Skjærbæk C, Fedorova TD, Okkels N, et al. Brain-first versus body-first Parkinson's disease: a multimodal imaging case-control study. *Brain*. (2020) 143:3077–88. doi: 10.1093/brain/awaa238

31. Knudsen K, Fedorova TD, Hansen AK, Sommerauer M, Haase AM, Svendsen KB, et al. Objective intestinal function in patients with idiopathic REM sleep behavior disorder. *Parkinsonism Relat Disord*. (2019) 58:28–34. doi: 10.1016/j.parkreldis.2018.08.011

32. Sharabi Y, Vatine GD, Ashkenazi A. Parkinson's disease outside the brain: targeting the autonomic nervous system. *Lancet Neurol*. (2021) 20:868–76. doi: 10.1016/S1474-4422(21)00219-2

33. Morais LH, Schreiber HL 4th, Mazmanian SK. The gut microbiota-brain axis in behaviour and brain disorders. *Nat Rev Microbiol*. (2021) 19:241–55. doi: 10.1038/s41579-020-00460-0

34. Margolis KG, Cryan JF, Mayer EA. The microbiota-gut-brain axis: from motility to mood. *Gastroenterology*. (2021) 160:1486–501. doi: 10.1053/j.gastro.2020.10.066

35. Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, et al. The microbiota-gut-brain axis. *Physiol Rev*. (2019) 99:1877–2013. doi: 10.1152/physrev.00018.2018

36. Wang Q, Luo Y, Ray Chaudhuri K, Reynolds R, Tan EK, Pettersson S. The role of gut dysbiosis in Parkinson's disease: mechanistic insights and therapeutic options. *Brain*. (2021) 144:2571–93. doi: 10.1093/brain/awab156

37. Rani L, Mondal AC. Unravelling the role of gut microbiota in Parkinson's disease progression: pathogenic and therapeutic implications. *Neurosci Res*. (2021) 168:100–12. doi: 10.1016/j.neures.2021.01.001

38. Dogra N, Mani RJ, Katare DP. The gut-brain axis: two ways signaling in Parkinson's disease. *Cell Mol Neurobiol*. (2022) 42:315–32. doi: 10.1007/s10571-021-01066-7

39. Sampson TR, Challis C, Jain N, Moiseyenko A, Ladinsky MS, Shastri GG, et al. A gut bacterial amyloid promotes α-synuclein aggregation and motor impairment in mice. *elife*. (2020) 9:e53111. doi: 10.7554/eLife.53111

40. Yang R, Gao G, Yang H. The pathological mechanism between the intestine and brain in the early stage of Parkinson's disease. *Front Aging Neurosci*. (2022) 14:861035. doi: 10.3389/fnagi.2022.861035

41. Aho VTE, Houser MC, Pereira PAB, Chang J, Rudi K, Paulin L, et al. Relationships of gut microbiota, short-chain fatty acids, inflammation, and the gut barrier in Parkinson's disease. *Mol Neurodegener*. (2021) 16:6. doi: 10.1186/s13024-021-00427-6

42. Nuzum ND, Loughman A, Szymlek-Gay EA, Teo WP, Hendy AM, Macpherson H. To the gut microbiome and beyond: the brain-first or body-first hypothesis in Parkinson's disease. *Front Microbiol*. (2022) 13:791213. doi: 10.3389/fmicb.2022.791213

43. Aho VTE, Pereira PAB, Voutilainen S, Paulin L, Pekkonen E, Auvinen P, et al. Gut microbiota in Parkinson's disease: temporal stability and relations to disease progression. *EBioMedicine*. (2019) 44:691–707. doi: 10.1016/j.ebiom.2019.05.064

44. Romano S, Savva GM, Bedarf JR, Charles IG, Hildebrand F, Narbad A. Meta-analysis of the Parkinson's disease gut microbiome suggests alterations linked to intestinal inflammation. *NPJ Parkinsons Dis*. (2021) 7:27. doi: 10.1038/s41531-021-00156-z

45. Nishiwaki H, Hamaguchi T, Ito M, Ishida T, Maeda T, Kashihara K, et al. Short-chain fatty acid-producing gut microbiota is decreased in Parkinson's disease but not in rapid-eye-movement sleep behavior disorder. *mSystems*. (2020) 5:e00797–20. doi: 10.1128/mSystems.00797-20

46. Nishiwaki H, Ito M, Ishida T, Hamaguchi T, Maeda T, Kashihara K, et al. Meta-analysis of gut dysbiosis in Parkinson's disease. *Mov Disord*. (2020) 35:1626–35. doi: 10.1002/mds.28119

47. Zheng SY, Li HX, Xu RC, Miao WT, Dai MY, Ding ST, et al. Potential roles of gut microbiota and microbial metabolites in Parkinson's disease. *Ageing Res Rev*. (2021) 69:101347. doi: 10.1016/j.arr.2021.101347

48. Mao L, Zhang Y, Tian J, Sang M, Zhang G, Zhou Y, et al. Cross-sectional study on the gut microbiome of Parkinson's disease patients in Central China. *Front Microbiol*. (2021) 12:728479. doi: 10.3389/fmicb.2021.728479

49. Toh TS, Chong CW, Lim SY, Bowman J, Cirstea M, Lin CH, et al. Gut microbiome in Parkinson's disease: new insights from meta-analysis. *Parkinsonism Relat Disord*. (2022) 94:1–9. doi: 10.1016/j.parkreldis.2021.11.017

50. Vascellari S, Palmas V, Melis M, Pisanu S, Cusano R, Uva P, et al. Gut microbiota and Metabolome alterations associated with Parkinson's disease. *mSystems*. (2020) 5:e00561–20. doi: 10.1128/mSystems.00561-20

51. Lin CH, Chen CC, Chiang HL, Liou JM, Chang CM, Lu TP, et al. Altered gut microbiota and inflammatory cytokine responses in patients with Parkinson's disease. *J Neuroinflammation*. (2019) 16:129. doi: 10.1186/s12974-019-1528-y

52. Xie A, Ensink E, Li P, Gordevičius J, Marshall LL, George S, et al. Bacterial butyrate in Parkinson's disease is linked to epigenetic changes and depressive symptoms. *Mov Disord*. (2022) 37:1644–53. doi: 10.1002/mds.29128

53. van Kessel SP, El Aidy S. Bacterial metabolites mirror altered gut microbiota composition in patients with Parkinson's disease. *J Parkinsons Dis*. (2019) 9:S359–70. doi: 10.3233/JPD-191780

54. Dalile B, Van Oudenhove L, Vervliet B, Verbeke K. The role of short-chain fatty acids in microbiota-gut-brain communication. *Nat Rev Gastroenterol Hepatol*. (2019) 16:461–78. doi: 10.1038/s41575-019-0157-3

55. Tan AH, Chong CW, Lim SY, Yap IKS, Teh CSJ, Loke MF, et al. Gut microbial ecosystem in Parkinson disease: new clinicobiological insights from multi-omics. *Ann Neurol*. (2021) 89:546–59. doi: 10.1002/ana.25982

56. Nuzum ND, Loughman A, Szymlek-Gay EA, Hendy A, Teo WP, Macpherson H. Gut microbiota differences between healthy older adults and individuals with Parkinson's disease: a systematic review. *Neurosci Biobehav Rev*. (2020) 112:227–41. doi: 10.1016/j.neubiorev.2020.02.003

57. Yang X, Ai P, He X, Mo C, Zhang Y, Xu S, et al. Parkinson's disease is associated with impaired gut-blood barrier for short-chain fatty acids. *Mov Disord*. (2022) 37:1634–43. doi: 10.1002/mds.29063

58. Chen SJ, Chen CC, Liao HY, Lin YT, Wu YW, Liou JM, et al. Association of fecal and plasma levels of short-chain fatty acids with gut microbiota and clinical severity in patients with Parkinson disease. *Neurology*. (2022) 98:e848–58. doi: 10.1212/WNL.0000000000013225

59. Wallen ZD, Appah M, Dean MN, Sesler CL, Factor SA, Molho E, et al. Characterizing dysbiosis of gut microbiome in PD: evidence for overabundance of opportunistic pathogens. *NPJ Parkinsons Dis*. (2020) 6:11. doi: 10.1038/s41531-020-0112-6

60. Chen SJ, Chen CC, Liao HY, Wu YW, Liou JM, Wu MS, et al. Alteration of gut microbial metabolites in the systemic circulation of patients with Parkinson's disease. *J Parkinsons Dis*. (2022) 12:1219–30. doi: 10.3233/JPD-223179

61. Chen SJ, Kuo CH, Kuo HC, Chen CC, Wu WK, Liou JM, et al. The gut metabolite Trimethylamine N-oxide is associated with Parkinson's disease severity and progression. *Mov Disord*. (2020) 35:2115–6. doi: 10.1002/mds.28246

62. Shan J, Qu Y, Wang S, Wei Y, Chang L, Ma L, et al. Regulation of neurotoxicity in the striatum and colon of MPTP-induced Parkinson's disease mice by gut microbiome. *Brain Res Bull*. (2021) 177:103–10. doi: 10.1016/j.brainresbull.2021.09.009

63. Zhou ZL, Jia XB, Sun MF, Zhu YL, Qiao CM, Zhang BP, et al. Neuroprotection of fasting mimicking diet on MPTP-induced Parkinson's disease mice via gut microbiota and metabolites. *Neurotherapeutics*. (2019) 16:741–60. doi: 10.1007/s13311-019-00719-2

64. Hou YF, Shan C, Zhuang SY, Zhuang QQ, Ghosh A, Zhu KC, et al. Gut microbiota-derived propionate mediates the neuroprotective effect of osteocalcin in a mouse model of Parkinson's disease. *Microbiome*. (2021) 9:34. doi: 10.1186/s40168-020-00988-6

65. Johnson ME, Stecher B, Labrie V, Brundin L, Brundin P. Triggers, facilitators, and aggravators: redefining Parkinson's disease pathogenesis. *Trends Neurosci*. (2019) 42:4–13. doi: 10.1016/j.tins.2018.09.007

66. Tran J, Anastacio H, Bardy C. Genetic predispositions of Parkinson's disease revealed in patient-derived brain cells. *NPJ Parkinsons Dis*. (2020) 6:8. doi: 10.1038/s41531-020-0110-8

67. Challis C, Hori A, Sampson TR, Yoo BB, Challis RC, Hamilton AM, et al. Gut-seeded α-synuclein fibrils promote gut dysfunction and brain pathology specifically in aged mice. *Nat Neurosci*. (2020) 23:327–36. doi: 10.1038/s41593-020-0589-7

68. Van Den Berge N, Ferreira N, Mikkelsen TW, Alstrup AKO, Tamgüney G, Karlsson P, et al. Ageing promotes pathological alpha-synuclein propagation and autonomic dysfunction in wild-type rats. *Brain*. (2021) 144:1853–68. doi: 10.1093/brain/awab061

69. Munoz-Pinto MF, Empadinhas N, Cardoso SM. The neuromicrobiology of Parkinson's disease: a unifying theory. *Ageing Res Rev*. (2021) 70:101396. doi: 10.1016/j.arr.2021.101396

70. Cardoso SM, Empadinhas N. The microbiome-mitochondria dance in prodromal Parkinson's disease. *Front Physiol*. (2018) 9:471. doi: 10.3389/fphys.2018.00471

71. Quinn PMJ, Moreira PI, Ambrósio AF, Alves CH. PINK1/PARKIN signalling in neurodegeneration and neuroinflammation. *Acta Neuropathol Commun*. (2020) 8:189. doi: 10.1186/s40478-020-01062-w

72. Liang Y, Cui L, Gao J, Zhu M, Zhang Y, Zhang HL. Gut microbial metabolites in Parkinson's disease: implications of mitochondrial dysfunction in the pathogenesis and treatment. *Mol Neurobiol*. (2021) 58:3745–58. doi: 10.1007/s12035-021-02375-0

73. Harland M, Torres S, Liu J, Wang X. Neuronal mitochondria modulation of LPS-induced neuroinflammation. *J Neurosci*. (2020) 40:1756–65. doi: 10.1523/JNEUROSCI.2324-19.2020

74. Chen SJ, Lin CH. Gut microenvironmental changes as a potential trigger in Parkinson's disease through the gut-brain axis. *J Biomed Sci*. (2022) 29:54. doi: 10.1186/s12929-022-00839-6

75. Nerius M, Doblhammer G, Tamgüney G. GI infections are associated with an increased risk of Parkinson's disease. *Gut*. (2020) 69:1154–6. doi: 10.1136/gutjnl-2019-318822

76. Matheoud D, Cannon T, Voisin A, Penttinen AM, Ramet L, Fahmy AM, et al. Intestinal infection triggers Parkinson's disease-like symptoms in Pink1−/− mice. *Nature*. (2019) 571:565–9. doi: 10.1038/s41586-019-1405-y

77. Cannon T, Sinha A, Trudeau LE, Maurice CF, Gruenheid S. Characterization of the intestinal microbiota during *Citrobacter rodentium* infection in a mouse model of

infection-triggered Parkinson's disease. *Gut Microbes*. (2020) 12:1830694–11. doi: 10.1080/19490976.2020.1830694

78. Miyazaki I, Isooka N, Imafuku F, Sun J, Kikuoka R, Furukawa C, et al. Chronic systemic exposure to low-dose rotenone induced central and peripheral neuropathology and motor deficits in mice: reproducible animal model of Parkinson's disease. *Int J Mol Sci*. (2020) 21:3254. doi: 10.3390/ijms21093254

79. Bhattarai Y, Si J, Pu M, Ross OA, McLean PJ, Till L, et al. Role of gut microbiota in regulating gastrointestinal dysfunction and motor symptoms in a mouse model of Parkinson's disease. *Gut Microbes*. (2021) 13:1866974. doi: 10.1080/19490976.2020.1866974

80. Dodiya HB, Forsyth CB, Voigt RM, Engen PA, Patel J, Shaikh M, et al. Chronic stress-induced gut dysfunction exacerbates Parkinson's disease phenotype and pathology in a rotenone-induced mouse model of Parkinson's disease. *Neurobiol Dis*. (2020) 135:104352. doi: 10.1016/j.nbd.2018.12.012

81. Ilieva NM, Wallen ZD, De Miranda BR. Oral ingestion of the environmental toxicant trichloroethylene in rats induces alterations in the gut microbiome: relevance to idiopathic Parkinson's disease. *Toxicol Appl Pharmacol*. (2022) 451:116176. doi: 10.1016/j.taap.2022.116176

82. Johnson AM, Ou ZA, Gordon R, Saminathan H. Environmental neurotoxicants and inflammasome activation in Parkinson's disease - a focus on the gut-brain axis. *Int J Biochem Cell Biol*. (2022) 142:106113. doi: 10.1016/j.biocel.2021.106113

83. Metta V, Leta V, Mrudula KR, Prashanth LK, Goyal V, Borgohain R, et al. Gastrointestinal dysfunction in Parkinson's disease: molecular pathology and implications of gut microbiome, probiotics, and fecal microbiota transplantation. *J Neurol*. (2022) 269:1154–63. doi: 10.1007/s00415-021-10567-w

84. Rota L, Pellegrini C, Benvenuti L, Antonioli L, Fornai M, Blandizzi C, et al. Constipation, deficit in colon contractions and alpha-synuclein inclusions within the colon precede motor abnormalities and neurodegeneration in the central nervous system in a mouse model of alpha-synucleinopathy. *Transl Neurodegener*. (2019) 8:5. doi: 10.1186/s40035-019-0146-z

85. Pellegrini C, D'Antongiovanni V, Miraglia F, Rota L, Benvenuti L, Di Salvo C, et al. Enteric α-synuclein impairs intestinal epithelial barrier through caspase-1-inflammasome signaling in Parkinson's disease before brain pathology. *NPJ Parkinsons Dis*. (2022) 8:9. doi: 10.1038/s41531-021-00263-x

86. Avagliano C, Coretti L, Lama A, Pirozzi C, De Caro C, De Biase D, et al. Dual-hit model of Parkinson's disease: impact of dysbiosis on 6-hydroxydopamine-insulted mice-neuroprotective and anti-inflammatory effects of butyrate. *Int J Mol Sci*. (2022) 23:6367. doi: 10.3390/ijms23126367

87. Dwyer Z, Chaiquin M, Landrigan J, Ayoub K, Shail P, Rocha J, et al. The impact of dextran sodium sulphate and probiotic pre-treatment in a murine model of Parkinson's disease. *J Neuroinflammation*. (2021) 18:20. doi: 10.1186/s12974-020-02062-2

88. Burgueño JF, Abreu MT. Epithelial toll-like receptors and their role in gut homeostasis and disease. *Nat Rev Gastroenterol Hepatol*. (2020) 17:263–78. doi: 10.1038/s41575-019-0261-4

89. Perez-Pardo P, Dodiya HB, Engen PA, Forsyth CB, Huschens AM, Shaikh M, et al. Role of TLR4 in the gut-brain axis in Parkinson's disease: a translational study from men to mice. *Gut*. (2019) 68:829–43. doi: 10.1136/gutjnl-2018-316844

90. Shao QH, Chen Y, Li FF, Wang S, Zhang XL, Yuan YH, et al. TLR4 deficiency has a protective effect in the MPTP/probenecid mouse model of Parkinson's disease. *Acta Pharmacol Sin*. (2019) 40:1503–12. doi: 10.1038/s41401-019-0280-2

91. Gholami M, Amoli M, Sharifi F. Overall corrections and assessments of "correlations between TLR polymorphisms and inflammatory bowel disease: a meta-analysis of 49 case-control studies". *Immunol Res*. (2019) 67:301–3. doi: 10.1007/s12026-019-09092-w

92. Villumsen M, Aznar S, Pakkenberg B, Jess T, Brudek T. Inflammatory bowel disease increases the risk of Parkinson's disease: a Danish nationwide cohort study 1977-2014. *Gut*. (2019) 68:18–24. doi: 10.1136/gutjnl-2017-315666

93. Weimers P, Halfvarson J, Sachs MC, Saunders-Pullman R, Ludvigsson JF, Peter I, et al. Inflammatory bowel disease and Parkinson's disease: a nationwide Swedish cohort study. *Inflamm Bowel Dis*. (2019) 25:111–23. doi: 10.1093/ibd/izy190

94. Zhu Y, Yuan M, Liu Y, Yang F, Chen WZ, Xu ZZ, et al. Association between inflammatory bowel diseases and Parkinson's disease: systematic review and meta-analysis. *Neural Regen Res*. (2022) 17:344–53. doi: 10.4103/1673-5374.317981

95. Li Y, Chen Y, Jiang L, Zhang J, Tong X, Chen D, et al. Intestinal inflammation and Parkinson's disease. *Aging Dis*. (2021) 12:2052–68. doi: 10.14336/AD.2021.0418

96. Inflammatory BT, Diseases B, Disease P's. *J Parkinsons Dis*. (2019) 9:S331–44. doi: 10.3233/JPD-191729

97. Lee HS, Lobbestael E, Vermeire S, Sabino J, Cleynen I. Inflammatory bowel disease and Parkinson's disease: common pathophysiological links. *Gut*. (2021) 70:408–17. doi: 10.1136/gutjnl-2020-322429

98. Halfvarson J, Brislawn CJ, Lamendella R, Vázquez-Baeza Y, Walters WA, Bramer LM, et al. Dynamics of the human gut microbiome in inflammatory bowel disease. *Nat Microbiol*. (2017) 2:17004. doi: 10.1038/nmicrobiol.2017.4

99. Lai SW, Liao KF, Lin CL, Sung FC. Irritable bowel syndrome correlates with increased risk of Parkinson's disease in Taiwan. *Eur J Epidemiol*. (2014) 29:57–62. doi: 10.1007/s10654-014-9878-3

100. Mishima T, Fukae J, Fujioka S, Inoue K, Tsuboi Y. The prevalence of constipation and irritable bowel syndrome in Parkinson's disease patients according to Rome III diagnostic criteria. *J Parkinsons Dis*. (2017) 7:353–7. doi: 10.3233/JPD-160982

101. Mertsalmi TH, But A, Pekkonen E, Scheperjans F. Irritable bowel syndrome and risk of Parkinson's disease in Finland: a nationwide registry-based cohort study. *J Parkinsons Dis*. (2021) 11:641–51. doi: 10.3233/JPD-202330

102. Yoon SY, Shin J, Heo SJ, Chang JS, Sunwoo MK, Kim YW. Irritable bowel syndrome and subsequent risk of Parkinson's disease: a nationwide population-based matched-cohort study. *J Neurol*. (2022) 269:1404–12. doi: 10.1007/s00415-021-10688-2

103. Lu S, Jiang HY, Shi YD. Association between irritable bowel syndrome and Parkinson's disease: a systematic review and meta-analysis. *Acta Neurol Scand*. (2022) 145:442–8. doi: 10.1111/ane.13570

104. Zhang X, Svn Z, Liv M, Yang Y, Zeng R, Huang Q, et al. Association between irritable bowel syndrome and risk of Parkinson's disease: a systematic review and meta-analysis. *Front Neurol*. (2021) 12:720958. doi: 10.3389/fneur.2021.720958

105. Ford AC, Sperber AD, Corsetti M, Camilleri M. Irritable bowel syndrome. *Lancet*. (2020) 396:1675–88. doi: 10.1016/S0140-6736(20)31548-8

106. Zeng J, Wang X, Pan F, Mao Z. The relationship between Parkinson's disease and gastrointestinal diseases. *Front Aging Neurosci*. (2022) 14:955919. doi: 10.3389/fnagi.2022.955919

107. Bhattarai Y, Muniz Pedrogo DA, Kashyap PC. Irritable bowel syndrome: a gut microbiota-related disorder? *Am J Physiol Gastrointest Liver Physiol*. (2017) 312:G52–62. doi: 10.1152/ajpgi.00338.2016

108. Liu B, Sjölander A, Pedersen NL, Ludvigsson JF, Chen H, Fang F, et al. Irritable bowel syndrome and Parkinson's disease risk: register-based studies. *NPJ Parkinsons Dis*. (2021) 7:5. doi: 10.1038/s41531-020-00145-8

109. Scott GD, Lim MM, Drake MG, Woltjer R, Quinn JF. Onset of skin, gut, and genitourinary prodromal Parkinson's disease: a study of 1.5 million veterans. *Mov Disord*. (2021) 36:2094–103. doi: 10.1002/mds.28636

110. Heinzel S, Aho VTE, Suenkel U, von Thaler AK, Schulte C, Deuschle C, et al. Gut microbiome signatures of risk and prodromal markers of Parkinson disease. *Ann Neurol*. (2021) 90:E1–E12. doi: 10.1002/ana.26128

111. Anis E, Xie A, Brundin L, Brundin P. Digesting recent findings: gut alpha-synuclein, microbiome changes in Parkinson's disease. *Trends Endocrinol Metab*. (2022) 33:147–57. doi: 10.1016/j.tem.2021.11.005

112. Zhu M, Liu X, Ye Y, Yan X, Cheng Y, Zhao L, et al. Gut microbiota: a novel therapeutic target for Parkinson's disease. *Front Immunol*. (2022) 13:937555. doi: 10.3389/fimmu.2022.937555

113. Travagli RA, Browning KN, Camilleri M. Parkinson disease and the gut: new insights into pathogenesis and clinical relevance. *Nat Rev Gastroenterol Hepatol*. (2020) 17:673–85. doi: 10.1038/s41575-020-0339-z

114. Mozaffari S, Nikfar S, Daniali M, Abdollahi M. The pharmacological management of constipation in patients with Parkinson's disease: a much-needed relief. *Expert Opin Pharmacother*. (2020) 21:701–7. doi: 10.1080/14656566.2020.1726319

115. Yu QJ, Yu SY, Zuo LJ, Lian TH, Hu Y, Wang RD, et al. Parkinson disease with constipation: clinical features and relevant factors. *Sci Rep*. (2018) 8:567. doi: 10.1038/s41598-017-16790-8

116. Lubomski M, Davis RL, Sue CM. Gastrointestinal dysfunction in Parkinson's disease. *J Neurol*. (2020) 267:1377–88. doi: 10.1007/s00415-020-09723-5

117. Knudsen K, Krogh K, Østergaard K, Borghammer P. Constipation in Parkinson's disease: subjective symptoms, objective markers, and new perspectives. *Mov Disord*. (2017) 32:94–105. doi: 10.1002/mds.26866

118. Xu J, Wang L, Chen X, Le W. New understanding on the pathophysiology and treatment of constipation in Parkinson's disease. *Front Aging Neurosci*. (2022) 14:917499. doi: 10.3389/fnagi.2022.917499

119. Pfeiffer RF. Autonomic dysfunction in Parkinson's disease. *Neurotherapeutics*. (2020) 17:1464–79. doi: 10.1007/s13311-020-00897-4

120. Fu SC, Shih LC, Wu PH, Hsieh YC, Lee CH, Lin SH, et al. Exploring the causal effect of constipation on Parkinson's disease through mediation analysis of microbial data. *Front Cell Infect Microbiol*. (2022) 12:871710. doi: 10.3389/fcimb.2022.871710

121. Cirstea MS, Yu AC, Golz E, Sundvick K, Kliger D, Radisavljevic N, et al. Microbiota composition and metabolism are associated with gut function in Parkinson's disease. *Mov Disord*. (2020) 35:1208–17. doi: 10.1002/mds.28052

122. Losurdo G, Salvatore D'Abramo F, Indellicati G, Lillo C, Ierardi E, Di Leo A. The influence of small intestinal bacterial overgrowth in digestive and extra-intestinal disorders. *Int J Mol Sci*. (2020) 21:3531. doi: 10.3390/ijms21103531

123. Li X, Feng X, Jiang Z, Jiang Z. Association of small intestinal bacterial overgrowth with Parkinson's disease: a systematic review and meta-analysis. *Gut Pathog*. (2021) 13:25. doi: 10.1186/s13099-021-00420-w

124. Wang H, Liu X, Tan C, Zhou W, Jiang J, Peng W, et al. Bacterial, viral, and fungal infection-related risk of Parkinson's disease: meta-analysis of cohort and case-control studies. *Brain Behav*. (2020) 10:e01549. doi: 10.1002/brb3.1549

125. Gravina AG, Priadko K, Ciamarra P, Granata L, Facchiano A, Miranda A, et al. Extra-gastric manifestations of *Helicobacter pylori* infection. *J Clin Med*. (2020) 9:3887. doi: 10.3390/jcm9123887

126. Huang HK, Wang JH, Lei WY, Chen CL, Chang CY, Liou LS. *Helicobacter pylori* infection is associated with an increased risk of Parkinson's disease: a population-based retrospective cohort study. *Parkinsonism Relat Disord*. (2018) 47:26–31. doi: 10.1016/j.parkreldis.2017.11.331

127. Dardiotis E, Tsouris Z, Mentis AA, Siokas V, Michalopoulou A, Sokratous M, et al. *H. pylori* and Parkinson's disease: meta-analyses including clinical severity. *Clin Neurol Neurosurg*. (2018) 175:16–24. doi: 10.1016/j.clineuro.2018.09.039

128. Cryan JF, O'Riordan KJ, Sandhu K, Peterson V, Dinan TG. The gut microbiome in neurological disorders. *Lancet Neurol*. (2020) 19:179–94. doi: 10.1016/S1474-4422(19)30356-4

129. Menozzi E, Macnaughtan J, Schapira AHV. The gut-brain axis and Parkinson disease: clinical and pathogenetic relevance. *Ann Med*. (2021) 53:611–25. doi: 10.1080/07853890.2021.1890330

130. Kaur G, Behl T, Bungau S, Kumar A, Uddin MS, Mehta V, et al. Dysregulation of the gut-brain axis, dysbiosis and influence of numerous factors on gut microbiota associated Parkinson's disease. *Curr Neuropharmacol*. (2021) 19:233–47. doi: 10.2174/18756190MTA3fMTUq5

131. Berding K, Vlckova K, Marx W, Schellekens H, Stanton C, Clarke G, et al. Diet and the microbiota-gut-brain axis: sowing the seeds of good mental health. *Adv Nutr*. (2021) 12:1239–85. doi: 10.1093/advances/nmaa181

132. Yang F, Wolk A, Håkansson N, Pedersen NL, Wirdefeldt K. Dietary antioxidants and risk of Parkinson's disease in two population-based cohorts. *Mov Disord*. (2017) 32:1631–6. doi: 10.1002/mds.27120

133. Alfonsetti M, Castelli V, d'Angelo M. Are we what we eat? Impact of diet on the gut-brain axis in Parkinson's disease. *Nutrients*. (2022) 14:380. doi: 10.3390/nu14020380

134. Molsberry S, Bjornevik K, Hughes KC, Healy B, Schwarzschild M, Ascherio A. Diet pattern and prodromal features of Parkinson disease. *Neurology*. (2020) 95:e2095–108. doi: 10.1212/WNL.0000000000010523

135. Maraki MI, Yannakoulia M, Stamelou M, Stefanis L, Xiromerisiou G, Kosmidis MH, et al. Mediterranean diet adherence is related to reduced probability of prodromal Parkinson's disease. *Mov Disord*. (2019) 34:48–57. doi: 10.1002/mds.27489

136. Metcalfe-Roach A, Yu AC, Golz E, Cirstea M, Sundvick K, Kliger D, et al. MIND and Mediterranean diets associated with later onset of Parkinson's disease. *Mov Disord*. (2021) 36:977–84. doi: 10.1002/mds.28464

137. Yin W, Löf M, Pedersen NL, Sandin S, Fang F. Mediterranean dietary pattern at middle age and risk of Parkinson's disease: a Swedish cohort study. *Mov Disord*. (2021) 36:255–60. doi: 10.1002/mds.28314

138. Bianchi VE, Rizzi L, Somaa F. The role of nutrition on Parkinson's disease: a systematic review. *Nutr Neurosci*. (2022) 22:1–24. doi: 10.1080/1028415X.2022.2073107

139. Terenzi D, Muth AK, Park SQ. Nutrition and gut-brain pathways impacting the onset of Parkinson's disease. *Nutrients*. (2022) 14:2781. doi: 10.3390/nu14142781

140. Jackson A, Forsyth CB, Shaikh M, Voigt RM, Engen PA, Ramirez V, et al. Diet in Parkinson's disease: critical role for the microbiome. *Front Neurol*. (2019) 10:1245. doi: 10.3389/fneur.2019.01245

141. Bianchi VE, Herrera PF, Laura R. Effect of nutrition on neurodegenerative diseases. A systematic review. *Nutr Neurosci*. (2021) 24:810–34. doi: 10.1080/1028415X.2019.1681088

142. Hegelmaier T, Lebbing M, Duscha A, Tomaske L, Tönges L, Holm JB, et al. Interventional influence of the intestinal microbiome through dietary intervention and bowel cleansing might improve motor symptoms in Parkinson's disease. *Cells*. (2020) 9:376. doi: 10.3390/cells9020376

143. Vojdani A, Gushgari LR, Vojdani E. Interaction between food antigens and the immune system: association with autoimmune disorders. *Autoimmun Rev*. (2020) 19:102459. doi: 10.1016/j.autrev.2020.102459

144. Vojdani A, Lerner A, Vojdani E. Cross-reactivity and sequence homology between alpha-synuclein and food products: a step further for Parkinson's disease synucleinopathy. *Cells*. (2021) 10:1111. doi: 10.3390/cells10051111

145. Lerner A. The intestinal luminal sources of α-synuclein: a gastroenterologist perspective. *Nutr Rev*. (2022) 80:282–93. doi: 10.1093/nutrit/nuab024

146. Leta V, Ray Chaudhuri K, Milner O, Chung-Faye G, Metta V, Pariante CM, et al. Neurogenic and anti-inflammatory effects of probiotics in Parkinson's disease: a systematic review of preclinical and clinical evidence. *Brain Behav Immun*. (2021) 98:59–73. doi: 10.1016/j.bbi.2021.07.026

147. Snigdha S, Ha K, Tsai P, Dinan TG, Bartos JD, Shahid M. Probiotics: potential novel therapeutics for microbiota-gut-brain axis dysfunction across gender and lifespan. *Pharmacol Ther*. (2022) 231:107978. doi: 10.1016/j.pharmthera.2021.107978

148. Sanders ME, Merenstein DJ, Reid G, Gibson GR, Rastall RA. Probiotics and prebiotics in intestinal health and disease: from biology to the clinic. *Nat Rev Gastroenterol Hepatol*. (2019) 16:605–16. doi: 10.1038/s41575-019-0173-3

149. Ibrahim A, Ali RAR, Manaf MRA, Ahmad N, Tajurruddin FW, Qin WZ, et al. Multi-strain probiotics (Hexbio) containing MCP BCMC strains improved constipation and gut motility in Parkinson's disease: a randomised controlled trial. *PLoS One*. (2020) 15:e0244680. doi: 10.1371/journal.pone.0244680

150. Tan AH, Lim SY, Chong KK, MAA M, Hor JW, Lim JL, et al. Probiotics for constipation in Parkinson disease: a randomized placebo-controlled study. *Neurology*. (2021) 96:e772–82. doi: 10.1212/WNL.0000000000010998

151. Barichella M, Pacchetti C, Bolliri C, Cassani E, Iorio L, Pusani C, et al. Probiotics and prebiotic fiber for constipation associated with Parkinson disease: an RCT. *Neurology*. (2016) 87:1274–80. doi: 10.1212/WNL.0000000000003127

152. Nemade D, Subramanian T, Shivkumar V. An update on medical and surgical treatments of Parkinson's disease. *Aging Dis*. (2021) 12:1021–35. doi: 10.14336/AD.2020.1225

153. Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, et al. Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review. *Mov Disord*. (2019) 34:180–98. doi: 10.1002/mds.27602

154. Tamtaji OR, Taghizadeh M, Daneshvar Kakhaki R, Kouchaki E, Bahmani F, Borzabadi S, et al. Clinical and metabolic response to probiotic administration in people with Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *Clin Nutr*. (2019) 38:1031–5. doi: 10.1016/j.clnu.2018.05.018

155. Hsieh TH, Kuo CW, Hsieh KH, Shieh MJ, Peng CW, Chen YC, et al. Probiotics alleviate the progressive deterioration of motor functions in a mouse model of Parkinson's disease. *Brain Sci*. (2020) 10:206. doi: 10.3390/brainsci10040206

156. Goya ME, Xue F, Sampedro-Torres-Quevedo C, Arnaouteli S, Riquelme-Dominguez L, Romanowski A, et al. Probiotic *Bacillus subtilis* protects against α-Synuclein aggregation in *C. elegans*. *Cell Rep*. (2020) 30:367–380.e7. doi: 10.1016/j.celrep.2019.12.078

157. Yoon G, Kim YK, Song J. Glucagon-like peptide-1 suppresses neuroinflammation and improves neural structure. *Pharmacol Res*. (2020) 152:104615. doi: 10.1016/j.phrs.2019.104615

158. Fang X, Tian P, Zhao X, Jiang C, Chen T. Neuroprotective effects of an engineered commensal bacterium in the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine Parkinson disease mouse model via producing glucagon-like peptide-1. *J Neurochem*. (2019) 150:441–52. doi: 10.1111/jnc.14694

159. Sun J, Li H, Jin Y, Yu J, Mao S, Su KP, et al. Probiotic *Clostridium butyricum* ameliorated motor deficits in a mouse model of Parkinson's disease via gut microbiota-GLP-1 pathway. *Brain Behav Immun*. (2021) 91:703–15. doi: 10.1016/j.bbi.2020.10.014

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Sleep structure and related clinical characteristics in drug-naïve Parkinson's disease with subjectively different sleep quality

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Background: Sleep disturbance is a common non-motor symptom of Parkinson's disease (PD). Most polysomnography (PSG) studies are conducted when patients are in their "on medication" state. Our study aimed to investigate changes in the sleep structure in drug-naive PD patients with poor subjective sleep quality based on polysomnography (PSG) and to explore potential correlations between sleep structure and clinical features of the disease.

Methods: A total of 44 drug-naive PD patients were included. All patients completed a standardized questionnaire to obtain demographic and clinical characteristics and underwent whole-night PSG recording. Patients with PSQI scores >5.5 were considered poor sleepers, and patients with PSQI scores <5.5 were considered to be good sleepers.

Results: There were 24 (54.5%) PD patients in the good sleeper group and 20 (24.5%) PD patients in the poor sleeper group. We observed that poor sleepers had severe non-motor symptoms (NMS) and worse life quality. The PSG displayed that they had a longer wake-up time after sleep onset (WASO) and lower sleep efficiency (SE). Correlation analysis revealed that the micro-arousal index was positively associated with UPDRS-III, and the N1 sleep percentage was negatively associated with the NMS score in good sleepers. For poor sleepers, rapid eye movement (REM) sleep percentage was negatively related to the Hoehn-Yahr (H-Y) stage, WASO increased with UPDRS-III, periodic limb movement index (PLMI) increased with the NMS score, and N2 sleep percentage was negatively related to the score of life quality.

Conclusion: Night awakening is the main manifestation of decreased sleep quality in drug-naive PD patients. Poor sleepers have severe non-motor symptoms and poor life quality. Additionally, the increase in nocturnal arousal events may predict the progression of motor dysfunction.

KEYWORDS

Parkinson's disease, sleep disturbances, non-motor symptoms, polysomnography, sleep structure, clinical features

1. Introduction

Parkinson's disease (PD) is a common chronic neurodegenerative disease that places an enormous material and mental burden on patients (1, 2). Although PD is characterized by motor symptoms, a broad spectrum of non-motor symptoms (NMS), including sleep disturbance, neuropsychiatric symptoms, and autonomic dysfunction, can be identified in people with PD (3). Sleep disturbances in PD include insomnia, rapid eye movement (REM) sleep behavior disorder, sleep-disordered breathing, restless legs syndrome, and circadian dysregulation, and affect a high percentage of people with PD (4, 5). The decline in sleep quality is a very common complaint among PD patients. One possible reason for the high prevalence of sleep complaints is that neurodegenerative diseases disrupt the circadian rhythm system at a faster rate than normal aging (6). Furthermore, there are strong correlations between sleep disturbances and other non-motor as well as motor symptoms such as nocturia, dystonia, and pain (7). Worse sleep quality has recently been reported to aggravate motor and non-motor symptoms in PD (8, 9). Many sleep problems may occur in the early stages of the disease and worsen as the disease progresses (10, 11), necessitating proper vigilance.

In the past, the evaluation of sleep quality relied mainly on a series of sleep scales. Many studies have used the Pittsburgh Sleep Quality Index (PSQI) and the Parkinson's Disease Sleep Scale (PDSS) for sleep assessment in PD patients (12). Although these instruments are rapidly administered and efficient, a detailed understanding of the sleep structure of patients with sleep complaints is still lacking. Currently, video-polysomnography (v-PSG), which is considered to be the most valuable method of diagnosing sleep disorders, is widely applied (13). PSG can not only quantitatively analyze the sleep structure but can also sensitively record the occurrence of specific sleep events. Previous studies using PSG revealed that, compared with healthy controls, patients with PD have shorter total sleep time, lower sleep efficiency, and increased sleep latency and wakefulness after sleep onset (14–16). However, anti-PD medication has an inevitable effect on sleep structures. The use of MAO-B inhibitors is related to sleep stages 2 and 3, while sleep stage 1 can be predicted by dopamine agonists (17).

In this respect, a cohort of drug-naive patients is essential to bringing new insights into the field of the non-motor spectrum of PD. This study aimed to investigate changes in the sleep structure in drug-naive PD patients with poor subjective sleep quality compared to those with good sleep quality using PSG technology and to explore the association between clinical features and sleep structure.

2. Materials and methods

2.1. Study participants

A total of 63 newly diagnosed PD patients were initially recruited from the Neurology Clinic of the Affiliated Brain Hospital of Nanjing Medical University from September 2021 to May 2022. Patients were diagnosed by at least two movement disorder disease specialists. Participants who met the following criteria were eligible for inclusion: if they met the diagnostic criteria of the UK Parkinson's Disease Brain Bank (18) and did not use any anti-PD medication before if they completed a standard questionnaire completely, or if they also cooperatively performed a PSG examination before taking any anti-PD medication. Exclusion criteria were as follows: (1) the presence of secondary parkinsonism, focal brain lesions (according to MRI evidence), and other psychiatric disorders; (2) patients taking hypnotics, antidepressants, or antipsychotics within the month prior to the PSG examination, because these drugs may affect sleep architecture; and (3) the presence of severe obstructive sleep apnea (apnea–hypopnea index was higher than 30), in which situation, there was manual intervention during the PSG, which could affect the reliability of the PSG. Finally, 44 patients were included in this study. This study was approved by the Ethics Committee of the Affiliated Brain Hospital of Nanjing Medical University (2021-KY007-01), and written informed consent was obtained from the study participants for research purposes.

2.2. Clinical evaluation

All subjects completed a standardized questionnaire designed to collect general information, including name, age, gender, body mass index (BMI), and disease duration at baseline. The Unified Parkinson's Disease Rating Scale (UPDRS) (19) and their Hoehn -Yahr stage (H-Y stage) (20) were used to assess comprehensive symptoms and to describe the severity of motor function. Non-motor symptoms were assessed using the Non-Motor Symptom Questionnaire (NMSQ) (21, 22). The Montreal Cognitive Assessment (MoCA) was used to evaluate cognitive function (23). Quality of life was assessed using the 39-item Parkinson's Disease Questionnaire (PDQ-39) (24). Subjective sleep assessment was performed using the Pittsburgh Sleep Quality Index (PSQI) (25) and the Parkinson's Disease Sleep Scale (PDSS) (26). The diagnosis of rapid eye movement behavior disorder (RBD), periodic limb movement disorder, and obstructive sleep apnea was made based on the PSG reports according to the International Classification of Sleep Disorders, Third Edition criteria (27). The PSQI is a self-report questionnaire that evaluates the subject's sleep during the past month. It includes 19 items, and the maximum possible score is 21. A PSQI global score of >5 discriminates sleep disturbance in patients with insomnia with a sensitivity of 99% and a specificity of 84% (28). The cutoff value to differentiate between good and poor sleepers is >5 points (25). We considered patients with PSQI scores >5.5 as poor sleepers and patients with PSQI scores <5.5 to be good sleepers.

2.3. Polysomnography technique

All patients underwent overnight video-PSG in an acclimatized, sound-proof sleep laboratory with a data acquisition time longer than 8 h. We used a Compumedics Grael-HD 64 (Compumedics Grael-HD, Melbourne, Australia) polygraph for signal acquisition. This instrument includes six electroencephalogram channels, two electrooculogram channels, one electromyogram channel,

TABLE 1 Demographic information and clinical characteristics.

Variables	Total	Good sleepers (N=24)	Poor sleepers (N=20)	*P*
Age, years	68.86 (7.06)	68.83 (8.67)	68.90 (4.93)	0.983[a]
Male patients/female patients, N	30/14	18/6	12/8	0.652[c]
BMI, kg/m^2	24.48 (3.06)	24.94 (2.60)	23.94 (3.60)	0.458[a]
Disease duration, years	1.25 (3.5)	1 (2.5)	2 (3.4)	0.172[b]
H-Y stage	2 (0)	2 (0)	2 (0.1)	0.398[b]
UPDRS III	19.73 (6.94)	18.08 (7.43)	21.70 (6.08)	0.232[a]
NMSQ	8.68 (4.49)	7.50 (4.40)	10.10 (4.38)	**0.026**[a]
MoCA	27 (4)	25 (5)	27 (1)	0.130[b]
PDSS	112 (40)	132 (17)	94.5 (13)	**0.001**[b]
PDQ-39	15.50 (41)	10 (21)	42.5 (38)	**0.010**[b]
Sleep disorders, N (%)				
RBD	16 (36.4%)	10	6	0.675[c]
PLMD	12 (27.3%)	8	4	0.646[c]
OSA	12 (27.3%)	10	2	0.162[c]

[a]Student's t-test, [b]Mann–Whitney U-test, [c]chi-square test. Data with a superscript a are expressed as mean (standard deviation, SD), those with a superscript b as median (interquartile range, IQR), and those with a superscript c as number (percentage). Bold values indicate statistically significant differences ($p < 0.05$).
BMI, body mass index; H-Y stage, Hoehn–Yahr stage; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III; NMSQ, Non-motor Symptoms Questionnaire; MoCA, Montreal Cognitive Assessment; PDSS, Parkinson's Disease Sleep Scale; PDQ-39, Parkinson's Disease Questionnaire-39; RBD, rapid eye movement sleep behavior disorder; PLMD, periodic limb movement disorder; OSA, obstructive sleep apnea.

one nasal pressure channel, one respiratory thermistor channel, one oximetry channel, one snore detector channel, one electrocardiography channel, one abdominal movement assessment channel, one thoracic movement assessment channel, one body position channel, and two leg movement sensors. Continuous audio and video recording were performed using infrared cameras. The EEG channels, including frontal (F3, F4), central (C3, C4), and occipital (O1, O2) channels, were placed according to the international 10–20 location system and linked to the mastoid electrodes as a reference. The staging and scoring were reviewed by a board-certified sleep physician according to the American Academy of Sleep Medicine (AASM) guidelines (13). Sleep stage percentages were calculated relative to total sleep time. Objective sleep parameters included total sleep time (TST; min), wake-up time after sleep onset (WASO; min), sleep efficiency (SE; %), sleep latency (SL; min), and the percentage of N1, N2, and N3 sleep, average heart rate (AHR; the number of events/min sleep), apnea–hypopnea index (number of events/hour sleep), micro-arousal index (number of events/hour sleep), and periodic limb movement index (PLMI; the total number of leg movements) during the entire night.

2.4. Statistical analysis

IBM SPSS 26.0 software was used for statistical analysis. Measurement data were expressed as mean (standard deviation, SD), median (interquartile range, IQR), number (N), or percentage (%). The Kolmogorov–Smirnov test was used to check the normality of the measurement data. A two-sample *t*-test was used for normally distributed data, and the Mann–Whitney *U*-test was used for non-normally distributed data. A chi-square test was conducted to analyze qualitative data. PSG data were compared by one-way analysis of covariance (ANCOVA) with adjustments for confounding factors, including UPDRS-III score and H-Y stage. In addition, the Spearman test was applied to analyze the correlation between sleep parameters and clinical characteristics. Linear regression was performed with the evaluation of the correlation coefficient. The statistical significance level was set at a $p < 0.05$.

3. Results

3.1. Demographic and clinical characteristics

Table 1 shows the demographic information and clinical characteristics of the patients. A total of 63 drug-naive PD patients were initially examined. A total of 13 patients who took hypnotics, antidepressants, or antipsychotics within the month prior to the PSG examination were excluded. Four patients were excluded due to incomplete PSG data, and two patients who had severe obstructive sleep apnea were also excluded. Finally, 44 patients were included in our study. Among them, 24 (54.5%) were good sleepers, and 20 (45.5%) were poor sleepers. Compared with good sleepers, poor sleepers had higher NMSQ and PDQ-39 scores and lower PDSS scores ($P = 0.026$, $P = 0.010$, $P = 0.001$, respectively). However, there were no significant differences in age, sex, BMI, disease duration, H-Y stage, UPDRS-III, or MoCA scores between the two groups. Furthermore, we observed that 36.4% of our PD

TABLE 2 Comparison of sleep scales between different sleep disorders.

	Without RBD	With RBD	*P*
PSQI	4 (6)	2 (7)	0.583[b]
PDSS	110.69 (22.33)	115.56 (24.45)	0.995[a]
	Without PLMD	With PLMD	*P*
PSQI	6.17 (4.81)	4.71 (3.52)	0.654[a]
PDSS	111 (24.1)	118.93 (18.71)	0.693[a]
	Without OSA	With OSA	*P*
PSQI	6.63 (4.62)	4.43 (4.24)	0.148[a]
PDSS	110.88 (20.89)	116.04 (27.1)	0.084[a]

[a]Student's t-test, [b]Mann–Whitney U-test. Variables with a superscript a are expressed as mean (standard deviation, SD) and those with a superscript b as median (interquartile range, IQR). Bold values indicate statistically significant differences ($p < 0.05$).
PSQI, Pittsburgh Sleep Quality Index; PDSS, Parkinson's Disease Sleep Scale; RBD, rapid eye movement sleep behavior disorder; PLMD, periodic limb movement disorder; OSA, obstructive sleep apnea.

cohort had RBD, 27.3% had PLMD, and 27.3% had OSA. We compared the distribution of various sleep disorders in good and poor sleepers, and no significant difference was found.

3.2. Comparison of sleep scales

The scores of patients with and without various sleep disorders on two sleep scales were compared separately; the results are summarized in Table 2. No significant differences were found for RBD, PLMD, or OSA patients.

3.3. Comparison of sleep parameters

Sleep parameters derived from PSG recordings are shown in Table 3. Poor sleepers differed significantly from good sleepers in terms of wake-up time after onset (WASO) and sleep efficiency (SE) ($P = 0.008$, $P = 0.004$, repetitively). There was no significant difference between the groups in total sleep time, sleep latency, REM latency, N1 sleep percentage, N2 sleep percentage, N3 sleep percentage, or the sleep disorder indices average heart rate (AHR), apnea–hypopnea index (AHI), micro-arousal index (MAI), and periodic limb movement index (PLMI).

3.4. Correlations between sleep architecture and clinical features

The correlations between sleep parameters and clinical features are presented in Table 4. For good sleepers, increasing MAI was related to higher UPDRS-III scores ($r = 0.680$, $P = 0.015$), and N1 sleep percentage increased with NMSQ scores ($r = -0.564$, $P = 0.036$). For poor sleepers, longer WASO was associated with higher UPDRS-III scores ($r = 0.640$, $P = 0.006$), PLMI increased with NMSQ scores ($r = 0.644$, $P = 0.014$), and lower N2 sleep percentage was related to higher PDQ-39 scores ($r = -0.685$, $P = 0.029$). We also observed that REM sleep latency increased with the H-Y stage in poor sleepers ($r = -0.696$, $P = 0.025$).

The regression analysis between clinical features and associated sleep parameters is summarized in Table 5. In good sleepers, MAI explained 46.8% of UPDRS-III variation ($P = 0.003$, $R^2 = 0.468$), and N1 sleep percentage explained 33.4% of NMSQ variation. For patients with poor sleep quality, PLMI accounted for 31.6% of NMSQ variation ($P = 0.033$, $R^2 = 0.316$), and N2 sleep percentage accounted for 36.7% of PDQ-39 variation ($P = 0.037$, $R^2 = 0.367$).

4. Discussion

A total of 44 patients were enrolled in this study, including 24 (54.5%) in the good sleeper group and 20 (45.5%) in the poor sleeper group. We observed that poor sleepers had severe non-motor symptoms and poor quality of life. They had longer wake-up times and lower sleep efficiency during night sleep according to PSG results. Furthermore, we found significant associations between nocturnal arousal events and motor symptom scores in all drug-naive PD patients. Our findings provide new insights into sleep problems in Parkinson's disease.

Our study evaluated the prevalence of three major sleep disorders in PD, including RBD (36.4%), PLMD (27.3%), and OSA (27.3%). The results are consistent with the frequencies reported in previous studies (29, 30). We did not find significant differences in PSQI or PDSS scores between the groups with and without these three sleep disorders. The results are consistent with those reported in some studies (31, 32), but contrary to other studies (33, 34). Differences between the results obtained in this study and other studies may be explained by the possible coexistence of other sleep problems in different PD cohorts and by the fact that only one or two questions on the PSQI and PDSS scales are strongly associated with specific types of sleep disorders. A previous study that tested the criterion validity of the PSQI in diagnosing the sleep disorders mentioned above found that it was not highly accurate for predicting the existence of these disorders (35). Thus, the PSQI is more suitable for screening for the presence of sleep alterations than for diagnosing specific types of sleep disorders. In our study, we divided the patients into two groups based on their PSQI scores. We compared the distribution of sleep disorders in good and poor sleepers, and no significant difference was found.

Changes in PSG in our study focused on drug-naive PD patients. After considering the distribution of different sleep disorders, we wanted to investigate the features of disturbed objective sleep parameters in patients suffering from reduced subjective sleep quality. Previous studies have reported that, compared with healthy controls, there were significant differences in sleep architecture patterns in PD patients (16); these differences include a decrease in TST, SE, N2 sleep percentage, and REM sleep percentage and an increase in WASO, N1 sleep percentage, REM sleep latency, and PLMI. Our study compared the sleep structure between good and poor sleepers in drug-naive patients. We observed that as patients' sleep quality began to decline,

TABLE 3 Comparison of sleep parameters.

	Total	Good sleepers	Poor sleepers	*P*
TST (SD), min	308.50 (110.70)	339.29 (99.66)	271.55 (116.94)	0.158[a]
WASO (SD), min	171.00 (79.12)	144.75 (49.87)	199.00 (64.75)	**0.008**[b]
SE, %	53.84 (16.67)	58.18 (14.74)	48.64 (18.10)	**0.004**[a]
SL(SD), min	23.00 (32.3)	27.50 (45.6)	23.00 (56.9)	0.974[b]
REML (SD), min	116.50 (198.5)	102.50 (88.0)	164.00 (349.3)	0.470[b]
REM Sleep% (SD), min	12.01 (8.25)	12.54 (9.67)	11.38 (6.61)	0.751[a]
N1 Sleep %	6.65 (12.30)	5.80 (12.30)	9.05 (12.78)	0.817[b]
N2 Sleep %	62.84 (12.43)	63.82 (13.30)	61.67 (11.90)	0.694[a]
N3 Sleep %	13.45 (27.50)	9.55 (27.05)	21.85 (22.28)	0.322[b]
AHR (SD)	60.39 (7.15)	59.88 (7.74)	61.00 (6.72)	0.725[a]
AH I(SD)	1.90 (7.0)	3.95 (8.0)	0.35 (3.3)	0.137[b]
MAI (SD)	12.95 (8.5)	15.80 (5.4)	9.7 (9.3)	0.974[b]
PLMI (SD)	31.25 (59.98)	47.71 (78.20)	11.50 (11.24)	0.459[a]

[a]Student's t-test, [b]Mann–Whitney U-test. Variables with a superscript a are expressed as mean (standard deviation, SD) and those with a superscript b as median (interquartile range, IQR). Bold values indicate statistically significant differences ($p < 0.05$). The p-value was adjusted for the UPDRS-III score and H-Y stage.
TST, total sleep time, WASO, wake time after sleep onset, SE, sleep efficiency, SL, sleep latency, REM, rapid eye movement, REML, REM sleep latency, N1 sleep, NREM sleep stage 1, N2 sleep, NREM sleep stage 2, N3 sleep, NREM sleep stage 3, AHR, average heart rate, AHI, apnea–hypopnea index, MAI, micro-arousal index, PLMI, periodic limb movement index.

the main changes were longer wake-up times after falling asleep and lower sleep efficiency. The differences in the findings may be explained by the progression of the disease and the use of anti-PD medication. In terms of neuropathologic evidence, sleep–wake disturbances in PD may reflect disruption of the neural circuitry that controls circadian rhythms (6). Altered peripheral clock gene expression and decreased function of the hypothalamic suprachiasmatic nucleus (SCN) are believed to be responsible for reduced melatonin output and sleep–wake disruption in PD patients (36, 37). Our results also revealed significant associations between the percentage of REM sleep and the H-Y stage in poor sleepers. Sleep-controlling neurons have recently been reported to be sensitive and vulnerable to α-synuclein (38), and the spread of pathology to the coeruleus/subcoeruleus complex may further disrupt REM sleep (39–41). With regard to anti-PD medication, one study has reported that higher amounts of dopaminergic medications, especially L-dopa, were related to sleep fragmentation and insomnia (42). These changes have been described as a progressive destructuring of the sleep structure (43). The mechanisms underlying sleep disturbances in PD remain speculative. Our observations may be an early objective manifestation of sleep disturbance in original ecological patients.

We consider sleep disturbances an integral part of PD rather than comorbidity. Our research explored the association between sleep parameters and typical clinical characteristics of PD, including the H-Y stage, the UPDRS-III score, the NMSQ score, and the PDQ-39 score. We also conducted an analysis of correlations between disease and PSG parameters, and no significant correlations were found. However, we observed that MAI was positively related to the UPDRS-III score in good sleepers and that WASO increased with the UPDRS-III score in poor sleepers. Both MAI and WASO were nocturnal arousal events, and dopamine may play a crucial role in the close association between these events and motor dysfunction. As we all know, PD is characterized by a progressive loss of dopaminergic neurons in the substantia nigra, and its metabolism and activity are also strongly influenced by the circadian clock (44). On the contrary, sleep dysfunction can disrupt the circadian rhythms that are generated by SCN, and the dysfunction of sleep and peripheral clocks, such as those in microglial and neuronal cells, leads to subsequent changes within and outside of the brain, including neuroinflammation, increased oxidative stress, and reduced metabolic clearance. These outcomes have been proposed to exacerbate Parkinson's disease progression (45–48). Therefore, the increase in nocturnal arousal events may be of great value in predicting the progression of motor dysfunction in PD. Our recent study found that N3 sleep (slow-wave sleep, SWS) is one of the important risk factors in PD patients with hallucinations (49). The deconstruction of the sleep structure is a process affected by many complex factors. The decrease in light sleep (including N1 sleep and N2 sleep) in the early stages of the disease causes more daytime fatigue. This may aggravate non-motor symptoms or quality of life burden in drug-naive PD patients.

Periodic limb movements during sleep (PLMS) have been reported to be associated with greater symptom severity, more subjective sleep disturbance, and decreased quality of life in PD patients (34, 50). We did not observe significant differences in PLMI variation in drug-naive PD patients with different subjective sleep quality. However, our results revealed an association between PLMI and non-motor symptoms in drug-naive patients with poor sleep quality. Evidence has confirmed that there are common pathophysiological pathways between PLMS and PD (51). Nigrostriatal degeneration may promote PLMS, whereas dopaminergic enhancement may control PLMS. In our drug-naive

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TABLE 4 Correlations between different sleep parameters and clinical features.

	Good sleepers							
	H-Y stage		UPDRS-III		NMSQ score		PDQ-39	
	r	*p*	r	*p*	r	*p*	r	*p*
TST	0.063	0.846	0.088	0.786	−0.091	0.778	0.174	0.589
WASO	0.209	0.514	−0.049	0.880	−0.361	0.249	−0.298	0.346
SE	0.000	1.000	0.175	0.586	−0.086	0.791	0.204	0.526
SL	0.000	1.000	−0.221	0.491	0.264	0.406	0.021	0.948
REML	−0.238	0.480	−0.478	0.128	0.121	0.722	−0.064	0.852
REM Sleep%	0.042	0.897	0.530	0.058	−0.007	0.982	0.119	0.712
N1 Sleep %	0.376	0.228	0.070	0.829	**−0.564**	**0.036**	−0.396	0.202
N2 Sleep %	−0.167	0.603	0.088	0.787	−0.236	0.461	−0.088	0.786
N3 Sleep %	−0.168	0.603	−0.309	0.329	0.564	0.056	0.446	0.146
AHR	−0.376	0.228	−0.553	0.062	−0.472	0.077	−0.533	0.074
AHI	−0.021	0.948	0.268	0.399	−0.268	0.399	−0.308	0.331
MAI	0.125	0.698	**0.680**	**0.015**	0.043	0.895	0.270	0.396
PLMI	−0.042	0.897	0.172	0.594	0.134	0.320	−0.053	0.871
	Poor sleepers							
	H-Y stage		UPDRS-III		NMSQ score		PDQ-39 score	
	r	*p*	r	*p*	r	*p*	r	*P*
TST	−0.609	0.062	−0.293	0.412	−0.301	0.399	0.006	0.987
WASO	0.609	0.062	**0.640**	**0.006**	0.153	0.672	−0.067	0.855
SE	−0.609	0.062	−0.524	0.120	−0.129	0.723	−0.067	0.855
SL	0.000	1.000	0.390	0.265	−0.288	0.419	−0.176	0.627
REML	0.274	0.476	0.151	0.699	−0.201	0.604	−0.283	0.460
REM Sleep%	**−0.696**	**0.025**	−0.354	0.316	−0.166	0.647	0.382	0.276
N1 Sleep %	−0.087	0.811	−0.134	0.712	0.522	0.122	0.442	0.200
N2 Sleep %	0.348	0.324	0.317	0.372	−0.313	0.379	**−0.685**	**0.029**
N3 Sleep %	0.087	0.811	−0.152	0.674	0.252	0.483	0.212	0.556
AHR	−0.225	0.533	0.567	0.055	0.070	0.848	0.600	0.067
AHI	0.301	0.064	−0.043	0.043	−0.488	0.153	0.524	0.120
MAI	−0.522	0.122	0.232	0.519	0.544	0.054	0.067	0.855
PLMI	0.435	0.209	0.134	0.712	**0.644**	**0.014**	0.164	0.651

Bold values indicate statistically significant differences ($p < 0.05$).

H-Y stage, Hoehn–Yahr stage; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III; NMSQ, Non-motor Symptoms Questionnaire; PDQ-39, Parkinson's Disease Questionnaire-39; TST, total sleep time, WASO, wake time after sleep onset, SE, sleep efficiency, SL, sleep latency, REM, rapid eye movement, REML, REM sleep latency, N1 sleep, NREM sleep stage 1, N2 sleep, NREM sleep stage 2, N3 sleep, NREM sleep stage 3, AHR, average heart rate, AHI, apnea–hypopnea index, MAI, micro-arousal index, PLMI, periodic limb movement index.

PD cohort, the regression model suggested that increasing PLMI was an independent variable predicting a higher NMSQ score in poor sleepers.

Several methodological considerations should be mentioned. First, although there have been some studies investigating the characteristics of objective sleep parameters in drug-naive PD patients, we conducted a more comprehensive clinical evaluation of these patients and further explored the relationship between sleep parameters and clinical features. Second, our study was based on PSG data. The majority of published studies related to sleep problems used subjective tools to measure sleep quality, while only a few such studies used objective methods. However, patients in our study did not undergo a second PSG examination to eliminate the first-night effect, which should be considered as a methodological and ethnic bias. In addition, we did not include healthy controls with and without sleep disorders such as OSA, RBD, and PLMS. Finally, our cohort consisted of a relatively small number of patients and was recruited in a single center. Further studies should include larger cohorts and conduct longitudinal follow-ups to confirm the correlations between sleep parameters and clinical characteristics.

TABLE 5 Linear regression analysis in good sleepers and in poor sleepers.

	B	β	t	*p*	F	Adjusted R^2
Good sleepers						
UPDRS-III						
MAI	0.897	0.718	3.265	0.009	10.660	0.468
NMSQ score						
N1%	−0.319	−0.628	−2.554	0.029	6.522	0.334
Poor sleepers						
NMSQ score						
PLMI	0.244	0.626	2.272	0.013	5.163	0.316
PDQ-39 score						
N2%	−1.106	0.444	−0.661	0.037	6.210	0.367

The p-value has been calculated using a linear logistic regression analysis.
UPDRS-III, Unified Parkinson's Disease Rating Scale Part III; NMSQ, Non-motor Symptoms Questionnaire; PDQ-39, Parkinson's Disease Questionnaire-39; N1 sleep, NREM sleep stage 1, N2 sleep, NREM sleep stage 2, MAI, micro-arousal index, PLMI, periodic limb movement index.

5. Conclusions

Our results showed that more than 50% of drug-naive PD patients have poor subjective sleep quality, mainly manifested by increased nocturnal awakening time and decreased sleep efficiency. Poor sleepers have severe non-motor symptoms and poor quality of life. Nocturnal arousal events, including MAI and WASO, may predict the progression of motor dysfunction. We provide new evidence for associations between sleep parameters and clinical characteristics in PD patients before they begin medication interference.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The study was approved by the Ethics Committee of the Affiliated Brain Hospital of Nanjing Medical University. All procedures were in accordance with the Declaration of Helsinki.

Author contributions

YJ and LZ conceived and designed the study. LZ, XJ, and JY obtained the funding. YJ, SZ, RG, YW, YC, DL, JZ, XJ, BS, and YP collected the data. YJ, SZ, RG, and YP conducted the data analysis. YJ drafted the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* (2019) 18:459–80.

2. Leta V, Urso D, Batzu L, Lau YH, Mathew D, Boura I, et al. Viruses, parkinsonism and Parkinson's disease: the past, present and future. *J Neural Transm (Vienna).* (2022) 129:1119–32. doi: 10.1007/s00702-022-02536-y

3. Falup-Pecurariu C, Diaconu Ş, Muntean M-L. Sleep Disturbances in Parkinson's Disease. In: Korczyn AD, Gálvez-Jiménez N, Lugo-Sanchez R, editors. *Non-motor Parkinson's Disease*. Cambridge: Cambridge University Press. (2022) p. 167–77. doi: 10.1017/9781009039291.016

4. Videnovic A. Disturbances of sleep and alertness in Parkinson's disease. *Curr Neurol Neurosci Rep.* (2018) 18:29. doi: 10.1007/s11910-018-0838-2

5. Diaconu S, Falup-Pecurariu C, Rus D-A, Mihăilescu G. Tulburările de somn asociate bolii Parkinson | [Sleep disorders associated with Parkinson's disease]. *Jurnal Medical Brasovean.* (2022) 2022:11–5. doi: 10.31926/jmb.2021.1.12

6. Nassan M, Videnovic A. Circadian rhythms in neurodegenerative disorders. *Nat Rev Neurol.* (2022) 18:1. doi: 10.1038/s41582-021-00577-7

7. van Wamelen DJ, Sauerbier A, Leta V, Rodriguez-Blazquez C, Falup-Pecurariu C, Rodriguez-Violante M, et al. Cross-sectional analysis of the Parkinson's disease non-motor international longitudinal study baseline non-motor characteristics, geographical distribution and impact on quality of life. *Sci Rep.* (2021) 11:9611. doi: 10.1038/s41598-021-88651-4

8. Yi Q, Yu-Peng C, Jiang-Ting L, Jing-Yi L, Qi-Xiong Q, Dan-Lei W, et al. Worse sleep quality aggravates the motor and non-motor symptoms in Parkinson's disease. *Front Aging Neurosci.* (2022) 14:887094. doi: 10.3389/fnagi.2022.887094

9. Tang X, Yang J, Zhu Y, Gong H, Sun H, Chen F, et al. High PSQI score is associated with the development of dyskinesia in Parkinson's disease. *NPJ Parkinsons Dis.* (2022) 8:124. doi: 10.1038/s41531-022-00391-y

10. Falup-Pecurariu C, Titova N, Ray Chaudhuri K. Editorial: movement disorders and sleep - underlying mechanisms, clinical aspects and treatment. *Front Neurol.* (2019) 10:1034. doi: 10.3389/fneur.2019.01034

11. Keir LHM, Breen DP. New awakenings: current understanding of sleep dysfunction and its treatment in Parkinson's disease. *J Neurol.* (2020) 267:288–94. doi: 10.1007/s00415-019-09651-z

12. Maiga B, Diop MS, Sangare M, Dembele K, Cisse L, Kone O, et al. Sleep quality assessment in 35 Parkinson's disease patients in the Fann Teaching Hospital, Dakar, Senegal. *Rev Neurol (Paris).* (2016) 172:242–7. doi: 10.1016/j.neurol.2015.11.006

13. Berry RB, Brooks R, Gamaldo C, Harding SM, Lloyd RM, Quan SF, et al. AASM scoring manual updates for 2017 (Version 2.4). *J Clin Sleep Med.* (2017) 13:665–6. doi: 10.5664/jcsm.6576

14. Ratti P-L, Nègre-Pagès L, Pérez-Lloret S, Manni R, Damier P, Tison F, et al. Subjective sleep dysfunction and insomnia symptoms in Parkinson's disease: insights from a cross-sectional evaluation of the French CoPark cohort. *Parkinsonism Relat Disord.* (2015) 21:1323–9. doi: 10.1016/j.parkreldis.2015.09.025

15. Cai G-E, Luo S, Chen L-N, Lu J-P, Huang Y-J, Ye Q-Y. Sleep fragmentation as an important clinical characteristic of sleep disorders in Parkinson's disease: a preliminary study. *Chin Med J (Engl).* (2019) 132:1788–95. doi: 10.1097/CM9.0000000000000329

16. Zhang Y, Ren R, Sanford LD, Yang L, Zhou J, Tan L, et al. Sleep in Parkinson's disease: A systematic review and meta-analysis of polysomnographic findings. *Sleep Med Rev.* (2020) 51:101281. doi: 10.1016/j.smrv.2020.101281

17. Martinez-Ramirez D, De Jesus S, Walz R, Cervantes-Arriaga A, Peng-Chen Z, Okun MS, et al. A Polysomnographic Study of Parkinson's Disease Sleep Architecture. *Parkinsons Dis.* (2015) 2015:570375. doi: 10.1155/2015/570375

18. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry.* (1992) 55:181–4. doi: 10.1136/jnnp.55.3.181

19. Fahn S. Recent developments in Parkinson's disease. *Macmillan health care information.* (1987) 2:293–304.

20. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology.* (1967) 17:427–42. doi: 10.1212/WNL.17.5.427

21. Chaudhuri KR, Martinez-Martin P, Schapira AHV, Stocchi F, Sethi K, Odin P, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. *Mov Disord.* (2006) 21:916–23. doi: 10.1002/mds.20844

22. van Wamelen DJ, Martinez-Martin P, Weintraub D, Schrag A, Antonini A, Falup-Pecurariu C, et al. The non-motor symptoms scale in Parkinson's disease: validation and use. *Acta Neurol Scand.* (2021) 143:1. doi: 10.1111/ane.13336

23. Ciesielska N, Sokołowski R, Mazur E, Podhorecka M, Polak-Szabela A, Kedziora-Kornatowska K. Is the montreal cognitive assessment (MoCA) test better suited than the mini-mental state examination (MMSE) in mild cognitive impairment (MCI) detection among people aged over 60? *Meta-analysis Psychiatr Pol.* (2016) 50:1039–52. doi: 10.12740/PP/45368

24. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. *Age Ageing.* (1997) 26:353–7. doi: 10.1093/ageing/26.5.353

25. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res.* (1989) 28:193–213. doi: 10.1016/0165-1781(89)90047-4

26. Chaudhuri KR, Pal S, DiMarco A, Whately-Smith C, Bridgman K, Mathew R, et al. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* (2002) 73:629–35. doi: 10.1136/jnnp.73.6.629

27. Sateia MJ. International classification of sleep disorders-third edition. *Chest.* (2014) 146:1387–94. doi: 10.1378/chest.14-0970

28. Backhaus J, Junghanns K, Broocks A, Riemann D, Hohagen F. Test-retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. *J Psychosom Res.* (2002) 53:737–40. doi: 10.1016/S0022-3999(02)00330-6

29. Peeraully T, Yong M-H, Chokroverty S, Tan E-K. Sleep and Parkinson's disease: a review of case-control polysomnography studies. *Mov Disord.* (2012) 27:1729–37. doi: 10.1002/mds.25197

30. Zhang J, Xu C-Y, Liu J. Meta-analysis on the prevalence of REM sleep behavior disorder symptoms in Parkinson's disease. *BMC Neurol.* (2017) 17:23. doi: 10.1186/s12883-017-0795-4

31. Inoue Y, Nanba K, Honda Y, Takahashi Y, Arai H. Subjective sleep quality and suggested immobilization test in restless leg syndrome and periodic limb movement disorder. *Psychiatry Clin Neurosci.* (2002) 56:293–4. doi: 10.1046/j.1440-1819.2002.00966.x

32. Shen Y, Shen Y, Dong Z-F, Pan P-L, Shi H-C, Liu C-F. Obstructive sleep apnea in Parkinson's disease: a study in 239 Chinese patients. *Sleep Med.* (2020) 67:237–43. doi: 10.1016/j.sleep.2019.11.1251

33. Sobreira-Neto MA, Pena-Pereira MA, Sobreira EST, Chagas MHN. Almeida CMOd, Fernandes RMF, et al. Obstructive sleep apnea and Parkinson's disease: characteristics and associated factors. *Arq Neuropsiquiatr.* (2019) 77:609–16. doi: 10.1590/0004-282x20190098

34. Covassin N, Neikrug AB, Liu L, Corey-Bloom J, Loredo JS, Palmer BW, et al. Clinical correlates of periodic limb movements in sleep in Parkinson's disease. *J Neurol Sci.* (2012) 316:131–6. doi: 10.1016/j.jns.2012.01.004

35. Nishiyama T, Mizuno T, Kojima M, Suzuki S, Kitajima T, Ando KB, et al. Criterion validity of the Pittsburgh sleep quality index and epworth sleepiness scale for the diagnosis of sleep disorders. *Sleep Med.* (2014) 15:422–9. doi: 10.1016/j.sleep.2013.12.015

36. Langston JW, Forno LS. The hypothalamus in Parkinson disease. *Ann Neurol.* (1978) 3:129–33. doi: 10.1002/ana.410030207

37. Breen DP, Vuono R, Nawarathna U, Fisher K, Shneerson JM, Reddy AB, et al. Sleep and circadian rhythm regulation in early Parkinson disease. *JAMA Neurol.* (2014) 71:589–95. doi: 10.1001/jamaneurol.2014.65

38. Dos Santos AB, Skaanning LK, Thaneshwaran S, Mikkelsen E, Romero-Leguizamón CR, Skamris T, et al. Sleep-controlling neurons are sensitive and vulnerable to multiple forms of α-synuclein: implications for the early appearance of sleeping disorders in α-synucleinopathies. *Cell Mol Life Sci.* (2022) 79:450. doi: 10.1007/s00018-022-04467-z

39. Hawkes CH, Del Tredici K, Braak H. A timeline for Parkinson's disease. *Parkinsonism Relat Disord.* (2010) 16:79–84. doi: 10.1016/j.parkreldis.2009.08.007

40. Braak H, Del Tredici K. Neuropathological staging of brain pathology in sporadic Parkinson's disease: separating the wheat from the chaff. *J Parkinsons Dis.* (2017) 7:S71–85. doi: 10.3233/JPD-179001

41. Diaconu Ş. Falup-Pecurariu O, ŢînŢ D, Falup-Pecurariu C. REM sleep behaviour disorder in Parkinson's disease (review). *Exp Ther Med.* (2021) 22:812. doi: 10.3892/etm.2021.10244

42. Chahine LM, Daley J, Horn S, Duda JE, Colcher A, Hurtig H, et al. Association between dopaminergic medications and nocturnal sleep in early-stage Parkinson's disease. *Parkinsonism Relat Disord.* (2013) 19:859–63. doi: 10.1016/j.parkreldis.2013.05.009

43. Diederich NJ, Vaillant M, Mancuso G, Lyen P, Tiete J. Progressive sleep 'destructuring' in Parkinson's disease. A polysomnographic study in 46 patients. *Sleep Med.* (2005) 6:313–8. doi: 10.1016/j.sleep.2005.03.011

44. Videnovic A, Lazar AS, Barker RA, Overeem S. The clocks that time us'–circadian rhythms in neurodegenerative disorders. *Nat Rev Neurol.* (2014) 10:683–93. doi: 10.1038/nrneurol.2014.206

45. Hunt J, Coulson EJ, Rajnarayanan R, Oster H, Videnovic A, Rawashdeh O. Sleep and circadian rhythms in Parkinson's disease and preclinical models. *Mol Neurodegener.* (2022) 17:2. doi: 10.1186/s13024-021-00504-w

46. Mattis J, Sehgal A. Circadian rhythms, sleep, and disorders of aging. *Trends Endocrinol Metab.* (2016) 27:192–203. doi: 10.1016/j.tem.2016.02.003

47. Leng Y, Musiek ES, Hu K, Cappuccio FP, Yaffe K. Association between circadian rhythms and neurodegenerative diseases. *Lancet Neurol.* (2019) 18:307–18. doi: 10.1016/S1474-4422(18)30461-7

48. Malhotra RK. Neurodegenerative disorders and sleep. *Sleep Med Clin.* (2022) 17:307–14. doi: 10.1016/j.jsmc.2022.02.009

49. Gu R, Zhu J, Zhong M, Jiang Y, Zhu S, Wang Y, et al. Characteristics of sleep structure in Parkinson's disease patients with hallucinations based on polysomnography. *Front Neurol.* (2022) 13:929569. doi: 10.3389/fneur.2022.929569

50. Sun S, Zhao X, Ren J, Cheng J, Zhou J, Su C. Characteristics of objective sleep and its related risk factors among parkinson's disease patients with and without restless legs syndrome. *Front Neurol.* (2021) 12:644385. doi: 10.3389/fneur.2021.644385

51. Iranzo A, Comella CL, Santamaria J, Oertel W. Restless legs syndrome in Parkinson's disease and other neurodegenerative diseases of the central nervous system. *Mov Disord.* (2007) 22:S424–S30. doi: 10.1002/mds.21600

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Dry eye in Parkinson's disease: a narrative review

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In Parkinson's disease (PD) patients, a wide range of ocular and visual disorders are present. Tear film instability, inflammation and dysfunction of the ocular surface, and the presence of symptoms of visual disturbance characterize dry eye, a multifactorial disease of the ocular surface. Based on a literature search, we discuss the frequency, pathogenesis, and influence on the quality of life of patients with dry eye in Parkinson's disease. Furthermore, we review the available means of diagnosis and management of dry eye. An improvement in awareness and recognition of dry eye is needed to provide suitable, personalized therapeutic options for PD patients, aiming to improve their quality of life, independence, and safety.

KEYWORDS

dry eye, Parkinson's disease, keratoconjunctivitis sicca, visual disturbances, diagnosis, management

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder presenting a wide range of non-motor symptoms including visual disturbances, with important implications for the quality of life of these patients. Visual disturbances in PD range from peripheral to central and include dry eye, diplopia, decreased blink rates, blepharitis, blepharospasm, visual hallucinations, retinal abnormalities, and convergence insufficiency (1). These disturbances lead to the appearance of ocular symptoms such as eye tearing, blurred vision, difficulty with reading, doubling of images, presence of passage hallucinations, impaired contrast sensitivity, and color vision and are frequently interconnected. For example, dopamine depletion and alpha-synuclein aggregation in the cell layers of the intra-retinal region have been shown to lead to a dysfunction in visual processing with impairment in color discrimination, contrast sensitivity, visual acuity, object, and motion perception (2, 3); double vision has been associated with the presence of visual hallucinations and convergence insufficiency (4). Dry eye disease was defined by the 2007 International Dry Eye Workshop (5) as "a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface that is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface". Symptoms of dry eyes include excess tearing, stinging or burning eyes, foreign body sensation, scratchiness, photophobia, and redness of the eye (6).

Dry eye disease has a prevalence of as high as 70% in PD patients (1, 7). Thus, patients with PD should be considered to be at increased risk of developing dry eyes. The aim of this study was to review the pathogenesis, clinical evaluation, impact on quality of life (QoL), and management of dry eye in Parkinson's disease.

Pathogenesis of dry eye in Parkinson's disease

Dysfunction of the tear-secreting glands and/or disorders of the ocular surface led to dry eye (8). The precorneal tear film is a hydrated gel, with its composition including water, electrolytes, mucins, soluble antimicrobial proteins (lactoferrin and lysosome), immunoglobulins, and growth factors that help regulate cellular processes (9, 10). A superficial lipid layer formed by hydrophilic polar lipids such as phospholipids and ceramides is adjacent to the aqueous-mucin layer (11). The aqueous-mucin layer is anchored by chemical attractions to the superficial corneal epithelium (Figure 1) (12). Its role is to protect and support the ocular surface.

The communication between the ocular surface (cornea and conjunctiva) and the tear-secreting glands (lacrimal glands and meibomian glands) occurs through a neural reflex arc: The sensory afferent information travels through the ophthalmic branch of the fifth cranial nerve (the trigeminal nerve) to the pons where the integration of signals with the input from cortical and other central nervous system centers is made. The efferent nerves are both parasympathetic (seventh cranial nerve—the facial nerve) and sympathetic (paraspinal sympathetic chain) fibers that travel to the lacrimal glands and are responsible for tear secretion (9). A decrease in aqueous tear secretion leads to an increase in tear film osmolarity and chronic inflammation that may severely affect the function and differentiation of the ocular surface epithelium (13).

In Parkinson's disease, several mechanisms are incriminated (Figure 2). With disease progression, the accumulation of aggregated alpha-synuclein was hypothesized to spread from the nigrostriatal dopaminergic system to the hypothalamus and neocortex in a caudo-rostral pattern, leading to cell dysfunction, degeneration, and a subsequent decrease in striatal dopamine levels (14). The neurochemical control of blinking is exerted by the dopaminergic, GABAergic, and cholinergic systems of the brainstem. Thus, the decreased levels of dopamine in the central nervous system (CNS) of PD patients give rise to significantly decreased blink rates (15). Blinking is crucial for maintaining an adequate tear film on the surface of the eyes. Second, it is acknowledged that abnormalities in autonomic function are ubiquitous in PD (16). The superior salivatory nucleus and the lacrimal nucleus in the pons give rise to general visceral (parasympathetic and sensory) efferent fibers that are carried to the geniculate ganglion within the intermediate nerve. Preganglionic parasympathetic fibers exit the geniculate ganglion forming the greater superficial petrosal nerve that joins the deep petrosal nerve toward the pterygopalatine ganglion. From there, parasympathetic postganglionic fibers synapse with the lacrimal glands (17). From the hypothalamus, descending autonomic fibers regulated by the ventral striatum and limbic system travel to the superior salivatory nucleus. Thus, the dysfunction of the autonomic system caused by the presence of Lewy bodies in the substantia nigra as well as the sympathetic and parasympathetic ganglia might explain the lacrimation disturbances found in PD patients (18). Furthermore, changes in meibum lipid composition and structure could contribute to the increased susceptibility to dry eye in PD patients (19). Tear proteins involved in lipid metabolism, oxidative stress, and immune response were found to be altered in Parkinson's disease patients (20).

Finally, antiparkinsonian medications were associated with dry eye syndrome (21). Benzhexol, pramipexole, and levodopa are known to cause dryness in mucous membranes due to their anticholinergic effects. Other examples include orphenadrine, benztropine, bornaprine, procyclidine, benapryzine, and methixine (22).

Clinical evaluation of dry eye

Subjective assessment

Dry eye can be assessed by using rating scales and questionnaires. The description, scoring system, and validity parameters of questionnaires can be found in Table 1. The Ocular Surface Disease Index (OSDI) is the most commonly used dry eye questionnaire. In PD patients, OSDI scores were significantly higher compared to healthy subjects (7).

Objective assessment

Tear function abnormalities in PD patients have been reported in the literature. Most authors reported more than one abnormal tear film test result, and, in some cases, the results were correlated with disease severity.

Slit lamp examination

A slit lamp examination can be used to diagnose moderate-to-severe dry eye by measuring the upper and lower tear menisci and by assessing the presence and grade of lid-parallel conjunctival folds (LIPCOFs), a sensitive predictor of dry eye. Based on the examination of conjunctival folds in the lower temporal quadrant, a grading system of three degrees has been proposed (23). The LIPCOF degree did not significantly differ between patients with Parkinson's disease and controls in a study by Nowacka et al. (7).

Therefore, more studies are needed in order to assess the usefulness of slit lamp examination for dry eye disease in PD.

Aqueous tear production (Schirmer test)

The insertion of a standardized filter paper strip into the lower conjunctival sac in order to measure the amount of wetting (millimeter units) after a period of 5 min is known as the Schirmer test. The screening threshold for dry eyes is 10 mm, with a value of 5 mm or less confirming the diagnosis (6).

Schirmer test scores were significantly lower in patients with Parkinson's disease than those in controls in a study by Demirci et al. (24) (6.52 ± 2.94 mm/5 min vs. 11.3 ± 6.16 mm/5 min). Similar results were obtained in three other studies (25–27) that followed the corneal parameters in PD patients compared to controls: 6.56 ± 4.75 mm/5 min vs. 12.81 ± 5.68 mm/5 min, 9.08 ± 4.46 mm/5 min vs. 17.16 ± 9.57 mm/5 min, and 4.3 ± 1.8 mm/5 min vs. 9.4 ± 3.0 mm/5 min, respectively. Schirmer's test scores were also found to be significantly affected in patients with

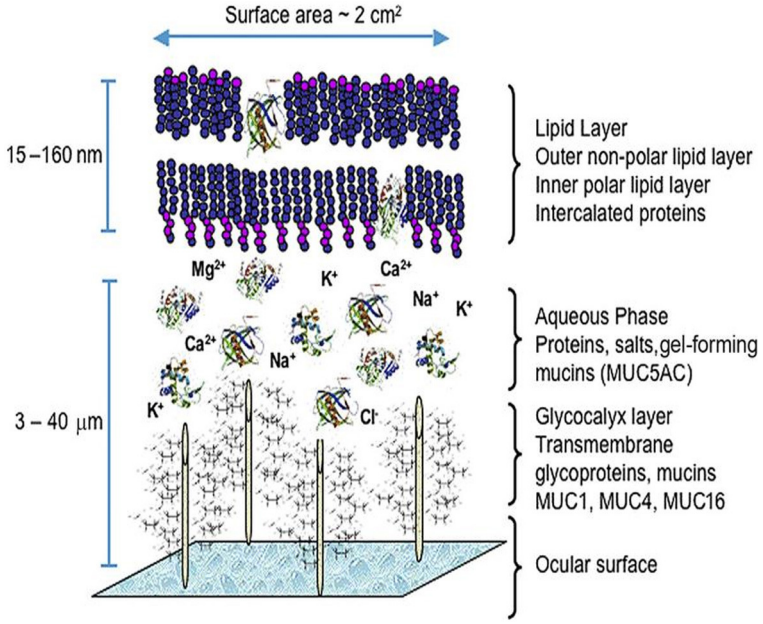

FIGURE 1
The precorneal tear film model. From Green-Church et al. (90), with permission.

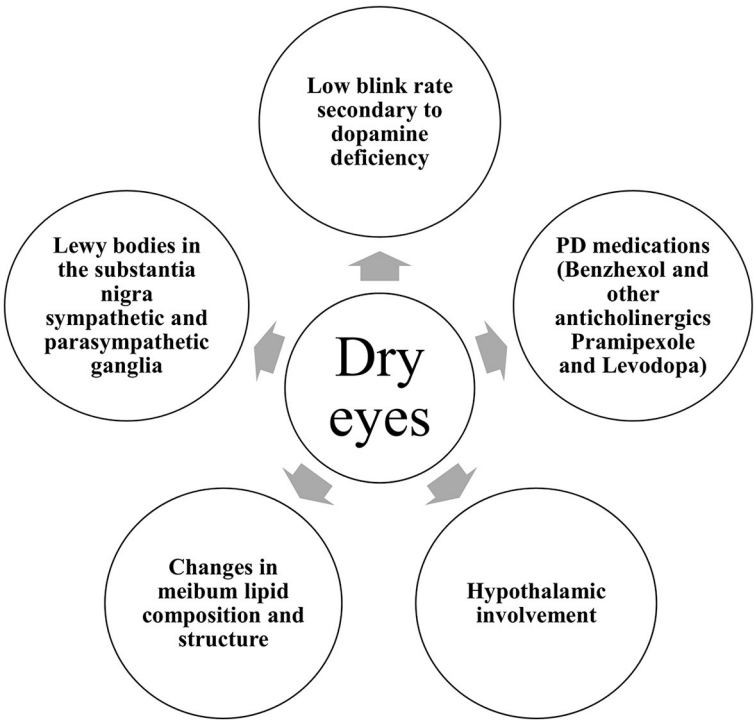

FIGURE 2
Mechanisms of dry eye in Parkinson's disease.

PD compared to healthy subjects (13.20 ± 10.45 vs. 17.49 ± 11.16 mm) in a study by Nowacka et al. (7).

The Schirmer test, therefore, is a useful method for evaluating and diagnosing dry eye in Parkinson's disease patients.

Staining of the ocular surface

Vital staining of the ocular surface using different dyes, such as lissamine green, rose bengal, and fluorescein, has been widely used to assess the integrity of the conjunctival and corneal epithelial cells.

TABLE 1 Description, scoring system, and validity parameters of available dry eye questionnaires.

Questionnaire	Description	Scoring	Validity parameters
Ocular surface disease index (OSDI)	The most used one. 12-item questionnaire; assessment of symptoms of ocular irritation and their impact on vision-related functioning. Subscales: vision-related function, ocular symptoms, and environmental triggers.	Total score of 0 to 100 Higher score = greater disability 0–12 = normal; 13–22 = mild dry eye; 23–32 = moderate dry eye; >33 = severe dry eye.	*Sensitivity* 0.60–0.92(higher in more severe diseases) *Specificity* 0.83 *Reliability* Internal consistency (Cronbach's α = 0.92 (0.84–0.94) Area under curve ROC = 0.970 Schiffman et al. (81)
Visual Functioning Questionnaire-25 (NEI-VFQ-25)	25-item questionnaire; shorter version of NEI-VFQ; assessment of the effect of visual impairment on the patient's health-related quality of life	Total score of 0 to 100 Higher score = greater disability	*Reliability** Internal consistency = between 0.66 and 0.94 for all subscales *for NEI-VFQ, longer 51-item-questionnaire Mangione et al. (82)
Standardized Patient Evaluation of Eye Dryness (SPEED) Questionnaire	Eight items; assessment of frequency and severity of symptoms, monitoring of diurnal and changes in symptoms over 3 months	Total score of 0–28 0–4 = mild dry eye; 5–7 = moderate dry eye; >8 = severe dry eye.	*Reliability* Internal consistency = between 0.86 and 0.95 Area under curve ROC = 0.928 Ngoet al. (83)
Dry Eye Questionnaire 5 (DEQ-5)	5-item questionnaire; assessment of the frequency of watery eye, discomfort and dryness, and late-day discomfort and dryness intensity; simplified version of the original DEQ	Total score of 0–22 >6 = dry eye; >12 = suspected Sjogren syndrome (SS).	*Sensitivity* 0.712 *Specificity* 0.827 *Reliability* Internal consistency = 0.819 Area under curve ROC = 0.835 Akowuah et al. (84)
Symptom Assessment in Dry Eyes (SANDE) Questionnaire	Two questions presented in a visual analog scale; assesses the frequency and severity of dry eye syndrome, and is useful in detecting changes in symptoms over time.	Visual analog scale Frequency of symptoms: rarely to all the time Severity of symptoms: very mild to very severe	*Reliability* Spearman coefficient correlation: $R = 0.64$; $P < 0.001$ (when compared to OSDI) Amparo et al. (85) *Repeatability* Intraclass correlation coefficient (ICC) = 0.53–0.76 Schaumberg et al. (86)
Dry Eye related Quality of life Score (DEQS)	15-item questionnaire; assessment of dry eye symptoms and influence on daily life, and the overall degree of quality of life impairment	Total score of 0–100 Higher score = greater disability	*Reliability* Internal consistency (Cronbach's α) = 0.93 *Repeatability* Intraclass correlation coefficient (ICC) = 0.91 Sakane et al. (87)
McMonnies Questionnaire	14-item questionnaire; helps detect dry eye, detects patients at risk for developing dry eye due to exposure to specific factors	Specific scoring systems available	*Sensitivity* 0.87–0.93 *Specificity* 0.85–0.89 *Reliability* Area under curve ROC = 0.94 Gothwal et al. (88)
The University of North Carolina Dry Eye Management Scale (UNC DEMS)	Single-item scale; provides a snapshot of a patient's overall experience: symptoms and quality of life over the last week	Visual analog scale From 1 (no symptoms) to 10 (severe symptoms)	*Reliability* Spearman coefficient correlation: $R = 0.80$; $P < 0.001$ (when compared to OSDI) *Repeatability* Test–retest reliability coefficient = 0.90 Grubbs et al. (89)

The damaged epithelial cell stain was in a bright color (green for fluorescein and lissamine green and purple for rose bengal) after the instillation of a drop of dye solution under cobalt-blue-filtered light (28).

Reddy et al. (29) determined the degree of ocular surface staining with rose bengal, lissamine green, and fluorescein sodium in patients with PD and progressive supranuclear palsy (PSP) compared to healthy subjects. A high percentage of PD and PSP patients had abnormal staining compared to healthy controls (none). This is in concordance with a study by Demirci et al. (24) that found higher corneal fluorescein staining in PD patients than that in the control group.

Staining of the ocular surface may prove useful in diagnosing dry eye disease in PD, but more studies are needed.

Tear film stability (tear break-up time)

By applying a fluorescein strip to the lower conjunctival sac and examining it under cobalt-blue-filtered light, the tear break-up time or TBUT can be determined (30). TBUT represents the time measured between the last blink and the appearance of the first dark spot, and a value under 10 s is considered abnormal (31).

TBUT was significantly lower in patients with Parkinson's disease than in healthy subjects in various studies (18, 24, 25, 32).

Biousse et al. (1) found that only TBUT was abnormal in PD patients compared to controls in terms of normal rose bengal staining and Schirmer test values. In another study, TBUT was not significantly different between the PD group and the control group, while Schirmer test results and meibomian gland function were significantly affected (7).

Studies are conflicting regarding the use of TBUT in properly diagnosing dry eye syndrome. More studies are needed in order to assess the usefulness of the test for Parkinson's disease patients.

Anterior segment optical coherence tomography

With high-resolution AS-OCT, cross-sectional images of the cornea can be obtained, allowing not only the examination of corneal layers (38) but also the measurement of corneal thickness and cross-sectional area, precise height, and volume of the tear meniscus (33).

Using AS-OCT, Ulusoy et al. (25) measured the thickness of each corneal sublayer in patients with Parkinson's disease in comparison to healthy individuals. They found that the thicknesses of the Bowman and stromal layers were significantly lower in PD patients. Furthermore, stromal thickness was negatively correlated with disease duration and severity and positively correlated with TBUT and Schirmer test scores. They concluded that reduced blinking rates and tear film dysfunction lead to corneal thinning in patients with PD.

Corneal thickness is an important indicator of corneal health. Central corneal thickness (CCT) was found to be significantly decreased in PD patients compared to healthy subjects in several studies (24).

Aksoy et al. (32) reported that the CCT, TBUT, and Schirmer test values decrease in correlation with disease severity (increasing Hoehn–Yahr scores). Demirci et al. (24) found corneal thickness to be significantly correlated with TBUT, blinking rates, and Schirmer test scores in PD patients.

Tamer et al. (18) measured the tear meniscus height in PD patients and controls and found abnormal tear meniscus height in 67.9% of the PD patients recruited in the study. Tear meniscus height was not linearly associated with the disease stage.

The use of optical coherence tomography to measure the thickness of corneal sublayers and tear meniscus proved to be a reliable method in evaluating the presence of dry eyes in Parkinson's disease patients.

Evaluation of blink rates

Blinking is necessary to maintain a healthy and regular tear film. Reduced blinking causes increased evaporation of aqueous components, resulting in subsequent contamination of the mucin layer and thinning of the tear film (34). Blinks are not only reduced but also are less effective with a decrease in amplitude and velocity in PD patients (35, 36). Due to impaired blinking, PD patients are at increased risk for dry eye. Inflammation, impairment of blinking, corneal sensitivity, and decreased tear secretion aggravate dry eye symptoms in PD (37).

PD patients were found to have significantly decreased blinking rates (BRs) compared to healthy controls (1, 18, 24, 27).

TABLE 2 Dry eye classification of severity.

	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)
Symptoms	+	++	+++
Signs	–	+ (reversible)	+ (irreversible → complications)

Symptoms: itching, dryness sensation, photophobia, ocular tiredness, and blurry vision.
Reversible signs: epithelial erosion, keratophakia filamentosa and punctata, short BUT, marginal blepharitis, and hyperemia.
Complications: corneal ulcers and neovascularization, keratinization, leukomas, retraction of conjunctival folds, and squamous epithelial metaplasia (permanent sequelae leading to reduced visual acuity).

Tamer et al. (18) found blinking rates to be inversely correlated with total abnormal tear tests and with disease severity (H-Y scores). This is in concordance with other studies that also found a significant negative correlation between blink rates and H-Y scores in PD patients (24, 25, 32).

Fitzpatrick et al. (38) found significantly decreased blink rates in PD patients compared to healthy individuals during different everyday tasks such as reading a book or watching a video. They found no correlation between BR and disease severity, duration, or treatment.

Decreased blink rates, therefore, could be an important indicator that further tear tests are needed in order to properly diagnose dry eye syndrome in PD patients at risk.

Dry eye staging

Based on the presence of symptoms and signs, dry eye can be classified into three grades of severity: grade 1 or mild, grade 2 or moderate, and grade 3 or severe (Table 2) (39).

Impact on the quality of life

In Parkinson's disease patients, both motor and non-motor symptoms (including ophthalmological problems) contribute significantly to a decreased quality of life (QoL). PD patients with dry eye experience several symptoms that further worsen QoL. These symptoms include dryness, itching, redness, ocular fatigue and pain, excessive tearing, and decreased visual acuity. The presence of ocular discomfort due to dry eye was associated with greater interference with activities of daily living and with higher scores on the OSDI (40).

In a study by Borm et al. (41), 53% of PD patients reported that the presence of ophthalmologic symptoms had a moderate-to-severe effect on their quality of life, compared with 16% of controls. The greatest interference was experienced while reading, driving a car, watching television, and working on a computer. In another study, Borm et al. (42) measured the impact on daily life using the VFQ-25 (Visual Functioning-25 questionnaire). In total, 44% of PD participants reported poor QoL due to the presence of relevant ophthalmological disturbances. The severity of visual disturbances is also correlated with an increased risk for falls as PD patients compensate for their motor and postural impairments with visual guidance (43, 44).

TABLE 3 Summary of treatment options for different stages of dry eye.

Early stage	Moderate stage	Severe stage
• Patient education • Elimination of environmental factors (e.g., air pollutants, hot and cold temperatures, and alcohol) • Elimination of precipitating medications (diuretics, beta-blockers, antihistamines, tricyclic antidepressants, antipsychotics, and antiparkinsonian drugs) • Artificial tear substitutes (cellulose ethers, carbomers, polyvinyl alcohol, sodium hyaluronate, and povidone) • Eyelid therapy (warm compresses and eyelid hygiene) • Correction of eyelid abnormalities (if present) • Treatment of contributing factors (e.g., blepharitis) • Treatment of underlying systemic disease	Early-stage treatment + • Anti-inflammatory agents (topical steroids or cyclosporin) • Supplementation with omega-3 fatty acids • Punctal plugs • Moisture chamber glasses	Moderate-stage treatment + • Oral anti-inflammatory agents (short-term corticosteroids or tetracycline) • Mucolytic agents • Autologous serum tears • Therapeutic contact lenses • Permanent punctal occlusion • Surgical intervention (tarsorrhaphy)

In patients suffering from dry eye, the prevalence of depression and anxiety is approximately three times higher than that in patients without dry eye disease (45). This is especially important because depression and anxiety are among the most frequently reported neuropsychiatric disturbances in PD with a prevalence of up to 90% (46). Thus, patients with dry eye and Parkinson's disease are at increased risk for depression and anxiety. Treatment of dry eye with over-the-counter lubricants of the ocular surface improved patient-reported satisfaction levels and QoL to as high as 75% for patients with mild symptoms and 65% for patients with severe symptoms (47). However, PD-related motor impairments might interfere with the self-administration of ocular products, with PD patients experiencing limited independence from being unable to handle eye drop instillation themselves, thus further decreasing their quality of life (48).

Management of dry eye in PD

Dry eye management usually begins with conventional over-the-counter ocular surface lubricants in the early stages and can progress to advanced therapies in more severe cases. In some of the cases, new therapies may be added to previous ones to increase the efficacy of the treatment. Treatment options are summarized in Table 3 (6, 49). However, symptomatic treatment of dry eye has not yet been studied, specifically for Parkinson's disease patients.

Patient education

Patient education is an important step in the care management of people with chronic illnesses such as Parkinson's disease because it provides support and information to patients and caregivers while also improving self-care, treatment compliance, patient wellness, and physical function through exercise. Many patient education programs have been developed worldwide with various improvements in QoL in PD patients (50–54).

Proper patient education is also essential for dry eye. The implementation of certain lifestyle and behavioral changes could alleviate dry eye symptoms (Figure 3). Exposure to air pollution or other environmental irritants, including tobacco smoke, should be limited. Cigarette smoking was found to have adverse effects on tear protein and on the lipid layer of the tear film and is associated with dry eye (55, 56). Excessive monitor usage should also be avoided. Dietary changes should be implemented with the consumption of omega-3 fatty acids and the limitation of alcohol intake (57).

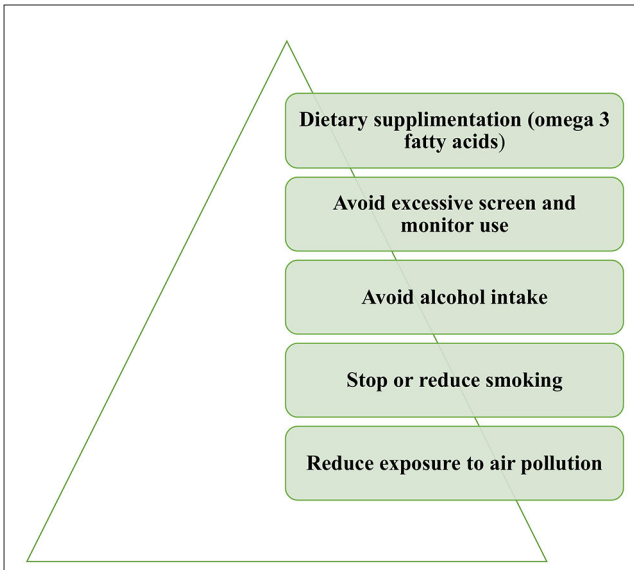

FIGURE 3
Lifestyle changes recommended for dry eye management.

Elimination of precipitating medications

Antiparkinsonian medications such as levodopa, benzhexol, or pramipexole are known determinants of dry eye. Other implicated medications are also antipsychotics and antidepressants, as depression and psychosis are two major neuropsychiatric comorbidities in PD patients.

While the elimination of precipitating medications is recommended, that is not always the case for Parkinson's disease patients. Antiparkinsonian medication is crucial for the improvement of PD for both motor and non-motor symptoms. Clinicians should consider, if possible, switching between classes of

antiparkinsonian medications if a certain treatment is considered to be the cause of dry eye symptoms. For example, amantadine was found to induce corneal endothelial toxicity in a dose-dependent manner (58), thus potentially being involved in treatment-induced dry eye.

On the other hand, levodopa replacement therapy has been shown to improve the blinking rates of PD patients (35). As discussed above, blinking is involved in the pathogenesis of dry eye, thus, an improvement in blinking might alleviate dry eye symptoms for these patients. The idea that patients should consciously increase their blink rates is difficult to achieve in the case of Parkinson's disease.

Artificial tear substitutes

Artificial tear substitutes are inorganic solutions containing electrolytes, surfactants, and viscosity agents that aim to lower the surface tension of the tear film, enhance tear volume by forming a hydrophilic layer on the ocular surface, and prevent bacterial growth, thus reducing the symptoms of dry eye (59). Cellulose ethers, carbomers, polyvinyl alcohol, sodium hyaluronate, or povidone are the main components of most artificial tear substitutes. Each tear substitute has its own properties; hence, treatment should be individualized according to each patient's deficit. In the general population, substitute treatment with added lubricants and osmoprotectants has been shown to increase patient satisfaction levels over a short period of time (60, 61). However, this may not be the case for Parkinson's disease patients. The application of artificial tear substitutes requires increased manual dexterity. As PD patients struggle with fine-motor dexterity tasks due to motor impairments, treatment adherence is expected to be low. It is well-known that treatment burden is a serious issue for both PD patients and their caregivers, causing poor adherence to treatment, poor quality of life, and poor health outcomes (62).

Advanced-stage therapies

In cases where artificial tear substitute treatment is insufficient, topical anti-inflammatory treatment may be efficient. Topical cyclosporine proved to have a high success rate for patients with mild-to-severe dry eye disease (63) and seemed to prevent the progression of dry eye symptoms over a period of 12 months (64). Topical corticosteroids have been reported to reduce corneal fluorescein staining and improve ocular irritation (65). Patients should be monitored, as prolonged treatment with corticosteroids may cause cataract formation and increased intraocular pressure.

In ocular surface diseases, obstruction of the lacrimal drainage to preserve the tears on the ocular surface can be achieved with punctal plugs, which are biocompatible silicone devices. The use of punctal plugs has been shown to decrease the use of tear substitutes and improve symptoms in dry eye patients (66). Complications of punctal plug use include partial migration or extrusion, which can cause local irritation or even canaliculitis and keratitis, loss, epiphora, punctal stenosis, and infectious complications (pyogenic granuloma) (67). Permanent punctal occlusion by laser or thermal cauterization can be beneficial in severe cases. An alternative for permanent punctal occlusion may be labial mucous membrane grafting, especially in patients with conjunctival cicatricial changes (68).

Moisture chamber glasses or spectacles (MCSs) are prosthetic devices that provide a comfortable and moister ocular environment by preventing the evaporation of tears and protecting the eyes from irritants such as wind, dust, or pollen. In a study by Shen et al. (69), significant improvements in ocular comfort and ocular parameters, tear meniscus height (TMH), non-invasive tear break-up time (NI-BUT), and tear film lipid layer thickness were found in the MCS group (dry eye subjects who wore MCSs for a period of 90 min) compared to the control group. MCSs are a feasible, non-invasive, alternative treatment for dry eye, especially for patients exposed to harsh environmental conditions.

The temporal or permanent closure of the eyelids (tarsorrhaphy) can be used in severe, refractory cases of dry eye. It allows a better distribution of the tear film on the surface of the eyes by decreasing the rate of evaporation of the tear film (70). It was proven to be very effective in the management of ocular surface problems, including dry eye, with a success rate as high as 90% and minor complications (71).

These treatments have not been specifically studied for Parkinson's disease patients.

Sjögren's syndrome and Parkinson's disease

Sjögren's syndrome (SS) is an autoimmune disorder characterized by the presence of dry mouth, dry eyes, and recurrent episodes of salivary gland enlargement due to keratoconjunctivitis sicca and focal lymphocytic sialadenitis (72). It has been associated with central nervous system abnormalities such as seizures, cognitive dysfunction, aseptic meningoencephalitis, focal cerebral deficits, multiple sclerosis-like symptoms, and movement disorders (73).

The risk of Parkinson's disease was found to be 1.37 times greater in patients with autoimmune rheumatic diseases than in controls in a nationwide population-based cohort study (74). Furthermore, the incidence of PD was higher in SS patients (2.5%; 215 out of 8,422 patients); thus, primary and secondary SS patients were considered to have a higher risk of developing Parkinson's disease (74). The pathogenesis of this phenomenon is unclear. It is thought to be due to an autoimmune process aimed against the basal ganglia that could involve anti-SSA and SSB antibodies or anti–beta2-glycoprotein IgG antibodies (75, 76).

Several cases of SS associated with Parkinsonism have been described in the literature (75, 77–79). In most cases, antiparkinsonian drugs did not improve the neurological signs and symptoms, while corticosteroid treatment variably improved the symptomatology in some cases.

A diagnosis of Sjögren's syndrome should be considered in patients with Parkinsonian features complaining of xerostomia and dry eye.

We recommend that dry eye assessment, a critical element of vision considered vital in Parkinson's disease, be added to the recently described dashboard system for the vitals of PD patients (80).

Conclusion

In Parkinson's disease patients' dry eye is a frequent complaint and has a negative impact on their health-related quality of life. Reduced blink rates due to dopamine depletion in the CNS, the presence of Lewy bodies in the substantia nigra, sympathetic and parasympathetic ganglia with subsequent autonomic system dysfunction, changes in meibum lipid composition and tear proteins, and changes in PD medications all play a role in the complex pathogenesis of this disorder. Various treatments for dry eye are available, but most of them, if not all, have not been specifically studied for Parkinson's disease patients. Instillation of artificial tear substitutes and removal of incriminated medications may not be feasible in PD patients. The care of these patients should always include an ophthalmologist as part of a multidisciplinary team. More studies are needed to explore this heterogenous syndrome in PD.

Author contributions

LU, SD, and CF-P worked on the conception and design of the article. LU carried out the search and drafted the article. KRC, CF-P, and SD revised the article for important intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Biousse V, Skibell BC, Watts RL, Loupe DN, Drews-Botsch C, Newman NJ, et al. Ophthalmologic features of Parkinson's disease. *Neurology.* (2004) 62:177–80. doi: 10.1212/01.WNL.0000103444.45882.D8

2. Weil RS, Schrag AE, Warren JD, Crutch SJ, Lees AJ, Morris HR, et al. Visual dysfunction in Parkinson's disease. *Brain.* (2016) 139:2827–43. doi: 10.1093/brain/aww175

3. Archibald NK, Clarke MP, Mosimann UP, Burn DJ. The retina in Parkinson's disease. *Brain.* (2009) 132:1128–45. doi: 10.1093/brain/awp068

4. Visser F, Vlaar AMM, Borm CDJM, Apostolov V, Lee YX, Notting IC, et al. Diplopia in Parkinson's disease: visual illusion or oculomotor impairment? *J Neurol.* (2019) 266:2457–64. doi: 10.1007/s00415-019-09430-w

5. Lemp MA, Baudouin C, Baum J, Dogru M, Foulks GN, Kinoshita S, et al. The definition and classification of dry eye disease: report of the definition and classification subcommittee of the international Dry Eye WorkShop. *Ocular Surf.* (2007) 5:75–92. doi: 10.1016/S1542-0124(12)70081-2

6. Módis L, Szalai E. Dry eye diagnosis and management. *Exp Rev Ophthalmol.* (2011) 6:67–79. doi: 10.1586/eop.10.89

7. Nowacka B, Lubiński W, Honczarenko K, Potemkowski A, Safranow K. Ophthalmological features of Parkinson disease. *Med Sci Monitor.* (2014) 20:2243–9. doi: 10.12659/MSM.890861

8. Bron AJ, Yokoi N, Gaffney E, Tiffany JM. Predicted phenotypes of dry eye: proposed consequences of its natural history. *Ocular Surf.* (2009) 7:78–92. doi: 10.1016/S1542-0124(12)70299-9

9. Pflugfelder SC, Solomon A, Stern ME, Palmer B. The diagnosis and management of dry eye: a twenty-five-year review. *Cornea.* (2000) 19:644–9. doi: 10.1097/00003226-200009000-00009

10. Van Setten G, Schultz G, Van Setten G, Van G, Schultz SG. Transforming growth factor-alpha is a constant component of human tear fluid. *Arch Clin Exp Ophthalmol.* (1994) 232:523–6. doi: 10.1007/BF00181994

11. Greiner JV, Glonek T, Korb DR, Booth R, Leahy CD. Phospholipids in meibomian gland secretion. *Ophthalm Res.* (1996) 28:44–9. doi: 10.1159/000267872

12. Pflugfelder SC, Liu Z, Monroy D, Li DQ, Carvajal ME, Price-Schiavi SA, et al. Detection of sialomucin complex (MUC4) in human ocular surface epithelium and tear fluid. *Invest Ophthalmol Vis Sci.* (2000) 41:1316–26.

13. Lemp MA, Bron AJ, Baudouin C, Bentez Del Castillo JM, Geffen D, Tauber J, et al. Tear osmolarity in the diagnosis and management of dry eye disease. *Am J Ophthalmol.* (2011) 151:792–8. doi: 10.1016/j.ajo.2010.10.032

14. Braak H, Ghebremedhin E, Rüb U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res.* (2004) 318:121–34. doi: 10.1007/s00441-004-0956-9

15. Karson CN. Blinking. *Bull Soc Belge Ophtalmol.* (1989) 237:443–57.

16. van Deursen DN, van den Heuvel OA, Booij J, Berendse HW, Vriend C. Autonomic failure in Parkinson's disease is associated with striatal dopamine deficiencies. *J Neurol.* (2020) 267:1922–30. doi: 10.1007/s00415-020-09785-5

17. Brackmann DE, Fetterman BL. Cranial nerve VII: facial nerve. In: G. G. Christopher, editor. *Textbook of Clinical Neurology*. 3rd ed. W.B. Saunders (Philadelphia, PA), (2007). p. 185–198.

18. Tamer C, Melek IM, Duman T, Öksüz H. Tear film tests in Parkinson's disease patients. *Ophthalmology.* (2005) 112:1795. doi: 10.1016/j.ophtha.2005.04.025

19. Blinchevsky S, Ramasubramanian A, Borchman D, Sayied S, Venkatasubramanian K. Meibum lipid composition and conformation in parkinsonism. *EC Ophthalmol.* (2021) 12:20–9.

20. Boerger M, Funke S, Leha A, Roser AE, Wuestemann AK, Maass F, et al. Proteomic analysis of tear fluid reveals disease-specific patterns in patients with Parkinson's disease – A pilot study. *Parkinson Relat Disord.* (2019) 63:3–9. doi: 10.1016/j.parkreldis.2019.03.001

21. Ekker MS, Janssen S, Seppi K, Poewe W, de Vries N, Theelen MT, et al. Ocular and visual disorders in Parkinson's disease: common but frequently overlooked. *Parkinson Relat Disord.* (2017) 40:1–10. doi: 10.1016/j.parkreldis.2017.02.014

22. Wong J, Lan W, Ong LM, Tong L. Non-hormonal systemic medications and dry eye. *Ocular Surf.* (2011) 9:212–26. doi: 10.1016/S1542-0124(11)70034-9

23. Höh H, Schirra F, Kienecker C, Ruprecht KW. Lid-parallel conjunctival folds are a sure diagnostic sign of dry eye. *Ophthalmologe.* (1995) 92:802–8.

24. Demirci S, Gunes A, Koyuncuoglu HR, Tok L, Tok O. Evaluation of corneal parameters in patients with Parkinson's disease. *Neurol Sci.* (2016) 37:1247–52. doi: 10.1007/s10072-016-2574-1

25. Ulusoy EK, Ulusoy DM. Evaluation of corneal sublayers thickness and corneal parameters in patients with Parkinson's disease. *Int J Neurosci.* (2021) 131:939–45. doi: 10.1080/00207454.2020.1761353

26. Sari ES, Koç R, Yazici A, Sahin G, Çakmak H, Kocatürk T, et al. Tear osmolarity, break-up time and schirmer's scores in Parkinson's disease. *Turk Oftalmol Dergisi.* (2015) 45:142–5. doi: 10.4274/tjo.46547

27. Çomoglu SS, Güven H, Acar M, Öztürk G, Koçer B. Tear levels of tumor necrosis factor-alpha in patients with Parkinson's disease. *Neurosci Lett.* (2013) 553:63–7. doi: 10.1016/j.neulet.2013.08.019

28. Lemp MA. Report of the National Eye Institute/Industry workshop on clinical trials in dry eyes. *CLAO J.* (1995) 21:221–32.

29. Reddy VC, Patel SV, Hodge DO, Leavitt JA. Corneal sensitivity, blink rate, and corneal nerve density in progressive supranuclear palsy and Parkinson disease. *Cornea.* (2013) 32:631–5. doi: 10.1097/ICO.0b013e3182574ade

30. Gulati A, Dana R. Keratoconjunctivitis sicca: clinical aspects. In: Foster CS, Azar DT, Dohlman CS, editors. *The Cornea (Scientific Foundations and Clinical Practice).* Philadelphia, PA: Lippincott Williams & Wilkins (2005). p. 603–27.

31. Lemp MA, Hamill JR. Factors affecting tear film breakup in normal eyes. *Arch Ophthalmol.* (1973) 89:103–5. doi: 10.1001/archopht.1973.01000040105007

32. Aksoy D, Ortak H, Kurt S, Cevik E, Cevik B. Central corneal thickness and its relationship to Parkinson's disease severity. *Can J Ophthalmol.* (2014) 49:152–6. doi: 10.1016/j.jcjo.2013.12.010

33. Milner MS, Beckman KA, Luchs JI, Allen QB, Awdeh RM, Berdahl J, et al. Dysfunctional tear syndrome: dry eye disease and associated tear film disorders - new strategies for diagnosis and treatment. *Curr Opin Ophthalmol.* (2017) 27:3–47. doi: 10.1097/01.icu.0000512373.81749.b7

34. Holly FJ. Physical chemistry of the normal and disordered tear film. *Transact Ophthalmol Soc United Kingdom (1962).* (1985) 104 (Pt 4):374–80.

35. Agostino R, Bologna M, Dinapoli L, Gregori B, Fabbrini G, Accornero N, et al. Voluntary, spontaneous, and reflex blinking in Parkinson's disease. *Mov Disord.* (2008) 23:669–75. doi: 10.1002/mds.21887

36. Korošec M, Zidar I, Reits D, Evinger C, VanderWerf F. Eyelid movement during blinking in patients with Parkinson's disease. *Mov Disord.* (2006) 21:1248–51. doi: 10.1002/mds.20930

37. Örnek N, Da? E, Örnek K. Corneal sensitivity and tear function in neurodegenerative diseases. *Curr Eye Res.* (2015) 40:423–8. doi: 10.3109/02713683.2014.930154

38. Fitzpatrick E, Hohl N, Silburn P, O'Gorman C, Broadley SA. Case-control study of blink rate in Parkinson's disease under different conditions. *J Neurol.* (2012) 259:739–44. doi: 10.1007/s00415-011-6261-0

39. Murube J, Németh J, Höh H, Kaynak-Hekimhan P, Horwath-Winter J, Agarwal A, et al. The triple classification of dry eye for practical clinical use. *Eur J Ophthalmol.* (2005) 15:660–7. doi: 10.1177/112067210501500602

40. Sayegh RR, Yu Y, Farrar JT, Kuklinski EJ, Shtein RM, Asbell PA, et al. Ocular discomfort and quality of life among patients in the dry eye assessment and management study. *Cornea.* (2021) 40:869–76. doi: 10.1097/ICO.0000000000002580

41. Borm CDJM, Visser F, Werkmann M, De Graaf D, Putz D, Seppi K, et al. Seeing ophthalmologic problems in Parkinson disease: results of a visual impairment questionnaire. *Neurology.* (2020) 94:e1539–47. doi: 10.1212/WNL.0000000000009214

42. Borm CDJM, Werkmann M, De Graaf D, Visser F, Hofer A, Peball M, et al. Undetected ophthalmological disorders in Parkinson's disease. *J Neurol.* (2022) 269:3821–32. doi: 10.1007/s00415-022-11014-0

43. Caudron S, Guerraz M, Eusebio A, Gros JP, Azulay JP, Vaugoyeau M, et al. Evaluation of a visual biofeedback on the postural control in Parkinson's disease. *Neurophysiol Clin.* (2014) 44:77–86. doi: 10.1016/j.neucli.2013.10.134

44. Ivers RQ, Cumming RG, Mitchell P, Attebo K. Visual impairment and falls in older adults: the blue mountains eye study. *J Am Geriatr Soc.* (1998) 46:58–64. doi: 10.1111/j.1532-5415.1998.tb01014.x

45. Wan KH, Chen LJ, Young AL. Depression and anxiety in dry eye disease: a systematic review and meta-analysis. *Eye.* (2016) 30:1558–67. doi: 10.1038/eye.2016.186

46. Timmer MHM, van Beek MHCT, Bloem BR, Esselink RAJ. What a neurologist should know about depression in Parkinson's disease. *Pract Neurol.* (2017) 17:359–68. doi: 10.1136/practneurol-2017-001650

47. Nichols KK, Bacharach J, Holland E, Kislan T, Shettle L, Lunacsek O, et al. Impact of dry eye disease on work productivity, and patients' satisfaction with over-the-counter dry eye treatments. *Investig Ophthalmol Vis Sci.* (2016) 57:2975–82. doi: 10.1167/iovs.16-19419

48. Guo LW, Akpek EK. The negative effects of dry eye disease on quality of life and visual function. *Turk J Med Sci.* (2020) 50:1611–5. doi: 10.3906/sag-2002-143

49. American Academy of Ophthalmology Cornea and External Disease Panel. *Preferred Practice Pattern. Guidelines for Dry Eye Syndrome.* San Francisco, CA: American Academy of Ophthalmology (2013).

50. Montgomery EB, Lieberman A, Singh G, Fries JF, Keller W. Patient education and health promotion can be in Parkinson's disease: a randomized controlled trial. *Am J Med.* (1994) 97:429–35. doi: 10.1016/0002-9343(94)90322-0

51. Simons G, Thompson SBN, Smith Pasqualini MC. An innovative education programme for people with Parkinson's disease and their carers. *Parkinson Relat Disord.* (2006) 12:478–85. doi: 10.1016/j.parkreldis.2006.05.003

52. A'Campo LEI, Wekking EM, Spliethoff-Kamminga NGA, le Cessie S, Roos RAC. The benefits of a standardized patient education program for patients with Parkinson's disease and their caregivers. *Parkinson Relat Disord.* (2010) 16:89–95. doi: 10.1016/j.parkreldis.2009.07.009

53. Macht M, Gerlich C, Ellgring H, Schradi M, Rusiñol ÀB, Crespo M, et al. Patient education in Parkinson's disease: formative evaluation of a standardized programme in seven European countries. *Patient Educ Couns.* (2007) 65:245–52. doi: 10.1016/j.pec.2006.08.005

54. Lindskov S, Westergren A, Hagell PA. controlled trial of an educational programme for people with Parkinson's disease. *J Clin Nurs.* (2007) 16:368–76. doi: 10.1111/j.1365-2702.2007.02076.x

55. Altinors DD, Akça S, Akova YA, Bilezikçi B, Goto E, Dogru M, et al. Smoking associated with damage to the lipid layer of the ocular surface. *Am J Ophthalmol.* (2006) 141:1016–21. doi: 10.1016/j.ajo.2005.12.047

56. Grus FH, Sabuncuo P, Augustin A, Pfeiffer N. Effect of smoking on tear proteins. *Graefe's Arch Clin Exp Ophthalmol.* (2002) 240:889–92. doi: 10.1007/s00417-002-0539-y

57. Lee BS, Kabat AG, Bacharach J, Karpecki P, Luchs J. Managing dry eye disease and facilitating realistic patient expectations: a review and appraisal of current therapies. *Clin Ophthalmol.* (2020) 14:119–26. doi: 10.2147/OPTH.S228838

58. Chang KC, Jeong JH, Kim MK, Wee WR, Lee JH, Jeon BS, et al. The effect of amantadine on corneal endothelium in subjects with Parkinson's disease. *Ophthalmology.* (2010) 117:1214–9. doi: 10.1016/j.ophtha.2009.10.039

59. Prashanth CN, Nagaraju R, Sujatha R. Artificial tear substitutes: which one & when? *J. Evol Med Dental Sci.* (2013) 2:4332–7. doi: 10.14260/jemds/843

60. Davitt WF, Bloomenstein M, Christensen M, Martin AE. Efficacy in patients with dry eye after treatment with a new lubricant eye drop formulation. *J Ocular Pharmacol Ther.* (2010) 26:347–53. doi: 10.1089/jop.2010.0025

61. Baudouin C, Cochener B, Pisella PJ, Girard B, Pouliquen P, Cooper H, et al. Randomized, phase III study comparing osmoprotective carboxymethylcellulose with sodium hyaluronate in dry eye disease. *Eur J Ophthalmol.* (2012) 22:751–61. doi: 10.5301/ejo.5000117

62. Tan QY, Cox NJ, Lim SER, Coutts L, Fraser SDS, Roberts HC, et al. The experiences of treatment burden in people with Parkinson's disease and their caregivers: a systematic review of qualitative studies. *J Parkinsons Dis.* (2021) 11:1597–617. doi: 10.3233/JPD-212612

63. Perry HD, Solomon R, Donnenfeld ED, Perry AR, Wittpenn JR, Greenman HE, et al. Evaluation of topical cyclosporine for the treatment of dry eye disease. *Arch Ophthalmol.* (2008) 126:1046–50. doi: 10.1001/archopht.126.8.1046

64. Rao SN. Topical cyclosporine 0.05% for the prevention of dry eye disease progression. *J Ocular Pharmacol Ther.* (2010) 26:157–63. doi: 10.1089/jop.2009.0091

65. Pflugfelder SC, Maskin SL, Anderson B, Chodosh J, Holland EJ, de Paiva CS, et al. A randomized, double-masked, placebo-controlled, multicenter comparison of loteprednol etabonate ophthalmic suspension, 0.5%, and placebo for treatment of keratoconjunctivitis sicca in patients with delayed tear clearance. *Am J Ophthalmol.* (2004) 138:444–57. doi: 10.1016/j.ajo.2004.04.052

66. Marcet MM, Shtein RM, Bradley EA, Deng SX, Meyer DR, Bilyk JR, et al. Safety and efficacy of lacrimal drainage system plugs for dry eye syndrome a report by the american academy of ophthalmology. *Ophthalmology.* (2015) 122:1681–7. doi: 10.1016/j.ophtha.2015.04.034

67. Best AL, Labetoulle M, and Legrand M, M'garrech M, Barreau E, Rousseau A. Punctal and canalicular plugs: indications, efficacy and safety. *J Francais d'Ophtalmol.* (2019) 42:e95–104. doi: 10.1016/j.jfo.2018.12.003

68. Osaki TH, Sant'Anna AE, Osaki MH. An alternative for permanent punctal occlusion: labial mucous membrane graft in the management of severe dry eye. *Ophthal Plast Reconstr Surg.* (2017) 33:395–96. doi: 10.1097/IOP.0000000000000950

69. Shen G, Qi Q, Ma X. Effect of moisture chamber spectacles on tear functions in dry eye disease. *Optomet Vis Sci.* (2016) 93:158–64. doi: 10.1097/OPX.0000000000000778

70. Valim V, Trevisani VFM, Sousa de Vilela JM, Belfort VS. Current approach to dry eye disease. *Clin Rev Aller Immunol.* (2015) 49:288–97. doi: 10.1007/s12016-014-8438-7

71. Cosar CB, Cohen EJ, Rapuano CJ, Maus M, Penne RP, Flanagan JC, et al. Tarsorrhaphy clinical experience from a cornea practice. *Cornea.* (2001) 20:787–91. doi: 10.1097/00003226-200111000-00002

72. Alexander E, Provost TT. Sjögren's syndrome. Association of cutaneous vasculitis with central nervous system disease. *Arch Dermatol.* (1987) 123:801–10. doi: 10.1001/archderm.1987.01660300123025

73. Alexander E. Central nervous system (CNS) manifestations of primary Sjögren's syndrome: an overview. *Scand J Rheumatol.* (1986) 61(Suppl):161–5.

74. Chang CC, Lin TM, Chang YS, Chen WS, Sheu JJ, Chen YH, et al. Autoimmune rheumatic diseases and the risk of Parkinson disease: a nationwide population-based cohort study in Taiwan. *Ann Med.* (2018) 50:83–90. doi: 10.1080/07853890.2017.1412088

75. Walker RH, Spiera H, Brin MF, Warren Olanow C. Parkinsonism associated with Sjögren's Syndrome: three cases and a review of the literature. *Mov Disord.* (1999) 14:262–8. doi: 10.1002/1531-8257(199903)14:2<262::AID-MDS1011>3.0.CO;2-6

76. Hassin-Baer S, Levy Y, Langevitz P, Nakar S, Ehrenfeld M. Anti-β2-glycoprotein I in Sjogren's syndrome is associated with parkinsonism. *Clin Rheumatol.* (2007) 26:743–7. doi: 10.1007/s10067-006-0398-8

77. Visser LH, Koudstaal PJ, Van De Merweb JP. Hemiparkinsonism in a patient with primary Sjögren's syndrome. A case report and a review of the literature. *Clin Neurol Neurosurg.* (1993) 95:141–5. doi: 10.1016/0303-8467(93)90009-6

78. Nishimura H, Tachibana H, Makiura N, Okuda B, Sugita M. Corticosteroid-responsive parkinsonism associated with primary Sjögren's syndrome. *Clin Neurol Neurosurg.* (1994) 96:327–31. doi: 10.1016/0303-8467(94)90124-4

79. Créange A, Brugieres P, Voisine MC, Degos JD. Primary Sjögren's syndrome presenting as progressive parkinsonism. *Mov Disord.* (1997) 12:121–3. doi: 10.1002/mds.870120124

80. Chaudhuri KR, Titova N, Qamar MA, Mură?an I, Falup-Pecurariu C. The dashboard vitals of Parkinson's: not to be missed yet an unmet need. *J Pers Med.* (2022) 12:1994. doi: 10.3390/jpm12121994

81. Schiffm an RM, Christianson MD, Gordon J, Hirsch JD, Reis BL. Reliability and validity of the ocular surface disease index. *Arch Ophthalmol.* (2000) 118:615–21. doi: 10.1001/archopht.118.5.615

82. Mangione CM, Lee PP, Pitts J, Gutierrez P, Berry S, Hays RD, et al. Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). *Arch Ophthalmol.* (1998) 116:1496–504. doi: 10.1001/archopht.116.11.1496

83. Ngo W, Situ P, Keir N, Korb D, Blackie C, Simpson T, et al. Psychometric properties and validation of the standard patient evaluation of eye dryness questionnaire. *Cornea.* (2013) 32:1204–10. doi: 10.1097/ICO.0b013e318294b0c0

84. Akowuah PK, Adjei-Anang J, Nkansah EK, Fummey J, Osei-Poku K, Boadi P, et al. Comparison of the performance of the dry eye questionnaire (DEQ-5) to the ocular surface disease index in a non-clinical population. *Contact Lens Anterior Eye.* (2022) 45:101441. doi: 10.1016/j.clae.2021.101441

85. Amparo F, Schaumberg DA, Dana R. Comparison of two questionnaires for dry eye symptom assessment: the ocular surface disease index and the symptom assessment in dry eye. *Ophthalmology.* (2015) 122:1498–503. doi: 10.1016/j.ophtha.2015.02.037

86. Schaumberg DA, Gulati A, Mathers WD, Clinch T, Lemp MA, Nelson JD, et al. Development and validation of a short global dry eye symptom index. *Ocular Surf.* (2007) 5:50–7. doi: 10.1016/S1542-0124(12)70053-8

87. Sakane Y, Yamaguchi M, Yokoi N, Uchino M, Dogru M, Oishi T, et al. Development and validation of the dry eye-related quality-of-life score questionnaire. *JAMA Ophthalmol.* (2013) 131:1331–8. doi: 10.1001/jamaophthalmol.2013.4503

88. Gothwal VK, Pesudovs K, Wright TA, McMonnies CW. McMonnies questionnaire: enhancing screening for dry eye syndromes with rasch analysis. *Investig Ophthalmol Vis Sci.* (2010) 51:1401–7. doi: 10.1167/iovs.09-4180

89. Grubbs J, Huynh K, Tolleson-Rinehart S, Weaver MA, Williamson J, Lefebvre C, et al. Instrument development of the UNC dry eye management scale. *Cornea.* (2014) 33:1186–92. doi: 10.1097/ICO.0000000000000243

90. Green-Church KB, Butovich I, Willcox M, Borchman D, Paulsen F, Barabino S, et al. The international workshop on meibomian gland dysfunction: report of the subcommittee on tear film lipids and lipid protein interactions in health and disease. *Invest Ophthalmol Vis Sci.* (2011) 52:1979–93. doi: 10.1167/iovs.10-6997d

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Effects of white matter hyperintensity on cognitive function in PD patients: a meta-analysis

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Background: Parkinson's disease (PD) is often accompanied by cognitive dysfunction, which imposes a heavy burden on patients, their families, and society. Early identification and intervention are particularly important, but reliable biomarkers for identifying PD-related cognitive impairment at an early stage are currently lacking. Although numerous clinical studies have investigated the association between brain white matter hyperintensity (WMH) and cognitive decline, the findings regarding the relationships between WMH and cognitive dysfunction in PD patients have been inconsistent. Therefore, this study aims to conduct a meta-analysis of the effect of WMH on PD cognitive function.

Methods: This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines. We systematically searched relevant literature from databases such as PubMed, Web of Science, EMBASE, CNKI, and CBM. The retrieval time was limited to database records created up until December 31, 2022. Additionally, we manually retrieved references for full-text reading. Statistical data analysis was performed using RevMan 5.3 and Stata 15.0 software.

Results: This study encompassed 23 individual studies and involved 2,429 patients with PD. The group of PD with mild cognitive impairment (PD-MCI) exhibited a significantly higher overall level of WMH than the group of PD with normal cognitive function (PD-NC) (SMD = 0.37, 95% CI: 0.21–0.52, $p < 0.01$). This finding was consistent across subgroup analyses based on different ethnicities (Asian or Caucasian), WMH assessment methods (visual rating scale or volumetry), and age matching. In addition to the overall differences in WMH load between the PD-MCI and PD-NC groups, the study found that specific brain regions, including periventricular white matter hyperintensity (PVH) and deep white matter hyperintensity (DWMH), had significantly higher WMH load in the PD-MCI group compared to the PD-NC group. The study also conducted a meta-analysis of WMH load data for PD with dementia (PDD) and PD without dementia (PDND), revealing that the overall WMH load in the PDD group was significantly higher than that in the PDND group (SMD = 0.98, 95% CI: 0.56–1.41, $p < 0.01$). This finding was consistent across subgroup analyses based on different ethnicities and age matching. Moreover, regarding specific brain regions (PVH or DWMH), the study found that the PDD group had significantly higher WMH load than the PDND group ($p < 0.01$).

Conclusion: WMH was associated with PD cognitive dysfunction. The early appearance of WMH may indicate PD with MCI.

KEYWORDS

Parkinson's disease, white matter hyperintensity, cognitive impairment, dementia, meta-analysis

Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder after Alzheimer's disease (AD). With the aging of the population, its incidence and prevalence have been increasing in recent years. Epidemiological studies have shown that PD affects 0.3% of the general population in developed countries, 1.0% of people aged over 60 years, and 3.0% of those over 80 years old (1). Initially, PD was characterized as a movement disorder with core motor symptoms such as resting tremors, bradykinesia, postural instability, and stiffness in the neck, trunk, and limbs. However, it is now recognized that PD also presents with non-motor symptoms (NMS) such as olfactory dysfunction, constipation, autonomic dysfunction, sleep disorders, cognitive impairment, anxiety, and depression (2). Clinical studies indicate that NMS may manifest several years or even decades before the onset of motor symptoms, which may have important diagnostic implications (3).

Cognitive dysfunction is a NMS in PD, encompassing both PD with mild cognitive impairment (PD-MCI) and PD with dementia (PDD). Clinical studies indicate that approximately 30% of newly diagnosed PD patients develop PD-MCI (4), while PDD affects roughly 80% of PD patients who have had the disease for over 10 years (5). Previous research has identified various risk factors for cognitive dysfunction in PD, including male gender, advanced age, higher Hoehn and Yahr scale stage, severity of motor symptoms, speech impairment, postural instability/gait difficulty subtype, depression, hallucinations, and educational level (6).

PD-MCI is a clinical syndrome characterized by cognitive and functional deficits that exhibit heterogeneity. It represents an intermediate stage between normal cognition and dementia, and can involve one or more cognitive domains. Clinical studies indicate that PD-MCI is an early stage of cognitive decline in PD and a significant risk factor for the progression of PD to PDD (7).

As PDD typically develops within an already established diagnosis of PD, detecting and diagnosing PD before the onset of dementia symptoms is crucial. PDD has a subtle onset and slow progression, primarily affecting attention, executive function, visual–spatial abilities, memory, and other cognitive domains. Executive dysfunction is particularly prominent and often accompanied by hallucinations, delusions, apathy, and emotional or personality changes (8). Compared with AD patients, there are some differences in the degree and features of cognitive deficits in individual cognitive domains: memory impairment is more pronounced in AD, while executive dysfunction is more common in PDD. Several risk factors have been identified for PDD, including age, time of diagnosis, akinetic-rigid subtype, disease severity, verbal fluency impairments, genetic factors, low education level, and postural instability (9).

PD-MCI can impact the lives of PD patients by diminishing their ability to communicate, access social support, and perform daily activities, which can be especially daunting for young patients facing societal, familial, and occupational pressures. In comparison, PDD has an even greater impact on the lives of PD patients (10). Hence, early and precise identification and diagnosis of cognitive dysfunction in PD are critical for reducing harm and enhancing patient outcomes. However, there is currently a lack of biological markers to accurately detect cognitive dysfunction in PD in clinical practice.

White matter hyperintensity (WMH), also known as leukoaraiosis (LA), is typically observed as merged or patchy areas of high-signal intensity on T2-weighted imaging (T2 WI) or fluid-attenuated inversion recovery (FLAIR) sequences in magnetic resonance imaging (MRI) scans of older adults (11). Generally, WMH is considered an imaging marker of white matter damage that increases with age, and the detection rate of WMH in Asians is generally significantly higher than that in Caucasians (12). In neuroimaging, WMH is typically classified into two subtypes: periventricular white matter hyperintensity (PVH) and deep white matter hyperintensity (DWMH). Research has found that WMH reflects chronic hypoperfusion of the brain's white matter, indicating axonal injury, myelin sheath damage, and gliosis. The core pathophysiological mechanism involves vascular damage caused by ischemia and hypoxia (13–16). Related studies have also found that WMH is involved in the entire process of cognitive impairment (17–22). In an 8-year cohort study, Kuller et al. found that individuals with significant WMH had a significantly increased risk of developing AD (HR = 1.5, 95%CI: 1.17–1.99) (23). Silbert et al. found that compared with baseline WMH load, WMH progression may be the most crucial risk factor for predicting cognitive dysfunction (19). Clinical studies have also found that WMH in different areas may have varying effects on cognitive function. Smith et al. found that executive dysfunction and memory were associated with the specific location of WMH rather than the overall volume of WMH (24). Subsequently, Sunwoo et al. found that WMH load (OR: 1.616, $P < 0.01$) and Cholinergic Pathways Hyperintensities Scale (CHIPS) score (OR: 1.084, $P < 0.01$) were related to the outcome of PDD (25). Lee et al. found that WMH was an independent factor related to PD cognitive dysfunction, regardless of age, gender, disease duration, severity, and cerebrovascular risk factors (26). However, Lee et al. (27) found that baseline WMH load was not related to dementia but longitudinal follow-up showed that WMH could predict the occurrence of PDD. In a cohort study, Hanning et al. (28) found that total WMH load was not related to the cognitive function of newly diagnosed PD patients. Overall, previous literature reports indicate significant differences in the relationship between WMH and PD cognitive impairment.

In recent years, there has been an increasing number of studies exploring the impact of WMH on cognitive impairment in

PD. Therefore, this study aims to conduct a systematic review and meta-analysis of literature published domestically and internationally in recent years regarding the effect of WMH on cognitive impairment in PD. The objective is to provide further clarification on the impact of WMH on cognitive function in PD, explore imaging markers for early identification of cognitive dysfunction in PD, and offer new evidence for early recognition and intervention of cognitive dysfunction in clinical practice.

Methods

Study design

This study adheres to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for epidemiological observational studies and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations for conducting systematic reviews and meta-analyses.

Study search and selection

This study systematically searched relevant literature in online databases, including PubMed, Web of Science, EMBASE, China National Knowledge Infrastructure (CNKI), and Chinese Biomedical Literature Database (CBM). The search was limited to the period from each database's establishment to December 31, 2022. Additionally, manual searches were conducted on the reference lists of full-text articles. Search terms used in this study mainly originated from subject headings and free words. The following search terms were utilized:

"Parkinson Disease," "Parkinson's Disease," "Parkinsonism," "paralysis agitans," "white matter hyperintensities," "white matter hyperintensity," "white matter lesion," "white matter lesions," "small vessel disease," "leukoaraiosis," "leukoencephalopathy," "leukoencephalopathies," "cognitive dysfunction," "cognitive dysfunctions," "cognitive decline," "cognitive declines," "cognitive impairment," "cognitive impairments," "neurocognitive disorder," "neurocognitive disorders," "mental deterioration," and "dementia."

The included studies met the following criteria: (1) PD patients included in this study were diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank Criteria from 1992 and/or the clinical diagnostic criteria for PD established by the Movement Disorders and Parkinson's Disease Group of the Chinese Medical Association Neurology Branch in 2016 and/or the Parkinson's disease diagnostic criteria by the Movement Disorder Society (MDS) in 2015. (2) The study provided relevant data on the cognitive function status grouping of PD patients (cognitive impairment group and non-cognitive impairment group) and the identification and quantification of WMH severity based on head MRI. (3) The study type was limited to cohort studies or case–control studies. (4) Studies that could provide mean ± standard deviation data suitable for meta-analysis were included. (5) The publication language was limited to Chinese or English.

The exclusion criteria were as follows: (1) PD patients with a history of or coexisting central nervous system diseases, peripheral nerve diseases that affect movement and/or autonomic function, and psychiatric illnesses unrelated to Parkinson's disease were excluded from this study. (2) Animal experiments were also excluded from this study. (3) Literature such as case reports, reviews, and commentaries that could not provide mean ± standard deviation data suitable for this study were excluded.

Investigators WZ and BC independently screened titles and abstracts of articles and determined whether to search for further articles based on the inclusion and exclusion criteria. Articles that could not be excluded were retrieved, and their full text was reviewed by TZ and YC. For articles with insufficient reported data for analysis, we contacted the corresponding author *via* email to request additional data. Any disagreements were resolved through discussions between the reviewers, and third reviewer SZ was consulted when necessary.

Data extraction

Two reviewers independently extracted relevant data, including the first author, publication year, research location, sample size, race, age, gender composition ratio, PD disease duration, Hoehn-Yahr stage, revised Unified Parkinson's Disease Rating Scale part III (UPDRS III), Montreal Cognitive Assessment (MoCA) or Mini-Mental State Examination (MMSE) scores, WMH distribution location, WMH evaluation method, and mean ± standard deviation data used for meta-analysis.

Quality assessment

The quality of the included literature was evaluated using the Newcastle-Ottawa Scale (NOS) (29), which consists of eight items and uses a semi-quantitative star system to assess the quality of the literature, with a maximum score of nine stars. The items include selection of study groups, comparability, and exposure or outcome evaluation. Studies with an NOS score of 5 or higher are considered to be of high quality (30). Additionally, Egger's tests were performed using Stata version 15.0 to quantitatively analyze potential publication bias.

Data synthesis and statistical analysis

RevMan 5.3 software was used for statistical analysis in this study. Continuous variables were represented using the weighted mean difference (MD) or standardized mean difference (SMD) and their corresponding 95% confidence intervals (CI). If the same method was used to assess WMH and cognitive function across studies, MD and its corresponding 95% CI were used for result analysis; otherwise, SMD and its corresponding 95% CI were used. The combined MD or SMD and their 95% CIs were calculated using either a random effects model or fixed effects model, and forest plots were generated to present individual studies and summary data. Heterogeneity between studies was assessed using the chi-square test and the I^2 statistic, with significant heterogeneity being considered when $p < 0.1$ for the chi-square test or $I^2 > 50\%$ (31–33). A random effects model was used for statistical analysis if significant heterogeneity was present; otherwise, a fixed effects model was employed (31–33). Sensitivity

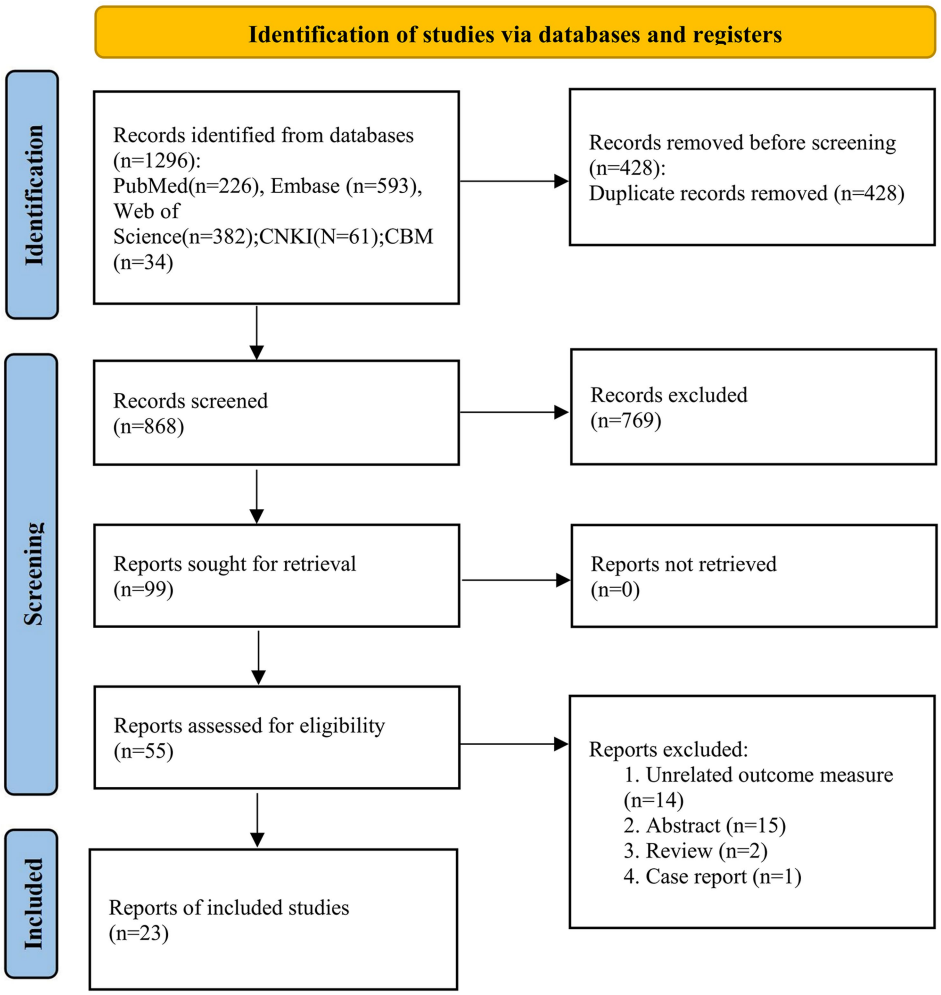

FIGURE 1
PRISMA search strategy flow diagram of studies selection process.

analyses were performed by omitting one study at a time to evaluate the robustness of the results.

Results

Search results

Using the established retrieval strategy and selected online databases, a total of 1,296 literature records were obtained. Through manual deduplication combined with literature management software, we reviewed and organized the titles and abstracts of 868 literature records and retrieved and read the full text of 99 articles. Finally, 23 studies were included in the meta-analysis. The literature search process is shown in Figure 1.

Study characteristics

This study included a total of 23 relevant studies involving 2,429 patients with PD. The publication dates of the included studies ranged from February 2006 to February 2021. Among them, 17 studies compared the severity of WMH between PD-MCI and PD-NC, while 7 studies compared the WMH status between PDD and PD without dementia (PDND). Only one study (34) simultaneously compared the WMH status between PD-MCI and PD-NC groups, as well as between PDD and PDND groups. The largest study enrolled 192 PD patients, while the smallest study enrolled 28. Of the included studies, 14 were from Asia, 8 were from Europe, and 1 was from the Americas. Except for two studies (35, 36), all included studies provided information on the course of PD. The evaluation of WMH was mainly performed through visual assessment or volumetric analysis of MRI scans of PD patients, with corresponding scale assessment data provided. Among them, 15 studies used visual assessment, 7 studies used volumetric analysis, and only one study (37) used both visual and volumetric assessment. The grouping of PD patients based on the degree of cognitive impairment was mainly determined by MMSE scores and/or MoCA scale. However, three studies did not use MMSE or MoCA to evaluate the degree of cognitive impairment in PD patients. One study (34) assessed the degree of cognitive impairment using various tests such as the Rey Auditory Verbal Learning Test (RAVLT), the Verbal Fluency Test (VFT), the Stroop Color-Word Test (SCWT), the

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TABLE 1 Basic characteristics and quality assessment of the included studies in PD-NC and PD-MCI groups.

First author/time	Age (years) N/M	Sample size N/M	Male (%) N/M	Country/Ethnicity	Duration of PD (years) N/M	UPDRS-III N/M	Location of WMH	WMH assessment	H-Y N/M	NOS
Dalaker et al. (39)	65.5 ± 9.2/ 69.4 ± 7.8	133/30	60.2%/63.3%	America/Caucasian	27.8 ± 19.7[a]/26.4 ± 20.8[a]	21.4 ± 9.9/23.7 ± 11.1	T	Volumetric	1.8 ± 0.6/2.0 ± 0.5	8
Kim et al. (38)	63.4 ± 12.0/70.0 ± 6.8	25/48	56.0%/33.3%	Korea/Asian	1.8 ± 0.8/1.9 ± 0.8	NA	T	Visual	1.4 ± 0.5/1.7 ± 0.8	5
Shin et al. (40)	66.6 ± 6.4/69.5 ± 6.9	44/87	40.9%/39.1%	Korea/Asian	2.2 ± 2.03/3.1 ± 3.06	17.9 ± 9.9/19.0 ± 9.3	T	Visual	NA	8
Kandiah et al. (41)	63.3 ± 7.5/68.9 ± 6.1	67/24	70.15%/75.00%	Singapore/Asian	5.3 ± 4.2/4.9 ± 2.6	NA	T/P/D	Volumetric	1.9 ± 0.3/1.8 ± 0.8	8
Wang et al. (42)	63.0 ± 8.0/65.0 ± 8.0	23/23	65.2%/47.80%	China/Asian	2.3 ± 1.7/3.1 ± 2.6	26 ± 12/32 ± 13	T/F/Pa/O/Te/D/B/I	Visual	1.9 ± 0.6/2.1 ± 0.7	7
Ham et al. (35)	69.0 ± 6.1/70.3 ± 8.1	41/46	36.6%/54.30%	Korea/Asian	NA	22.9 ± 9.4/29.4 ± 10.9	T	Visual	NA	8
Amboni et al. (43)	65.8 ± 6.5/65.2 ± 8.7	21/21	66.7%/85.70%	Italy/Caucasian	5.9 ± 2.6/6.6 ± 3.7	13.1 ± 5.3/14.3 ± 8.5	T	Volumetric	1.5 ± 0.6/1.5 ± 0.4	8
Baggio et al. (44)	64.0 ± 9.8/66.1 ± 12.2	43/22	53.5%/63.60%	Spain/Caucasian	10.8 ± 5.1/8.8 ± 4.0	14.1 ± 7.5/18.2 ± 8.7	T	Volumetric	NA	8
Mak et al. (45)	63.4 ± 7.6/ 69.4 ± 6.4	65/25	72.3%/76.00%	Singapore/Asian	5.4 ± 4.3/5.0 ± 2.7	17.5 ± 7.0/20.0 ± 8.4	T/P/D	Volumetric	1.9 ± 0.4/1.8 ± 0.4	8

[a]This item is measured in months.

Trail Making Test Part B (TMT-B), the Raven's Colored Progressive Matrices (RCPM), the Clock Drawing Test, and the Token Test. Another study (38) utilized the Korean version of MMSE, the Clinical Dementia Rating (CDR) scale, and the Clinical Dementia Rating sum of boxes (CDR-SB) to evaluate the degree of cognitive impairment in PD patients. Finally, one study (37) employed MMSE scores and the Mattis Dementia Rating Scale to evaluate the severity of cognitive impairment, but no MMSE-related data were found in the latter two studies. All of the included studies were assessed as high-quality studies according to the NOS. The basic characteristics of the included studies and the results of quality assessment are shown in Tables 1–3.

Quality assessment

The NOS scores of the included studies ranged from 5 to 8, with no study being assessed as low quality. The methodological quality of the included meta-analysis studies is detailed in Tables 1–3. The Egger test using Stata 15 showed no evidence of publication bias.

Effects of total WMH in PD-MCI versus PD-NC

Data comparing the total WMH load between PD-MCI and PD-NC groups were available in 17 studies (28, 34, 35, 37–46, 48–50), which included a total of 1656 PD patients. Due to high heterogeneity (32), a random-effects model was used for statistical analysis. The meta-analysis results showed that the overall WMH load in the PD-MCI group was significantly higher than that in the PD-NC group (SMD = 0.37, 95% CI: 0.21–0.52, $p < 0.01$), as presented in Figure 2.

Subgroup analyses were performed based on relevant factors of interest in clinical practice, such as different WMH assessment methods (visual rating scale and volumetric analysis), PD patients' belonging to different ethnic groups (Asian or Caucasian) and whether they were age-matched. The subgroup analyses revealed that: (1) both visual rating scale-based assessment (SMD = 0.39, 95% CI: 0.17–0.61, $p < 0.01$) and volumetric analysis-based assessment (SMD = 0.35, 95% CI: 0.12–0.59, $p < 0.01$) showed significant differences in WMH load between PD-MCI and PD-NC groups, as presented in Figure 3; (2) the WMH load in both Asian (SMD = 0.47, 95% CI: 0.21–0.73, $p < 0.01$) and Caucasian (SMD = 0.26, 95% CI: 0.10–0.43, $p < 0.01$) PD-MCI groups was significantly higher than that in the PD-NC group, as shown in Figure 4; (3) additionally, in the age-matched subgroup (SMD = 0.26, 95% CI: 0.05–0.48, $p = 0.02$) and the age-unmatched subgroup (SMD = 0.46, 95% CI: 0.24–0.69, $p < 0.01$), the WMH load in the PD-MCI group was significantly higher than that in the PD-NC group, as shown in Figure 5.

Effects of PVH in PD-MCI versus PD-NC

This study included five studies (41, 45, 47, 49, 50) that compared the PVH load between the PD-MCI and PD-NC groups, with a total of 503 PD patients. The heterogeneity test suggested high heterogeneity; therefore, a random-effects model was used for data analysis. The results indicated that the PVH load in the PD-MCI group was significantly higher than that in the PD-NC group

TABLE 2 Basic features and quality evaluation of included studies in PD-NC and PD-MCI groups.

First author/ time	Age (years) N/M	Sample size N/M	Male (%) N/M	Country/ Ethnicity	Duration of PD (years) N/M	UPDRS-III N/M	Location of WMH	WMH assessment	H-Y N/M	NOS
Oh et al. (46)	62.5 ± 9.4/68.8 ± 6.6	53/76	50.9%/42.10%	Korea/Asian	1.9 ± 1.8/ 1.7 ± 1.6	NA	T	Visual	1.5 ± 0.7/1.7 ± 0.6	7
Li et al. (47)	63.45 ± 7.65/64.28 ± 8.05	45/43	53.33%/51.16	China/Asian	2.85 ± 1.38/ 3.46 ± 2.25	25.85 ± 10.57/33.65 ± 12.46	P/D/B/I	Visual	1.80 ± 0.50/2.27 ± 0.65	8
Dunet et al. (37)	78.1 ± 6.1/81.8 ± 3.8	15/13	67%/54%	Switzerland, France/ Caucasian	5.7 ± 3.6/ 6.5 ± 5.1	NA	T	Visual/Volumetric	NA	6
Stojkovic et al. (48)	61.5 ± 8.1/65.6 ± 7.9	46/61	65.2%/64%	Italy/Caucasian	7.2 ± 5.4/ 8.9 ± 5.3	36.5 ± 13.6/44.5 ± 11.9	T	Volumetric	2.1 ± 0.9/2.4 ± 0.8	8
Hanning et al. (28)	64.0 ± 9.0 63.0 ± 10.0	29/79	59%/69%	Germany/ Caucasian	NA	14 (8; 22)/18 (14;28)		Visual	1.5 (1;2)/2 (1.3;2.5)	6
Huang et al. (49)	61.3 ± 9.5/65.4 ± 7.8	81/94	58.0%/55.3%	Singapore/ Asian	14.85 ± 9.05[a]/10.97 ± 7.29[a]	17.3 ± 7.5/25.1 ± 11.1	T/P	Volumetric	1.7 ± 0.4/1.8 ± 0.4	8
Li et al. (50)	60.4 ± 3.3/60.2 ± 3.0	30/29	56.7%/58.6%	China/Asian	2.5 ± 1.0/5.7 ± 1.1	10.3 ± 1.9/21.6 ± 2.5	P/D /T/O/ Te/F/B/I	Visual	1.3 ± 0.3/2.2 ± 0.2	7
Nicoletti et al. (34)	64.4 ± 10.4/67.5 ± 7.4	84/55	61.9%/63.6%	Italy/Caucasian	3.0 ± 2.9/3.0 ± 2.7	25.4 ± 14.5/27.4 ± 11.9	T	Visual	1.9 ± 0.6/2.2 ± 0.7	8

NA, not available; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; H-Y staging, Hoehn and Yahr staging; NOS, Newcastle-Ottawa Scale; N, PD-NC; M, PD-MCI; T, Total WMH (White matter hyperintensity); D, Deep; P, Periventricular; I, Infratentorial; B, Basal ganglia; O, Occipital lobe; Te, Temporal lobe; Pa, Parietal lobe; F, Frontal lobe; The data is presented as mean ± standard deviation or percentage; a, This item is measured in months; b, Data is presented as median (first quartile; third quartile).

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TABLE 3 Basic characteristics and quality assessment of the included studies in PDND and PDD groups.

First author/ time	Age (years) N/D	Sample size N/D	Male (%) N/D	Country/ Ethnicity	Duration of PD (years) N/D	UPDRS-III N/D	Location of WMH	WMH Assessment	H-Y N/D	NOS
Beyer et al. (51)	71.3/ 73.9	19/16	52.6%/ 62.50%	Norway/ Caucasian	12.7 ± 6.4/12.5 ± 7.4	27.2 ± 13.1/42.3 ± 12.4	T, P, F、Pa、O、DW、B、I	Visual	2.3 ± 0.6/3.1 ± 0.6	8
Daida et al. (52)	62.2 ± 10.3/ 70.7 ± 9.0	103/21	38.8%/ 81.9%	Japan/Asian	11.1 ± 6.2/9.5 ± 6.3	NA	T、P、DW	Visual	2.8 ± 0.8/3.6 ± 0.9	8
Lee et al. (26)	65.5 ± 6.5/ 70.2 ± 7.0	11/35	54.5%/ 31.40%	Korea/ Asian	1.4 ± 1.06/1.9 ± 1.7	8.5 ± 7.1/22.5 ± 12.7	T、P、DW、I、B、	Visual	1.5 ± 0.7/2.2 ± 0.9	7
Joki et al. (36)	74.5 ± 5.5/ 75.7 ± 6.2	50/50	52%/ 64%	Japan/Asian	NA	NA	T、P、DW	Visual	NA	8
Sławek et al. (53)	61.9 ± 9.1/ 67.9 ± 8.7	135/57	45.9%/ 50.9%	Poland/ Caucasian	5.9 ± 4.6/8.7 ± 6.3	29.6 ± 15.3/ 42.9 ± 18.9	T、P、DW	Visual	2.0 ± 0.7/2.4 ± 0.7	8
Nicoletti et al. (34)	65.3 ± 9.5/	121/18	66.7% /66.7%	Italy/Caucasian	2.9 ± 2.8/3.4 ± 2.8	25.1 ± 12.7/33.1 ± 16.5	T	Visual	2.1 ± 0.7/1.9 ± 0.6	8
Tanaka et al. (54)	62.2 ± 10.2/71.6 ± 8.4	27/110	40.0%/ 70.40%	Japan/Asian	11.1 ± 6.1/10.1 ± 6.7	NA	P、DW	Visual	2.8 ± 0.8/3.7 ± 0.8	6

NA, not available; UPDRS-III, Unified Parkinson's Disease Rating Scale part III; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; HY, Hoehn and Yahr scale stage; NOS, Newcastle-Ottawa Scale; N, PDND; D, PDD; T, total WMH; DW, deep matter; P, periventricular matter; I, infratentorial matter; B, basal ganglia; O, occipital lobe; Te, temporal lobe; Pa, parietal lobe; F, frontal lobe. The data is presented as mean ± standard deviation or percentage.

(SMD = 0.47, 95% CI: 0.10–0.84, $p = 0.01$), as demonstrated in Figure 6.

Effects of DWMH in PD-MCI versus PD-NC

A total of five studies (41, 45, 47, 50) met the inclusion criteria and provided relevant data for comparing the DWMH load between the PD-MCI and PD-NC groups, with a total of 374 PD patients. The results of the random-effects model analysis revealed that the DWMH load in the PD-MCI group was significantly higher than that in the PD-NC group (SMD = 0.57, 95% CI: 0.28–0.86, P<0.01), as presented in Figure 7.

Effects of total WMH in PDD versus PDND

This study included a total of six studies (26, 34, 36, 42, 51–53) that provided data for comparing the total WMH load between the PDD and PDND groups, with a total of 636 PD patients. It is noteworthy that all six studies used visual rating scales to evaluate the severity of WMH. The results of the random-effects model analysis revealed that the overall WMH load in the PDD group was significantly higher than that in the PDND group (SMD = 0.98, 95% CI: 0.56–1.41, $p < 0.01$), as demonstrated in Figure 8.

Further subgroup analyses based on whether different races and ages were matched found that: (1) among Asians (SMD = 1.32, 95%CI: 0.82–1.81, p < 0.01) and Caucasians (SMD = 0.58, 95% CI: 0.32–0.84, p < 0.01), the overall WMH load in the PDD group was significantly higher than that in the PDND group, as presented in Figure 9; (2) in the age-matched group, the overall WMH load in the PDD group was significantly higher than that in the PDND group (SMD = 0.93, 95% CI: 0.60–1.27, $p < 0.01$); however, there was no significant difference in the total WMH load between the PDD and PDND groups in the non-age-matched group (SMD = 1.12, 95% CI: −0.14-2.38, $p = 0.08$), as shown in Figure 10.

Effects of PVH in PDD versus PDND

This study included a total of six studies (26, 36, 51–54) that provided relevant data for comparing the PVH load between the PDD and PDND groups, with a total of 375 PD patients. The results of the random-effects model analysis revealed that the PVH load in the PDD group was significantly higher than that in the PDND group (SMD = 0.83, 95% CI: 0.48–1.19, $p < 0.01$), as demonstrated in Figure 11.

Effects of DWMH in PDD versus PDND

A total of five studies (26, 36, 52–54) reported relevant data for comparing the DWMH load between the PDD and PDND groups. The heterogeneity test showed no significant heterogeneity; therefore, a fixed-effects model was used for statistical analysis. The results revealed no significant difference in DWMH load between the PDD and PDND groups (SMD = 0.55, 95% CI: 0.36–0.73, $p < 0.01$), as presented in Figure 12.

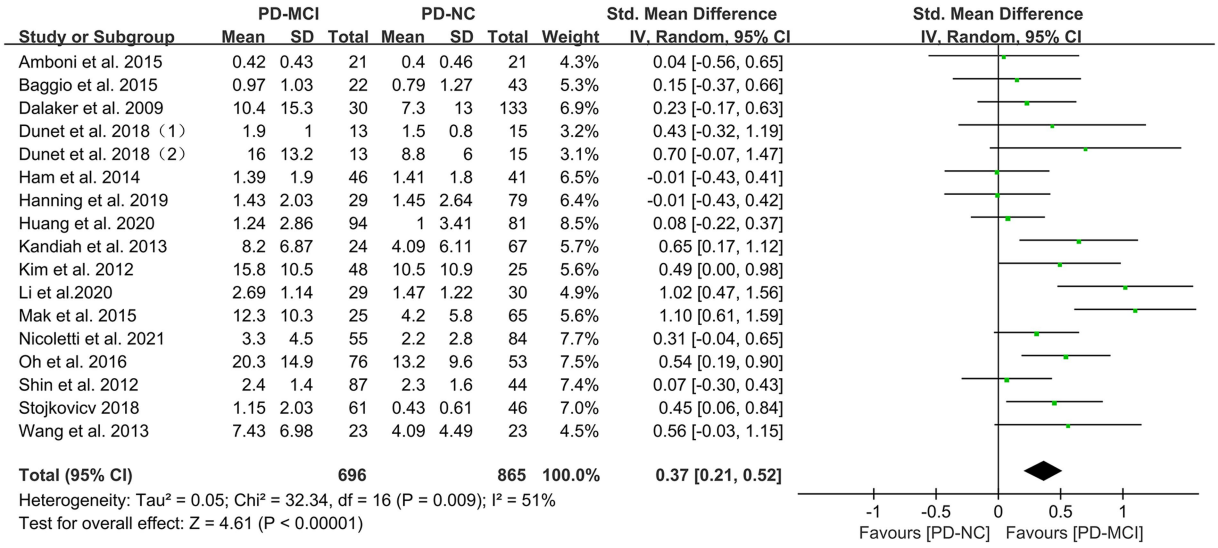

FIGURE 2
Forest plot and meta-analysis of total WMH between PD-MCI and PD-NC.

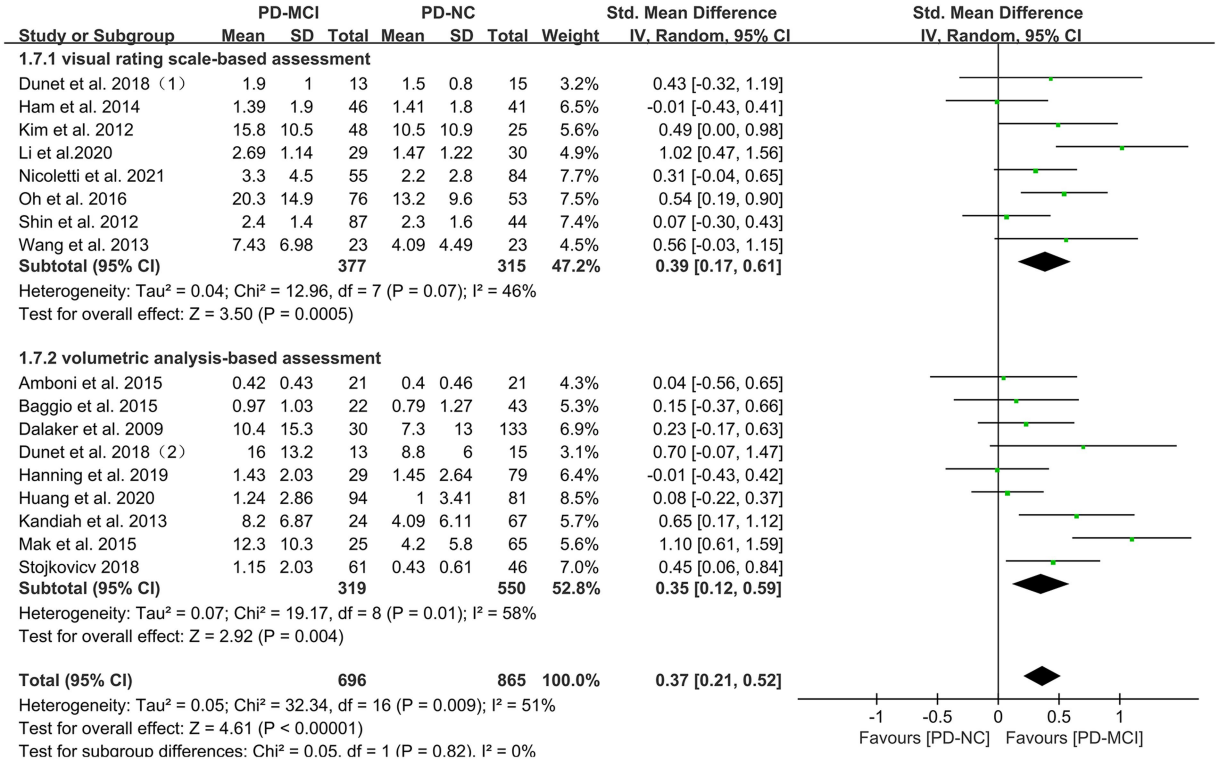

FIGURE 3
Forest plot and meta-analysis of WMH between PD-MCI and PD-NC: a subgroup analysis based on different assessment modalities.

Sensitivity analysis

This study conducted sensitivity analyses for all explored outcome measures, and the results demonstrated that the study findings were stable and reliable.

Discussion

Our research systematically retrieved literature on the relationship between WMH and cognitive impairment in PD. We conducted a meta-analysis to investigate the impact of WMH load on cognitive

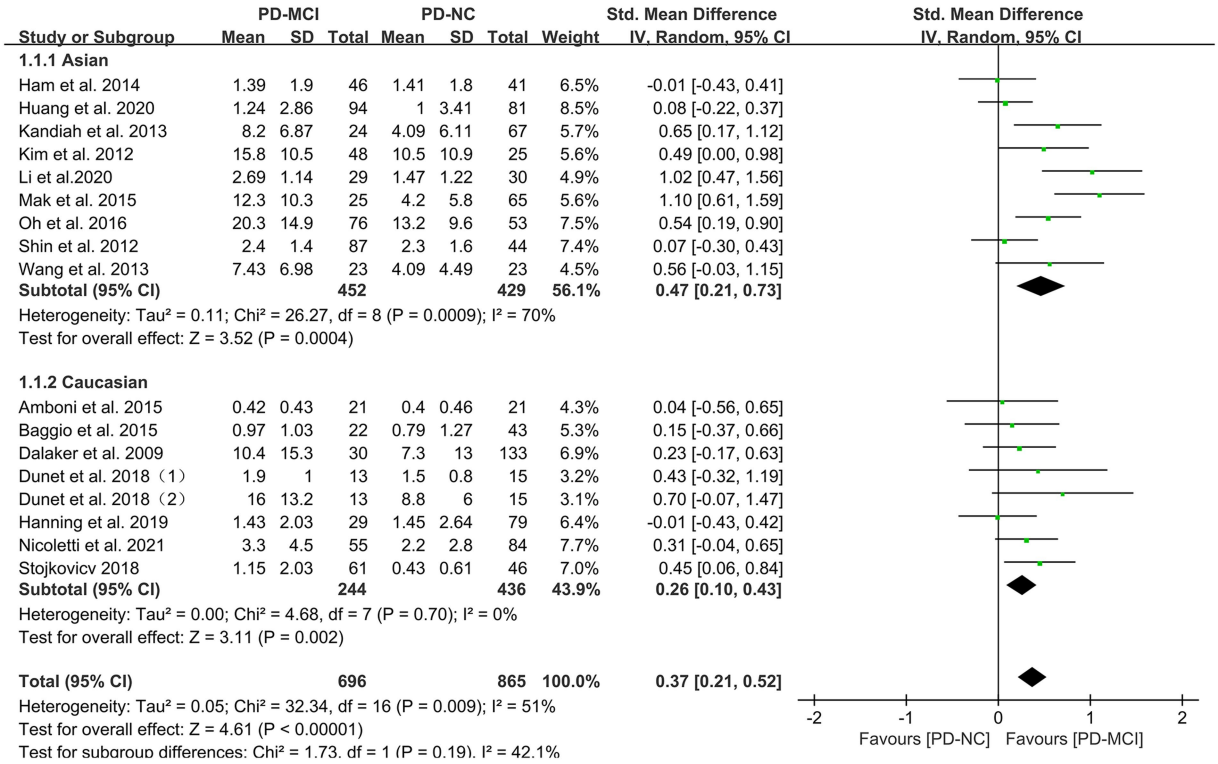

FIGURE 4
Forest plot and meta-analysis of WMH between PD-MCI and PD-NC: a subgroup analysis based on different ethnicities.

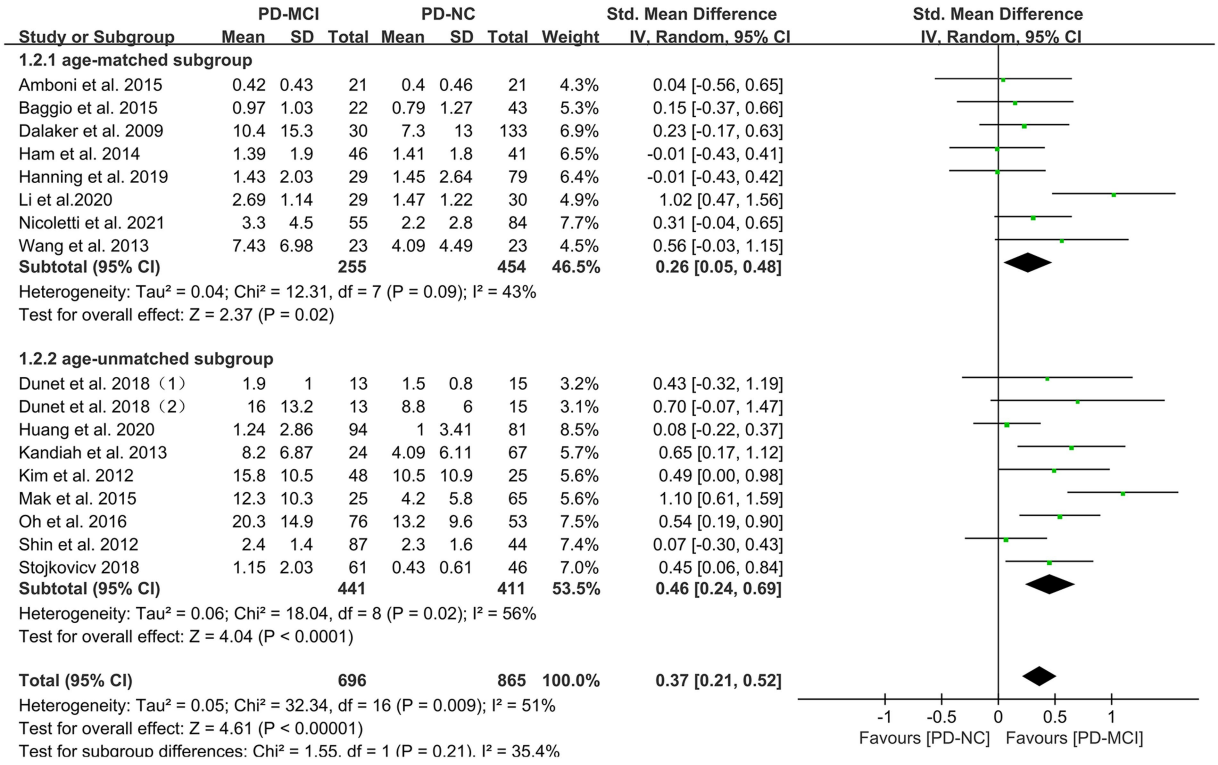

FIGURE 5
Forest plot and meta-analysis of WMH between PD-MCI and PD-NC: a subgroup analysis based on age.

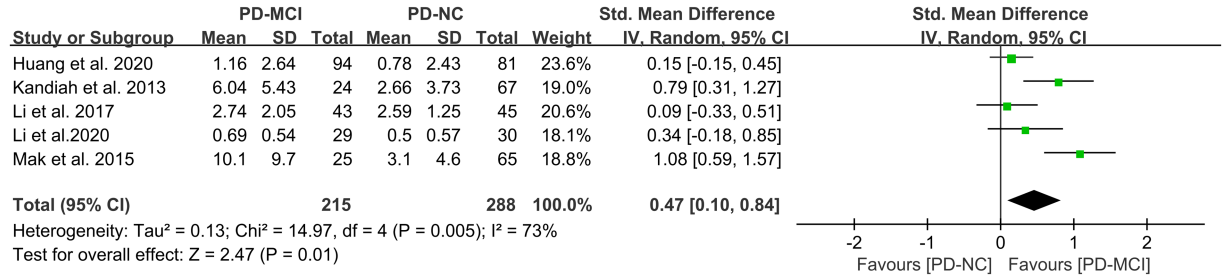

FIGURE 6
Forest plot and meta-analysis of PVH between PD-MCI and PD-NC.

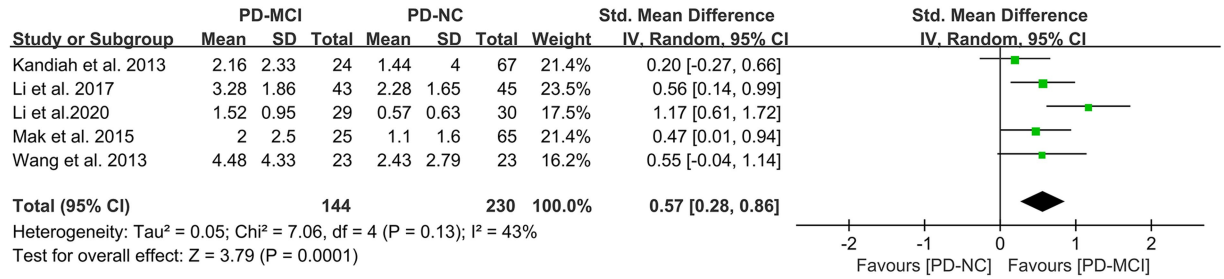

FIGURE 7
Forest plot and meta-analysis of DWMH between PD-MCI and PD-NC.

function in PD, which is of clinical significance for doctors. A total of 19 case–control studies and 4 longitudinal cohort studies with 2,429 participants were included. The study found that the severity of WMH may play an important role in the cognitive decline of PD, even in the early stages of cognitive impairment, and may serve as an imaging biomarker for early cognitive dysfunction in PD patients.

In a cross-sectional study, Dalaker et al. (39) compared the total load of WMH in 163 newly diagnosed untreated PD patients and 102 age-matched healthy controls but found no significant difference in the overall WMH load between the two groups. Subgroup analysis of PD-MCI and PD-NC did not reveal any significant differences between the two groups. Similarly, Baggio et al. (44) and Amboin et al. (43) also did not find a relationship between WMH and cognitive impairment in PD. However, Kandiah et al. (41) found that the overall WMH load in PD-MCI patients was significantly higher than in PD-NC patients; even after adjusting for age and vascular risk factors such as diabetes, hypertension, hyperlipidemia, smoking, etc., the overall WMH load in the PD-MCI group remained significantly increased. Mak et al. (45) also reported similar findings. However, a recent longitudinal study by Nicoletti et al. (34) found that baseline WMH load was not associated with the risk of PD-MCI, and severe baseline WMH was the strongest predictor of PDD. In our study, we compared the WMH load between the PD-NC and PD-MCI groups and found that the WMH load in the PD-MCI group was significantly higher than in the PD-NC group, suggesting that WMH may play an important role in early cognitive impairment in PD.

The evaluation of WMH can be classified into two methods: visual rating scales and volumetric assessments. Visual rating scales are commonly used as they are simple and quick; however, they have some subjective bias and ceiling effects, and their reliability and sensitivity are lower compared to volumetric measurement methods. Therefore, our study conducted subgroup analyses based on different WMH assessment methods, and found that even after excluding potential subjective bias in visual rating scales, significant associations between WMH and PD-MCI were still observed using the volumetric assessment.

As WMH load increases with age, and the prevalence of WMH positivity is significantly higher in Asians than in Caucasians (12), our study conducted subgroup analyses based on age-matching and ethnicity (Asian or Caucasian). We found that the impact of WMH load on early cognitive function in PD was not influenced by ethnicity or age; regardless of age-matching or ethnicity, the severity of WMH was significantly correlated with cognitive impairment in PD patients. Due to limitations in accessing research data, this study did not specifically explore the effects of WMH load on cognitive domains in PD.

Vesely et al. found that the impact of WMH load on cognitive function may vary in specific brain regions (55). In a cohort study, Kandiah et al. (41) reported that baseline PVH load significantly increased in the PD-MCI group compared to PD-NC, while there was no significant difference in DWMH load. Further univariate analysis revealed that PVH was significantly higher in PD-MCI than PD-NC; after adjusting for age and hippocampal volume in multivariate analysis, PVH only showed a certain trend, and DWMH was not a predictor of PD-MCI risk. Subsequently, Mak et al. (45) found that the overall WMH and PVH load were significantly higher in the PD-MCI group than in the PD-NC group, while there was no significant association between DWMH

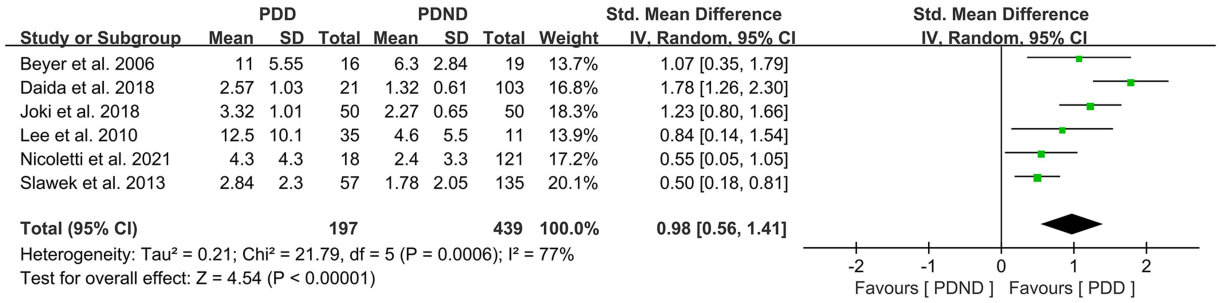

FIGURE 8
Forest plot and meta-analysis of total WMH between PDD and PDND.

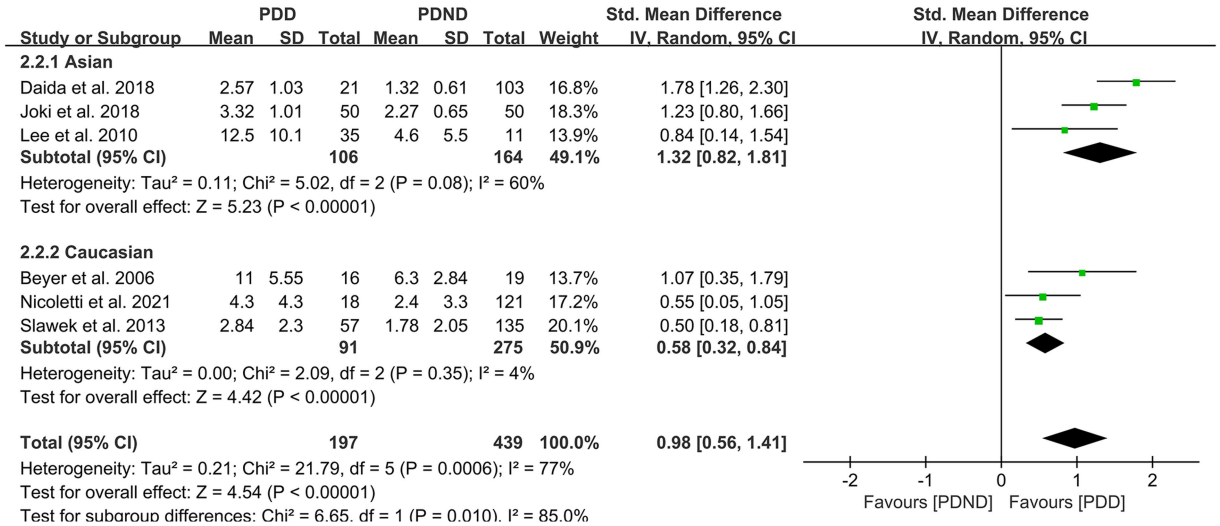

FIGURE 9
Forest plot and meta-analysis of WMH between PDD and PDND: a subgroup analysis based on different ethnicities.

and PD-MCI. Interestingly, Li et al. (47) observed in a study of cognitive impairment in 120 PD patients that compared to PD-NC, DWMH load was significantly increased in PD-MCI, while there was no significant difference in PVH load between the two groups. Further multiple regression analysis demonstrated that the correlation between PD cognitive impairment and DWMH score was the highest. In our study, we found that both PVH and DWMH load were significantly associated with early cognitive function in PD patients, suggesting that both PVH and DWMH may affect early cognitive function in PD.

Two studies (42, 50) provided data on the correlation between lobar WMH load, basal ganglia WMH load, and PVH load with cognitive impairment in PD. Li et al. (50) reported that only frontal lobe WMH load showed a significant difference between the PD-MCI group and the PD-NC group, while Wang et al. (42) found no significant differences in WMH load in various brain regions between the PD-NC and PD-MCI groups. Due to limitations in accessing data, the effects of WMH load in different brain regions on cognitive impairment in PD were not explored based on each region's WMH load. Future research on the effects of WMH in different brain regions on cognitive function in PD is expected to provide further insights into the impact of WMH in different brain areas on cognitive dysfunction in PD.

PD-MCI is the most crucial risk factor for PD progression to PDD (7). Compared to PD-MCI, PDD has a more significant impact on patients' daily lives. Beyer et al. (51) first explored the impact of WMH on cognitive impairment in PD in 2006 and found that compared with the PDND group, the levels of DWMH load and PVH load were significantly higher in the PDD group. Multiple linear regression analysis revealed that DWMH was the only variable significantly correlated with MMSE scores. Subsequently, Joki et al. (36) observed that PVH load was significantly increased in PDD patients compared to PDND patients, while there was no significant difference in DWMH load between the two groups. In contrast, Slawek et al. (53) found in a study of 192 PD patients and 184 age-and gender-matched healthy controls that overall WMH load and DWMH load were related to cognitive impairment in PD patients, while no significant correlation was found with PVH. Further multivariate analysis showed that DWMH could predict PDD. Our study conducted a meta-analysis of studies on overall WMH load and PDD, and found that overall WMH load affects cognitive function in PDD patients. Further subgroup analysis revealed that both Asian and Caucasian WMH load were related to cognitive function in PDD, while there was no significant

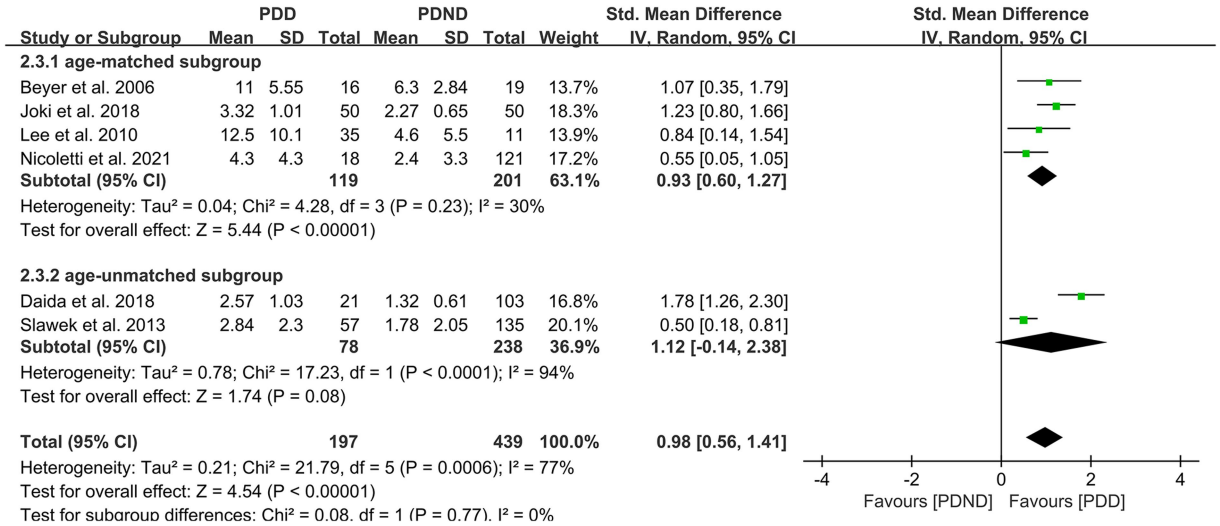

FIGURE 10
Forest plot and meta-analysis of WMH between PDD and PDND: a subgroup analysis based on age.

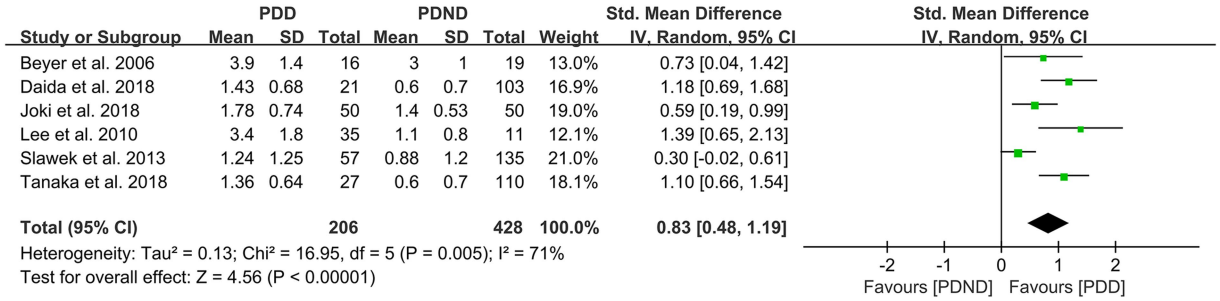

FIGURE 11
Forest plot and meta-analysis of PVH between PDD and PDND.

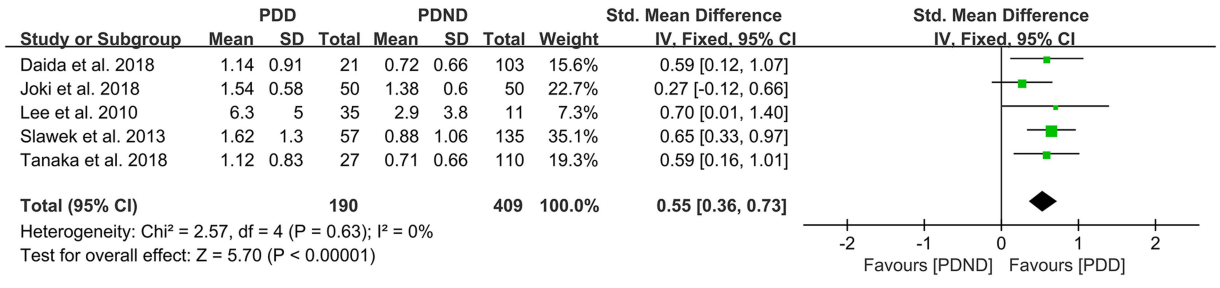

FIGURE 12
Forest plot and meta-analysis of DWMH between PDD and PDND.

difference in WMH load between different age PDD and PDND groups, suggesting that age may confound the relationship between WMH and PDD. In future research, special attention should be paid to the impact of age on the relationship between WMH load and cognitive function in PDD.

Limitations

This study has several limitations. First, unpublished data, case reports in abstract form, and non-English or Chinese literature were not included, which may have led to selection bias. Second,

due to differences in analysis methods and designs among different studies, the comparability of data was limited, which may have had some impact on the research results. Third, due to data availability, this study did not analyze the relationship between WMH in different brain regions and cognitive domains in PD. Fourthly, this study did not take into account various sources of variation, including vascular risk factors, UPDRS scores, and the duration of PD. Therefore, more high-quality multicenter studies are still needed in the future to clarify the relationship between WMH and cognitive impairment in PD and provide more high-quality evidence-based medicine for clinical practice. This will allow for early and accurate identification and diagnosis of cognitive impairment in PD, reducing its harm and improving patient prognosis.

Conclusion

WMH is associated with cognitive dysfunction in PD, and the severity of WMH may impact cognitive dysfunction in PD. Additionally, the early appearance of WMH may suggest the presence of MCI in PD.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

SZ proposed the concept of the review. WZ and BC performed data collection, analysis, and interpretation under the supervision of SZ and TZ. YC, YS, XF, ML, and YF provided reagents, materials, and analysis. WZ and BC wrote the manuscript. All authors approved the final version of the manuscript for submission.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Lee A, Gilbert RM. Epidemiology of Parkinson disease. *Neurol Clin*. (2016) 34:955–65. doi: 10.1016/j.ncl.2016.06.012

2. Doorn KJ, Lucassen PJ, Boddeke HW, Prins M, Berendse HW, Drukarch B, et al. Emerging roles of microglial activation and non-motor symptoms in Parkinson's disease. *Prog Neurobiol*. (2012) 98:222–38. doi: 10.1016/j.pneurobio.2012.06.005

3. Haehner A, Hummel T, Hummel C, Sommer U, Junghanns S, Reichmann H. Olfactory loss may be a first sign of idiopathic Parkinson's disease. *Mov Disord*. (2007) 22:839–42. doi: 10.1002/mds.21413

4. Wang LJ, Feng SJ, Nie K. Chinese guidelines for the diagnosis and treatment of mild cognitive impairment in Parkinson's disease (2020 edition). *Chin J Nerv Ment Dis*. (2021) 47:1–12. doi: 10.3969/j.issn.1002-0152.2021.01.001

5. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Arch Neurol*. (2003) 60:387–92. doi: 10.1001/archneur.60.3.387

6. Marinus J, Zhu K, Marras C, Aarsland D, van Hilten JJ. Risk factors for non-motor symptoms in Parkinson's disease. *Lancet Neurol*. (2018) 17:559–68. doi: 10.1016/S1474-4422(18)30127-3

7. Janvin CC, Larsen JP, Aarsland D, Hugdahl K. Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. *Mov Disord*. (2006) 21:1343–9. doi: 10.1002/mds.20974

8. Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord*. (2007) 22:1689–707; quiz 837. doi: 10.1002/mds.21507

9. Vasconcellos LF, Pereira JS. Parkinson's disease dementia: diagnostic criteria and risk factor review. *J Clin Exp Neuropsychol*. (2015) 37:988–93. doi: 10.1080/13803395.2015.1073227

10. Holden HM, Schweer CN, Troster AI. Impact of mild cognitive impairment on quality of life in young and typical onset Parkinson's disease. *Mov Disord Clin Pract*. (2022) 9:69–75. doi: 10.1002/mdc3.13353

11. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. (2013) 12:822–38.

12. Han F, Zhai FF, Wang Q, Zhou LX, Ni J, Yao M, et al. Prevalence and risk factors of cerebral small vessel disease in a Chinese population-based sample. *J Stroke*. (2018) 20:239–46. doi: 10.5853/jos.2017.02110

13. Thomas AJ, Perry R, Barber R, Kalaria RN, O'Brien JT. Pathologies and pathological mechanisms for white matter hyperintensities in depression. *Ann N Y Acad Sci*. (2002) 977:333–9. doi: 10.1111/j.1749-6632.2002.tb04835.x

14. Thomas AJ, O'Brien JT, Barber R, McMeekin W, Perry R. A neuropathological study of periventricular white matter hyperintensities in major depression. *J Affect Disord*. (2003) 76:49–54.

15. Gouw AA, Seewann A, Vrenken H, van der Flier WM, Rozemuller JM, Barkhof F, et al. Heterogeneity of white matter hyperintensities in Alzheimer's disease: post-mortem quantitative MRI and neuropathology. *Brain*. (2008) 131:3286–98. doi: 10.1093/brain/awn265

16. Murray ME, Vemuri P, Preboske GM, Murphy MC, Schweitzer KJ, Parisi JE, et al. A quantitative postmortem MRI design sensitive to white matter hyperintensity differences and their relationship with underlying pathology. *J Neuropathol Exp Neurol*. (2012) 71:1113–22. doi: 10.1097/NEN.0b013e318277387e

17. DeCarli C, Murphy DGM, Tranh M, Grady CL, Haxby JV, Gillette JA, et al. The effect of white matter hyperintensity volume on brain structure, cognitive performance, and cerebral metabolism of glucose in 51 healthy adults. *Neurology*. (1995) 45:2077–84. doi: 10.1212/WNL.45.11.2077

18. Fazekas F, Kapeller P, Schmidt R, Offenbacher H, Payer F, Fazekas G. The relation of cerebral magnetic resonance signal hyperintensities to Alzheimer's disease. *J Neurol Sci*. (1996) 142:121–5.

19. Silbert LC, Howieson DB, Dodge H, Kaye JA. Cognitive impairment risk: white matter hyperintensity progression matters. *Neurology*. (2009) 73:120–5. doi: 10.1212/WNL.0b013e3181ad53fd

20. Brickman AM, Zahodne LB, Guzman VA, Narkhede A, Meier IB, Griffith EY, et al. Reconsidering harbingers of dementia: progression of parietal lobe white matter hyperintensities predicts Alzheimer's disease incidence. *Neurobiol Aging*. (2015) 36:27–32. doi: 10.1016/j.neurobiolaging.2014.07.019

21. Lee S, Viqar F, Zimmerman ME, Narkhede A, Tosto G, Benzinger TLS, et al. White matter hyperintensities are a core feature of Alzheimer's disease: evidence from the

dominantly inherited Alzheimer network. *Ann Neurol*. (2016) 79:929–39. doi: 10.1002/ana.24647

22. Chang T-C, Chen Y-C, Huang Y-C, Lin W-C, Lu C-H. Systemic oxidative stress and cognitive function in Parkinson's disease with different PWMH or DWMH lesions. *BMC Neurol*. (2021) 21:16. doi: 10.1186/s12883-020-02037-z

23. Kuller LH, Lopez OL, Newman A, Beauchamp NJ, Burke G, Dulberg C, et al. Risk factors for dementia in the cardiovascular health cognition study. *Neuroepidemiology*. (2003) 22:13–22. doi: 10.1159/000067109

24. Smith EE, Salat DH, Jeng J, McCreary CR, Fischl B, Schmahmann JD, et al. Correlations between MRI white matter lesion location and executive function and episodic memory. *Neurology*. (2011) 76:1492–9. doi: 10.1212/WNL.0b013e318217e7c8

25. Sunwoo MK, Jeon S, Ham JH, Hong JY, Lee JE, Lee JM, et al. The burden of white matter hyperintensities is a predictor of progressive mild cognitive impairment in patients with Parkinson's disease. *Eur J Neurol*. (2014) 21:922–e50. doi: 10.1111/ene.12412

26. Lee SJ, Kim JS, Yoo JY, Song IU, Kim BS, Jung SL, et al. Influence of white matter hyperintensities on the cognition of patients with Parkinson disease. *Alzheimer Dis Assoc Disord*. (2010) 24:227–33. doi: 10.1097/WAD.0b013e3181d71a13

27. Lee SJ, Lee DG. The cross-sectional and longitudinal relationships between white matter hyperintensities and dementia in patients with Parkinson's disease: a retrospective analysis of 132 patients in a single center. *Arch Gerontol Geriatr*. (2016) 62:133–7. doi: 10.1016/j.archger.2015.10.006

28. Hanning U, Teuber A, Lang E, Trenkwalder C, Mollenhauer B, Minnerup H. White matter hyperintensities are not associated with cognitive decline in early Parkinson's disease – the Denopa Cohort. *Parkinsonism Relat Disord*. (2019) 69:61–7. doi: 10.1016/j.parkreldis.2019.10.016

29. Stang A. Critical Evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. (2010) 25:603–5. doi: 10.1007/s10654-010-9491-z

30. Wells GA, Shea B, Connell O D, Peterson J, Welch V, Losos M, et al.. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. (2000). Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

31. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. (2002) 21:1539–58. doi: 10.1002/sim.1186

32. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. (2003) 327:557–60. doi: 10.1136/bmj.327.7414.557

33. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: q statistic or I2 index? *Psychol Methods*. (2006) 11:193–206. doi: 10.1037/1082-989X.11.2.193

34. Nicoletti A, Luca A, Baschi R, Cicero CE, Mostile G, Davì M, et al. Vascular risk factors, white matter lesions and cognitive impairment in Parkinson's disease: the pacos longitudinal study. *J Neurol*. (2021) 268:549–58. doi: 10.1007/s00415-020-10189-8

35. Ham JH, Yi H, Sunwoo MK, Hong JY, Sohn YH, Lee PH. Cerebral microbleeds in patients with Parkinson's disease. *J Neurol*. (2014) 261:1628–35. doi: 10.1007/s00415-014-7403-y

36. Joki H, Higashiyama Y, Nakae Y, Kugimoto C, Doi H, Kimura K, et al. White matter hyperintensities on MRI in dementia with Lewy bodies, Parkinson's disease with dementia, and Alzheimer's disease. *J Neurol Sci*. (2018) 385:99-104. doi: 10.1016/j.jns.2017.12.018

37. Dunet V, Fartaria MJ, Deverdun J, Le Bars E, Maury F, Castelnovo G, et al. Episodic memory decline in Parkinson's disease: relation with white matter hyperintense lesions and influence of quantification method. *Brain Imaging Behav*. (2019) 13:810–8. doi: 10.1007/s11682-018-9909-x

38. Kim JS, Oh YS, Lee KS, Kim YI, Yang DW, Goldstein DS. Association of cognitive dysfunction with neurocirculatory abnormalities in early Parkinson disease. *Neurology*. (2012) 79:1323–31. doi: 10.1212/WNL.0b013e31826c1acd

39. Dalaker TOLarsen JP, Dwyer MG, Aarsland D, Beyer MK, Alves G, et al. White matter hyperintensities do not impact cognitive function in patients with newly diagnosed Parkinson's disease. *Neuroimage*. (2009) 47:2083–9. doi: 10.1016/j.neuroimage.2009.06.020

40. Shin J, Choi S, Lee JE, Lee HS, Sohn YH, Lee PH. Subcortical white matter hyperintensities within the cholinergic pathways of Parkinson's disease patients according to cognitive status. *J Neurol Neurosurg Psychiatry*. (2012) 83:315–21. doi: 10.1136/jnnp-2011-300872

41. Kandiah N, Zainal NH, Narasimhalu K, Chander RJ, Ng A, Mak E, et al. Hippocampal volume and white matter disease in the prediction of dementia in Parkinson's disease. *Parkinsonism Relat Disord*. (2014) 20:1203–8. doi: 10.1016/j.parkreldis.2014.08.024

42. Wang L, Zhu XQ, Jiang CJ, Chen XW, Sun ZW. Influence of leukoaraiosis on the cognition of patients with Parkinson disease. *Natl. Med J China*. (2013) 93:177–81. doi: 10.3760/cma.j.issn.0376-2491.2013.03.006

43. Amboni M, Tessitore A, Esposito F, Santangelo G, Picillo M, Vitale C, et al. Resting-state functional connectivity associated with mild cognitive impairment in Parkinson's disease. *J Neurol*. (2015) 262:425–34. doi: 10.1007/s00415-014-7591-5

44. Baggio H-C, Segura B, Sala-Llonch R, Marti M-J, Valldeoriola F, Compta Y, et al. Cognitive impairment and resting-state network connectivity in Parkinson's disease. *Hum Brain Mapp*. (2015) 36:199–212. doi: 10.1002/hbm.22622

45. Mak E, Dwyer MG, Ramasamy DP, Au WL, Tan LCS, Zivadinov R, et al. White matter hyperintensities and mild cognitive impairment in Parkinson's disease. *J Neuroimaging*. (2015) 25:754–60. doi: 10.1111/jon.12230

46. Oh Y-S, Kim J-S, Park H-E, Song I-U, Park J-W, Yang D-W, et al. Association between urine protein/creatinine ratio and cognitive dysfunction in Lewy body disorders. *J Neurol Sci*. (2016) 362:258–62. doi: 10.1016/j.jns.2016.01.061

47. Li XY, Wang Y, Shen HW. Correlation between leukoaraiosis and the cognitive impairment in Parkinson disease patients. *Chin. J. Front. Med. Sci.* (2017) 9:62–6. doi: 10.16766/j.cnki.issn.1674-4152.001433

48. Stojkovic T, Stefanova E, Soldatovic I, Markovic V, Stankovic I, Petrovic I, et al. Exploring the relationship between motor impairment, vascular burden and cognition in Parkinson's disease. *J Neurol*. (2018) 265:1320–7. doi: 10.1007/s00415-018-8838-3

49. Huang X, Wen MC, Ng SYE, Hartono S, Chia NSY, Choi X, et al. Periventricular white matter hyperintensity burden and cognitive impairment in early Parkinson's disease. *Eur J Neurol*. (2020) 27:959–66. doi: 10.1111/ene.14192

50. Li J, Tong QL, Chen WA, Zhang X. Study on the relationship between cognitive function and leukoaraiosis in different brain region of patients with Parkinson's disease. *Chin J Gen Pract*. (2020) 18 1083–5+121. doi: 10.12037/YXQY.2017.05-12

51. Beyer MK, Aarsland D, Greve OJ, Larsen JP. Visual rating of white matter hyperintensities in Parkinson's disease. *Mov Disord*. (2006) 21:223–9. doi: 10.1002/mds.20704

52. Daida K, Tanaka R, Yamashiro K, Ogawa T, Oyama G, Nishioka K, et al. The presence of cerebral microbleeds is associated with cognitive impairment in Parkinson's disease. *J Neurol Sci*. (2018) 393:39–44. doi: 10.1016/j.jns.2018.08.009

53. Sławek J, Roszmann A, Robowski P, Dubaniewicz M, Sitek EJ, Honczarenko K, et al. The impact of MRI white matter hyperintensities on dementia in Parkinson's disease in relation to the homocysteine level and other vascular risk factors. *Neurodegener Dis*. (2013) 12:1–12. doi: 10.1159/000338610

54. Tanaka R, Shimo Y, Yamashiro K, Ogawa T, Nishioka K, Oyama G, et al. Association between abnormal nocturnal blood pressure profile and dementia in Parkinson's disease. *Parkinsonism Relat Disord*. (2018) 46:24–9. doi: 10.1016/j.parkreldis.2017.10.014

55. Vesely B, Rektor I. The contribution of white matter lesions (WML) to Parkinson's disease cognitive impairment symptoms: a critical review of the literature. *Parkinsonism Relat Disord*. (2016) 22:S166–70. doi: 10.1016/j.parkreldis.2015.09.019

Glossary

ARWMC	age-related white matter changes
BBB	blood–brain barrier
CHIPS score	the Cholinergic Pathways Hyperintensities Scale
CI	confidence intervals
CVR	cerebrovascular reactivity
DWMH	deep white matter hyperintensity
Erkinjunntti	the Erkinjunntti rating scales
Fazekas	the Fazekas visual rating scales
FLAIR	fluid-attenuated inversion recovery
H–Y stage	Hoehn and Yahr scale stage
MCI	Mild cognitive impairment
MD	mean differences
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MOOSE	the Meta-Analysis of Observational Studies in Epidemiology guidelines
MRI	magnetic resonance imaging
Na	no available
NOS	Newcastle-Ottawa Scale
PD	Parkinson's Disease
PDD	PD dementia
PD-MCI	Parkinson's disease mild cognitive impairment
PD-NC	Parkinson's disease with no cognitive impairment
PDND	non-demented PD
PVH	periventricular hyperintensity
Scheltens scale	the Scheltens visual rating scales.
SMD	standard mean difference
UKPDS	the use of British Parkinson's Disease Society
UPDRS-III	Unified Parkinson's Disease Rating Scale part III
WMH	White matter hyperintensity

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Pain in monogenic Parkinson's disease: a comprehensive review

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Pain, a challenging symptom experienced by individuals diagnosed with Parkinson's disease (PD), still lacks a comprehensive understanding of its underlying pathophysiological mechanisms. A systematic investigation of its prevalence and impact on the quality of life in patients affected by monogenic forms of PD has yet to be undertaken. This comprehensive review aims to provide an overview of the association between pain and monogenic forms of PD, specifically focusing on pathogenic variants in *SNCA*, *PRKN*, *PINK1*, *PARK7*, *LRRK2*, *GBA1, VPS35, ATP13A2, DNAJC6, FBXO7*, and *SYNJ1*. Sixty-three articles discussing pain associated with monogenic PD were identified and analyzed. The included studies exhibited significant heterogeneity in design, sample size, and pain outcome measures. Nonetheless, the findings of this review suggest that patients with monogenic PD may experience specific types of pain depending on the pathogenic variant present, distinguishing them from non-carriers. For instance, individuals with *SNCA* pathogenic variants have reported painful dystonia, lower extremity pain, dorsal pain, and upper back pain. However, these observations are primarily based on case reports with unclear prevalence. Painful lower limb dystonia and lower back pain are prominent symptoms in *PRKN* carriers. A continual correlation has been noted between *LRRK2* mutations and the emergence of pain, though the conflicting research outcomes pose challenges in reaching definitive conclusions. Individuals with *PINK1* mutation carriers also frequently report experiencing pain. Pain has been frequently reported as an initial symptom and the most troublesome one in *GBA1*-PD patients compared to those with idiopathic PD. The evidence regarding pain in *ATP13A2, PARK7, VPS35, DNAJC6, FBXO7,* and *SYNJ1*pathogenic variants is limited and insufficient. The potential linkage between genetic profiles and pain outcomes holds promising clinical implications, allowing for the potential stratification of patients in clinical trials and the development of personalized treatments for pain in monogenic PD. In conclusion, this review underscores the need for further research to unravel the intricate relationship between pain and monogenic forms of PD. Standardized methodologies, larger sample sizes, and longitudinal studies are essential to elucidate the underlying mechanisms and develop targeted therapeutic interventions for pain management in individuals with monogenic PD.

KEYWORDS

Parkinson's disease, monogenic, genetic, pain, inheritance

1. Introduction

Parkinson's disease (PD) is a complex disorder with significant clinical variability, potentially influenced by genetic factors, affecting not only motor but also non-motor symptoms (NMS) including pain (1, 2). Pain in PD encompasses various categories, including musculoskeletal pain, chronic pain, fluctuation-related pain, nocturnal pain, orofacial pain, discoloration, edema/swelling, and radicular pain, as categorized by the King's Parkinson's Disease Pain Scale (3).

Despite of its high prevalence, with reports of up to 85% of PD patients experiencing pain (4–6), it remains underdiagnosed and undertreated, even if it significantly impacts the quality of life (7–12). Lower Back Pain (LBP) is the most common pain site in PD, surpassing its prevalence in healthy older adults (13). Shoulder pain can even precede the PD diagnosis (14), with 12% of PD patients reporting it as their initial symptom (15). Motor complications in PD patients correlate with a higher risk of pain, and pain potentially exacerbates parkinsonian symptoms (5, 16). Given the complexity of pain etiology and the limited therapeutic options for its management, a comprehensive and accurate classification of pain types are crucial for improved patient outcomes (12).

Pathogenic variants in PD-causative genes have been associated with diverse disease symptoms (17, 18). For example, cognitive decline affects 70% of PD patients with pathogenic alpha-synuclein (*SNCA*) gene variants, while only 23% of Leucine-Rich Repeat Kinase 2 (*LRRK2*) carriers exhibit cognitive impairment (18). Rigidity and bradykinesia are nearly universal in *SNCA* patients, with dystonia less frequently observed (18). Despite these observations, data on pain in monogenic forms of PD remain limited. Case reports and small case–control studies indicate variations in pain presentation among different genetic forms of PD. For instance, a PD patient with an *SNCA* pathogenic variant exhibited dorsal pain as a primary symptom (19), while another patient with the Leu347Pro PTEN-induced putative protein kinase 1 (*PINK1*) pathogenic variant developed long-term right-sided pain following right-hand tremor onset (20).

Reports also suggest pain as an initial symptom in PD patients with the G2019S *LRRK2* variant (21). Yet, these reports rarely explore the longitudinal progression of pain or compare pain experiences among carriers of different pathogenic variants under similar conditions. Consequently, the question of whether genetic status directly leads to the emergence of pain or is associated with different types in PD remains unanswered.

This review aims to investigate the hypothesis that genotypes may influence the pain phenotype in PD patients. We assess the presence, types, severity, and onset time of pain in PD patients and their relationship with different variants in pathogenic genes. By synthetizing existing literature, this review seeks to enhance our understanding of pain in monogenic forms of PD and offer insights for future research and clinical management.

2. Methods

2.1. Search strategy

To ensure methodological rigor, this review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (22). The initial literature search encompassed databases such as MEDLINE (PubMed), Embase (Elsevier), and Cochrane databases. We sought articles published from inception until March 2023. The search strategy employed a combination of subject headings and MeSH terms, including "Parkinson's disease" OR "Parkinson disease" OR "PD," AND "gene" OR "genetic" OR "monogenic" OR "*SNCA*" OR "PRKN" OR "Parkin" OR "PINK1" OR "DJ1" OR "LRRK2" OR "ATP13A2" OR "GBA1" OR "DNAJC6" OR "FBXO7" OR "SYNJ1" OR "PARK1" OR "PARK2" OR "PARK4" OR "PARK6" OR "PARK7" OR "PARK8" OR "PARK9" OR "PARK15" OR "PARK19" OR "PARK20," AND "pain" OR "pain sensation" OR "somatosensory discomfort." The search was conducted without restrictions on language, year of publication, study type, or publication status.

Two independent investigators (PA and CTC) conducted the search, and the search results, including abstracts and full-text articles, were organized using reference management software. In addition to the electronic search, references from included studies and review articles were screened to augment the dataset.

Monogenic forms of PD result from the inheritance of a pathogenic variant of a single gene, contributing to approximately 30% of familial cases and 3–5% of sporadic cases (23). While the PD causative gene landscape has sparked some debate, several genes, including, *SNCA*, Parkin RBR E3 Ubiquitin Protein Ligase (*PRKN*), *PINK1*, *LRRK2*, and deglycase DJ-1 (*PARK7*) are widely as acknowledged as monogenic PD genes by most experts (24, 25). This review incorporates vacuolar protein sorting 35 (*VPS35*), with only one confirmed pathogenic variant (26), ATPase Cation Transporting 13A2 (*ATP13A2*), F- box protein 7 (*FBXO7*), DnaJ Heat Shock Protein Family (Hsp40) Member C6 (*DNAJC6*), and Synaptojanin-1 (*SYNJ1*) based on a recent comprehensive review (25).

We have included findings related to the *GBA1* gene (Glucosylceramidase) which elevate the risk of developing PD. Pain reports are common among *GBA1* carriers, making this addition significant to our review (27).

Specific pathogenic variants linked to PD and pain syndromes are discussed within the text, while those variants reported only in individual cases are further summarized in Table 1 for comprehensive reference.

2.2. Selection criteria

To ensure the relevance and quality of selected articles, the following inclusion criteria were applied: (A) Published papers that specifically focused on pain symptoms in patients with monogenic pathogenic variants associated with PD and (B) Articles that provided information on autosomal dominant (AD) or recessive (AR) forms of PD or on patients carrying at least one pathogenic variant in the *SNCA*, *PRKN*, *PINK1*, *PARK7*, *LRRK2*, *GBA1*, *VPS35*, *ATP13A2*, *DNAJC6*, *FBXO7*, or *SYNJ1* genes, and reporting cases of PD-related pain. Furthermore, a meta-summary was conducted to consolidate the overall findings from the selected studies.

The exclusion criteria were as follows: (A) Articles that included PD patients carrying gene pathogenic variants other than those listed

TABLE 1 Pain in monogenic PD: summary of the data extracted from the included studies concerning clinical studies.

Gene/ Symbol/ Inheritance	Protein product	Variants type	Authors/year	Type of study	Sample size	Pain-related information	Other clinical features
SNCA/ PARK1, PARK4/ AD	Alpha-synuclein	*SNCA* missense (H50Q)	Appel-Cresswell et al. (2013) (28)	Case series/ report	110 fully sequenced 1105 patients and 875 control TaqMan sequencing	Painful dystonic flexion on walking in carriers.	Bilateral action tremor, micrographia, and decreased walking speed with shuffling.
		SNCA missense (G51D)	Lesage et al. (2013) (29)	Case series/ report	4 patients	Lower extremity pain in 1 out of 3 carriers.	Left hemibody rest tremor.
		Mosaicism of duplication and triplication in oral mucosal cells	Perandones et al. (2014) (19)	Case series/ report	2 cases	Dorsal pain in 1 out of 2 patients	First presented with dorsal pain and gait disorders, secondary to rigidity and bradykinesia of the lower left leg.
		Triplication	Byers et al. (2011) (30)	Case series/ report	1 case	Upper back pain	Fatigue, tremors, and decreased dexterity as initial symptoms.
PRKN/ PARK2/ AR	Parkin	Homozygous Exon 3 deletion	Capecci et al. (2004) (31)	Case series/ report	1 patient	Painful dystonic posture during off phases.	Psychomotor slowness, mood depression, insomnia.
		Intron 5 splice mutation/ intron 5 splice mutation and exon 8 deletion	Khan et al. (2002) (32)	Case series/ report	10 patients	Lower limb pain/leg pain, pain with "OFF-periods" and painful dystonic cramps of the feet.	Bilateral leg tremor.
		Homozygous exon 4 deletion	Dogu et al. (2004) (33)	Case series/ report	12 siblings	Left foot severe pain as first complaint and left foot dystonia two years later in one patient.	N/A
		Compound heterozygous Parkin mutation (a deletion of exon 7 and a missense mutation in exon 12)	Djarmati et al. (2004) (34)	Case series/ report	75 unrelated patients	4% with pain and 24% with dystonia as their onset symptom. No clarification about Parkin mutation carriers was among them.	N/A
		Different deletions*	Ohsawa et al. (2005) (35)	Case series/ report	9 Parkin patients and 8 idiopathic PD	Tingling sensation with foot sensory loss in 2 out of 9 Parkin patients. Significant decrease of SNAP amplitude in 8 out of 9 Parkin patients.	N/A
		1 homozygous exon 2 deletion, 13 compound heterozygous, and 10 had single mutant allele	Khan et al. (2003) (36)	Case series/ report	115 PD patients (24 Parkin patients)	Painful 'OFF' periods in homozygous patients.	N/A
		Homozygous for 202A deletion	Nisipeanu et al. (2001) (37)	Case series/ report	4 brothers	Low back pain	N/A
		3 *PRKN* deletion patients (2 homozygous and 1 heterozygous)	Bouhouche et al. (2017) (38)	Case series/ report	18 consanguineous patients	No pain for 3 Parkin patients.	N/A
		9 homozygous deletion mutations and 7 had a heterozygous point mutation	Shyu et al. (2005) (39)	Cross-sectional	230 PD (30 Parkin carriers)	50% of patients with tingling pains over both lower legs.	The same patients complained of profound dizziness.
		15 heterozygous, 3 homozygous, and 7 compound heterozygous including different kinds of deletions or duplications	Monroy-Jaramillo et al. (2014) (40)	Cross-sectional	122 non-related EOPD patients (25 Parkin mutation) and 120 HC	The patient with exon 9 deletion experienced pain.	N/A
		93 carried two mutations and 25 had one mutation	Lesage et al. (2007) (41)	Cross-sectional	435 patients	Painful contractions with objective mild sensory neuropathy in the lower limbs 1 out of 3 sisters with single heterozygous deletion of exon 3.	Left foot dystonia in the other sisters. No pain was mentioned. Another sister had a mild decrease in sensory nerve action potentials in the lower limbs without pain.

(Continued)

TABLE 1 (Continued)

Gene/ Symbol/ Inheritance	Protein product	Variants type	Authors/year	Type of study	Sample size	Pain-related information	Other clinical features
		Different Parkin mutations	Doherty et al. (2013) (42)	Case-control	5 Parkin, 5 pathologically confirmed PD, and 4 HC	FOG and painful OFF-period dystonia in *PRKN* carriers.	N/A
		Parkin heterozygous mutation	Gierthmühlen et al. (2010) (43)	Case-control	9 Parkin carriers and 9 HC	Somatosensory disturbances (Sensory gain for the cold pain threshold in 5 out 9 parkin carriers. Sensory gain for the hot pain threshold in one carrier).	N/A
		Different kinds of mutation	Koziorowski et al. (2013) (44)	Case-control	150 EOPD patients and 230 HC	43% of Parkin carriers had "other symptoms" including pain and dystonia as an onset symptom in comparison with 13 % for non-carriers.	N/A
		202A deletion (12 homozygous, 1 heterozygous)	Hassin-Baer et al. (2011) (45)	Cohort	13 PD patients and 15 family members	Severe LBP (8 out of 13) Painful dystonia (2 out of 13)	N/A
		Different Parkin mutations	Elia et al. (2014) (46)	Cohort	44 patients	Lower limb pain in 3 patients.	All patients had lower limb walking task-specific dystonia.
PINK1/ PARK6/ AR	PTEN-induced putative kinase 1	One with homozygous transition in exon 7 (Q456>X)	Zadikoff et al. (2006) (47)	Case series/ report	11 PD patients	Back, and extremity pain, and painful wearing-off dystonia are frequent complaints.	N/A
		Homozygous A217D mutation	Norman et al. (2017) (48)	Case series/ report	1 EOPD patient (family of Moroccan origin)	Back and shoulder pain.	N/A
		5 heterozygous for Arg246Gln & Arg276Gln	Biswas et al. (2010) (49)	Case series/ report	250 patients and 205 HC	Pain in legs, calves, knees, spine, and back.	N/A
		27 variants including 1 homozygous T→C substitution in exon 5 (Leu347Pro)	Rogaeva et al. (2004) (20)	Case series/ report	289 PD patients and 80 HC in the first stage and 150 HC for estimating the mutation frequencies	Pain on the right side after 10 years.	Right-hand tremor as an onset symptom.
		1 homozygous L347P	Kilarski et al. (2012) (50)	Case series/ report	136 EOPD	Pain as an onset symptom.	Lower limb tremor as an onset symptom.
		1 homozygous nonsense mutation in exon 3 (Tyr258Stop)	Tan et al. (2006) (51)	Case series/ report	80 sporadic EOPD patients	Painful paresthesia	An urge to move her lower limbs was accompanied by painful paresthesia with a cramp-like feeling distally.
		1 homozygous L539F *PINK1* and 1 homozygous Q456X *PINK1* mutation	Bouhouche et al. (2017) (52)	Case series/ report	19 unrelated PD patients	No pain reported	N/A
		Different mutations in exon2*	Djarmati et al. (2006) (53)	Cross-sectional	92 EOPD patients	Right shoulder pain in 2 heterozygous patients [mutation (952A>T in exon 2: Met318Leu)]	Four variants were found and three of them (c.558GC, c.626CT, and c.952AT) are likely to be pathogenic.
		Different kinds of mutations	Ibanez et al. (2006) (54)	Case-control	53 patients without *PINK1* mutations 34 *PINK1* patients, and 174 HC	Painful episodes of torticollis and levodopa-induced painful dystonia episodes in 1 homozygous Q456X *PINK1* mutation patient.	N/A
		PINK1 mutation	Gierthmühlen et al. (2009) (55)	Case-control	14 family members with *PINK1* mutation and 14 HC	Somatosensory impairment (higher mechanical pain, and pain pressure thresholds in *PINK1* carriers than HC).	N/A

(Continued)

TABLE 1 (Continued)

Gene/ Symbol/ Inheritance	Protein product	Variants type	Authors/year	Type of study	Sample size	Pain-related information	Other clinical features
		Different substitution mutations*	Koziorowski et al. (2013) (44)	Case-control	150 EOPD patients and 230 HC	No pain reported	N/A
LRRK2/ PARK8/ AD	Leucine-rich repeat kinase 2	Heterozygous N1437H mutation	Puschmann et al. (2012) (56)	Case series/ report	1 patient for clinical study and 7 brains for genetic study.	Severe painful dystonia in ON state.	N/A
		11 G2019S mutation	Bras et al. (2005) (57)	Case series/ report	128 PD patients	Painful cervical dystonia was responsive to levodopa in 2 carriers.	N/A
		3 G2019S mutation (2 familial and 1 idiopathic patient)	Gosal et al. (2005) (58)	Case series/ report	273 PD patients	Idiopathic patient Painful left foot dystonia after 9 years of onset symptoms in an idiopathic patient.	The same patient had heaviness in the right arm and leg, which caused some walking difficulties as an onset symptom.
		One p.R1441G mutation, one p.G2019S, and 103 G2385R	Hatano et al. (2014) (59)	Case series/ report	871 PD patients (430 sporadic PD and 441 probands with familial PD)	Severe wasting painful dyskinesia after 13 years of disease onset in a patient with both R1441G and G2385R mutations in *LRRK2*.	Bradykinesia and tremors in the left lower limb as onset symptoms.
		Three with G2019S mutation	Gatto et al. (2013) (21)	Case series/ report	55 PD patients	Pain as an onset symptom in one carrier with abnormal MMSE.	N/A
		LRRK2 mutation	Khlebtovsky et al. (2018) (60)	Cross-sectional	28 PD patients	Higher heat pain threshold in LRRK2 carriers than non-carriers.	N/A
		2 with R1441C and 2 with G2019S mutation	Hedrich et al. (2006) (61)	Cross-sectional	First included: 98 EOPD, 42 LOPD patients. Further included: 220 EOPD patients and 200 HC	Joint pain was the initial symptom in one patient with R1441C LRRK2 mutation.	N/A
		8 heterozygous R1441C mutation, 1 heterozygous G2019S mutation	Criscuolo et al. (2011) (62)	Cross-sectional	192 PD patients	Pain in 5 R1441C carriers vs. one no-carrier	N/A
		G2019S mutation	Bouhouche et al. (2017) (52)	Cross-sectional	100 unrelated PD patients	No significant difference in pain prevalence.	N/A
		G2385R or R1628P LRRK2 variants	Li et al. (2015) (63)	Cross-sectional	1225 PD patients	No differences in the NMS phenotype.	N/A
		LRRK2 Gly2019Ser mutation	Healy et al. (2008) (64)	Case-control	24 world populations, 19 376 patients	126 out of 301 *LRRK2* PD patients (42%) had dystonia, mostly painful foot dystonia "OFF-period"(25%for idiopathic PD).	N/A
		7 PD patients and 2 PD relatives (at-risk group) had *LRRK2* mutation	Baig et al. (2015) (65)	Case-control	769 PD patients, 98 at risk (first-degree PD relatives), and 287 HC	The pain was reported among symptoms in 55.6% of PD patients and 1.2% of relatives.	N/A
		G2385R mutation	An et al. (2008) (66)	Case-control	600 PD patients and 334 unrelated HC	No significant difference between genotypes in pain as an onset symptom.	N/A
		LRRK2 G2385R or R1628P	Wang et al. (2014) (67)	Case-control	223 *LRRK2*-PD carriers and 1366 iPD.	No difference in pain between *LRRK2* PD patients and idiopathic PD.	N/A
		LRRK2 R1628P mutation	Zhang et al. (2009) (68)	Case-control	600 patients and 459 unrelated HC	No significant difference in pain as an onset symptom among genotypes.	N/A
		7 heterozygous G2019S mutation	Luciano et al. (2010) (69)	Cohort	791 individuals	Knee pain was reported among symptoms in one individual who developed PD.	N/A

(Continued)

TABLE 1 (Continued)

Gene/ Symbol/ Inheritance	Protein product	Variants type	Authors/year	Type of study	Sample size	Pain-related information	Other clinical features
ATP13A2/ PARK9/ AR	ATPase 13A2	1 homozygous deletion (c.2822delG)	Martino et al. (2015) (70)	Case series/ report	1 PD patient	Pain in the right hand	Right-arm dystonic posturing is an onset symptom.
		Two with W258X mutation	Bouhouche et al. (2017) (52)	Cross-sectional	19 PD patients	No pain among their symptoms.	N/A
DJ-1/ *PARK7*/ AR	DJ-1	1 heterozygous deletion of exon5	Djarmati et al. (2004) (34)	Case series/ report	75 unrelated PD patients	Pain as an onset symptom in 3 out of 75 (4%). No mention if the DJ-1 carrier was one of them.	N/A
GBA1/ AD	Glucocerebrosidase	15 with *GBA* mutations	Bonner et al. (2020) (71)	Case series/ report	20 PD patients (15 with PD-*GBA* and 5 with idiopathic PD)	The pain was reported as the most bothersome symptom in 17 patients (12 *GBA*-PD patients) *GBA*-PD patients reported rigidity and stiffness often combined with pain.	Sleep disruption was reported as caused by pain in 2 patients. No clarification if patients were *GBA* carriers.
		N370S (homozygous)	Rodriguez-Porcel et al. (2017) (72)	Case series/ report	2 *GBA*-PD patients	A cramp-like pain	N/A
		3 heterozygous D409H and 1 heterozygous R463H	Kresojevic et al. (2015) (73)	Cross-sectional	578 PD patients	Pain is an initial symptom in all carrier patients.	N/A
		Different heterozygous mutations	Jesús et al. (2016) (74)	Case-control	532 iPD patients (62 carriers) and 542 HC (43 carriers)	37.9% of deleterious and 40% of benign *GBA* carriers vs. 34.4% of non-carriers had pain	Among other NMS, REM sleep disorder was significantly more common among *GBA* carriers than non-carriers
		12 heterozygous including five N370S, two L444P, and other different mutations	McNeill et al. (2012) (75)	Case-control	220 PD patients (12 PD-*GBA* and 20 non-*GBA* mutations PD patients)	Unexplained pain was more common among *GBA*-PD patients than sporadic (58% vs. 10%, p=0.005).	N/A
		L444P mutation	Wang et al. (2014) (67)	Case-control	49 *GBA*-PD and 1366 iPD	No differences concerning bodily pain between groups.	N/A
		Different kinds of point mutations or deletion	Neumann et al. (2009) (76)	Case-control	790 PD and 257 controls	A patient with R463C mutation experienced pain in the left shoulder and lower back pain, also a patient with G193E reported back pain	N/A

*Type of mutations is fully described in the manuscript.
SNCA, alpha-synuclein; *PRKN*, Parkin RBR E3 Ubiquitin Protein Ligase; *PINK1*, PTEN induced putative protein kinase 1; *LRRK2*, Leucine-Rich Repeat Kinase 2; *ATP13A2*, ATPase Cation Transporting 13A2; DJ-1, deglycase; and *GBA*, Glucosylceramidase; N/A, non-applicable; PD, Parkinson's disease; iPD, idiopathic Parkinson's disease; HC, healthy controls; AA, AG, GG, different genotypes of SNPs which have different base pair; FOG, Freezing of gait; EOPD, Early-onset Parkinson's disease; SNAP, Sural Sensory Nerve Action Potential; T→C, T to C transition (mutation); MMSE, Mini-Mental State Examination; PD-*GBA*, *GBA* carrier PD patients.

above or patients with other pain-related diseases, X-linked dystonia-parkinsonism, or rapid-onset dystonia-parkinsonism, and (B) Redundant publications.

The assessment of the retrieved occurred in two phases. Initially, titles and abstracts were screened based on the inclusion/exclusion criteria. Subsequently, the full text of the remaining articles was reviewed for final selection. Any articles that did not provide pertinent information regarding pain in monogenic forms of PD, even after a thorough full-text revision, were excluded from the analysis.

2.3. Specific aim

This review aimed to investigate the presence of pain in individuals with monogenic variants associated with PD. The primary objectives were to ascertain whether particular gene pathogenic variants within the spectrum of monogenic PD genes correlate with the presence of pain and, more specifically, to explore whether these pathogenic variants are associated with specific types of pain.

3. Results

3.1. Identification of studies

A consolidated master list comprising 541 potentially eligible articles was generated from the contributions of the two reviewers. Duplicate entries within the list were identified and removed, resulting in 534 unique articles. A preliminary screening of the titles and abstracts was conducted by the study team, which led to the exclusion of 3 due to the lack of relevance to the search terms. Furthermore, several papers were flagged for full-text review but were subsequently

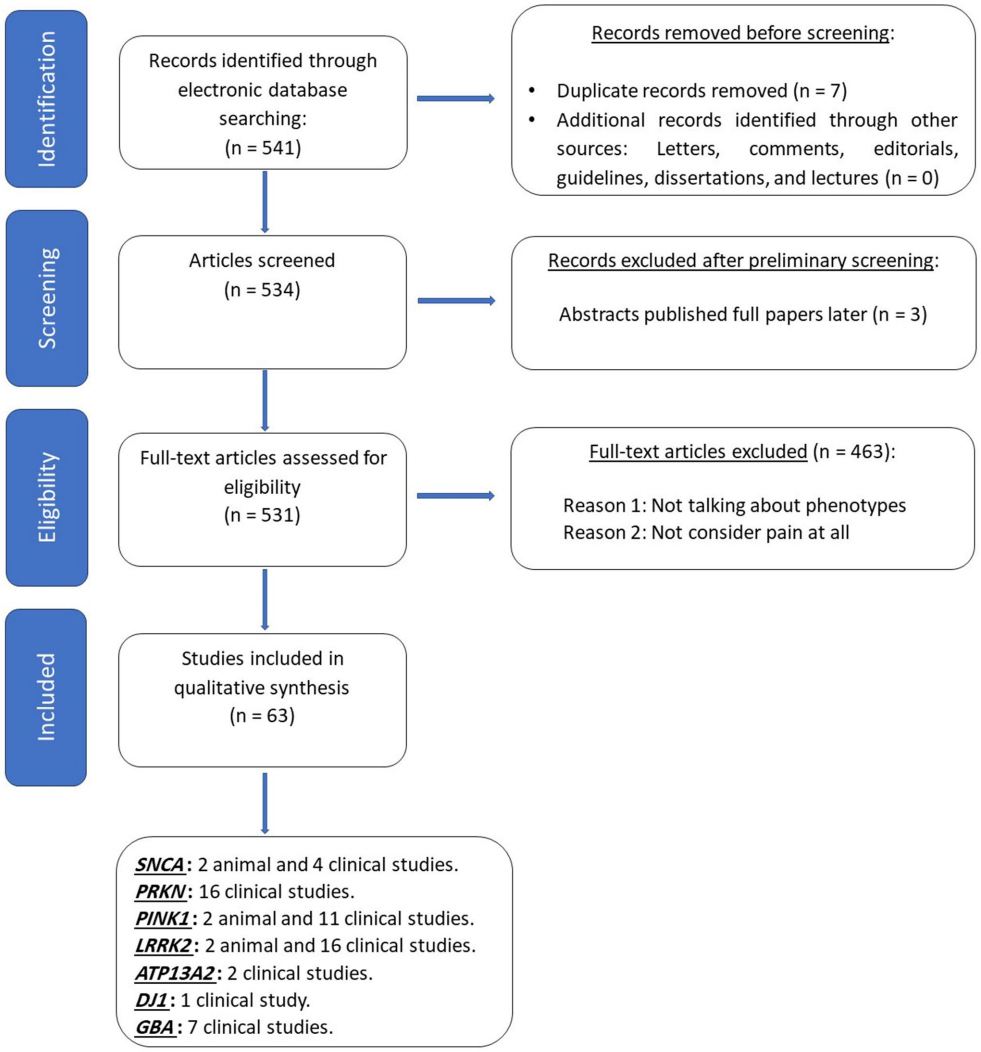

FIGURE 1
PRISMA's diagram depicts the flow of information through the different phases of the comprehensive review, which included searches of databases. *SNCA*, alpha- synuclein; *PRKN*, Parkin RBR E3 Ubiquitin Protein Ligase; *PINK1*, PTEN induced putative protein kinase 1; LRRK2, Leucine-Rich Repeat Kinase 2; ATP13A2, ATPase Cation Transporting 13A2; *PARK7*, deglycase; *GBA*, Glucosylceramidase.

excluded as they did not contain any mention of pain within the reported symptoms. This process led to the exclusion of 463 articles.

In total, 63 articles met eligibility criteria for inclusion in this review. These selected articles encompassed six studies conducted on animal models, twenty-eight case series or case reports, eleven cross-sectional studies, fifteen case–control studies, and three prospective cohort studies (Figure 1). Each selected study underwent a comprehensive review, and pertinent data were extracted.

For each gene, we provide a general description and a summary of clinical studies, while details related to animal models will be presented in Table 2.

3.2. Monogenic forms of PD

More than 40 distinct chromosomal loci and 21 disease-causing genes associated with PD have been identified (77, 78). Among these, specific regions house known genes responsible for monogenic PD. Recognized monogenic PD genes include *SNCA, PRKN, PINK1, PARK7, LRRK2, GBA1, VPS35, ATP13A2, DNAJC6, FBXO7,* and *SYNJ1* (25, 78). In monogenic PD, a pathogenic variant in a single gene is sufficient to manifest the PD phenotype (79).

All of the above mentioned genes exhibit autosomal inheritance patterns (79). In general, phenotypes resembling idiopathic PD (iPD) are more commonly observed in cases of AD inheritance, whereas young-onset parkinsonism resembling iPD or parkinsonism with atypical features is more commonly associated with AR inheritance (78).

Our review encompasses 11 out of 19 known PD-causing genes identified in the most recent comprehensive genetic database of PD (80). The exclusion of the remaining genes is due to insufficient data supporting their pathogenic role in PD and subsequent studies failed to replicate the pathogenic variant (81, 82).

TABLE 2 Pain in monogenic PD: summary of the data extracted from the included studies concerning animal models.

Gene/ Symbol/ Inheritance	Protein product	Variants type	Authors/year	Sample size	Pain-related information
SNCA/ PARK1, PARK4/ AD	Alpha-synuclein	Higher expression of alpha-Synuclein	Vivacqua et al. (2009) (84)	At least 3 rats	The abnormal pain in PD may be caused by the pathological changes related to alpha-Synuclein
		SNCA missense (A53T)	Valek et al. (2021) (85)	32 mice	*PINK1*-/-*SNCA* A53T double mutant mice show early prodromal sensory neuropathy. Loss of thermal sensitivity is an initial sign of sensory dysfunction.
PINK1/ PARK6/ AR	PTEN-induced putative kinase 1	*Pink1*−/−	Johnson et al. (2020) (86)	Rat model in PD	Abnormal nociceptive responses and faster thermal withdrawal latencies in *PINK1* -/- rats.
		Pink1−/−	Yi et al. (2019) (87)	Rat model in PD	*PINK1*-positive cells participate in the development of pain following mitochondrial autophagy.
LRRK2/ PARK8/ AD	Leucine-rich repeat kinase 2	R1441G mutation in *LRRK2*	Bichler et al. (2013) (88)	*LRRK2* BAC (Bacterial Artificial Chromosome) transgenic (Tg) mice and control ones (NTg)	Pain sensitivity.
		Gain of function mutation in *LRRK2*	Valek et al. (2019) (89)	*LRRK2*/Park8 transgenic PD mice and rats	Not develop any sensory deficits.

No animal studies concerning pain in the following gene mutations were found: *PRKN*/PARK2 (Parkin), *ATP13A1*/PARK9 (ATPase 13A2), DJ-1/*PARK7* (deglycase), *GBA1* (Glucocerebrosidase). *SNCA*, alpha-synuclein; *PINK1*, PTEN, induced putative protein kinase 1; *LRRK2*, Leucine-Rich Repeat Kinase 2; AR, Autosomal Recessive; AD, Autosomal Dominant; BAC, Bacterial Artificial Chromosome; Tg, transgenic; NTg, non-transgenic.

Approximately 15% of individuals with PD have a family history of the disorder, with the current known monogenic forms accounting for approximately 30% of familial PD cases (16, 83).

The selected articles included in this review primarily focus on genes *SNCA, PRKN, LRRK2, PINK1, PARK7,* and *GBA1* which are associated with either Early Onset PD (EOPD) or Late Onset PD (LOPD). We also sought information on *ATP13A2, DNAJC6, FBXO7,* and *SYNJ1,* which are rare causes of atypical PD However, our search did not yield any reports specifically addressing pain in relation to these genes.

A summary of the review results is provided in Table 1, providing an overview of key findings related to of pain in the context of monogenic PD.

3.2.1. *SNCA* (PARK1, 4)

The *SNCA* gene plays an important role in AD PD, with missense mutations and copy number gains (duplication or triplication) being established causes of PD. While pathogenic missense variants in *SNCA* are rare in the general population, duplications and triplications are also rare but more frequent, with approximately 60 reported families to date (90).

SNCA has six exons that encode alpha-synuclein, a 140-amino acid cytoplasmic protein highly abundant in neurons, particularly in the substantia nigra pars compacta (SNc), where it regulates dopamine neurotransmission (83, 91). Pathogenic *SNCA* variantscan lead to cytoplasmic accumulation of alpha-synuclein, promoting oxidative stress and metabolic dysfunction in the SNc (92).

Specific pathogenic variants in the *SNCA* that are associated with PD. Parkinson's disease-1 (PARK1) results from a point pathogenic variant (missense) in *SNCA*, while *SNCA* gene duplication and triplication lead to Parkinson's disease-4 (PARK-4) (93). To date, eight pathogenic missense variants have been identified in *SNCA*, all located within the N-terminal amphipathic region of alpha-synuclein. These variants interfere with the alpha-helix-mediated interaction with membranes, contributing to the pathogenesis of PD (94–100).

The most common of these eight missense variants is A53T (18, 80). The number of cases for other missense variants (A30G, A30P, E46K, H50Q, G51D, A53E, and A53V) are small, and some, like H50Q, are not significantly enriched in cases compared to controls (18). Therefore, sufficient evidence may not exist to classify all of them as pathogenic variants (18).

PD patients with *SNCA* gene pathogenic variants typically exhibite earlier age of disease onset than iPD, rapid disease progression, positive response to levodopa treatment, and often present with prominent NMS (101).

This review included six studies, two animal models and four clinical studies (all case series/reports), that investigated *SNCA* pathogenic variants and their potential association with pain. Out of the initially identified articles, 61 were excluded as they did not mention pain or other phenotypes related to *SNCA* pathogenic variants.

Regarding animal studies, Vivacqua et al. reported that higher levels of alpha-synuclein expression in spinal cord areas known to be involved in pain modulation and transmission (84). Another study showed that *PINK1*−/− *SNCA* A53T double mutant mice, which develop a PD-like disease, exhibited a loss of thermal sensitivity as an initial sign of sensory dysfunction (85).

Among clinical studies, one case report study described a novel *SNCA* missense pathogenic variant, G51D, in a patient with lower extremity pain among her symptoms (29). Additionally, two other

case reports detailed dorsal and upper back pain in carriers with *SNCA* duplication and triplication (19, 30).Another case report described painful dystonic flexion of the toes while walking in a patient with H50Q variant, although this variant's pathogenicity remains under debate (28).

3.2.2. *PRKN* (PARK2)

The *PRKN* gene is associated with an AR form of the disorder (79, 102, 103). Homozygous and compound-heterozygous pathogenic variants in *PRKN* are causative of PD, while heterozygous pathogenic variants may predispose to PD symptoms with low penetrance, making them potential genetic risk factors (104, 105).

PRKN comprises12 exons and encodes Parkin, a 465 amino acid protein (79, 106). Parkin is widely expressed in human tissues, with significant abundance in the brain, especially the substantia nigra pars compacta (SNc) (106).

Approximately 60 *PRKN* pathogenic and non-pathogenic variants have been identified, including deletions and duplications, which can complicate *PRKN* genotyping (107, 108). According to published data, up to 18% of EOPD patients globally and 27.6% of AR families carry *PRKN* pathogenic variants (23, 109). Among PD-*PRKN* patients, exon 3 deletion is the most frequent pathogenic variant (17). All *PRKN* pathogenic variants result in the loss of Parkin function, leading to a loss of Ubiquitin E3 ligase activity and subsequent neurodegeneration (110).

Monogenic PD associated with *PRKN* typically presents with early onset, slow symptom progression, and a positive response to dopaminergic treatment but is often accompanied by complications such as dystonia and prominent freezing of gait (111, 112).

Sixteen studies in this review provided information on the association between *PRKN* pathogenic variants and pain, including clinical data. These studies included eight case series/reports, three cross-sectional, three case–control studies, and two cohorts. One hundred fifty-six eight clinical studies and one animal study were excluded because they did not mention pain as a symptom or did not involve carriers pathogenic variant carriers.

A cohort study has reported painful limb dystonia as a symptom among *PRKN* pathogenic variant carriers (45). Besides, another cohort study described eight cases with lower limb dystonia activated by walking, Three of those cases also presented with lower limb pain unrelated to dystonic spasms (46).

A case–control study mentioned painful dystonia among three PRKN missense pathogenic carriers and general pain in another missense carrier, while one case report study described painful dystonic posture during off phases in a homozygous exon 3 deletion patient (31, 42). Three case reports described painful foot dystonia among deletion carriers, with four patients in one study also experiencing LBP (32, 33, 37).

Notably, a case series reported 24% dystonia among the patients but did without specifying whether they were *PRKN* pathogenic variant carriers (34). A case–control study reported "other symptoms" including pain and dystonia, as an onset symptoms in 43% of *PRKN* carriers compared to 13% of non-carriers (44).

Musculoskeletal pain has also been associated with *PRKN* pathogenic variants (R275W, exon 3 duplication and homozygous deletion) in two studies (40, 41).

In a cross-sectional study, a carrier of *PRKN* exon 9 deletion reported experiencing pain as a symptom, although the specific type of pain was not described (40). Another cross-sectional study noted painful contractions as an onset symptom in a patient with exon 3 deletion (41). Additionally, a homozygous *PRKN* pathogenic variant carrier required hospitalization due to painful OFF periods (36).

Sensory symptoms and signs, such as tingling sensation and a significant decrease in Sural Sensory Nerve Action Potential (SNAP) amplitude, were reported in two studies (35, 39). Besides, a case–control study observed a sensory gain in cold and hot pain thresholds among carriers (43).

On the other hand, there was a study screened 145 PD patients for *LRRK2* pathogenic variant, 19 of whom carried a *PRKN* pathogenic variant. They reported their clinical data, including pain, and no specific mention of pain was reported for any of the pathogenic variant carriers (38).

3.2.3. *PINK1* (PARK6)

Pathogenic variants in the *PINK1* gene are the second most common cause of AR EOPD (79). *PINK1* comprises 6 exons encoding PTEN-induced putative kinase 1, a 581 amino acid serine/threonine kinase (113). In normal conditions, wild-type *PINK1* plays a protective role against neuronal apoptosis in neural cell lines. However, pathogenic variants associated with PARK6 disrupt this protective function, leading to the degeneration of dopaminergic neurons (114). Most *PINK1* pathogenic variants are located in exon 7, with Q456X variant being the most frequent (79).

Individuals with *PINK1* monogenic PD typically have an onset age of around 32 years and experience slow disease progression, often with a favorable response to levodopa treatment and sleep benefits (115).

Thirteen studies have investigated the potential relationship between pain and *PINK1* pathogenic variants. These studies include two animal studies and eleven clinical research articles (seven case series/reports, one cross-sectional study, and three case–control studies). Forty-one clinical studies were excluded from the analysis because they did not mention pain as a symptom.

Regarding animal studies, a study found that thermal withdrawal latencies were significantly shorter in *PINK1*−/− rats than in wild-type rats over time, indicating altered pain responses (86). The second team used a rat model with neuropathic pain to investigate the role of *PINK1* and observed increased expression of *PINK1* in pain-related areas compared to control rats (87).

A case–control study reported painful episodes of torticollis and painful dystonia in a homozygous Q456X *PINK1* pathogenic variant carrier (54). Similarly, Zadikoff et al. described a homozygous Q456X *PINK1* pathogenic variant carrier who frequently experienced back and limb pain and painful wearing-off dystonia (47).

Multiple case reports, one case–control, and one cross-sectional study support the observation that pain is frequently encountered in patients with *PINK1* pathogenic variants, often manifesting in various body regions, particularly the neck, back, and shoulders. However, these studies did not provide detailed descriptions of the specific type and characteristics of the reported pain (20, 48–50, 53, 55).

Additionally, a case report study highlighted a patient with a novel homozygous nonsense *PINK1* pathogenic variant. This patient exhibited an urge to move her lower limbs accompanied by painful paresthesia and a sensation of distal cramping (51).

On the other hand, one case report (a homozygous Q456X carrier) and one case–control study specifically assessed pain symptoms in individuals carrying *PINK1* mutations, but neither of them reported pain as a symptom among the *PINK1* carriers (38, 44). In the case–control study, the prevalence of pain among *PINK1* carriers was 0%, while it was 13% in the non-carrier group, it was 13, and 43% in *PRKN* carriers (44).

3.2.4. *LRRK2* (PARK8)

Pathogenic variants in the *LRRK2* gene are the most common genetic cause of AD PD (24, 116), affecting both familial and sporadic forms of the disease (117). The *LRRK2* gene is a large gene consisting of 51 exons and encodes a 2,527 amino acid cytoplasmic protein called leucine-rich repeat kinase 2 (118). One of the critical functions of *LRRK2* is its regulation of protein synthesis through the miRNA pathway, and impairment in this pathway has been implicated in *LRRK2*-related pathogenesis (119).

More than 40 pathogenic variants have been identified in the *LRRK2* gene among PD patients, with eight of them known to cause PD (93). Among them, the most common and well-characterized *LRRK2* pathogenic variant is G2019S, with a prevalence ranging from 0 to 42% depending on ethnicity, followed by R1441C (120, 121).

LRRK2-PD patients typically presents as a LOPD, often respond well to levodopa treatment, and have fewer NMS than iPD cases (122, 123).

Among the identified studies involving *LRRK2*-associated PD patients, 18 included information on pain symptoms, while 124 studies did not mention pain or other sensory symptoms and were excluded from the analysis. Of the 18 studies, two were animal studies, and the remaining 16 were clinical consisting of five case series/reports, five cross-sectional studies, five case–control studies, and one cohort study.

Evidence from mouse studies investigating the association between *LRRK2* and pain observed similar pain sensitivity than controls without developing sensory deficits (88, 89).

Multiple studies have described the presence of painful dystonia in different cohorts of *LRRK2* pathogenic variant carriers. Three studies reported painful dystonia among G2019S pathogenic variant carriers. A case–control study reported that 42% of carriers experienced painful foot dystonia during the "OFF period" (64). Another case report described a patient who reported painful foot dystonia (58). Furthermore, a study reported painful cervical dystonia in one individual, which showed a positive response to levodopa treatment (57).

Severe wearing-off and dyskinesia with off-time pain have been reported in a *LRRK2* pathogenic variant carrier (59). Unspecified pain and joint pain have been reported as onset symptoms by three PD patients, all carriers of pathogenic variants, two G2019S and one R1441C (21, 61, 69). A case–control study found that pain is one of the most common NMS experienced by PD patients with *LRRK2* pathogenic mutations, affecting over half of the subjects (65). In a cross-sectional study, pain was observed in five R1441C carriers but only in one non-carrier, although the difference was not statistically significant ($p = 0.155$). The specific type and characteristics of the reported pain were not described in detail (62).

Notably, a case report documented a patient with severe and painful ON-dystonia who carried a *LRRK2* N1437H variant which is not recognized among the established pathogenic variants (56). Furthermore, McGill test recorded neuropathic disturbances were reported for *LRRK2* pathogenic variant carriers with a mean of 8.3 8.3 ± 14 compared to 0 for non-carriers. Additionally, *LRRK2* mutation carriers displayed a higher heat pain threshold compared to non-carriers (44.1 ± 4.82 vs. 40.6 ± 4.5°C, $p = 0.058$), suggesting a clear difference in terms of pain perception (60).

The final five included studies for this gene reported pain among individual carrying *LRRK2* pathogenic variants. However, after analysis, no statistically significant difference in the prevalence of pain emerged between the carrier and non-carrier groups (52, 63, 66–68).

3.2.5. *PARK7* (DJ-1)

PARK7 pathogenic variants are associated with AR PD and are relatively uncommon, constituting approximately 1 to 2% of EOPD cases (124). The *PARK7* gene is comprised of 8 exons, with the initial two being noncoding, and it encodes DJ-1, a 189 amino acid protein which exhibits neuroprotective and antioxidant properties (125, 126). Pathogenic variants within *PARK7* result in the production of a mutated DJ-1 protein characterized by reduced activity due to misfolding (127, 128).

Individual carrying *PARK7* pathogenic variant typically experience disease onset at an average age of 27 years and often exhibit prominent NMS, including mental health disorders and cognitive decline. Dystonia is highly prevalent, affecting approximately 73% of those with DJ-1 pathogenic variant (129).

Among the 26 studies examining *PARK7* pathogenic variants, only one case series/report study mentioned the presence of pain.

Djarmati et al. conducted a screening of 75 unrelated PD patients and identified one individual carrying a heterozygous deletion of exon 5 in *PARK7*. Among the 75 cases, three individuals presented pain as an onset symptom (4%); however, the authors did not specify whether the *PARK7* pathogenic variant carrier was one of the three PD patients reporting pain (34).

3.2.6. *VPS35* (PARK17)

VPS35 is responsible for encoding the vacuolar protein sorting ortholog 35, which is a critical component of a large complex involved in the transportation of proteins from endosomes to the trans-Golgi network. Pathogenic variants in *VPS35* were initially identified in 2011 and represent a rare cause of AD LOPD (18, 130).

Exome analysis has revealed that the D620N is the sole confirmed pathogenic variant associated wit PD thus far (131). Monogenic PD linked to *VPS35* exhibits high heritability but low penetrance. The clinical phenotype of *VPS35*-related PD closely resembles that of iPD, although the average age of onset is typically around 50 years old (132).

Among the twelve studies conducted on individual carrying *VPS35* variants, 67 patients were included, all of whom were heterozygous carriers (18). Out of these 67 heterozygous patients, who presented a total of 10 different potentially disease-causing variants, 50 (75%) carried the pathogenic D620N variant (18). While these studies did report various symptoms in these patients, NMS were the least commonly reported (6.2%) and none of the studies specifically mentioned the presence of pain (18).

3.2.7. *GBA1*

Pathogenic variants in the *GBA1* gene are not considered causative for PD, but they represent the most prevalent genetic susceptibility factor for the development of the disease (133, 134).

While *GBA1* pathogenic variants do not exhibit complete penetrance, heterozygote carriers face a fivefold increased risk of developing PD, while homozygotes have a 10- to 20-fold elevated risk (135). The penetrance of *GBA* pathogenic variant carriers to develop PD has been estimated as 13.7% by the age of 60 years and 29.7% by the age of 80 years (135).

Furthermore, due to their higher frequency in most PD populations compared to known monogenic PD genes such as *LRRK2*, *SNCA*, and *PRKN* (136), *GBA1* pathogenic variants are regarded as the most significant genetic risk factor for PD (137). Recent genome-wide association studies have confirmed that approximately 8–12% of PD patients carry *GBA1* pathogenic variants (138).

The *GBA1* gene, located on chromosome 1q22, encodes the enzyme glucocerebrosidase, and is associated with AR Gaucher disease (GD) (136). Approximately 130 *GBA1* pathogenic variants have been reported in PD patients (27, 139). Similar to GD, L444P and N370S are the two most frequent pathogenic variants. Severe pathogenic variants such as L444P are associated with a higher risk of developing PD, earlier age of onset, and more severe motor and NMS (140).

We included seven articles (comprising four case–control studies, two case series/reports, and one cross-sectional study). Eighteen articles were excluded because they did not mention pain among the reported symptoms.

While no distinctive symptoms have been reported to differentiate *GBA1* pathogenic variant carriers from individuals with iPD (141), pain appears to be an exception. Some patients with GD develop progressive parkinsonian symptoms (142), and notably, pain has been more frequently reported as an initial symptom in *GBA1*-PD patients compared to individuals with iPD.

Shoulder pain and LBP (76), unexplained pain (58% vs. 10%, $p = 0.005$) (75), and cramp-like pain as the primary source of disability at a young age (72) have all been reported more frequently among *GBA1* pathogenic variant carriers compared to non-carriers. In a case series pain was identified as the most bothersome symptom in 12 out of 15 *GBA1*-PD patients also reporting rigidity and stiffness, often accompanied by pain. One patient described painful dyskinesia as the most bothersome symptom, and two reported pain-related sleep problems (71).

In a cross-sectional study, pain was reported more frequently as an initial symptom in the *GBA1*-PD compared to the iPD 10.3 vs. (3.0%) ($p = 0.039$), with four patients reporting shoulder pain as their initial symptom. The most significant finding of this study is that the presenting symptoms of PD are similar in *GBA1* carriers and non-carriers for all parameters except for pain (73).

On the other hand, two case–control studies mentioned that *GBA1*-PD patients experienced bodily pain among their symptoms, although no statistically significant differences were reported between *GBA1*-PD and the iPD group ($p = 0.7$) (67, 74).

Considering that symptoms tend not be more severe among patients carrying pathological variants like L444P, it becomes intriguing to explore whether pain is more closely associated with severe variants (137). Contrary to this argument, based on existing studies, while two patients with N370S variant (considered mild) reported cramp-like pain (72), 49 patients with L444P variant (classified as severe) found no significant differences in terms of bodily pain compared to individuals with iPD (67).

3.2.8. *ATP13A2* (PARK9)

Pathogenic variants in the *ATP13A2* gene are responsible for Kufor-Rakeb syndrome (KRS), an AR atypical form of PD (143). The *ATP13A2* gene consists of 29 exons and encodes a protein of 1,180 amino acids (144). The *ATP13A2* protein plays a role in reducing intracellular concentrations of manganese ions (Mn2+), thereby offering protection against apoptosis (145). Pathogenic variants in *ATP13A2* lead to disruptions in the proteasomal pathway and premature degradation of *ATP13A2* mRNA, contributing to the development of KRS (146).

Since the discovery of *ATP13A2* pathogenic variants in 2006 (144), only a limited number of studies have been conducted and published. Among the 16 studies we assessed, one cross-sectional study and one case series/report did mention pain as a symptom, while the remaining 14 studies did not mention pain or other associated phenotypes and were consequently excluded.

In one cross-sectional study, a *ATP13A2* pathogenic variant was identified in two patients who did not have pain as one of their symptoms (38). Additionally, a case report documented arm dystonic posturing as the onset symptom in a homozygous patient with 2822delG variant who was unresponsive to anticholinergics and levodopa; however this variant has not yet been definitively established as a pathogenic variant for PD (70).

3.2.9. *DNAJC6* (PARK19A, b)

DNAJC6, located on 1p31.3, encodes auxilin, and its loss of function can lead to EOPD (147). In animal studies, the absence of auxilin has been linked to synaptic vesicle endocytosis disruptions, which have adverse effects on synaptic neurotransmission, homeostasis, and signaling (148). However, the precise mechanism by which auxilin deficiency induces dopaminergic neurodegeneration and unusual neurological symptoms remains incompletely understood (148).

Homozygous pathogenic variants in *DNAJC6* are responsible for atypical parkinsonism, exhibiting AR inheritance pattern (149, 150). PARK19A is characterized by onset in the first or second decade of life and rapid disease progression, while PARK-19B onset occurs between the third and fifth decades, featuring a slower progressive course, and similar features to classic iPD (149–151).

Three separate case-report studies identified Juvenile-onset PD, PARK-19A, among patients with homozygous pathogenic variant in the *DNAJC6* gene, including two loss-of-function and one nonsense variant; however, none of these cases reported pain as a symptom (149, 150, 152). Another study reported homozygous pathogenic variants in two unrelated families with PARK-19B and no instances of pain were among their reported symptoms (151).

Finally, in a comprehensive analysis utilizing whole exome sequencing *DNAJC6* potential pathogenic variants were explored in 6 juvenile parkinsonism patients. Homozygous nonsense R256* *DNAJC6* pathogenic variants were confirmed for all affected children and none of them reported pain among their symptoms (153).

3.2.10. *FBXO7* (PARK15)

FBXO7 a gene comprising ten exons is located on chromosome 22q12.3, encodes a member of the F-box protein family known as F-Box Protein 7, characterized by an approximately 40 amino acid motif (154). Pathogenic variants in *FBXO7* are responsible for an AR parkinsonian syndrome. The typical presenting symptoms include

bradykinesia and tremor, and patients affected by this disorder frequently exhibit pyramidal signs, dysarthria, and dyskinesia (155).

To date, eight studies have identified cases carrying *FBXO7* variants, predominantly associated with an early-onset parkinsonian and pyramidal syndrome (155–161). Notably, only one study reported a classical PD presentation in two siblings, caused by a new *FBXO7* pathogenic variant, L34R (162). None of these studies discuss or mention pain as one of the associated symptoms.

3.2.11. *SYNJ1* (PARK20)

SYNJ1, located on 21q22.11 and comprised of 33 exons, encodes Synaptojanin 1 protein. Pathogenic variant in *SYNJ1* Are associated to AR EOPD (163).

Remarkably, independently and simultaneously, two studies identified the same homozygous missense pathogenic variant in the *SYNJ1* gene, R258Q. In both studies affected patients were thoroughly screened for all known genes, and R258Q *SYNJ1* was the sole pathogenic variant identified. Two affected siblings in each study suffered from EOPD, and none of them mention pain among their symptoms (164, 165).

4. Discussion

This review was conducted to assess the presence of pain in patients with monogenic PD-related pathogenic variants, encompassing genes such as *SNCA, PRKN, PINK1, LRRK2, ATP13A2, PARK7, VPS35, GBA1, DNAJC6, FBXO7,* and *SYNJ1*. The central findings of this review offer valuable insights into the connection between specific gene pathogenic variants and the occurrence of pain in individuals with PD.

As a summary: (1) for the *SNCA* gene, two point mutations were associated with lower extremity pain and painful foot dystonic flexion while walking (28, 29). Gene duplications and triplications were also linked to dorsal and upper back pain (19, 30); (2) *PRKN* carriers reported painful lower limb dystonia and lower back pain as prominent symptoms (31–33, 36, 37, 42, 45, 46). Additionally, musculoskeletal pain, sensory loss, tingling sensation, and reduced SNAP amplitude suggested a central origin for abnormal sensitivity in *PRKN* pathogenic variant carriers (35, 39–41, 43); (3) Pain was observed in *PINK1* pathogenic variants. Homozygote carriers of the Q456X as the most frequent pathogenic variant experienced painful dystonia (47, 54), and pain was reported in various body parts, with a preference for the neck, back, and shoulders (20, 48–50, 53, 55). *PINK1* pathogenic variants were also associated with abnormal central somatosensory processing (51); (4) The *LRRK2* pathogenic variants are associated with pain, with painful dystonia reported in G2019S carriers (57, 58, 64) and G2019S and R1441C carriers reporting unspecified joint pain as their onset symptom (21, 61, 69). Multiple studies indicated that *LRRK2* pathogenic variant carriers experienced different types of pain as part of their symptoms (52, 56, 59, 60, 62, 63, 66–68); (5) Limited studies have assessed pain in *ATP13A2* pathogenic variant carriers. However, pain was reported in a few cases, suggesting a potential link between *ATP13A2* and pain (70); (6) Among *GBA1* pathogenic variant carriers, pain was reported as one of the most prevalent early symptoms, with some patients exclusively experiencing shoulder pain as an initial presentation (73). A case series study found that almost all *GBA1*-PD patients reported pain as their most bothersome symptom (71). Glucosylceramide accumulation, associated with *GBA1* pathogenic variants, may contribute to PD-associated sensory neuropathies and pain (166). Low *GBA1* activity has also been observed in PD patients without *GBA1* pathogenic variants, indicating its involvement in developing or progressing PD-associated sensory neuropathy (167). It would be indeed interesting to explore whether pain is more associated with severe pathological variants in PD-related genes. However, based on the available studies, there does not appear to be a significant difference in the prevalence of pain between individuals with severe pathological variants and those with iPD (67, 137); (7) No results were available regarding pain in *PARK7*, *VPS35, DNAJC6, FBXO7,* and *SYNJ1* pathogenic variants. The most common pain subtypes linked with Monogenic Parkinson's disease are summarized in Figure 2.

The findings discussed in this review provide valuable insights into the connection between specific monogenic variants in PD-related genes and pain in PD. Certain genes roles, including *SNCA, PRKN, PINK1,* and *LRRK2*, have been extensively studied providing potential perspectives into the underlying mechanisms of pain in PD.

In the case of *SNCA*, animal studies have indicated that abnormal pain in PD may be attributed to pathological changes related to alpha-synuclein- presence in unmyelinated areas of the spinal cord (84, 85). Clinical studies further support the presence of various pain manifestations in *SNCA* pathogenic variant carriers, such as painful dystonic flexion while walking and dorsal and upper back pain (19, 28, 29).

Similarly, *PRKN* pathogenic variant carriers have been found to experience painful lower limb dystonia and lower back pain, accompanied by reduced SNAP amplitude (31–33, 35–37, 39–43, 45, 46). These findings suggest the involvement of sensory axonal neuropathy and suggest that reduced SNAP amplitude may serve as a diagnostic indicator for *PRKN*-related PD.

PINK1 pathogenic variant carriers, they exhibit distinct somatosensory profiles and clinical entities compared to iPD, suggesting a primary hypofunction of nociceptive and non-nociceptive systems in *PINK1*-associated PD (43). Studies have proposed that specific *PINK1* pathogenic variants, such as the L347P, may be associated with pain in PD patients (20). Moreover, abnormalities in nociceptive processing have been reported in *PINK1* pathogenic variant carriers, indicating a potential role of abnormal central somatosensory processing in pain generation (43). Interestingly, these abnormalities seem to lead to hypoalgesia rather than hyperalgesia, contrasting with the findings in sporadic PD cases (168). The study of E3 ligase dysfunction has provided insights into the pathophysiology of PD, particularly about the *PRKN* gene (169). The single-base pair deletion in *PRKN* observed in four brothers with refractory back pain may be attributed to a lack of E3 activity, potentially contributing to lower back pain in PD patients (37). E3 ligases play a crucial role in the ubiquitin-proteasome pathway involved in protein turnover, and dysfunction in this pathway has been implicated in PD (169).

Additional research is needed to better understand the connection between *LRRK2* and pain as while multiple clinical studies have suggested that individuals with LRRK2 pathogenic variants experience different pain types (21, 58, 64, 88), animal models findings also suggest that pain sensitivity remains unchanged in the presence of *LRRK2* pathogenic variants (89, 123).

In the context of other monogenic variants, such as *ATP13A2, PARK7, VPS35*, *DNAJC6, FBXO7* and *SYNJ1* the current literature

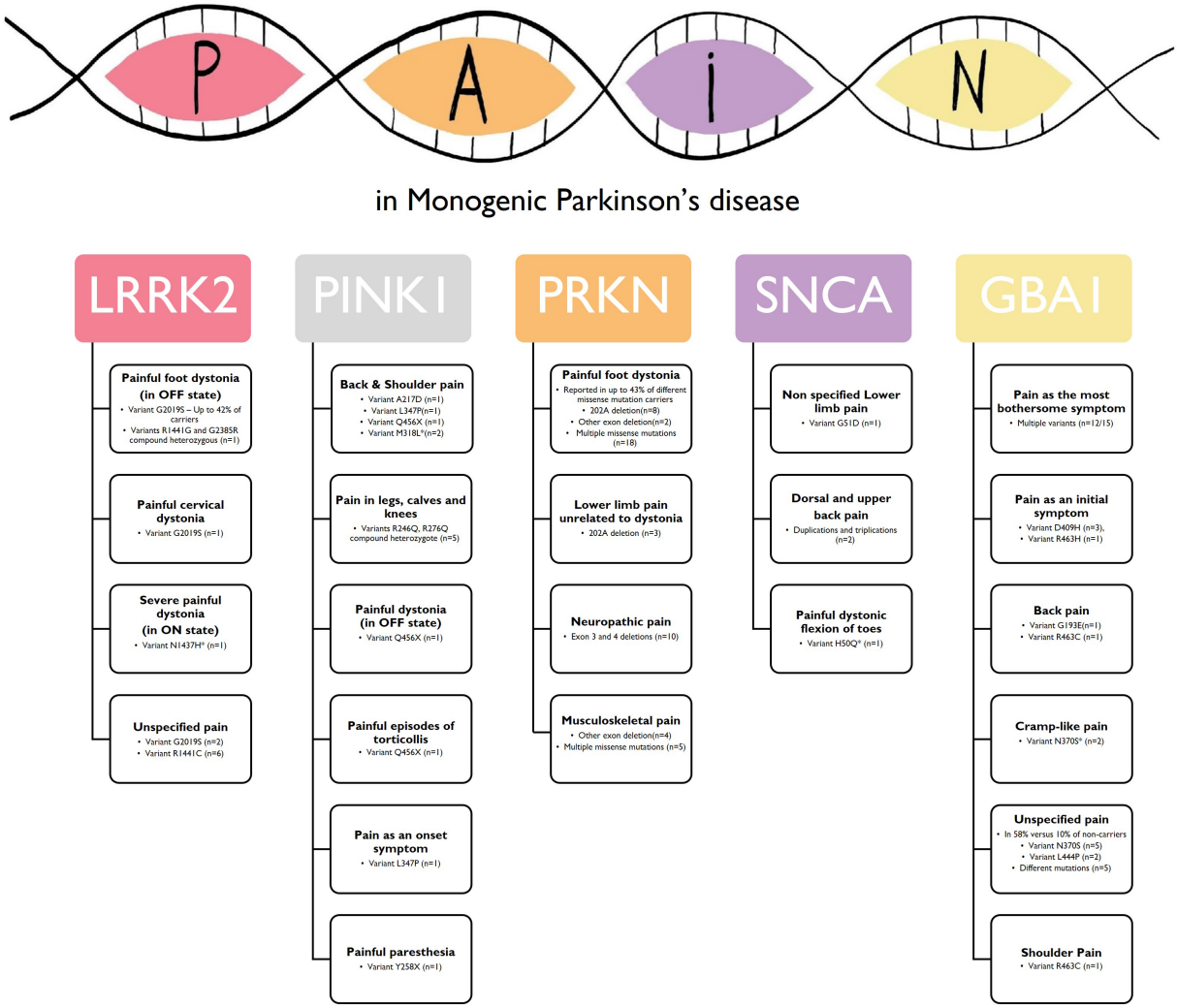

FIGURE 2
Common pain subtypes linked with Monogenic Parkinson's disease. This figure illustrates the most commonly pain subtypes reported in individuals with monogenic forms of Parkinson's disease (PD) associated with specific genes. The figure provides an overview of the pain profiles observed in relation to each gene pathogenic variant using the descriptors used in the original articles. *LRRK2*, Leucine-Rich Repeat Kinase 2; *PINK1*, PTEN induced putative protein kinase 1; *PRKN*, Parkin RBR E3 Ubiquitin Protein Ligase; *SNCA*, alpha-synuclein; *GBA*, Glucosylceramidase – *Variants that are not yet established as pathogenic for PD.

provides inconclusive results or insufficient data regarding their association with pain in PD. Additional studies are required to clarify the potential links between these genes and pain symptoms in PD patients.

Genetic associations with *GBA1* variants have demonstrated an influence the occurrence of pain in PD. Patients carrying *GBA1* variants have reported higher rates of pain compared to non-carriers (71, 73). Recent studies suggest that approaches targeting glucocerebrosidase activity or refolding may reduce PD pain and sensory loss (166). Even in PD patients without *GBA1* variants, low *GBA1* activity has been observed, indicating a prevalent loss of *GBA1* function that may contribute to developing or progressing PD-associated sensory neuropathy (135). These findings suggest that elevated levels of glucosylceramides may underlie sensory neuropathies characterized by the loss of thermal sensation and mechanical hypersensitivity in PD patients, irrespective of the presence of chronic pain.

Overall, this comprehensive review underscores the complex relationship between monogenic pathogenic variants in PD-related genes and the presence of pain in PD. To advance our understanding of the underlying mechanisms and identify potential targets for the treatment of pain in PD further investigations are essential. While this review provides a solid foundation for future research, it also sheds light on several limitations that require attention. The absence of pain assessment in numerous studies and the lack of detailed pain characteristics impede a comprehensive understanding of pain in monogenic PD-related pathogenic variants. Furthermore, the predominance of case series/reports and the limited information available for specific gene pathogenic variants underscores the necessity for more robust studies with larger sample sizes and systematic evaluation of pain symptoms. It is because of these limitation specific frequencies or data about the prevalence of pain in monogenic forms of PD remain unclear. Addressing this knowledge gap is of paramount importance and needs the implementation of more focused and structured study designs regarding pain in PD. Finally, gaining a deeper understanding of pain as a potential prodromal symptom in monogenic PD could provide insights into early indicators and predictive markers, allowing for more timely and targeted interventions.

5. Conclusion

In conclusion, the existing evidence suggests that specific types of pain are commonly observed in individuals with monogenic forms of PD, particularly those associated with *SNCA, PRKN, PINK1, LRRK2*, and *GBA1* genes. Pain in PD can potentially serve as a clinical marker, sometimes as a prodromal symptom as in individuals with *PRKN* and *GBA1* pathogenic variants, but also as a potential marker of progression other genes pathogenic variants.

Given the subjective nature of pain, its effective management requires standardized and objective standards of care. Future investigations should prioritize the collection of high-quality, standardized pain data, to enable direct comparison across studies and facilitate large-scale meta-analyses. Establishing connections between genetic profiles with pain symptoms could have significant clinical implications, such as guiding the selection of diagnostic tests, facilitating patient stratification for clinical trials, and ultimately enabling personalized treatment approaches for individuals with monogenic PD.

Author contributions

VB contributed to the study's design, planning, supervision, and manuscript review. PA and CT-C were involved in the planning, literature search, and manuscript writing. BA participated in the study's original design and search strategy. All authors critically reviewed and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Ford B. Pain in Parkinson's disease. *Mov Disord*. (2010) 25:S98–S103. doi: 10.1002/mds.22716

2. Ha AD, Jankovic J. Pain in Parkinson's disease. *Mov Disord*. (2012) 27:485–91. doi: 10.1002/mds.23959

3. Chaudhuri KR, Rizos A, Trenkwalder C, Rascol O, Pal S, Martino D, et al. King's Parkinson's disease pain scale, the first scale for pain in PD: an international validation: King's PD pain scale validation. *Mov Disord*. (2015) 30:1623–31. doi: 10.1002/mds.26270

4. Broen MPG, Braaksma MM, Patijn J, Weber WEJ. Prevalence of pain in Parkinson's disease: a systematic review using the modified QUADAS tool: prevalence of pain in Parkinson's disease. *Mov. Disord*. (2012) 27:480–4. doi: 10.1002/mds.24054

5. Defazio G, Gigante A, Mancino P, Tinazzi M. The epidemiology of pain in Parkinson's disease. *J Neural Transm*. (2013) 120:583–6. doi: 10.1007/s00702-012-0915-7

6. Toda K, Harada T. Prevalence, classification, and etiology of pain in Parkinson's disease: association between Parkinson's disease and fibromyalgia or chronic widespread pain. *Tohoku J Exp Med*. (2010) 222:1–5. doi: 10.1620/tjem.222.1

7. Ford B. Pain in Parkinson disease: the hidden epidemic. *Nat Rev Neurol*. (2009) 5:242–3. doi: 10.1038/nrneurol.2009.50

8. Mao CJ, Chen JP, Zhang XY, Chen Y, Li SJ, Li J, et al. Parkinson's disease patients with pain suffer from more severe non-motor symptoms. *Neurol Sci*. (2015) 36:263–8. doi: 10.1007/s10072-014-1942-y

9. Quittenbaum BH, Grahn B. Quality of life and pain in Parkinson's disease: a controlled cross-sectional study. *Parkinsonism Relat Disord*. (2004) 10:129–36. doi: 10.1016/j.parkreldis.2003.12.001

10. Rodríguez-Violante M, Alvarado-Bolaños A, Cervantes-Arriaga A, Martinez-Martin P, Rizos A, Chaudhuri KR. Clinical determinants of Parkinson's disease-associated pain using the King's Parkinson's disease pain scale. *Mov Disord Clin Pract*. (2017) 4:545–51. doi: 10.1002/mdc3.12469

11. Tinazzi M. Pain and motor complications in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. (2006) 77:822–5. doi: 10.1136/jnnp.2005.079053

12. Buhmann C, Kassubek J, Jost WH. Management of Pain in Parkinson's disease. *J Parkinsons Dis*. (2020) 10:S37–48. doi: 10.3233/JPD-202069

13. Tueth LE, Duncan RP. Musculoskeletal pain in Parkinson's disease: a narrative review. *Neurodegener Dis Manag*. (2021) 11:373–85. doi: 10.2217/nmt-2021-0011

14. Stamey W, Davidson A, Jankovic J. Shoulder pain: a presenting symptom of Parkinson disease. *JCR J Clin Rheumatol*. (2008) 14:253–4. doi: 10.1097/RHU.0b013e3181826d43

15. Cleeves L, Findley L. Frozen shoulder and other shoulder disturbancies in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. (1989) 52:813–4. doi: 10.1136/jnnp.52.6.813-b

16. Barbeau A, Roy M. Familial subsets in idiopathic Parkinson's disease. *Can J Neurol Sci J Can Sci Neurol*. (1984) 11:144–50. doi: 10.1017/S0317167100046308

17. Kasten M, Hartmann C, Hampf J, Schaake S, Westenberger A, Vollstedt EJ, et al. Genotype-phenotype relations for the Parkinson's disease genes *Parkin*, *PINK1*, *DJ1*: MDSGene systematic REVIEW: MDSGene REVIEW: *Parkin*, *PINK1*, *DJ1*. *Mov Disord*. (2018) 33:730–41. doi: 10.1002/mds.27352

18. Trinh J, Zeldenrust FMJ, Huang J, Kasten M, Schaake S, Petkovic S, et al. Genotype-phenotype relations for the Parkinson's disease genes *SNCA*, *LRRK2*, VPS35: MDSGene systematic review: MDSGene systematic review: *SNCA*, *LRRK2*, *VPS35*. *Mov Disord*. (2018) 33:1857–70. doi: 10.1002/mds.27527

19. Perandones C, Giugni JC, Calvo DS, Raina GB, De Jorge LL, Volpini V, et al. Mosaicism of alpha-synuclein gene rearrangements: report of two unrelated cases of early-onset parkinsonism. *Parkinsonism Relat Disord*. (2014) 20:558–61. doi: 10.1016/j.parkreldis.2013.11.014

20. Rogaeva E, Johnson J, Lang AE, Gulick C, Gwinn-Hardy K, Kawarai T, et al. Analysis of the *PINK1* gene in a large cohort of cases with Parkinson disease. *Arch Neurol [Internet]*. (2004) 61:1898–904. doi: 10.1001/archneur.61.12.1898

21. Gatto EM, Parisi V, Converso DP, Poderoso JJ, Carreras MC, Martí-Massó JF, et al. The LRRK2 G2019S mutation in a series of Argentinean patients with Parkinson's disease: clinical and demographic characteristics. *Neurosci Lett*. (2013) 537:1–5. doi: 10.1016/j.neulet.2013.01.011

22. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med*. (2018) 169:467–73. doi: 10.7326/M18-0850

23. Domingo A, Klein C. Genetics of Parkinson disease. *Handb Clin Neurol*. (2018):211–27. doi: 10.1016/B978-0-444-63233-3.00014-2

24. Cook L, Schulze J, Verbrugge J, Beck JC, Marder KS, Saunders-Pullman R, et al. The commercial genetic testing landscape for Parkinson's disease. *Parkinsonism Relat Disord*. (2021) 92:107–11. doi: 10.1016/j.parkreldis.2021.10.001

25. Jia F, Fellner A, Kumar KR. Monogenic Parkinson's disease: genotype, phenotype, pathophysiology, and genetic testing. *Genes*. (2022) 13:471. doi: 10.3390/genes13030471

26. Zimprich A, Benet-Pagès A, Struhal W, Graf E, Eck SH, Offman MN, et al. A mutation in VPS35, encoding a subunit of the Retromer complex, causes late-onset Parkinson disease. *Am J Hum Genet*. (2011) 89:168–75. doi: 10.1016/j.ajhg.2011.06.008

27. Zhang Y, Shu L, Sun Q, Zhou X, Pan H, Guo J, et al. Integrated genetic analysis of racial differences of common GBA variants in Parkinson's disease: a meta-analysis. *Front Mol Neurosci*. (2018) 11:43. doi: 10.3389/fnmol.2018.00043

28. Appel-Cresswell S, Vilarino-Guell C, Encarnacion M, Sherman H, Yu I, Shah B, et al. Alpha-synuclein p.H50Q, a novel pathogenic mutation for Parkinson's disease: α-Synuclein p.H50q, a novel mutation for Pd. *Mov Disord*. (2013) 28:811–3. doi: 10.1002/mds.25421

29. Lesage S, Anheim M, Letournel F, Bousset L, Honoré A, Rozas N, et al. G51D α-synuclein mutation causes a novel parkinsonian-pyramidal syndrome: *SNCA* G51D in parkinsonism. *Ann Neurol*. (2013) 73:459–71. doi: 10.1002/ana.23894

30. Byers B, Cord B, Nguyen HN, Schüle B, Fenno L, Lee PC, et al. *SNCA* triplication Parkinson's Patient's iPSC-derived DA neurons accumulate α-Synuclein and are susceptible to oxidative stress. *PLoS One*. (2011) 6:e26159 doi: 10.1371/journal.pone.0026159

31. Capecci M, Passamonti L, Annesi F, Annesi G, Bellesi M, Candiano ICC, et al. Chronic bilateral subthalamic deep brain stimulation in a patient with homozygous deletion in the Parkin gene. *Mov Disord*. (2004) 19:1450–2. doi: 10.1002/mds.20250

32. Khan NL. Progression of nigrostriatal dysfunction in a parkin kindred: an [18F] dopa PET and clinical study. *Brain*. (2002) 125:2248–56. doi: 10.1093/brain/awf237

33. Dogu O, Johnson J, Hernandez D, Hanson M, Hardy J, Apaydin H, et al. A consanguineous Turkish family with early-onset Parkinson's disease and an exon 4 parkin deletion: a Turkish Parkin family. *Mov Disord*. (2004) 19:812–6. doi: 10.1002/mds.20028

34. Djarmati A, Hedrich K, Svetel M, Schäfer N, Juric V, Vukosavic S, et al. Detection of *Parkin* (*PARK2*) and *DJ1* (*PARK7*) mutations in early-onset Parkinson disease: *Parkin* mutation frequency depends on ethnic origin of patients: MUTATION IN BRIEF. *Hum Mutat*. (2004) 23:525–5. doi: 10.1002/humu.9240

35. Ohsawa Y, Kurokawa K, Sonoo M, Yamada H, Hemmi S, Iwatsuki K, et al. Reduced amplitude of the sural nerve sensory action potential in PARK2 patients. *Neurology*. (2005) 65:459–62. doi: 10.1212/01.wnl.0000171859.85078.3d

36. Khan NL, Graham E, Critchley P, Schrag AE, Wood NW, Lees AJ, et al. Parkin disease: a phenotypic study of a large case series. *Brain*. (2003) 126:1279–92. doi: 10.1093/brain/awg142

37. Nisipeanu P, Inzelberg R, Abo Mouch S, Carasso RL, Blumen SC, Zhang J, et al. Parkin gene causing benign autosomal recessive juvenile parkinsonism. *Neurology*. (2001) 56:1573–5. doi: 10.1212/WNL.56.11.1573

38. Bouhouche A, Tesson C, Regragui W, Rahmani M, Drouet V, Tibar H, et al. Mutation analysis of consanguineous Moroccan patients with Parkinson's disease combining microarray and gene panel. *Front Neurol*. (2017) 8:567. doi: 10.3389/fneur.2017.00567

39. Shyu WC, Lin SZ, Chiang MF, Pang CY, Chen SY, Hsin YL, et al. Early-onset Parkinson's disease in a Chinese population: 99mTc-TRODAT-1 SPECT, Parkin gene analysis and clinical study. *Parkinsonism Relat Disord*. (2005) 11:173–80. doi: 10.1016/j.parkreldis.2004.12.004

40. Monroy-Jaramillo N, Guerrero-Camacho JL, Rodríguez-Violante M, Boll-Woehrlen MC, Yescas-Gómez P, Alonso-Vilatela ME, et al. Genetic mutations in early-onset Parkinson's disease Mexican patients: molecular testing implications. *Am J Med Genet B Neuropsychiatr Genet*. (2014) 165:235–44. doi: 10.1002/ajmg.b.32228

41. Lesage S, Magali P, Lohmann E, Lacomblez L, Teive H, Janin S, et al. Deletion of the *parkin* and *PACRG* gene promoter in early-onset parkinsonism. *Hum Mutat*. (2007) 28:27–32. doi: 10.1002/humu.20436

42. Doherty KM, Silveira-Moriyama L, Parkkinen L, Healy DG, Farrell M, Mencacci NE, et al. Parkin disease: a Clinicopathologic entity? *JAMA Neurol*. (2013) 70:571–9. doi: 10.1001/jamaneurol.2013.172

43. Gierthmühlen J, Schumacher S, Deuschl G, Fritzer E, Klein C, Baron R, et al. Somatosensory function in asymptomatic *Parkin*- mutation carriers: sensory symptoms and Parkinson's disease. *Eur J Neurol*. (2010) 17:513–7. doi: 10.1111/j.1468-1331.2009.02797.x

44. Koziorowski D, Hoffman-Zacharska D, Sławek J, Jamrozik Z, Janik P, Potulska-Chromik A, et al. Incidence of mutations in the PARK2, *PINK1*, *PARK7* genes in polish early-onset Parkinson disease patients. *Neurol Neurochir Pol*. (2013) 47:319–24. doi: 10.5114/ninp.2013.36756

45. Hassin-Baer S, Hattori N, Cohen OS, Massarwa M, Israeli-Korn SD, Inzelberg R. Phenotype of the 202 adenine deletion in the *parkin* gene: 40 years of follow-up: phenotype of the 202A deletion in the *parkin* gene. *Mov Disord*. (2011) 26:719–22. doi: 10.1002/mds.23456

46. Elia AE, Del Sorbo F, Romito LM, Barzaghi C, Garavaglia B, Albanese A. Isolated limb dystonia as presenting feature of Parkin disease. *J Neurol Neurosurg Psychiatry*. (2014) 85:827–8. doi: 10.1136/jnnp-2013-307294

47. Zadikoff C, Rogaeva E, Djarmati A, Sato C, Salehi-Rad S, St. George-Hyslop P, et al. Homozygous and heterozygous *PINK1* mutations: considerations for diagnosis and care of Parkinson's disease patients. *Mov Disord*. (2006) 21:875–9. doi: 10.1002/mds.20854

48. Norman BP, Lubbe SJ, Tan M, Warren N, Morris HR. Early onset Parkinson's disease in a family of Moroccan origin caused by a p.A217D mutation in *PINK1*: a case report. *BMC Neurol*. (2017) 17:153. doi: 10.1186/s12883-017-0933-z

49. Biswas A, Sadhukhan T, Majumder S, Misra AK, Das SK, Variation Consortium IGet al. Evaluation of *PINK1* variants in Indian Parkinson's disease patients. *Parkinsonism Relat Disord*. (2010) 16:167–71. doi: 10.1016/j.parkreldis.2009.10.005

50. Kilarski LL, Pearson JP, Newsway V, Majounie E, Knipe MDW, Misbahuddin A, et al. Systematic review and UK-based study of *PARK2 (parkin), PINK1, PARK7 (DJ-1)* and *LRRK2* in early-onset Parkinson's disease: *PARK2, PINK1, PARK7, LRRK2* in EOPD. *Mov Disord*. (2012) 27:1522–9. doi: 10.1002/mds.25132

51. Tan EK, Yew K, Chua E, Puvan K, Shen H, Lee E, et al. *PINK1* mutations in sporadic early-onset Parkinson's disease. *Mov Disord*. (2006) 21:789–93. doi: 10.1002/mds.20810

52. Bouhouche A, Tibar H, Ben El Haj R, El Bayad K, Razine R, Tazrout S, et al. *LRRK2* G2019S mutation: prevalence and clinical features in Moroccans with Parkinson's disease. *Park Dis*. (2017) 2017:1–7. doi: 10.1155/2017/2412486

53. Djarmati A, Hedrich K, Svetel M, Lohnau T, Schwinger E, Romac S, et al. Heterozygous*PINK1* mutations: a susceptibility factor for Parkinson disease? *Mov Disord*. (2006) 21:1526–30. doi: 10.1002/mds.20977

54. Ibáñez P, Lesage S, Lohmann E, Thobois S, Michele GD, Borg M, et al. Mutational analysis of the *PINK1* gene in early-onset parkinsonism in Europe and North Africa. *Brain*. (2006) 129:686–94. doi: 10.1093/brain/awl005

55. Gierthmuhlen J, Lienau F, Maag R, Hagenah JM, Deuschl G, Fritzer E, et al. Somatosensory processing in a German family with *PINK1* mutations: its potential role in Parkinson disease. *J Neurol Neurosurg Psychiatry*. (2009) 80:571–4. doi: 10.1136/jnnp.2008.158659

56. Puschmann A, Englund E, Ross OA, Vilariño-Güell C, Lincoln SJ, Kachergus JM, et al. First neuropathological description of a patient with Parkinson's disease and LRRK2 p.N1437H mutation. *Parkinsonism Relat Disord*. (2012) 18:332–8. doi: 10.1016/j.parkreldis.2011.11.019

57. Bras JM, Guerreiro RJ, Ribeiro MH, Januario C, Morgadinho A, Oliveira CR, et al. G2019S dardarin substitution is a common cause of Parkinson's disease in a Portuguese cohort. *Mov Disord*. (2005) 20:1653–5. doi: 10.1002/mds.20682

58. Gosal D, Ross OA, Wiley J, Irvine GB, Johnston JA, Toft M, et al. Clinical traits of LRRK2-associated Parkinson's disease in Ireland: a link between familial and idiopathic PD. *Parkinsonism Relat Disord*. (2005) 11:349–52. doi: 10.1016/j.parkreldis.2005.05.004

59. Hatano T, Funayama M, Kubo S, Ichiro MIF, Oji Y, Mori A, et al. Identification of a Japanese family with LRRK2 p.R1441G-related Parkinson's disease. *Neurobiol Aging*. (2014) 35:2656.e17–23. doi: 10.1016/j.neurobiolaging.2014.05.025

60. Khlebtovsky A, Roditi Y, Djaldetti R. Comparison of thermal sensation and pain thresholds in LRRK2 carriers and non carriers with Parkinson's disease. (2023) Available at: https://www.mdsabstracts.org/abstract/comparison-of-thermal-sensation-and-pain-thresholds-in-lrrk2-carriers-and-non-carriers-with-parkinsons-disease/

61. Hedrich K, Winkler S, Hagenah J, Kabakci K, Kasten M, Schwinger E, et al. RecurrentLRRK2 (Park8) mutations in early-onset Parkinson's disease. *Mov Disord*. (2006) 21:1506–10. doi: 10.1002/mds.20990

62. Criscuolo C, De Rosa A, Guacci A, Simons EJ, Breedveld GJ, Peluso S, et al. The *LRRK2* R1441C mutation is more frequent than G2019S in Parkinson's disease patients from southern Italy: *LRRK2* R1441C mutation more frequent in southern Italy. *Mov Disord*. (2011) 26:1732–6. doi: 10.1002/mds.23735

63. Li DW, Gu Z, Wang C, Ma J, Tang BS, Chen SD, et al. Non-motor symptoms in Chinese Parkinson's disease patients with and without LRRK2 G2385R and R1628P variants. *J Neural Transm*. (2015) 122:661–7. doi: 10.1007/s00702-014-1281-4

64. Healy DG, Falchi M, O'Sullivan SS, Bonifati V, Durr A, Bressman S, et al. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. *Lancet Neurol*. (2008) 7:583–90. doi: 10.1016/S1474-4422(08)70117-0

65. Baig F, Lawton M, Rolinski M, Ruffmann C, Nithi K, Evetts SG, et al. Delineating nonmotor symptoms in early Parkinson's disease and first-degree relatives. *Mov Disord*. (2015) 30:1759–66. doi: 10.1002/mds.26281

66. An XK, Peng R, Li T, Burgunder JM, Wu Y, Chen WJ, et al. LRRK2 Gly2385Arg variant is a risk factor of Parkinson's disease among Han-Chinese from mainland China. *Eur J Neurol*. (2008) 15:301–5. doi: 10.1111/j.1468-1331.2007.02052.x

67. Wang C, Cai Y, Gu Z, Ma J, Zheng Z, Tang BS, et al. Clinical profiles of Parkinson's disease associated with common leucine-rich repeat kinase 2 and glucocerebrosidase genetic variants in Chinese individuals. *Neurobiol Aging*. (2014) 35:725.e1–6. doi: 10.1016/j.neurobiolaging.2013.08.012

68. Zhang Z, Burgunder JM, An X, Wu Y, Chen W, Zhang J, et al. *LRRK2* R1628P variant is a risk factor of Parkinson's disease among Han-Chinese from mainland China: LRRK2 R1628P variant. *Mov Disord*. (2009) 24:1902–5. doi: 10.1002/mds.22371

69. Luciano MS, Lipton RB, Wang C, Katz M, Zimmerman ME, Sanders AE, et al. Clinical expression of *LRRK2* G2019S mutations in the elderly: clinical LRRK2 G2019S expression in the elderly. *Mov Disord*. (2010) 25:2571–6. doi: 10.1002/mds.23330

70. Martino D, Melzi V, Franco G, Kandasamy N, Monfrini E, Di Fonzo A. Juvenile dystonia-parkinsonism syndrome caused by a novel p.S941Tfs1X ATP13A2 (PARK9) mutation. *Parkinsonism Relat Disord*. (2015) 21:1378–80. doi: 10.1016/j.parkreldis.2015.09.036

71. Bonner N, Bozzi S, Morgan L, Mason B, Peterschmitt MJ, Fischer TZ, et al. Patients' experiences of Parkinson's disease: a qualitative study in glucocerebrosidase and idiopathic Parkinson's disease. *J Patient Rep Outcomes*. (2020) 4:65. doi: 10.1186/s41687-020-00230-9

72. Rodriguez-Porcel F, Espay AJ, Carecchio M. Parkinson disease in Gaucher disease. *J Clin Mov Disord*. (2017) 4:7. doi: 10.1186/s40734-017-0054-2

73. Kresojević N, Janković M, Petrović I, Kumar KR, Dragašević N, Dobričić V, et al. Presenting symptoms of GBA-related Parkinson's disease. *Parkinsonism Relat Disord*. (2015) 21:804–7. doi: 10.1016/j.parkreldis.2015.04.028

74. Jesús S, Huertas I, Bernal-Bernal I, Bonilla-Toribio M, Cáceres-Redondo MT, Vargas-González L, et al. GBA variants influence motor and non-motor features of Parkinson's disease. *PLoS One*. (2016) 11:e0167749 doi: 10.1371/journal.pone.0167749

75. McNeill A, Duran R, Hughes DA, Mehta A, Schapira AHV. A clinical and family history study of Parkinson's disease in heterozygous *glucocerebrosidase* mutation carriers. *J Neurol Neurosurg Psychiatry*. (2012) 83:853–4. doi: 10.1136/jnnp-2012-302402

76. Neumann J, Bras J, Deas E, O'Sullivan SS, Parkkinen L, Lachmann RH, et al. Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. *Brain*. (2009) 132:1783–94. doi: 10.1093/brain/awp044

77. Deng H, Wang P, Jankovic J. The genetics of Parkinson disease. *Ageing Res Rev*. (2018) 42:72–85. doi: 10.1016/j.arr.2017.12.007

78. Marras C, Lang A, van de Warrenburg BP, Sue CM, Tabrizi SJ, Bertram L, et al. Nomenclature of genetic movement disorders: recommendations of the international Parkinson and movement disorder society task force: nomenclature of genetic movement disorders. *Mov Disord*. (2016) 31:436–57. doi: 10.1002/mds.26527

79. Klein C, Westenberger A. Genetics of Parkinson's disease. *Cold Spring Harb Perspect Med*. (2012) 2:a008888–8. doi: 10.1101/cshperspect.a008888

80. Li B, Zhao G, Zhou Q, Xie Y, Wang Z, Fang Z, et al. Gene4PD: a comprehensive genetic database of Parkinson's disease. *Front Neurosci*. (2021) 15:679568. doi: 10.3389/fnins.2021.679568

81. Elwan M, Schaefer AM, Craig K, Hopton S, Falkous G, Blakely EL, et al. Changing faces of mitochondrial disease: autosomal recessive *POLG* disease mimicking myasthenia gravis and progressive supranuclear palsy. *BMJ Neurol Open*. (2022) 4:e000352. doi: 10.1136/bmjno-2022-000352

82. Bilguvar K, Tyagi NK, Ozkara C, Tuysuz B, Bakircioglu M, Choi M, et al. Recessive loss of function of the neuronal ubiquitin hydrolase UCHL1 leads to early-onset progressive neurodegeneration. *Proc Natl Acad Sci*. (2013) 110:3489–94. doi: 10.1073/pnas.1222732110

83. Selvaraj S, Piramanayagam S. Impact of gene mutation in the development of Parkinson's disease. *Genes Dis*. (2019) 6:120–8. doi: 10.1016/j.gendis.2019.01.004

84. Vivacqua G, Yin JJ, Casini A, Li X, Li YH, D'Este L, et al. Immunolocalization of alpha-synuclein in the rat spinal cord by two novel monoclonal antibodies. *Neuroscience*. (2009) 158:1478–87. doi: 10.1016/j.neuroscience.2008.12.001

85. Valek L, Tran B, Wilken-Schmitz A, Trautmann S, Heidler J, Schmid T, et al. Prodromal sensory neuropathy in *Pink1* $^{-/-}$ *SNCA* ^{A53T} double mutant Parkinson mice. *Neuropathol Appl Neurobiol*. (2021) 47:1060–79. doi: 10.1111/nan.12734

86. Johnson RA, Kelm-Nelson CA, Ciucci MR. Changes to ventilation, vocalization, and thermal nociception in the *Pink1*−/− rat model of Parkinson's disease. *J Parkinsons Dis*. (2020) 10:489–504. doi: 10.3233/JPD-191853

87. Yi MH, Shin J, Shin N, Yin Y, Lee SY, Kim CS, et al. *PINK1* mediates spinal cord mitophagy in neuropathic pain. *J Pain Res*. (2019) 12:1685–99. doi: 10.2147/JPR.S198730

88. Bichler Z, Lim HC, Zeng L, Tan EK. Non-motor and motor features in LRRK2 transgenic mice. *PLoS One*. (2013) 8:e70249 doi: 10.1371/journal.pone.0070249

89. Valek L, Auburger G, Tegeder I. Sensory neuropathy and nociception in rodent models of Parkinson's disease. *Dis Model Mech*. (2019) 12. doi: 10.1242/dmm.039396

90. Blauwendraat C, Makarious MB, Leonard HL, Bandres-Ciga S, Iwaki H, Nalls MA, et al. A population scale analysis of rare *SNCA* variation in the UK biobank. *Neurobiol Dis*. (2021) 148:105182. doi: 10.1016/j.nbd.2020.105182

91. Giasson BI, Duda JE, Murray IVJ, Chen Q, Souza JM, Hurtig HI, et al. Oxidative damage linked to neurodegeneration by selective α-Synuclein nitration in Synucleinopathy lesions. *Science*. (2000) 290:985–9. doi: 10.1126/science.290.5493.985

92. Lotharius J. Impaired dopamine storage resulting from alpha-synuclein mutations may contribute to the pathogenesis of Parkinson's disease. *Hum Mol Genet*. (2002) 11:2395–407. doi: 10.1093/hmg/11.20.2395

93. Lesage S, Brice A. Parkinson's disease: from monogenic forms to genetic susceptibility factors. *Hum Mol Genet*. (2009) 18:R48–59. doi: 10.1093/hmg/ddp012

94. Hoffman-Zacharska D, Koziorowski D, Ross OA, Milewski M, Poznański J, Jurek M, et al. Novel A18T and pA29S substitutions in α-synuclein may be associated with sporadic Parkinson's disease. *Parkinsonism Relat Disord*. (2013) 19:1057–60. doi: 10.1016/j.parkreldis.2013.07.011

95. Kiely AP, Asi YT, Kara E, Limousin P, Ling H, Lewis P, et al. α-Synucleinopathy associated with G51D *SNCA* mutation: a link between Parkinson's disease and multiple system atrophy? *Acta Neuropathol (Berl)*. (2013) 125:753–69. doi: 10.1007/s00401-013-1096-7

96. Krüger R, Kuhn W, Müller T, Woitalla D, Graeber M, Kösel S, et al. AlaSOPro mutation in the gene encoding α-synuclein in Parkinson's disease. *Nat Genet*. (1998) 18:106–8. doi: 10.1038/ng0298-106

97. Pasanen P, Myllykangas L, Siitonen M, Raunio A, Kaakkola S, Lyytinen J, et al. A novel α-synuclein mutation A53E associated with atypical multiple system atrophy and Parkinson's disease-type pathology. *Neurobiol Aging*. (2014) 35:2180.e1–5. doi: 10.1016/j.neurobiolaging.2014.03.024

98. Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, et al. Mutation in the α-Synuclein gene identified in families with Parkinson's disease. *Science*. (1997) 276:2045–7. doi: 10.1126/science.276.5321.2045

99. Proukakis C, Dudzik CG, Brier T, MacKay DS, Cooper JM, Millhauser GL, et al. A novel -synuclein missense mutation in Parkinson disease. *Neurology*. (2013) 80:1062–4. doi: 10.1212/WNL.0b013e31828727ba

100. Zarranz JJ, Alegre J, Gómez-Esteban JC, Lezcano E, Ros R, Ampuero I, et al. The new mutation, E46K, of α-synuclein causes parkinson and Lewy body dementia: new α-Synuclein gene mutation. *Ann Neurol*. (2004) 55:164–73. doi: 10.1002/ana.10795

101. Kasten M, Klein C. The many faces of alpha-synuclein mutations: the many faces of alpha-Synuclein mutations. *Mov Disord*. (2013) 28:697–701. doi: 10.1002/mds.25499

102. Klein C, Lohmann K. Parkinson disease(s): is "Parkin disease" a distinct clinical entity? *Neurology*. (2009) 72:106–7. doi: 10.1212/01.wnl.0000333666.65522.8d

103. Klein C, Schlossmacher MG. Parkinson disease, 10 years after its genetic revolution: multiple clues to a complex disorder. *Neurology*. (2007) 69:2093–104. doi: 10.1212/01.wnl.0000271880.27321.a7

104. Castelo Rueda MP, Raftopoulou A, Gögele M, Borsche M, Emmert D, Fuchsberger C, et al. Frequency of heterozygous Parkin (PRKN) variants and penetrance of Parkinson's disease risk markers in the population-based CHRIS cohort. *Front Neurol*. (2021) 12:706145. doi: 10.3389/fneur.2021.706145

105. Zhu W, Huang X, Yoon E, Bandres-Ciga S, Blauwendraat C, Cade JH, et al. Heterozygous *PRKN* mutations are common but do not increase the risk of Parkinson's disease [internet]. *Neurology*. (2021). doi: 10.1101/2021.08.11.21261928

106. Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, et al. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature*. (1998) 392:605–8. doi: 10.1038/33416

107. Klein C, Schumacher K, Jacobs H, Hagenah J, Kis B, Garrels J, et al. Association studies of Parkinson's disease andparkin polymorphisms. *Ann Neurol*. (2000) 48:126–7. doi: 10.1002/1531-8249(200007)48:1<126::AID-ANA22>3.0.CO;2-K

108. Hedrich K, Eskelson C, Wilmot B, Marder K, Harris J, Garrels J, et al. Distribution, type, and origin ofParkin mutations: review and case studies. *Mov Disord*. (2004) 19:1146–57. doi: 10.1002/mds.20234

109. Lesage S, Lunati A, Houot M, Romdhan SB, Clot F, Tesson C, et al. Characterization of recessive Parkinson disease in a large multicenter study. *Ann Neurol*. (2020) 88:843–50. doi: 10.1002/ana.25787

110. Dawson TM, Dawson VL. The role of parkin in familial and sporadic Parkinson's disease: the role of Parkin in familial and sporadic PD. *Mov Disord*. (2010) 25:S32–9. doi: 10.1002/mds.22798

111. Ishikawa A, Tsuji S. Clinical analysis of 17 patients in 12 Japanese families with autosomal-recessive type juvenile parkinsonism. *Neurology*. (1996) 47:160–6. doi: 10.1212/WNL.47.1.160

112. Grünewald A, Kasten M, Ziegler A, Klein C. Next-generation phenotyping using the *Parkin* example: time to catch up with genetics. *JAMA Neurol*. (2013) 70:1186. doi: 10.1001/jamaneurol.2013.488

113. Valente EM, Abou-Sleiman PM, Caputo V, Muqit MMK, Harvey K, Gispert S, et al. Hereditary early-onset Parkinson's disease caused by mutations in *PINK1*. *Science*. (2004) 304:1158–60. doi: 10.1126/science.1096284

114. Petit A, Kawarai T, Paitel E, Sanjo N, Maj M, Scheid M, et al. Wild-type *PINK1* prevents basal and induced neuronal apoptosis, a protective effect abrogated by Parkinson disease-related mutations. *J Biol Chem*. (2005) 280:34025–32. doi: 10.1074/jbc.M505143200

115. Bonifati V, Rohe CF, Breedveld GJ, Fabrizio E, De Mari M, Tassorelli C, et al. Early-onset parkinsonism associated with *PINK1* mutations: frequency, genotypes, and phenotypes. *Neurology*. (2005) 65:87–95. doi: 10.1212/01.wnl.0000167546.39375.82

116. Paisán Ruíz C, Jain S, Evans EW, Gilks WP, Simón J, van der Brug M, et al. Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. *Neuron*. (2004) 44:595–600. doi: 10.1016/j.neuron.2004.10.023

117. Rui Q, Ni H, Li D, Gao R, Chen G. The role of LRRK2 in neurodegeneration of Parkinson disease. *Curr Neuropharmacol*. (2018) 16:1348–57. doi: 10.2174/1570159X16666180222165418

118. Nuytemans K, Theuns J, Cruts M, Van Broeckhoven C. Genetic etiology of Parkinson disease associated with mutations in the *SNCA*, *PARK2*, *PINK1*, *PARK7*, and *LRRK2* genes: a mutation update. *Hum Mutat*. (2010) 31:763–80. doi: 10.1002/humu.21277

119. Gehrke S, Imai Y, Sokol N, Lu B. Pathogenic LRRK2 negatively regulates microRNA-mediated translational repression. *Nature*. (2010) 466:637–41. doi: 10.1038/nature09191

120. Iwaki H, Blauwendraat C, Makarious MB, Bandrés-Ciga S, Leonard HL, Gibbs JR, et al. Penetrance of Parkinson's disease in *LRRK2* p.G2019S carriers is modified by a polygenic risk score. *Mov Disord*. (2020 May) 35:774–80. doi: 10.1002/mds.27974

121. Correia Guedes L, Ferreira JJ, Rosa MM, Coelho M, Bonifati V, Sampaio C. Worldwide frequency of G2019S LRRK2 mutation in Parkinson's disease: a systematic review. *Parkinsonism Relat Disord*. (2010) 16:237–42. doi: 10.1016/j.parkreldis.2009.11.004

122. Deng H, Le W, Guo Y, Hunter CB, Xie W, Jankovic J. Genetic and clinical identification of Parkinson's disease patients withLRRK2 G2019S mutation. *Ann Neurol*. (2005) 57:933–4. doi: 10.1002/ana.20510

123. Alcalay RN, Mejia-Santana H, Mirelman A, Saunders-Pullman R, Raymond D, Palmese C, et al. Neuropsychological performance in LRRK2 G2019S carriers with Parkinson's disease. *Parkinsonism Relat Disord*. (2015) 21:106–10. doi: 10.1016/j.parkreldis.2014.09.033

124. Pankratz N, Pauciulo MW, Elsaesser VE, Marek DK, Halter CA, Wojcieszek J, et al. Mutations in DJ-1 are rare in familial Parkinson disease. *Neurosci Lett*. (2006) 408:209–13. doi: 10.1016/j.neulet.2006.09.003

125. Bonifati V, Rizzu P, van Baren MJ, Schaap O, Breedveld GJ, Krieger E, et al. Mutations in the *DJ-1* gene associated with autosomal recessive early-onset parkinsonism. *Science*. (2003) 299:256–9. doi: 10.1126/science.1077209

126. Meulener MC, Xu K, Thomson L, Ischiropoulos H, Bonini NM. Mutational analysis of DJ-1 in *Drosophila* implicates functional inactivation by oxidative damage and aging. *Proc Natl Acad Sci*. (2006) 103:12517–22. doi: 10.1073/pnas.0601891103

127. Anderson PC, Daggett V. Molecular basis for the structural instability of human DJ-1 induced by the L166P mutation associated with Parkinson's disease. *Biochemistry*. (2008) 47:9380–93. doi: 10.1021/bi800677k

128. Malgieri G, Eliezer D. Structural effects of Parkinson's disease linked DJ-1 mutations. *Protein Sci*. (2008) 17:855–68. doi: 10.1110/ps.073411608

129. Weissbach A, Wittke C, Kasten M, Klein C. 'Atypical' Parkinson's disease – genetic. (2019) 207–235. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0074774219300972

130. Vilariño-Güell C, Wider C, Ross OA, Dachsel JC, Kachergus JM, Lincoln SJ, et al. VPS35 mutations in Parkinson disease. *Am J Hum Genet*. (2011) 89:162–7. doi: 10.1016/j.ajhg.2011.06.001

131. Ando M, Funayama M, Li Y, Kashihara K, Murakami Y, Ishizu N, et al. *VPS35* mutation in Japanese patients with typical Parkinson's disease: *VPS35* mutation in Japanese PD. *Mov Disord*. (2012) 27:1413–7. doi: 10.1002/mds.25145

132. Sharma M, Ioannidis JPA, Aasly JO, Annesi G, Brice A, Bertram L, et al. A multi-Centre clinico-genetic analysis of the *VPS35* gene in Parkinson disease indicates reduced penetrance for disease-associated variants. *J Med Genet*. (2012) 49:721–6. doi: 10.1136/jmedgenet-2012-101155

133. Cerri S, Ghezzi C, Ongari G, Croce S, Avenali M, Zangaglia R, et al. GBA mutations influence the release and pathological effects of small extracellular vesicles from fibroblasts of patients with Parkinson's disease. *Int J Mol Sci*. (2021) 22:2215. doi: 10.3390/ijms22042215

134. Zhao F, Bi L, Wang W, Wu X, Li Y, Gong F, et al. Mutations of glucocerebrosidase gene and susceptibility to Parkinson's disease: An updated meta-analysis in a European population. *Neuroscience*. (2016) 320:239–46. doi: 10.1016/j.neuroscience.2016.02.007

135. Beavan M, McNeill A, Proukakis C, Hughes DA, Mehta A, Schapira AHV. Evolution of prodromal clinical markers of Parkinson disease in a *GBA* mutation–positive cohort. *JAMA Neurol*. (2015) 72:201–8. doi: 10.1001/jamaneurol.2014.2950

136. Sidransky E, Lopez G. The link between the GBA gene and parkinsonism. *Lancet Neurol*. (2012) 11:986–98. doi: 10.1016/S1474-4422(12)70190-4

137. Granek Z, Barczuk J, Siwecka N, Rozpędek-Kamińska W, Kucharska E, Majsterek I. GBA1 gene mutations in α-Synucleinopathies—molecular mechanisms underlying pathology and their clinical significance. *Int J Mol Sci*. (2023) 24:2044. doi: 10.3390/ijms24032044

138. Avenali M, Blandini F, Cerri S. Glucocerebrosidase defects as a major risk factor for Parkinson's disease. *Front Aging Neurosci*. (2020) 12:97. doi: 10.3389/fnagi.2020.00097

139. Velez-Pardo C, Lorenzo-Betancor O, Jimenez-Del-Rio M, Moreno S, Lopera F, Cornejo-Olivas M, et al. The distribution and risk effect of GBA variants in a large cohort of PD patients from Colombia and Peru. *Parkinsonism Relat Disord*. (2019) 63:204–8. doi: 10.1016/j.parkreldis.2019.01.030

140. Ryan E, Seehra G, Sharma P, Sidransky E. GBA1-associated parkinsonism: new insights and therapeutic opportunities. *Curr Opin Neurol*. (2019) 32:589–96. doi: 10.1097/WCO.0000000000000715

141. Riboldi GM, Di Fonzo AB. GBA, Gaucher disease, and Parkinson's disease: from genetic to clinic to new therapeutic approaches. *Cells*. (2019) 8:364. doi: 10.3390/cells8040364

142. Tayebi N. Gaucher disease with parkinsonian manifestations: does glucocerebrosidase deficiency contribute to a vulnerability to parkinsonism? *Mol Genet Metab*. (2003) 79:104–9. doi: 10.1016/S1096-7192(03)00071-4

143. Lill CM. Genetics of Parkinson's disease. *Mol Cell Probes*. (2016) 30:386–96. doi: 10.1016/j.mcp.2016.11.001

144. Ramirez A, Heimbach A, Gründemann J, Stiller B, Hampshire D, Cid LP, et al. Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. *Nat Genet*. (2006) 38:1184–91. doi: 10.1038/ng1884

145. Tan J, Zhang T, Jiang L, Chi J, Hu D, Pan Q, et al. Regulation of intracellular manganese homeostasis by Kufor-Rakeb syndrome-associated ATP13A2 protein. *J Biol Chem*. (2011) 286:29654–62. doi: 10.1074/jbc.M111.233874

146. Park JS, Blair NF, Sue CM. The role of ATP13A2 in Parkinson's disease: clinical phenotypes and molecular mechanisms: ATP13A2 in Parkinson's disease. *Mov Disord*. (2015) 30:770–9. doi: 10.1002/mds.26243

147. Vidyadhara DJ, Somayaji M, Wade N, Yücel B, Zhao H, Shashaank N, et al. Dopamine transporter and synaptic vesicle sorting defects underlie auxilin-associated Parkinson's disease. *Cell Rep*. (2023) 42:112231. doi: 10.1016/j.celrep.2023.112231

148. Yim YI, Sun T, Wu LG, Raimondi A, De Camilli P, Eisenberg E, et al. Endocytosis and clathrin-uncoating defects at synapses of auxilin knockout mice. *Proc Natl Acad Sci*. (2010) 107:4412–7. doi: 10.1073/pnas.1000738107

149. Edvardson S, Cinnamon Y, Ta-Shma A, Shaag A, Yim YI, Zenvirt S, et al. A deleterious mutation in *DNAJC6* encoding the neuronal-specific Clathrin-Uncoating co-chaperone Auxilin, is associated with juvenile parkinsonism. *PLoS One*. (2012) 7:e36458 doi: 10.1371/journal.pone.0036458

150. Köroğlu Ç, Baysal L, Cetinkaya M, Karasoy H, Tolun A. *DNAJC6* is responsible for juvenile parkinsonism with phenotypic variability. *Parkinsonism Relat Disord*. (2013) 19:320–4. doi: 10.1016/j.parkreldis.2012.11.006

151. Olgiati S, Quadri M, Fang M, Rood JPMA, Saute JA, Chien HF, et al. *D NAJC 6* mutations associated with early-onset Parkinson's disease: *DNAJC6* mutations in Parkinson's disease. *Ann Neurol*. (2016) 79:244–56. doi: 10.1002/ana.24553

152. Elsayed LEO, Drouet V, Usenko T, Mohammed IN, Hamed AAA, Elseed MA, et al. A novel nonsense mutation in *DNAJC 6* expands the phenotype of autosomal-recessive juvenile-onset Parkinson's disease. *Ann Neurol*. (2016) 79:335–7. doi: 10.1002/ana.24591

153. Ng J, Cortès-Saladelafont E, Abela L, Termsarasab P, Mankad K, Sudhakar S, et al. *DNAJC6* mutations disrupt dopamine homeostasis in juvenile Parkinsonism-Dystonia. *Mov Disord*. (2020) 35:1357–68. doi: 10.1002/mds.28063

154. Kipreos ET, Pagano M. The F-box protein family. *Genome Biol*. (2000) 1:REVIEWS3002. doi: 10.1186/gb-2000-1-5-reviews3002

155. Wei L, Ding L, Li H, Lin Y, Dai Y, Xu X, et al. Juvenile-onset parkinsonism with pyramidal signs due to compound heterozygous mutations in the F-box only protein 7 gene. *Parkinsonism Relat Disord*. (2018) 47:76–9. doi: 10.1016/j.parkreldis.2017.11.332

156. Shojaee S, Sina F, Banihosseini SS, Kazemi MH, Kalhor R, Shahidi GA, et al. Genome-wide linkage analysis of a parkinsonian-pyramidal syndrome pedigree by 500 K SNP arrays. *Am J Hum Genet*. (2008) 82:1375–84. doi: 10.1016/j.ajhg.2008.05.005

157. Fonzo AD, Dekker MCJ, Montagna P, Baruzzi A, Yonova EH, Guedes LC, et al. FBXO7 mutations cause autosomal recessive, early-onset parkinsonian-pyramidal syndrome. *Neurology*. (2009) 72:240–5. doi: 10.1212/01.wnl.0000338144.10967.2b

158. Paisán-Ruiz C, Guevara R, Federoff M, Hanagasi H, Sina F, Elahi E, et al. Early-onset L-dopa-responsive parkinsonism with pyramidal signs due to *ATP13A2, PLA2G6, FBXO7* and *spatacsin* mutations: complex recessive Parkinsonisms. *Mov Disord*. (2010) 25:1791–800. doi: 10.1002/mds.23221

159. Keller Sarmiento IJ, Afshari M, Kinsley L, Silani V, Akhtar RS, Simuni T, et al. Novel bi-allelic FBXO7 variants in a family with early-onset typical Parkinson's disease. *Parkinsonism Relat Disord*. (2022) 104:88–90. doi: 10.1016/j.parkreldis.2022.10.014

160. Gündüz A, Eken AG, Bilgiç B, Hanagasi HA, Bilgüvar K, Günel M, et al. FBXO7–R498X mutation: phenotypic variability from chorea to early onset parkinsonism within a family. *Parkinsonism Relat Disord*. (2014) 20:1253–6. doi: 10.1016/j.parkreldis.2014.07.016

161. Conedera S, Apaydin H, Li Y, Yoshino H, Ikeda A, Matsushima T, et al. FBXO7 mutations in Parkinson's disease and multiple system atrophy. *Neurobiol Aging*. (2016) 40:192.e1–5. doi: 10.1016/j.neurobiolaging.2016.01.003

162. Lohmann E, Coquel AS, Honoré A, Gurvit H, Hanagasi H, Emre M, et al. A new F-box protein 7 GENE MUTATION CAUSING TYPICAL Parkinson's disease: *FBXO7* GENE MUTATION CAUSING TYPICAL PD. *Mov Disord*. (2015) 30:1130–3. doi: 10.1002/mds.26266

163. Lesage S, Mangone G, Tesson C, Bertrand H, Benmahdjoub M, Kesraoui S, et al. Clinical variability of SYNJ1-associated early-onset parkinsonism. *Front Neurol*. (2021) 12:648457. doi: 10.3389/fneur.2021.648457

164. Quadri M, Fang M, Picillo M, Olgiati S, Breedveld GJ, Graafland J, et al. Mutation in the *SYNJ1* gene associated with autosomal recessive. *Early-Onset Parkinsonism Hum Mutat*. (2013) 34:1208–15. doi: 10.1002/humu.22373

165. Krebs CE, Karkheiran S, Powell JC, Cao M, Makarov V, Darvish H, et al. The Sac1 domain of *SYNJ 1* identified mutated in a family with early-onset progressive P arkinsonism with generalized seizures. *Hum Mutat*. (2013) 34:1200–7. doi: 10.1002/humu.22372

166. Klatt-Schreiner K, Valek L, Kang J, Khlebtovsky A, Trautmann S, Hahnefeld L, et al. High glucosylceramides and low anandamide contribute to sensory loss and pain in Parkinson's disease. *Mov Disord*. (2020) 35:1822–33. doi: 10.1002/mds.28186

167. Alcalay RN, Levy OA, Waters CH, Fahn S, Ford B, Kuo SH, et al. Glucocerebrosidase activity in Parkinson's disease with and without *GBA* mutations. *Brain*. (2015) 138:2648–58. doi: 10.1093/brain/awv179

168. Buhidma Y, Rukavina K, Chaudhuri KR, Duty S. Potential of animal models for advancing the understanding and treatment of pain in Parkinson's disease. *Npj Park Dis*. (2020) 6:1. doi: 10.1038/s41531-019-0104-6

169. George AJ, Hoffiz YC, Charles AJ, Zhu Y, Mabb AM. A comprehensive atlas of E3 ubiquitin ligase mutations in neurological disorders. *Front Genet*. (2018) 9:29. doi: 10.3389/fgene.2018.00029

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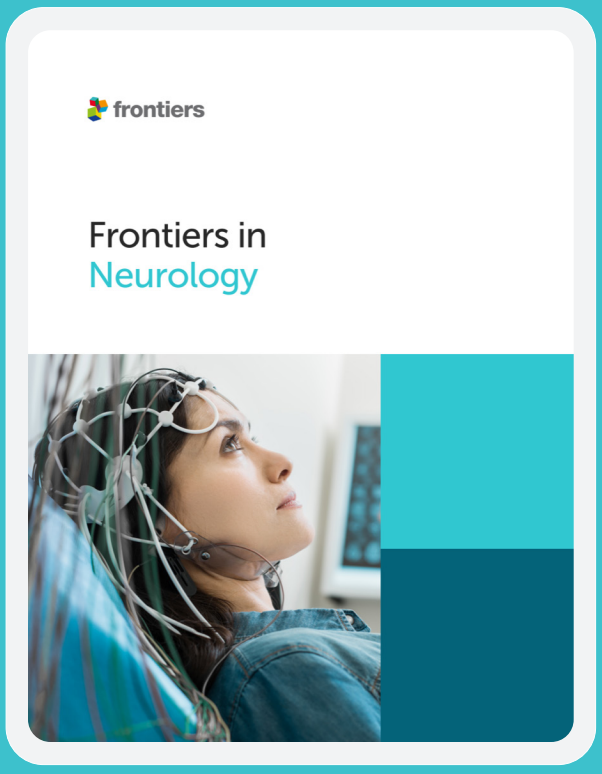

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