The Canadian Journal of Neurological Sciences (2024), **51**, 650–659
doi:10.1017/cjn.2023.336

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Original Article

Impact of Non-Motor Symptoms on Quality of Life in Patients with Early-Onset Parkinson's Disease

Ameya Patwardhan, Nitish Kamble, Amitabh Bhattacharya, Vikram Holla, Ravi Yadav and Pramod Kumar Pal
Department of Neurology, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, Karnataka, India

ABSTRACT: ***Background:*** Early-onset Parkinson's disease (EOPD) refers to patients with Parkinson's disease (PD) whose age at disease onset is less than 50 years. Literature on the non-motor symptoms (NMS) in these patients is very limited in the Indian context. We aimed to study the NMS in patients with EOPD and its impact on the quality of life (QoL). ***Methods:*** We included 124 patients with EOPD with a mean age at disease onset between 21 and 45 years and 60 healthy controls (HC). NMS were assessed using validated scales, and the QoL domains were evaluated using the PD QoL–39 scale (PDQ-39). ***Results:*** The mean age at disease onset in EOPD patients was 37.33 ± 6.36 years. Majority of the patients were male (66.12%). The average disease duration was 6.62 ± 5.3 years. EOPD patients exhibited a significantly higher number of NMS per patient (7.97 ± 4.69) compared to HC (1.3 ± 1.39; $p < 0.001$). The most common NMS reported were urinary dysfunction, body pain, poor sleep quality, constipation, anxiety, depression, cognitive impairment, and REM sleep behavior disorder. The total NMS burden correlated with the QoL measures. Distinctive patterns of QoL subdomain involvement were identified, with sleep/fatigue, mood/cognition, and urinary dysfunction independently influencing QoL metrics. ***Conclusions:*** Our study provides valuable insights into the NMS profile and its impact on QoL in patients with EOPD, addressing an important knowledge gap in the Indian context. By understanding the specific NMS and their influence on QoL, healthcare professionals can develop targeted interventions to address these symptoms and improve the overall QoL.

RÉSUMÉ : ***Contexte :*** On entend par maladie de Parkinson précoce (MPP) une maladie dont les symptômes apparaissent avant l'âge de 50 ans. La documentation sur les symptômes non moteurs (SNM) de ce type de maladie est maigre en Inde. Aussi l'étude visait-elle à examiner les SNM chez les patients atteints de la MPP et leurs répercussions sur la qualité de vie (QV). ***Méthode :*** Ont participé à l'étude 124 patients atteints de la MPP chez qui les premiers symptômes sont apparus en moyenne entre l'âge de 21 ans et de 45 ans, ainsi que 60 témoins en bonne santé (TBS). Les SNM ont été évalués à l'aide d'échelles validée, et les domaines de la QV, à l'aide de l'échelle d'évaluation de la qualité de vie à 39 questions, dans la maladie de Parkinson, la PDQ-39. ***Résultats :*** L'âge moyen d'apparition de la MPP était de 37,33 ± 6,36 ans, et la durée moyenne de la maladie s'élevait à 6,62 ± 5,3 ans. La majorité des personnes touchées était des hommes (66,12 %). Les sujets atteints de la MPP présentaient un nombre significativement plus élevé de SNM par patient (7,97 ± 4,69) que les TBS (1,3 ± 1,39; $p < 0,001$). Les SNM déclarés le plus souvent étaient des troubles urinaires, des douleurs corporelles, une mauvaise qualité de sommeil, la constipation, l'anxiété, la dépression, des troubles cognitifs et des troubles de comportement du sommeil durant la phase de mouvements oculaires rapides. Une corrélation a été établie entre le fardeau total des SNM et les mesures de la QV. Des types particuliers d'atteinte à la QV dans certains sous-domaines, soit le sommeil et la fatigue, l'humeur et la cognition et les troubles urinaires, influant de manière indépendante les mesures de la QV, se sont dégagés de l'étude. ***Conclusion :*** L'étude a permis de dresser un tableau valable des SNM et de leurs répercussions sur la QV chez les patients atteints de la MPP, ce qui comble une lacune importante en matière de connaissances en Inde. En ayant une meilleure compréhension de ces SNM particuliers et de leur incidence sur la QV, les professionnels de la santé peuvent élaborer des interventions ciblées dans le but d'atténuer ces symptômes et d'améliorer la QV en général.

Keywords: Early onset Parkinson's disease; Non-motor symptoms; Parkinson's disease; Quality of life

(Received 23 July 2023; final revisions submitted 27 December 2023; date of acceptance 27 December 2023; First Published online 5 January 2024)

Introduction

Early-onset Parkinson's disease (EOPD) refers to patients with Parkinson's disease (PD) having age at onset (AAO) less than or equal to 45 years but onset up to age of 50 years is included by some authors.[1] EOPD comprises of about 3%–6% of all cases of PD.[2] Although EOPD shares many common characteristics with late-onset PD (LOPD), several features appear to cluster in earlier onset presentations, conferring a phenotypic homogeneity to early-onset cases.

EOPD patients may experience a poorer health related quality of life (QoL) than older onset counterparts due to psychosocial consequences and comorbid depression. A study comparing QoL

Corresponding author: P. K. Pal; Email: palpramod@hotmail.com
Cite this article: Patwardhan A, Kamble N, Bhattacharya A, Holla V, Yadav R, and Pal PK. (2024) Impact of Non-Motor Symptoms on Quality of Life in Patients with Early-Onset Parkinson's Disease. *The Canadian Journal of Neurological Sciences* **51**: 650–659, https://doi.org/10.1017/cjn.2023.336

in early onset and late onset PD found that EOPD has worse overall QoL scores, independent of presence of depression.[3] Another study from Iran corroborated this finding of significantly worse depression and the "emotional" domain score of QoL in the EOPD cohort.[4] EOPD patients with Parkin mutations have a worse QoL than the non-genetic EOPD patients, with significant contribution from non-motor symptoms (NMS) such as depression and excessive daytime sleepiness.[5] These findings indicate a need to systematically study the NMS that adversely impacts the QoL in patients with EOPD. Few studies from India that have examined NMS and its relation to QoL reveals an almost 100% prevalence of NMS, commonly fatigue, pain, anxiety, and urinary symptoms.[6,7,8] Initial studies on NMS in the Indian population did not find any difference in NMS with respect to age or age at onset. Another study found one or more NMS in all the patients and all the individual NMS domains were affecting the QoL.[6] Yet another study found that fatigue, lightheadedness and pain were the most prevalent NMS, with the total NMS score being the most important determinant of QoL.[9] However, the EOPD population was not specifically examined in these studies. Hence, we aimed to assess the NMS in patients with EOPD and compare with healthy controls, using standardized scales, and to determine how this influenced the quality-of-life metrics.

Methods

This cross-sectional observational study was conducted in the department of Neurology at the National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru, India which is a tertiary care center in South India. The study was approved by the Institute Ethics Committee (IEC NO.NIMH/DO/IEC (BS & NS DIV) 2018–19). EOPD patients diagnosed using UKPDS Brain bank criteria[10] with age at onset (AAO) less than or equal to 45 years were included. Although a cut-off of 50 years is now recommended by the International MDS Task Force, previous studies have variably used an upper limit of 40-50 years to define EOPD.[1] Clinical characterization, motor and non-motor assessments, and QoL assessment were performed using validated scales. Furthermore, 60 healthy age and gender-matched controls were also included.

Motor Assessments

Motor assessment was performed using the unified Parkinson's disease rating scale (UPDRS) part-III (overnight levodopa OFF and supramaximal levodopa dose ON state) and Hoehn and Yahr staging. We calculated the total levodopa equivalent daily dose (T-LEDD) using the formula given by Tomlinson et al.[11] Hence, the T-LEDD is equal to (Levodopa × 1) + (Levodopa CR × 0.75) + (Pramipexole × 100) + (Ropinirole × 20) + (Amantadine × 1) + (Rasagiline × 100) + (Selegiline × 10) + (Levodopa X 0.33 if entacapone is used irrespective of dose) + (Levodopa × 0.5 if tolcapone is used irrespective of the dose).[11] None of the patients were on any newer medications such as safinamide, opicapone, and istradefylline, the LEDD of which cannot be calculated using the above formula.

The EOPD patients were categorized into three clinical phenotypes as tremor dominant (PD-TD), postural instability, and gait difficulty (PD-PIGD) and mixed type. This categorization was based on the formula, which is a "ratio of mean tremor score (sum of items 20 and 21 in UPDRS part III "OFF score" divided by 4) to the mean bradykinesia/rigidity score (sum of items 22–27 and 31 in UPDRS part III "OFF score" divided by 15)." Patients with a ratio more than 1.0 were classified into PD-TD, and ratio less than 0.8 were classified into PD-PIGD variant. Patients with mixed phenotype had ratio between 0.8 and 1.0.[12]

NMS Assessments

The NMS scales that were used included Epworth Sleepiness scale (ESS),[13,14] Non motor symptom scale (NMSS),[15] NMS-Quest,[16] Impulse control disorders questionnaire (QUIP scale),[17] Hospital anxiety and depression rating scales (HADS),[18] REM sleep behavioral disorder screening questionnaire (RBDSQ),[19] Pittsburgh sleep quality index (PSQI),[20] Montreal cognitive Assessment (MoCA),[21] and the Parkinson's Disease Questionnaire −39 (PDQ 39).[22] All these scales were applied to all the study participants. Permission to use MDS owned scales was obtained for the purpose of the study.

The non-motor scales were applied as follows:

a. The PDQ-39 Summary Index (PDQSI) was used as the quality-of-life metric, calculated by dividing the sum of subdomain scores by eight.[22]
b. A score of above 10 on ESS was considered to be a significant marker for excessive daytime sleepiness.[14]
c. Scores of 6 or more on the 13 item RBDSQ were considered to be significant and suggestive of the presence of RBD.[19]
d. Poor quality of sleep was defined as the global score of > 5 on the six-domain self-rated PSQI.[20]
e. A cutoff of more than 10 was used for the diagnosis of clinically definite anxiety or depression on the HADS. A score between 8 and 10 was used to define "borderline anxiety" and "borderline depression."[18]
f. A score of less than 26 was used to define cognitive impairment on the MoCA.[21]
g. QUIP, which is specifically devised for use in PD, was used to assess impulse control disorders (ICDs) with very high sensitivity.[17]
h. NMS-Quest was used as the patient-rated questionnaire for the assessment of nine non-motor domains with a maximum score of 30.[16]
i. NMSS for PD was used as the observer-rated scale to assess the burden of NMS which was rated as follows - 0 (no burden), 1–20 (mild burden), 21–40 (moderate burden), 41–70 (severe burden), > 70 (very severe burden).[15]

Statistical Analysis

The data collected were tabulated in Microsoft Excel spreadsheets and analyzed using SPSS version 16. Comparison was performed between NMS in EOPD vs NMS in healthy controls. Correlation was examined between different groups of NMS and QoL measures. The mean and standard deviation were calculated for continuous variables and expressed categorical variables as frequencies and percentages. All the variables were tested for normal distribution using the Shapiro–Wilks test. The Mann–Whitney *U* test was employed for analysis of continuous independent variables not following normal distribution, and the independent *t*-test was employed for variables that following normal distribution. For comparison between the groups, the Kruskal–Wallis test was employed. The analysis of categorical variables was done by Pearson Chi-Square test. The strength of the association was tested between the two continuous variables with Pearson's Correlation Coefficient or Spearman rank correlation depending upon the normality of the data. A p-value of ≤ 0.05 was considered as significant.

https://doi.org/10.1017/cjn.2023.336 Published online by Cambridge University Press

Results

Demographics and Clinical Characteristics

A total of 124 patients and 60 controls were included in the study. The mean age of the patients was 43.98 ± 7.47 years, and the mean AAO was 37.33 ± 6.36 years. The mean age of controls was 43.25 ± 13.58. There was a male preponderance among the cases (M:F = 82:42) and healthy controls (M:F = 36:24). Majority of the patients had AAO between 40-45 years of age (45.96 %) and 30–39 years of age (45.96%). The mean duration of illness for EOPD patients was 6.62 ± 5.30 years. A positive family history was found in 15 patients (12.09 %). The mean T-LEDD was 589.73 ± 307.12 mg/day (range 60–1600 mg/day). Levodopa was prescribed for 82.25% patients. A dopaminergic agonist (DA) was prescribed in 66.12% patients, which comprised of Pramipexole (78.04%) and Ropinirole (19.96%). A DA was started as the first drug in 66.12% patients, whereas Levodopa was started as the first drug in 33.88% patients. Peak dose dyskinesias were seen in 26.62% patients.

Motor Assessment

The UPDRS part III 'OFF' score was 35.33 ± 13.30. whereas the UPDRS part III 'ON' score was 14.27 ± 9.06. The mean percentage improvement in UPDRS part III score was 59.84 ± 17.55 %. Majority of the patients (86.29%) had PD-TD, 5.64% had PD- PIGD, and 8.06% had mixed motor phenotype.

Assessment of Non-Motor Symptoms

A high proportion of patients (61.29%) were found to have poor sleep quality on the PSQI assessments. The total percentage of EOPD patients having excessive day time sleepiness was 17.74%. RBD was present in 20.26 % of the patients. On the PD-NMS questionnaire, 31.4% (n = 39) patients reported one of the symptoms pertaining to RBD. Evidence of depression on screening with HADS was present in 36.8%, whereas anxiety was present in 44%. One or more impulse control disorder (ICD) was present in 16.12%, of which dopamine dysregulation syndrome (DDS) was the most common (60%). Evidence of cognitive impairment was found in 29.6% patients.

Gastrointestinal symptoms including dysphagia and/or constipation were reported by 40.9% patients, while a large number of patients reported urinary dysfunction (73.6%). About one-fourth (25.6%) of EOPD patients reported sexual dysfunction. Other significant NMS detected included body pain (68%), anosmia (22.4%), involuntary weight gain/loss (14.67%), and excessive sweating (13.63%). Results of non-motor assessments are summarized in Table 1.

Subgroup analyses:

A. ***Age-group differences:*** Differences in NMS were examined between patients with AAO between<40 years and those with AAO 40 years or above. There was no significant difference between the total NMSS burden (p = 0.12), Global PSQI scores (p = 0.07), ESS score (p = 0.09), QUIP scores (p = 0.29), RBDSQ scores (p = 0.12), HADS-depression score (p = 0.91), and HADS-anxiety score (p = 0.88). However, the mean PDQ-39 Summary index score was significantly higher in patients who had AAO 40 years or more compared to those with AAO below 40 years (p = 0.02).
B. ***Comparison between early and late PD:*** Patients with a duration of illness greater than five years (late PD) had a significantly higher UPDRS part III "OFF" score (40.008 vs 31.148, $p = 0.0002$). However, the LEDD values were comparable between the two groups (p = 0.81). No difference was observed between the two groups in the ESS scores (p = 0.76), total NMS burden (p = 0.76), MoCA score (p = 0.10), PSQI score (p = 0.39), or QoL summary index scores (p = 0.75). However, the overall NMS burden correlated with longer duration of illness (p = 0.04).
C. ***Effect of use of dopamine agonist (DA) on NMS:*** There was no significant difference in EDS (p = 0.50), PSQI score (p = 0.21), QUIP score (p = 0.33), HADS – depression score (p = 0.73), HADS-anxiety (p = 0.85), or total NMS burden (p = 0.90).

Comparison of NMS Between Cases and Healthy Controls

Other than excessive day time sleepiness, all other non-motor scores were significantly worse in cases compared to healthy controls, and the MOCA scores were significantly better in healthy controls compared to cases (Table 2 and Figures 1 and 2).

Correlation Studies

A. ***Correlation between NMS and clinical characteristics***: A significant positive correlation was seen between the values of ESS, PSQI (Global score), HADS (Anxiety), and QUIP score with UPDRS (OFF) score and a significant negative correlation between MoCA score and the UPDRS (OFF) score. NMSS burden correlated with longer duration of illness. A significant positive correlation was found between age at assessment and poor sleep quality, RBDSQ scores, and total NMS burden, whereas a negative correlation was found between MoCA scores and age at assessment (Table 3).
B. ***Correlation of NMS with QoL of EOPD patients:*** QoL was found to be dependent on multiple NMS. A positive correlation was seen between the summary index scores and ESS score, NMSS (total) score, QUIP score, and NMS Quest score (Table 4). Correlation was examined between NMS subdomains and QoL metrics. A significant positive correlation was found between PDQSI and the domains of mood/cognition, sleep/fatigue, urinary dysfunction, and "miscellaneous domains" of weight change and excessive sweating (Table 4).

Quality of Life Subdomains

Eight QoL subdomains scores based on the PDQ-39 were calculated. The subdomain scores were as follows: "ADL" = 38.99 ± 22.64, 'Mobility'= 43.34 ± 23.17, "Emotional" = 41.16 ± 23.77, "Stigma"= 41.11 ± 31.52, "Social support" = 8.63 ± 17.00, "Cognition" = 21.21 ± 15.61, "Communication" = 22.85 ± 18.49, and "Bodily discomfort" = 19.03 ± 15.92.

Discussion

This study assessed the spectrum of NMS in patients with EOPD and their influence on the QoL measures using validated scales.

A number of salient demographic features of our cohort are worth a mention. These include a significant male preponderance, which may reflect gender inequalities in accessing medical care, in addition to biological factors. Being a tertiary care center, patients with relatively advanced stage of the illness were seen, as indicated by the high mean duration of illness (6.62 ± 5.30 years), T-LEDD (555.60 ± 296.32 mg/day), and high UPDRS III scores

https://doi.org/10.1017/cjn.2023.336 Published online by Cambridge University Press

Table 1: Non-motor symptom scores in EOPD patients

NMS Scale/Domain	EOPD (Total) $N = 124$	EOPD (Sporadic) $N = 109$	EOPD (familial) $N = 15$
ESS:			
Mean ± SD Score	6.26 ± 4.58	6.27 ± 4.54	6.2 ± 4.80
Lower Normal	62 (50%)	53 (48.62%)	9 (60%)
Higher Normal	41 (33.06%)	40 (36.695)	1 (6.66%)
Mild EDS	10 (8.06%)	6 (5.50%)	4 (26.66%)
Moderate EDS	8 (6.45%)	7 (6.42%)	1 (6.66%)
Severe EDS	3 (4.83%)	3 (2.75%)	0
RBDSQ:			
RBD+ (RBDSQ>5)	26 (20.96%)	24 (22.01%)	2 (13.33%)
RBD– (RBDSQ<5)	98 (79.04%)	85 (79.99%)	13 (86.67%)
PSQI:			
Poor Sleep Quality (PSQI>5)	76 (61.29%)	65 (59.63%)	11 (73.33%)
Good sleep quality (PSQI ≤ 5)	48 (38.70%)	44 (42.30%)	4 (26.66%)
MoCA:			
Cognitive Impairment (MOCA ≤ 26)	36 (29.03%)	30 (27.52%)	6 (40%)
No Cognitive Impairment (MOCA≥26)	88 (70.97%)	79 (72.48%)	9 (60%)
HADS (Anxiety):			
Mean ± SD Score	9.21 ± 4.53	9.25 ± 4.62	8.86 ± 3.75
None (0–7)	40 (32.25%)	35 (32.11%)	5 (33.33%)
Borderline (8–10)	31 (25%)	27 (24.77%)	4 (26.67%)
Definite (>10)	53 (42.74%)	47 (43.11%)	6 (40%)
HADS (Depression):			
Mean ± SD Score	9.18 ± 4.54	8.85 ± 4.42	8.86 ± 3.73
None (0–7)	43 (34.67%)	39 (35.77%)	4 (26.67%)
Borderline (8–10)	36 (29.03%)	32 (29.35%)	4 (26.67%)
Definite (>10)	45 (36.29%)	38 (34.86%)	7 (46.66%)
QUIP (Impulse Control disorders):	20 (16.13%)	18 (14.63%)	2 (13.33%)
	Hypersexuality (20%)	Hypersexuality (27.7%)	Compulsive eating
	Compulsive eating	Compulsive	(100%)
	(40%)	buying (11.11%)	DDS (50%)
	DDS (60%)	Compulsive	
	Compulsive buying	eating (33.33%)	
	(10%)	Hobbyism (11.11) %	
	Hobbyism (10%)	DDS (55.55%)	
Non motor symptom burden:			
None (0)	3 (2.41%)	3 (2.75%)	0
Mild (1–20)	33 (26.61%)	31 (28.44%)	2 (13.33%)
Moderate (21–40)	38 (30.64%)	35 (32.11%)	3 (20%)
Severe (41–70)	34 (27.41%)	30 (27.52%)	4 (26.66%)
Very Severe (>70)	16 (12.90%)	10 (9.17%)	6(40%)
NMSS PD: Mean ± SD Score	38.93 ± 30.03	35.63 ± 27.00	63.5 ± 37.59
NMS–Quest			
Mean ± SD Score	7.97 ± 4.69	7.98 ± 4.81	6.26 ± 5.19
NMSS PD Domains			
Cardiovascular	0.73 ± 1.38	0.73 ± 1.40	0.80 ± 1.27

(*Continued*)

https://doi.org/10.1017/cjn.2023.336 Published online by Cambridge University Press

Table 1: (*Continued*)

NMS Scale/Domain	EOPD (Total) *N* = 124	EOPD (Sporadic) *N* = 109	EOPD (familial) *N* = 15
Sleep/fatigue	6.58 ± 5.21	6.35 ± 5.12	8.20 ± 5.58
Mood/Cognition	13.90 ± 14.71	11.88 ± 10.30	28.6 ± 27.80
Perceptual problems/hallucinations	0.71 ± 2.02	0.69 ± 1.99	0.93 ± 2.17
Attention	3.24 ± 3.67	3.00 ± 3.45	4.93 ± 4.65
Gastrointestinal symptoms	2.13 ± 3.21	2.01 ± 2.98	2.93 ± 4.47
Urinary dysfunction	5.55 ± 6.10	5.29 ± 5.90	7.40 ± 7.15
Sexual dysfunction	1.40 ± 3.17	1.32 ± 3.21	2.85 ± 1.40
Pain	2.58 ± 2.20	2.49 ± 2.12	2.59 ± 2.58
Anosmia	1.15 ± 2.47	1.08 ± 2.44	2.62 ± 1.15
Sweating	0.66 ± 1.99	0.57 ± 1.90	1.26 ± 2.46
Weight change	0.56 ± 1.50	0.49 ± 1.32	1.0 ± 2.39
QoL (PDQSI)	30.39 ± 14.21	29.54 ± 14.10	36.55 ± 13.48

DDS = dopamine dysregulation syndrome; EOPD = early onset Parkinson's disease; ESS = Epworth Sleepiness scale; HADS– hospital anxiety and depression scale; MoCA = Montreal cognitive assessment; NMS = Quest–Non motor symptom questionnaire; NMS Scale for PD–Non–motor scale for PD, PDQSI = Parkinson Disease QoL Summary Index; PSQI = Pittsburgh sleep quality index; RBDSQ = REM behavioral disorder screening questionnaire.

Table 2: Comparison of non-motor symptoms scores in EOPD and healthy controls

Scale (Mean ± *SD*)	EOPD cases *N* = 124	Controls *N* = 60	P value of test Statistic (T test)
Age	43.98 ± 7.47	43.25 ± 13.58	0.70
Gender Distribution (M:F)	82:42	36:24	0.26
ESS	6.27 ± 4.56	5.28 ± 2.90	0.08
RBDSQ	3.17 ± 2.81	0.87 ± 0.99	**<0.001**
PSQI	7.33 ± 4.10	2.11 ± 2.17	**<0.001**
HADS (Depression)	9.10 ± 4.49	1.90 ± 2.06	**<0.001**
HADS (Anxiety)	9.19 ± 4.54	3.90 ± 3.14	**<0.001**
NMS-Quest	7.97 ± 4.69	1.30 ± 1.39	**<0.001**
QUIP	1.98 ± 5.37	0.05 ± 0.22	**<0.001**

EOPD = early onset Parkinson's disease; ESS = Epworth Sleepiness scale; HADS– hospital anxiety and depression scale; MoCA = Montreal cognitive assessment; NMS = Quest–Non motor symptom questionnaire; NMS Scale for PD–Non–motor scale for PD, PDQSI = Parkinson Disease QoL Summary Index; PSQI = Pittsburgh sleep quality index; RBDSQ = REM behavioral disorder screening questionnaire.

(35.33 ± 13.30). We also observed PD-TD as the major phenotype in our cohort.

A positive family history in first-degree relatives was observed in as many as 12.09% of our patients, consistent with previous studies.[23,24] Detection of certain genetic mutations in EOPD can have prognostic value and provides clue toward the expected non-motor profile. Prominent NMS features including anxiety, depression, and dementia are seen in PARK-DJ1(PARK7), while anxiety, ICD, and apathy are common in PARK-PINK1(PARK6).[25] Parkin mutations (PARK2), which are the most commonly implicated mutation in sporadic and familial EOPD across the globe, are known to present with less frequent cognitive impairment but may have ICDs more often.[25] With expanding knowledge of monogenic forms of PD, it is likely that their NMS signatures will eventually be elucidated more completely.

We applied a combination of multiple validated NMS scales that enabled comprehensive assessment of individual NMS domains. Our study showed that a high proportion of EOPD patients who had a poor sleep quality, with EDS in 17.74% and RBD in 20.26% patients, comparable to previous studies that have reported prevalence range of 15%–26%.[26] Mood-related symptoms (anxiety and depression) were also comparable to previously reported estimates of 30%–48%.[27] It is likely that sleep dysfunction, anxiety, and depression in EOPD are interrelated and has a multifactorial causation, with contribution from both biological and psychosocial factors. Other studies support the observation of higher incidence of anxiety in EOPD as compared to LOPD patients.[28] Anxiety may be a feature of "non-motor wearing off" phenomenon that is experienced by some patients in later stages of the disease, which is supported by our finding of a significant correlation between UPDRS part III OFF scores and HADS (anxiety) scores. There was a significant correlation between the anxiety scores and the UPDRS part III OFF scores that suggest, patients with more severe motor phenotype are more susceptible to anxiety. In contrast to the large study from India, we did not find any difference between the anxiety and depression scores and the age at disease onset.[7] Our study showed a slightly higher prevalence

https://doi.org/10.1017/cjn.2023.336 Published online by Cambridge University Press

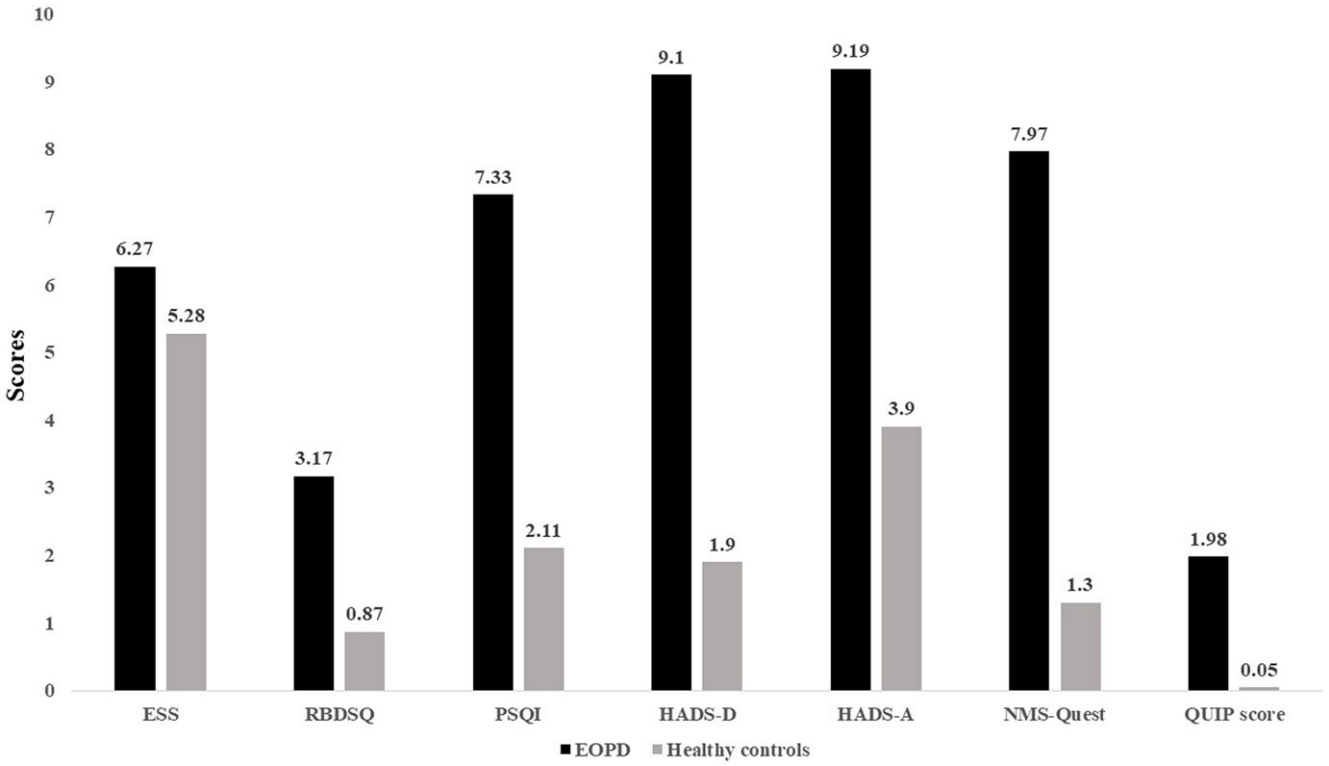

Figure 1: NMS scores in EOPD and healthy controls.

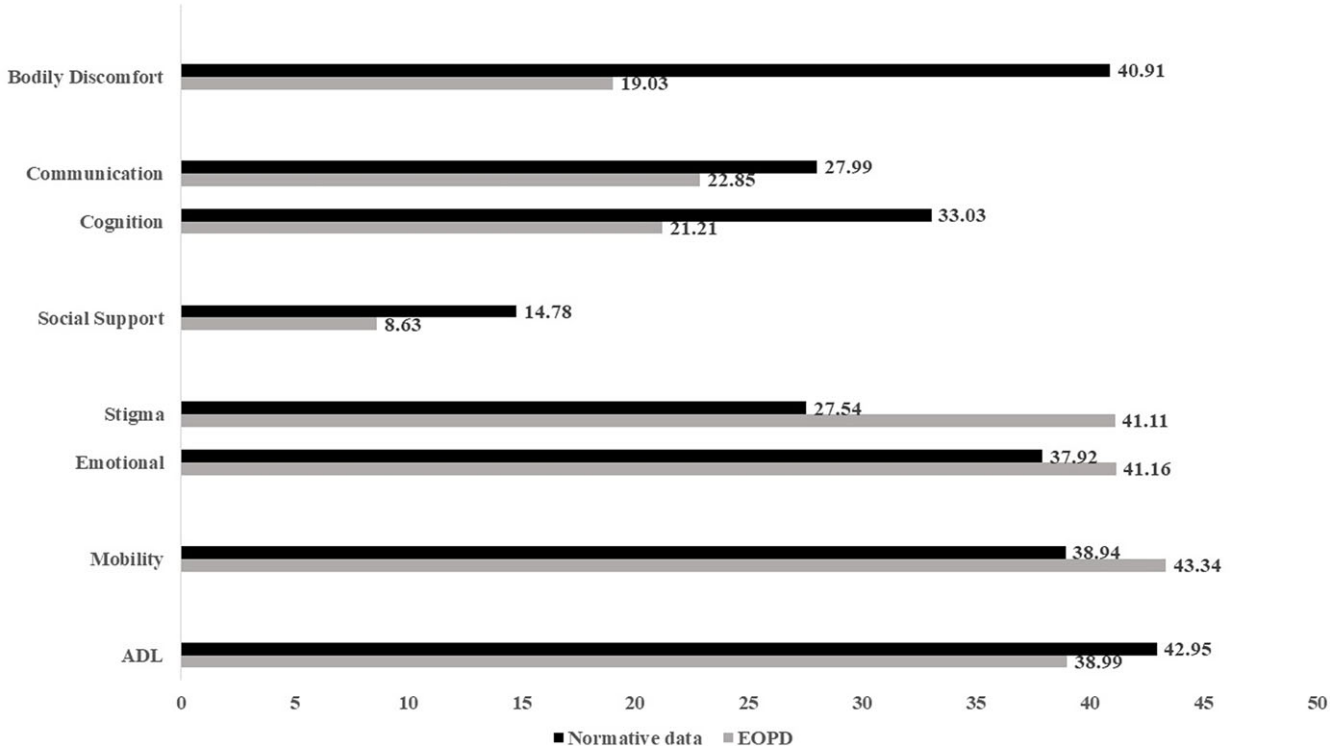

Figure 2: Quality of life domains in EOPD and healthy controls.

https://doi.org/10.1017/cjn.2023.336 Published online by Cambridge University Press

Table 3: Correlation between clinical characteristics and non-motor symptoms

	ESS	RBDSQ	PSQI (Global score)	HADS (Depression)	HADS (Anxiety)	MoCA	NMSS (Total score)	QUIP	Summary Index
AAO	0.39	0.13	0.21	0.55	0.43	0.18	0.07	0.53	**0.03**
Age at Assessment	**0.042**	**0.011**	**0.027**	0.26	0.12	**0.049**	**0.029**	0.27	0.10
Gender	0.64	0.97	0.64	0.06	0.12	0.09	**0.04**	0.32	0.91
Duration of Illness	0.55	0.13	0.082	0.52	0.42	0.15	**0.04**	0.26	0.83
UPDRS part III (OFF)	**0.006**	0.06	0.08	0.08	**0.05**	**0.007**	0.12	**0.004**	0.19
UPDRS part III (ON)	**0.01**	0.38	–	0.06	0.09	**0.002**	**0.01**	**0.01**	0.21
Side of Onset	0.44	0.84	0.57	0.12	0.13	0.41	0.65	0.96	0.39
T-LEDD	0.65	0.44	0.08	0.07	0.15	**0.03**	0.47	**0.04**	0.90
Motor Phenotype	0.88	0.59	0.97	0.83	0.16	0.09	0.47	0.78	0.83

AAO = age at onset; DDS = dopamine dysregulation syndrome; EOPD = early onset Parkinson's disease; ESS = Epworth Sleepiness scale; HADS– Hospital anxiety and depression scale; MoCA = Montreal cognitive assessment; NMS = Quest–Non motor symptom questionnaire; NMS Scale for PD–Non–motor scale for PD, PDQSI = Parkinson Disease QoL Summary Index; PSQI = Pittsburgh sleep quality index; RBDSQ = REM behavioral disorder screening questionnaire.

Table 4: Correlation of QoL in EOPD with NMS

Scale	Correlation coefficient (Spearman's rho)	"*p*" value
ESS	0.25	0.005
RBDSQ	0.14	0.12
PSQI	0.05	0.55
HADS (Depression)	0.13	0.14
HADS (Anxiety)	0.10	0.26
PD – NMSQ Score	0.29	0.01
QUIP	0.22	0.01
MoCA	– 0.07	0.48
NMSS (Total score)	0.31	0.001
NMSS-Cardiovascular	0.09	0.32
NMSS-Sleep/Fatigue	0.27	0.004
NMSS-Mood/Cognition	0.40	0.005
NMSS-Perceptual problems/ hallucinations	0.15	0.10
NMSS-Attention/Memory	0.15	0.11
NMSS-Gastrointestinal dysfunction	0.10	0.28
NMSS-Urinary dysfunction	0.20	0.032
NMSS-Miscellaneous		
Pain	– 0.02	0.79
Change in taste/smell	0.04	0.61
Excessive sweating	0.199	0.037
Weight change	0.276	0.004

DDS = dopamine dysregulation syndrome; EOPD = Early onset Parkinson's disease; ESS = Epworth Sleepiness scale; HADS– hospital anxiety and depression scale; MoCA = Montreal cognitive assessment; NMS = Quest–Non motor symptom questionnaire; NMS Scale for PD–Non–motor scale for PD, PDQSI = Parkinson Disease QoL Summary Index; PSQI = Pittsburgh sleep quality index; RBDSQ = REM behavioral disorder screening questionnaire.

of cognitive impairment of around 29%, compared to previous estimates of 10%–20% in EOPD,[29,30] possibly reflecting a more advanced stage of the disease. It is also likely that MoCA may have overestimated the scores on cognitive impairment in the present study with English being the second language in many of our patients.

The prevalence of ICD (16 %) was consistent with previous studies which have reported a variable prevalence range of 3%–40%.[31] The ICD prevalence is known to be higher in EOPD patients than late-onset PD patients.[32] This may be related to the use of higher use of DA in EOPD, as in our cohort, compared to LOPD. However, the subgroup analysis failed to show correlation between DA use and occurrence of ICDs. Our cohort also featured several other features known to be associated with development of ICD including male preponderance and higher T-LEDD.[25] The most common ICD in our EOPD cohort was dopamine dysregulation syndrome, which is consistent with previous studies.[32]

The incidence of gastrointestinal dysfunction, urinary dysfunction, anosmia, and autonomic dysfunction is similar to that of other studies in EOPD.[24,33] It is hypothesized that urinary dysfunction may be a component of a distinct non-motor subphenotype characterized by autonomic dysfunction, RBD, and depression and may be a marker of a more severe PD phenotype.[34] It is likely that genetic subtypes featuring these NMS such as GBA, SNCA, and VPS-related EOPD may have been present in our cohort, but lack of genetic data at present precludes further correlation. The overall NMS burden was comparable to findings from a previous EOPD study.[33]

EOPD patients had significantly higher NMS burden as compared to age-matched healthy controls. This corroborates with other studies that have demonstrated more frequent and severe NMS in patients with PD compared to healthy aging individuals.

Few studies have specifically looked at NMS and QoL determinants in EOPD in the Indian context. The first main publication on YOPD in India examined mainly motor features, and some NMS such as cognitive impairment and autonomic dysfunction.[35] More recently, a number of studies have examined NMS in PD in the last decade and have commonly reported pain, fatigue, urinary symptoms, anxiety, and depression.[6,9] Depression was found to be one of the main determinants of QoL in these studies. However, these studies did not specifically examine the EOPD cohort. The pattern of NMS seen in our EOPD cohort is similar to these studies reported in literature previously. Compared to another large multicenter observational study from India that comprehensively described both motor and NMS in EOPD, we

https://doi.org/10.1017/cjn.2023.336 Published online by Cambridge University Press

Table 5: Literature on NMS in EOPD from India and internationally: a comparative perspective

Author, country, Year	Age cutoff and number of Subjects	Mean age at onset for EOPD Mean ± SD (years)	Gender (M : F)	Duration of illness for EOPD (years) Mean ± SD	Main NMS features in EOPD	Strengths/Limitations of the study
Kim et al.[39] 2020, Korea	LOPD (AAO ≥ 70 years, $n = 63$), MOPD (50–69 years, $n = 268$), YOPD AAO < 50 years, $n = 74$)	46.6 ± 5.3	44 : 30	6.5 ± 7.3	Higher depression and anxiety scores, lower tremor scores and SCOPA-AUT scores, and slower progression of cognitive impairment in EOPD	Longitudinal study with a large sample size. However, QoL determinants were not specifically examined.
Lanfranco De Carolis et al.[40] 2023, Italy	LOPD (AAO ≥ 70 years, $n = 37$), MOPD (50 to 69 years, $n = 72$), YOPD AAO < 50 years, $n = 22$)	45.9 ± 3.5	15 : 7	–	NMS more frequent in MOPD and LOPD than EOPD	Small sample size of EOPD group and retrospective nature of the study were major limitations
Zhou MZ et al.[41] 2013, China	EOPD (≤45 years, $n = 13$), MOPD (45–64 years, $n = 103$), OOPD (≥65 years, $n = 114$)	40.1 ± 3.3	5 : 8	9.3 ± 5.1	HDRS and HARS score similar between groups. Linear effect between AAO and ESS scores (P = 0.011). Autonomic symptoms, neuropsychiatric symptoms less frequent in EOPD	Comprehensive assessment of NMS was performed. However, QoL determinants were not studied.
Zhou Z et al.[42] 2022, China	AAO < 50 years, ($n = 1217$)	44.12 ± 5.54	–	–	The most critical determinants of prognosis were motor and some NMSs, especially the UPDRS total score, motor complications, RBD, and autonomic dysfunction.	Longitudinal study with a large sample cohort. Additionally, classification within EOPD was explored: mild motor and non-motor dysfunction /slow progression (cluster I), intermediate (cluster II), and severe motor and non-motor dysfunction/malignant (cluster III).
Hu T et al.[43] 2018, China	EOPD: AAO ≤ 45 years, ($n = 106$), LOPD: > 45 years ($n = 463$)	37.1 ± 7.2	58 : 48	2.1 ± 1.6	Sleep/fatigue, attention/ memory, and miscellaneous are the most affected subdomains. NMS, especially sleep/ fatigue, mood/ apathy, attention/ memory, and GI symptoms were determinants of decreased QoL	NMS were studied in drug naive patients, thus minimizing potential confounding effect of medication on NMS.
Bovenzi R et al.[44] 2023, Italy	AAO < 50 years, ($n = 193$)	43.93 ± 5.47	107 : 86	5.0 ± 5.07	Only a minor part of EOPD patients (30%) had concurrent RBD and constipation at onset. Neuropsychiatric symptoms (depression, anxiety, apathy, and psychosis) affected upto 50% of patients. ICD were common (37.5%)	Longitudinal assessment was an advantage. Several limitations, included retrospective design, data gaps in assessment of NMS, and absence of a control group
Guo X et al.[45] 2013, China	AAO < 50 years, ($n = 135$) LOPD: $n = 387$	41.8 ± 6.1	–	5.0 ± 4.4	More severe NMS in LOPD than EOPD. Positive correlation with age, LEDD, and NMSS scores in LOPD but not in EOPD.	Cross-sectional design, large sample size. Standardised scales used.
Kukkle et al.[7] 2022, India	(JP, < 20 years, $n = 25$), young-onset (YOPD, 20–40 years, $n = 333$), and early-onset (EOPD, 40–50 years, $n = 310$)	38.7 ± 8.1	455 : 213	8 ± 6	Panic attacks and depression more common in YOPD and sleep-related issues more common in EOPD subjects.	Multicenter collaborative study, systematic NMS scale application, and data collection. QoL determinants were not specifically examined.
Tran TN et al.[38] 2021, Vietnam	YOPD (AAO ≤ 40 years, $n = 89$)	35.46 ± 3.96	47 : 42	6.68 ± 4.48	Fatigue was the most common NMS (75%). Sleep/fatigue and mood/cognition domains predicted QoL.	QoL subdomains were examined and non-motor predictors of QoL were determined. Cross-sectional nature of the study is a limitation.
Current study 2023, India	Patients with AAO ≤ 45 years ($n = 124$), age and gender matched controls ($n = 60$)	37.33 ± 6.36	82 : 42	6.62 ± 5.3	Most common NMS were urinary dysfunction, body pain, poor sleep quality, constipation, anxiety, and depression.	Comprehensive assessment of NMS using validated scales. Limitations include cross-sectional assessment, large gender ratio difference, and lack of genetic testing data.

AAO = age at onset; EOPD = early onset Parkinson's disease; HARS = Hamilton Anxiety rating scale; HDRS = Hamilton Depression Rating Scale; LOPD = late- onset Parkinson's disease; NMS-Quest-Non motor symptom questionnaire, MOPD = middle-onset Parkinson's disease; SCOPA-AUT = Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire; QoL = quality of life; YOPD = young onset Parkinson's Disease.

https://doi.org/10.1017/cjn.2023.336 Published online by Cambridge University Press

applied a wider range of scales to assess NMS and particularly focused on assessment of QoL determinants and QoL subdomains, which was not examined specifically in that study.[7] However, the age cutoff in the present study (45 years) was different from this other major work from India. In the international context, there have been few longitudinal NMS studies, specifically focusing on EOPD, that have shed light on NMS progression over time and in different stages of the disease. Further details of comparison of major NMS studies from India and internationally can be found in Table 5.

Quality of Life

Previous studies have shown that NMS that can adversely affect QoL include RBD, ICD, chronic pain, depression, constipation, and upper gastrointestinal dysfunction.[3,36,37] Our study confirmed some findings from previous studies, as we demonstrated a significant contribution of total NMS burden and presence of ICDs to the QoL measures. In addition, EDS was identified to be another significant determinant. A recent Vietnamese study examined the association between NMS domains and QoL in EOPD and found that the domains of sleep/fatigue and Mood/cognition were the most likely to affect QoL metrics.[38] Mood/cognition and sleep/fatigue were the domains that showed the highest degree of correlation with QoL, in concordance with the Vietnamese study. While the Vietnamese study found that 7 out of 8 NMS subdomains contributed to QoL, we found a significant role of the following 4 NMS subdomains: sleep/fatigue, mood/cognition, urinary dysfunction, and miscellaneous features. Our study is one of the first Indian studies to report data on QoL subdomains. These distinctive patterns of NMS subdomain involvement and their impact on QoL provide novel insights and scientific basis for designing interventions directed at improving the QoL of this group of patients.

A comprehensive cross-sectional evaluation of NMS was done, which was lacking in previous studies that studied only one or a few of the NMS components. However, longitudinal characterization and fluctuations of NMS were not studied and needs further exploration in future studies. The scales employed were screening tools and further confirmatory tests such as polysomnography for RBD, autonomic function testing for suspected autonomic dysfunction, and neuropsychological examination were not done. Furthermore, there was huge gender ratio difference in our study that might significantly alter the results. Genetic data of these patients will be useful to perform genotype–phenotype characterization.

Conclusions

This study done in a large cohort of EOPD patients showed a high overall non-motor symptom burden. In addition to motor disability, non-motor features of excessive day time sleepiness and presence of impulse control disorders were found to significantly influence the QoL of these patients. Within NMS subdomains, sleep/fatigue, mood/cognition, and urinary dysfunction significantly contributed to health-related QoL. Therefore, a comprehensive assessment of non-motor symptoms needs to be incorporated in routine clinical assessment of this group of patients.

Funding. None.

Competing interests. During the preparation of this work, the author(s) used ChatGPT in order to improve language and readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Statement of authorship. A.P: Conceptualization, data curation, formal analysis, methodology, investigation, and original draft, N.K: Conceptualisation, data curation, formal analysis, investigation, review and editing, A.B: methodology, visualization, validation, review and editing, V.H: methodology, investigation, review and editing, R.Y: conceptualization, project administration, supervision, validation, review and editing, P.K.P: conceptualization, project administration, supervision, validation, review and editing.

References

1. Mehanna R, Smilowska K, Fleisher J, et al. Age cutoff for early-onset Parkinson's disease: recommendations from the international parkinson and movement disorder society task force on early onset parkinson's disease. Mov Disord Clin Pract. 2022;9:869–78. DOI: 10.1002/MDC3.13523.
2. Willis AW, Schootman M, Kung N, Racette BA, Willis A. Epidemiology and neuropsychiatric manifestations of young onset Parkinson's disease in the United States. Parkinsonism Relat Disord. 2013;19:202–6. DOI: 10.1016/j.parkreldis.2012.09.014.
3. Knipe MDW, Wickremaratchi MM, Wyatt-Haines E, Morris HR, Ben-Shlomo Y. Quality of life in young- compared with late-onset Parkinson's disease. Mov Disord. 2011;26:2011–8. DOI: 10.1002/mds.23763.
4. Fereshtehnejad SM, Hadizadeh H, Farhadi F, Shahidi GA, Delbari A, Lökk J. Comparison of the psychological symptoms and disease-specific quality of life between early- and typical-onset Parkinson's disease patients. Parkinsons Dis. 2014;2014:819260–7. DOI: 10.1155/2014/819260.
5. Zhou XY, Liu FT, Chen C, et al. Quality of life in newly diagnosed patients with parkin-related Parkinson's disease. Front Neurol. 2020;11:580910. DOI: 10.3389/fneur.2020.580910.
6. Kumar A, Patil S, Singh VK, et al. Assessment of non-motor symptoms of Parkinson's disease and their impact on the quality of life: an observational study. Ann Indian Acad Neurol. 2022;25:909–15. DOI: 10.4103/aian.aian_647_21.
7. Kukkle PL, Goyal V, Geetha TS, et al. Clinical study of 668 Indian subjects with juvenile, young, and early onset Parkinson's disease. Can J Neurol Sci. 2022;49:93–101. DOI: 10.1017/cjn.2021.40.
8. de Souza A, Kakode VRP, D.'Costa Z, Bhonsle SK. Nonmotor symptoms in Indian patients with Parkinson's disease. Basal Ganglia. 2015;5:89–93. DOI: 10.1016/j.baga.2015.09.002.
9. Karri M, Ramasamy B, Kalidoss R. Prevalence of non-motor symptoms in Parkinson's disease and its impact on quality of life in tertiary care center in India. Ann Indian Acad Neurol. 2020;23:270–4. DOI: 10.4103/aian.AIAN_10_19.
10. Marsili L, Rizzo G, Colosimo C. Diagnostic criteria for Parkinson's disease: from James Parkinson to the concept of prodromal disease. Front Neurol. 2018;9:156. DOI: 10.3389/FNEUR.2018.00156.
11. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord. 2010;25:2649–53. DOI: 10.1002/MDS.23429.
12. Schiess MC, Zheng H, Soukup VM, Bonnen JG, Nauta HJW. Parkinson's disease subtypes: clinical classification and ventricular cerebrospinal fluid analysis. Parkinsonism Relat Disord. 2000;6:69–76. DOI: 10.1016/S1353-8020(99)00051-6.
13. Walker NA, Sunderram J, Zhang P, en Lu S, Scharf MT. Clinical utility of the epworth sleepiness scale. Sleep Breath. 2020;24:1759–65. DOI: 10.1007/S11325-020-02015-2/METRICS.
14. Arnulf I. Excessive daytime sleepiness in parkinsonism. Sleep Med Rev. 2005;9:185–200. DOI: 10.1016/j.smrv.2005.01.001.
15. Storch A, Schneider CB, Klingelhöfer L, et al. Quantitative assessment of non-motor fluctuations in Parkinson's disease using the non-motor symptoms scale (NMSS). J Neural Transm. 2015;122:1673–84. DOI: 10.1007/S00702-015-1437-X/METRICS.

16. Romenets SR, Wolfson C, Galatas C, 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.
17. Martinez-Martin P, Rodriguez-Blazquez C, Catalan MJ. Independent and complementary validation of the QUIP-RS in advanced Parkinson's disease. Mov Disord Clin Pract. 2018;5:341–342. DOI: 10.1002/MDC3.12603.
18. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361–70. DOI: 10.1111/J.1600-0447.1983.TB09716.X.
19. Stiasny-Kolster K, Mayer G, Schäfer S, Möller JC, Heinzel-Gutenbrunner M, Oertel WH. The REM sleep behavior disorder screening questionnaire—A new diagnostic instrument. Mov Disord. 2007;22:2386–93. DOI: 10.1002/MDS.21740.
20. 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.
21. Nasreddine ZS, Phillips NA, Bédirian 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.
22. 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.
23. Schrag A, Schott JM. Epidemiological, clinical, and genetic characteristics of early-onset parkinsonism. Lancet Neurol. 2006;5:355–63. DOI: 10.1016/S1474-4422(06)70411-2.
24. Mehanna R, Moore S, Hou JG, Sarwar AI, Lai EC. Comparing clinical features of young onset, middle onset and late onset Parkinson's disease. Parkinsonism Relat Disord. 2014;20:530–4. DOI: 10.1016/j.parkreldis.2014.02.013.
25. Liu X, Le W. Profiling non-motor symptoms in monogenic Parkinson's disease. Front Aging Neurosci. 2020;12:591183. DOI: 10.3389/FNAGI.2020.591183.
26. Gjerstad MD, Boeve B, Wentzel-Larsen T, Aarsland D, Larsen JP. Occurrence and clinical correlates of REM sleep behaviour disorder in patients with Parkinson's disease over time. J Neurol Neurosurg Psychiatry. 2008;79:387–91. DOI: 10.1136/JNNP.2007.116830.
27. Ray S, Agarwal P. Depression and anxiety in Parkinson disease. Clin Geriatr Med. 2020;36:93–104. DOI: 10.1016/j.cger.2019.09.012.
28. Rai N, Goyal V, Kumar N, et al. Neuropsychiatric co-morbidities in non-demented Parkinson's disease. Ann Indian Acad Neurol. 2015;18:33. DOI: 10.4103/0972-2327.144287.
29. Chaudhary S, Joshi D, Pathak A, Mishra VN, Chaurasia RN, Gupta G. Comparison of cognitive profile in young- and late-onset Parkinson's disease patients. Ann Indian Acad Neurol. 2018;21:130. DOI: 10.4103/AIAN.AIAN_262_17.
30. Tang H, Huang J, Nie K, et al. Cognitive profile of parkinson's disease patients: a comparative study between early-onset and late-onset Parkinson's disease. Int J Neurosci. 2015;126:227–34. DOI: 10.3109/00207454.2015.1010646.
31. Lim SY, Tan ZK, Ngam PI, et al. Impulsive-compulsive behaviors are common in Asian Parkinson's disease patients: assessment using the QUIP. Parkinsonism Relat Disord. 2011;17:761–4. DOI: 10.1016/j.parkreldis.2011.07.009.
32. Vela L, Martínez Castrillo JC, García Ruiz P, et al. The high prevalence of impulse control behaviors in patients with early-onset Parkinson's disease: a cross-sectional multicenter study. J Neurol Sci. 2016;368:150–4. DOI: 10.1016/j.jns.2016.07.003.
33. Špica V, Pekmezović T, Svetel M, Kostić VS. Prevalence of non-motor symptoms in young-onset versus late-onset Parkinson's disease. J Neurol. 2013;260:131–7. DOI: 10.1007/S00415-012-6600-9/METRICS.
34. 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.
35. Muthane UB, Swamy HS, Satishchandra P, Subhash MN, Rao S, Subbakrishna D. Early onset Parkinson's disease: are juvenile- and young-onset different? Mov Disord. 1994;9:539–44. DOI: 10.1002/mds.870090506.
36. Muslimović D, Post B, Speelman JD, Schmand B, de Haan RJ. Determinants of disability and quality of life in mild to moderate Parkinson disease. Neurology. 2008;70:2241–47. DOI: 10.1212/01.wnl.0000313835.33830.80.
37. Mehanna R, Jankovic J. Young-onset Parkinson's disease: its unique features and their impact on quality of life. Parkinsonism Relat Disord. 2019;65:39–48. DOI: 10.1016/j.parkreldis.2019.06.001.
38. Tran TN, Le Ha UN, Nguyen TM, et al. The effect of non-motor symptoms on health-related quality of life in patients with young onset Parkinson's disease: a single center Vietnamese cross-sectional study. Clin Park Relat Disord. 2021;5:100118. DOI: 10.1016/J.PRDOA.2021.100118.
39. Kim R, Shin JH, Park S, Kim HJ, Jeon B. Longitudinal evolution of non-motor symptoms according to age at onset in early Parkinson's disease. J Neurol Sci. 2020;418:117157. DOI: 10.1016/j.jns.2020.117157.
40. Carolis LD, Galli S, Bianchini E, et al. Age at onset influences progression of motor and non-motor symptoms during the early stage of parkinson's disease: a monocentric retrospective study. Brain Sci. 2023;13:157. DOI: 10.3390/brainsci13020157.
41. Zhou MZ, Gan J, Wei YR, et al. The association between non-motor symptoms in Parkinson's disease and age at onset. Clin Neurol Neurosurg. 2013;115:2103–7. DOI: 10.1016/j.clineuro.2013.07.027.
42. Zhou Z, Zhou X, Xiang Y, et al. Subtyping of early-onset Parkinson's disease using cluster analysis: a large cohort study. Front Aging Neurosci. 2022;14:1040293. DOI: 10.3389/fnagi.2022.1040293.
43. Hu T, Ou R, Liu H, et al. Gender and onset age related-differences of non-motor symptoms and quality of life in drug-naïve Parkinson's disease. Clin Neurol Neurosurg. 2018;175:124–9. DOI: 10.1016/j.clineuro.2018.11.001.
44. Bovenzi R, Conti M, Degoli GR, et al. Shaping the course of early-onset Parkinson's disease: insights from a longitudinal cohort. Neurol Sci. 2023;44:3151–9. DOI: 10.1007/s10072-023-06826-5.
45. Guo X, Song W, Chen K, et al. Gender and onset age-related features of non-motor symptoms of patients with Parkinson's disease–a study from Southwest China. Parkinsonism Relat Disord. 2013;19:961–5. DOI: 10.1016/j.parkreldis.2013.06.009.

https://doi.org/10.1017/cjn.2023.336 Published online by Cambridge University Press