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The Burden of Non-Motor Symptoms in Parkinson's Disease: A Cross-Sectional Study on Clinical Correlates and Quality of Life in Quetta, Pakistan

Amanullah Kakar[1], Ainullah Kakar[1], Riaz Ahmed[1], Muhammad Qahir[1], Abdul Bari Nasar[1], Ihsan ul Haq[1], Muhammad Essa[1]

[1]Department of Neurology, BMC Hospital, Quetta, Balochistan, Pakistan.

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Correspondence to: Muhammad Essa, Department of Neurology, BMC Hospital, Quetta, Balochistan, Pakistan.
Email: dressakhan777@gmail.com

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All authors equally contributed to the study and approved the final manuscript.

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ABSTRACT

Background: Parkinson's disease (PD) patients' quality of life (QoL) is greatly impacted by non-motor symptoms (NMS), however, there is still a lack of a thorough definition of these symptoms in varied regional populations like Pakistan. This study aimed to delineate non-motor symptoms (NMS), their correlations with clinical characteristics, and their influence on quality of life (QoL) in a cohort of Parkinson's disease (PD) patients from Quetta, Pakistan. **Methods:** This cross-sectional study encompassed 86 Parkinson's disease patients prospectively recruited from the Neurology Outpatient Department of Bolan Medical Complex Hospital in Quetta. Demographic data, disease features, quality of life (PDQ-39, Schwab & England ADL), and biomarkers were gathered. Statistical analyses encompassed descriptive statistics, bivariate analyses, and multivariate analyses (linear and logistic regression). **Results:** The study population exhibited a mean age of 64.3±9.1 years, with a male predominance of 67.4%. A significant prevalence of NMS was noted, encompassing cognitive impairment (mean MoCA: 21.8±3.9), severe depression (23.3), and sleep problems (median PDSS-2: 20). Quality of life was markedly diminished (median PDQ-39: 48). Prolonged disease duration (rho = 0.45, $p<0.001$) and advanced H&Y stage (H = 18.2, p=0.001) were predictive with increased NMS burden. **Conclusion:** Non-motor symptoms are exceedingly frequent and substantially affect the quality of life in Parkinson's disease patients from Quetta, Pakistan. The advancement of disease and depression are significant indicators of NMS burden. These findings underscore the essential requirement for regular NMS screening and comprehensive care strategies to enhance patient outcomes in this marginalized community.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder predominantly characterised by motor symptoms including tremor, stiffness, bradykinesia, and postural instability[1-3]. Although these motor symptoms are frequently the primary and most identifiable indicators, serving as the foundation for clinical diagnosis, the comprehensive impact of Parkinson's disease extends much beyond motor impairment[4, 5]. Non-motor symptoms (NMS) are widely acknowledged as a vital and widespread component of the disease, often manifesting years prior to the appearance of motor symptoms and significantly affecting patients' quality of life (QoL)[6-8]. These varied symptoms include a broad spectrum of neuropsychiatric, sleep-related, autonomic, and sensory disorders[9-12]. NMS may encompass severe cognitive impairment, mood disorders including depression and anxiety, various sleep disturbances such as insomnia and REM sleep behavior disorder, autonomic dysfunctions like constipation and orthostatic hypotension, and sensory abnormalities such as pain and olfactory dysfunction[13-16]. The prevalence, severity, and specific characteristics of NMS can significantly differ among persons with PD, impacted by factors such as disease duration, the intensity of motor symptoms, and distinct patient characteristics, demanding a tailored therapy approach[17, 18].

NMS in PD are frequently underdiagnosed and poorly treated in clinical practice, despite their substantial impact, especially in a variety of socioeconomic and geographic circumstances[19-21]. Comprehending the complete spectrum of NMS and its associations with clinical factors is crucial for thorough patient care and for formulating tailored treatment approaches[19, 22, 23]. Global research has illuminated the spectrum of NMS; nonetheless, geographical disparities in genetic predisposition, environmental influences, healthcare accessibility, and cultural norms might affect its

presentation and consequences. There is a lack of comprehensive studies precisely delineating NMS in PD cohorts from areas such as Balochistan, Pakistan, where distinct demographic and socioeconomic factors may exert a considerable influence.

This study seeks to fill the knowledge gap by offering a thorough characterization of NMS in a cohort of Parkinson's disease patients from Quetta, Pakistan. By concentrating on this particular demographic, we aim to comprehend the distinct obstacles encountered by these patients, uncover common non-motor symptoms, and investigate their associations with recognized clinical indicators. The study aims to evaluate the overall quality of life in this group and uncover possible predictors of non-motor symptom burden, including clinical factors. the study aims to provide significant insights into the complex nature of PD in this neglected community, ultimately guiding culturally appropriate and effective management techniques to enhance patient outcomes and quality of life.

METHODOLOGY

This study is a cross-sectional examination of data from the Parkinson's Disease Non-Motor Symptoms International Longitudinal Study (NILS). The study concentrated on a group of 86 patients with Parkinson's disease (PD). The primary objectives of this study were to thoroughly characterize non-motor symptoms (NMS) in this cohort, investigate their correlations with various clinical factors, and assess their impact on the overall quality of life (QoL) of the patients.

Study Setting and Participants

The study was conducted at the Neurology Department of Bolan Medical Complex Hospital, Quetta, Pakistan. Participants were included if they met MDS Clinical Diagnostic Criteria for idiopathic PD (Postuma et al., 2015), were ≥40 years old, and provided informed consent[24]. Exclusions included atypical parkinsonism, severe cognitive impairment (MoCA score <10), or acute medical/psychiatric conditions.

Data were predominantly gathered from patients with Parkinson's disease in 2023. All clinical evaluations were conducted during standard patient appointments by qualified neurologists and a research assistant, guaranteeing uniformity and compliance with established protocols.

Clinical Assessments

Demographic data (age, gender, ethnicity, education, socioeconomic level) were collected through structured interviews. Disease variables including disease duration, motor severity (MDS-UPDRS Part III; Goetz et al., 2008), Hoehn & Yahr (H&Y) Staging, and Levodopa Equivalent Daily Dose (LEDD; Tomlinson et al., 2010)[25, 26].

Non-motor symptoms (NMS) were evaluated using validated tools: cognition (MoCA; Nasreddine et al., 2005), sleep (PDSS-2; Chaudhuri et al., 2002; ESS; Johns, 1991), autonomic dysfunction (SCOPA-AUT; Visser et al., 2004), and sensory symptoms (UPSIT; Doty et al., 1984; KPPS; Chaudhuri et al., 2015)[27-31]. Comorbidities, including hypertension, diabetes, and dementia, were validated during clinical evaluation.

Statistical Analysis

All statistical analyses were conducted utilizing SPSS (version 28). Descriptive statistics comprised mean ± SD or median (IQR) for continuous data, and frequency (%) for categorical variables. The Shapiro-Wilk test was employed to evaluate normality. Bivariate analysis employed Spearman's rank correlation, Mann-Whitney U test, Kruskal-Wallis test, and Chi-square test. Multivariate analysis using linear regression for NMS burden and quality of life, adjusted for age, sex, disease duration, and LEDD, with assumptions verified. Logistic regression was employed for binary outcomes. The quality of life (QoL) was evaluated with the PDQ-39 and the Schwab & England Activities of Daily Living (ADL) Scale.

RESULTS

This study is a cross-sectional analysis of a cohort of 86 patients with Parkinson's disease (PD). The primary goals of this study were to thoroughly delineate non-motor symptoms (NMS) in this cohort, investigate their correlations with diverse clinical factors, and evaluate their influence on the overall quality of life (QoL) of the patients.

Demographic and Clinical Characteristics

The cohort comprised patients with a mean age of 64.3±9.1 years, demonstrating a notable male predominance (67.4 male, 32.6 female) (Table 1). Ethno-demographic analysis revealed that the majority of patients identified as Baloch (86.0%), followed by Pashtun (10.5%). Educational attainment reflected regional socioeconomic trends, with nearly half of the patients (48.8%) having completed primary-level education.

From a clinical perspective, the median disease duration was 6 years (Interquartile Range [IQR]: 4–9 years). Motor severity, as assessed by the Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS Part III), averaged 34.1±11.5. A significant proportion of patients (44.2%) were classified as Hoehn & Yahr (H&Y) stage 2 (Table 1). The median levodopa equivalent daily dose (LEDD) was 500 mg (IQR: 350–700 mg).

Non-Motor Symptoms (NMS) and Comorbidities

Cognitive impairment was a prominent feature, with a mean Montreal Cognitive Assessment (MoCA) score of 21.8±3.9 (Table 2). Mood disorders were highly prevalent, with 23.3% of patients experiencing severe depression (Beck Depression Inventory [BDI] score ≥20), and an additional 32.6% reporting moderate depressive symptoms.

Sleep disturbances were also common, indicated by a median Parkinson's Disease Sleep Scale-2 (PDSS-2) score of 20 (IQR: 15–25). Furthermore, 41.9% of the cohort exhibited abnormal daytime sleepiness, as defined by an Epworth Sleepiness Scale (ESS) score >10. Autonomic dysfunction was evident, with a mean Scales for Outcomes in Parkinson's Disease-Autonomic (SCOPA-AUT) score of 15.2±5.6, and orthostatic hypotension was observed in 29.1% of patients. Sensory deficits were notable, including a median University of Pennsylvania Smell Identification Test (UPSIT) olfaction score of 18 (IQR: 12–22) and a median King's Parkinson's Disease Pain Scale (KPPS) severity score of 8 (IQR: 4–12).

Common comorbidities identified within the cohort included hypertension (46.5%), diabetes (25.6%), and dementia (20.9%) (Table 2).

Treatment and Biomarkers

Regarding treatment, the majority of patients were on dopamine agonists (72.1%), and a substantial proportion (34.9%) utilized MAO-B inhibitors. Physical therapy was a common adjunctive treatment, received by 55.8% of the patients (Table 3). Biomarker analysis provided insights into the underlying pathology: the median cerebrospinal fluid (CSF) alpha-synuclein level was 850 pg/mL (IQR: 650–1100 pg/mL consistent with dopaminergic depletion characteristic of Parkinson's disease.

Quality of Life (QoL) and Lifestyle Factors

The quality of life was significantly impaired within the cohort, reflected by a median Parkinson's Disease Questionnaire-39 (PDQ-39) score of 48 (IQR: 35–62). Activities of daily living (ADL) were also affected, with a mean Schwab & England ADL score of 68±14 (Table 4). Lifestyle factors of note included low physical activity (60.5) and a history of current or former smoking (30.2).

Predictors of NMS Burden

Bivariate analysis (Table 5) revealed several significant predictors of higher NMS burden. Both disease duration (Spearman's rho = 0.45, p<0.001) and advanced H&Y stage (Kruskal-Wallis H = 18.2, p=0.001) demonstrated strong positive correlations with increased NMS burden. Severe depression (BDI ≥20) was also significantly associated with worse NMS (Mann-Whitney U = 480, p=0.006). Interestingly, a higher CSF alpha-synuclein level was found to correlate with a lower NMS burden (rho = -0.31, p=0.008), suggesting a potential protective or inverse relationship that warrants further investigation.

Table 1

Demographic and Clinical Characteristics (n = 86)

Variable	Category/Subgroup	Statistics
Demographics		
Age (years)	Continuous	Mean = 64.3 ± 9.1
Sex	Male	58 (67.4%)
	Female	28 (32.6%)
Ethnicity	Baloch	74 (86.0%)
	Pashtun	9 (10.5%)
	Other	3 (3.5%)
Education Level	Primary	42 (48.8%)
	Secondary	30 (34.9%)
	Tertiary	14 (16.3%)
Clinical Variables		
Disease Duration (years)	Continuous	Median = 6 (IQR: 4–9)
Hoehn & Yahr Stage	Stage 1	12 (14.0%)
	Stage 2	38 (44.2%)
	Stage 3	28 (32.6%)
	Stage 4	6 (7.0%)
	Stage 5	2 (2.3%)
Levodopa Equivalent Daily Dose (mg)	Continuous	Median = 500 (IQR: 350–700)
MDS-UPDRS Part III (motor severity)	Continuous	Mean = 34.1 ± 11.5

Table 2

Non-Motor Symptoms (NMS) and Comorbidities (n = 86)

Variable	Category/Subgroup	Statistics
Cognition		
MoCA Score	Continuous	Mean = 21.8 ± 3.9
Mood/Apathy		
Beck Depression Inventory (BDI)	Mild (≤13)	38 (44.2%)
	Moderate (14–19)	28 (32.6%)
	Severe (≥20)	20 (23.3%)
Sleep		
PDSS-2 Total Score	Continuous	Median = 20 (IQR: 15–25)
Epworth Sleepiness Scale (ESS)	Normal (≤10)	50 (58.1%)
	Abnormal (>10)	36 (41.9%)
Autonomic Dysfunction		
SCOPA-AUT Total Score	Continuous	Mean = 15.2 ± 5.6
Orthostatic Hypotension	Present	25 (29.1%)
Sensory Symptoms		
UPSIT Olfaction Score	Continuous	Median = 18 (IQR: 12–22)
King's PD Pain Scale (KPPS)	Continuous	Median = 8 (IQR: 4–12)
Comorbidities		
Hypertension	Present	40 (46.5%)
Diabetes	Present	22 (25.6%)
Dementia	Present	18 (20.9%)

Table 3

Treatment and Biomarkers (n = 86)

Variable	Category/Subgroup	Statistics
Treatment		
Dopamine Agonist Use	Yes	62 (72.1%)
MAO-B Inhibitor Use	Yes	30 (34.9%)
Physical Therapy	Yes	48 (55.8%)
Biomarkers		
CSF Alpha-Synuclein (pg/mL)	Continuous	Median = 850 (IQR: 650–1100)

Table 4

Quality of Life and Lifestyle Factors (n = 86)

Variable	Category/Subgroup	Statistics
Quality of Life		
PDQ-39 Total Score	Continuous	Median = 48 (IQR: 35–62)
Schwab & England ADL Scale (%)	Continuous	Mean = 68 ± 14
Lifestyle		
Physical Activity (IPAQ)	Low	52 (60.5%)
	Moderate	24 (27.9%)
	High	10 (11.6%)
Smoking Status	Never	60 (69.8%)
	Current/Former	26 (30.2%)

Table 5

Bivariate Analysis of NMS Burden (Total NMSS Score)

Variable	Statistical Test	Result	p-value
Age	Spearman's rho	r = 0.28	0.01
Disease Duration	Spearman's rho	r = 0.45	<0.001
Hoehn & Yahr Stage	Kruskal-Wallis	H = 18.2	0.001
Depression (BDI ≥20 vs. <20)	Mann-Whitney U	U = 480	0.006
Orthostatic Hypotension	Mann-Whitney U	U = 610	0.03
CSF Alpha-Synuclein	Spearman's rho	r = -0.31	0.008

DISCUSSION

This study presents a detailed cross-sectional examination of non-motor symptoms (NMS) in a cohort of 86 Parkinson's disease (PD) patients from Quetta, Pakistan, providing new insights into the clinical profile, NMS burden, and quality of life (QoL) in this understudied group. Our findings underscore the considerable frequency and influence of NMS, aligning with global literature, while also uncovering distinctive traits relevant to the regional context.

Our study revealed a significant prevalence of NMS across multiple dimensions, including cognitive impairment, mood problems, sleep difficulties, autonomic dysfunction, and sensory impairments. The average MoCA score of 21.8±3.9 signifies a significant degree of cognitive impairment, consistent with prior studies indicating that cognitive decline is a prevalent and frequently early characteristic of Parkinson's Disease (Gonzalez-Latapi et al., 2021)[32]. The elevated prevalence of severe depression (23.3) and moderate depressive symptoms (32.6) highlights the significant neuropsychiatric load within this cohort, aligning with the universal recognition of depression as one of the most devastating non-motor symptoms in Parkinson's disease (Prange et al., 2022)[33]. Likewise, sleep disruptions, shown by a median PDSS-2 score of 20 (Liguori et al., 2021) and a significant prevalence (41.9) of atypical daytime sleepiness (Shkodina, 2025), underscore the widespread occurrence of sleep-related problems in Parkinson's disease patients[34, 35]. These findings align with worldwide studies that regularly identify non-motor symptoms as significant factors in diminished quality of life in Parkinson's disease.

Our demographic research indicated a male predominance of 67.4% and a substantial representation of Baloch ethnicity at 86.0%, mirroring the demographics of the local community. The significant percentage of patients with primary-level education (48.8%) is an essential socioeconomic determinant that may affect disease perception, healthcare-seeking behaviors, and treatment adherence, potentially influencing the reported clinical profiles. The median disease duration of 6 years and an average MDS-UPDRS Part III score of 34.1±11.5 (Goetz et al., 2008) indicate a moderately advanced disease stage in numerous patients, corroborated by 44.2% being classified as Hoehn & Yahr stage 2. These qualities provide an essential background for comprehending the severity and complexity of the observed NMS.

The study also discovered substantial determinants of NMS burden. According to existing literature, both prolonged disease duration (Spearman's rho = 0.45, $p<0.001$) and elevated H&Y stage (Kruskal-Wallis H = 18.2, $p=0.001$) were significantly correlated with increased NMS burden. This underscores that as Parkinson's disease advances, the non-motor difficulties tend to proliferate and escalate. The correlation between severe depression (BDI ≥20) and exacerbated NMS (Mann-Whitney U = 480, $p=0.006$) underscores the interconnectedness of mood disorders and other NMS, indicating that mitigating depression may yield broader advantages for comprehensive NMS care. A higher amount of CSF alpha-synuclein was intriguingly associated with a reduced load of non-motor symptoms (rho = -0.31, $p=0.008$). This data necessitates additional validation, although it potentially implies a complicated interplay between alpha-synuclein pathology and non-motor symptom manifestation, or even signifies distinct Parkinson's disease endophenotypes in which elevated soluble alpha-synuclein may be protective or suggestive of a specific disease subtype.

The observed decline in quality of life, indicated by a median PDQ-39 score of 48 and a mean Schwab & England ADL score of 68±14, highlights the significant influence of Parkinson's disease and its related non-motor symptoms on everyday activities and overall well-being. This underscores the imperative for comprehensive management techniques that encompass not only motor symptom control but also the proactive diagnosis and treatment of non-motor symptoms (NMS). The elevated prevalence of comorbidities such as hypertension and diabetes, along with lifestyle factors like insufficient physical activity and smoking, constitutes considerable health problems that may influence Parkinson's disease pathogenesis and non-motor symptom manifestation.

The strengths of this study encompass its prospective data collection from a distinct geographic cohort, yielding unique insights into the features of PD in a group frequently underrepresented in global research. The utilization of a thorough set of validated measures for non-motor symptom assessment, quality of life, and biomarkers enhances the reliability of the findings. The limitations encompass the cross-sectional design, which prevents the determination of causative linkages or the monitoring of NMS progression over time. The sample size of 86 patients, albeit substantial for a regional study, may restrict the generalizability of certain findings and the statistical power for more detailed subgroup analysis.

The clinical implications of this study are significant. The significant prevalence and impact of NMS require regular screening and prompt care for these symptoms in PD patients in this area. Clinicians must exercise heightened vigilance for cognitive deficits, affective problems, and sleep difficulties. The established predictors of NMS burden enable doctors to recognize individuals at elevated risk for severe NMS, facilitating preventive care. Future research should concentrate on longitudinal studies to monitor the progression of NMS in this cohort, examine the underlying mechanisms of the inverse connection between CSF alpha-synuclein and NMS burden, and assess the efficacy of tailored therapies for NMS in this particular population.

CONCLUSION

This cross-sectional study thoroughly delineated non-motor symptoms (NMS) in 86 patients with Parkinson's disease (PD) from Quetta, Pakistan. Our findings validate the considerable prevalence and notable impact of NMS, including cognitive impairment, mood disorders, sleep disturbances, autonomic dysfunction, and sensory abnormalities, on patient quality of life (QoL) within this regional population.

Significant clinical indicators, including prolonged disease duration and elevated Hoehn & Yahr stage, forecast an augmented burden of non-motor symptoms (NMS). The significant correlation between severe depression and exacerbated NMS underscores the necessity for a comprehensive neuropsychiatric evaluation. The inverse relationship between CSF alpha-synuclein concentrations and non-motor symptom load necessitates additional exploration of its implications for Parkinson's disease endophenotypes or protective mechanisms.

The observed decline in quality of life highlights the need for comprehensive management that extends beyond the control of motor symptoms, stressing the importance of proactive diagnosis and treatment of non-motor symptoms. This study offers significant data from an underserved group, promoting regular NMS monitoring and early intervention for PD patients in the area. Future longitudinal studies are essential to comprehend the evolution of NMS, evaluate the functions of biomarkers, and formulate tailored, culturally appropriate therapies to enhance outcomes and quality of life for individuals with PD in Pakistan.

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