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A prospective study of cognitive impairment in Parkinson's disease: clinical, neuropsychological, and neuroimaging correlates

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Abstract

Aim: Parkinson's disease (PD) is a progressive neurodegenerative disorder marked by dopaminergic neuron loss, leading to motor and non-motor symptoms. Cognitive impairment in PD (PD-CI), ranging from mild cognitive deficits to dementia, significantly reduces quality of life and increases caregiver burden. This study aims to identify predictors of PD-CI, potentially supporting early interventions.

Methods: This one-year prospective observational study included 80 idiopathic PD patients recruited from Al-Azhar University Hospitals. Inclusion followed the Movement Disorder Society (MDS) Clinical Diagnostic Criteria for PD, with evaluations conducted at baseline, 3, 6, and 12 months. Patients underwent clinical assessments [Unified Parkinson's Disease Rating Scale, Part III (UPDRS-III), Hoehn and Yahr (H-Y), Beck Depression Inventory (BDI), and Hamilton Anxiety Rating Scale (HAM-A)], cognitive evaluations [Brief International Cognitive Assessment for MS (BICAMS) and Montreal Cognitive Assessment (MoCA)], magnetic resonance imaging (MRI), and laboratory testing. Exclusion criteria included conditions such as cerebellar abnormalities, early dementia diagnoses, and other Parkinsonism causes.

Results: Cognitive impairment was observed in 41.25% of patients. Those with cognitive impairment were older, had a longer disease duration, and exhibited higher fasting blood glucose (FBS) levels and lower thyroid-stimulating hormone (TSH) levels compared to patients without cognitive impairment ($p < 0.05$). Brain atrophy was detected in 4 (5%) patients in a subset of patients with PD, which was particularly pronounced in regions associated with cognitive function, such as the hippocampus and frontal lobe. Higher H-Y, UPDRS-III, and BDI scores correlated with cognitive decline, while lower MoCA and Symbol Digit Modalities Test (SDMT) scores predicted impairment ($p < 0.05$).

Conclusions: Cognitive impairment in PD is associated with advanced age, longer disease duration, metabolic factors, and structural brain changes. These findings suggest the potential for a predictive model to identify early cognitive decline in PD, enabling timely intervention and improved patient outcomes.

Keywords

Parkinson's disease, cognitive impairment, predictors, neurodegeneration, early intervention

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder with a main finding of a loss of neurons along the substantia nigra [1]. Subsequently, a wide range of manifestations could develop, including predominant motor symptoms such as tremors, rigidity, bradykinesia, and gait disturbance [1, 2]. Additionally, non-motor symptoms are frequently seen in PD patients, including cognitive impairment, sleep abnormalities, and mood changes like depression and anxiety [3].

PD follows Alzheimer's disease as the most common neurological illness. PD has a substantial worldwide burden [4], with a prevalence rate of 1% in those over 60 years old and 3% in people over 80 [4, 5]. Despite appearing in the later stages, four out of five of those patients are expected to have PD cognitive impairment (PD-CI), ranging from mild deterioration to PD dementia (PDD) [6]. This is supported by Hely et al. [7], who followed PD patients for 20 years and concluded that 83% of surviving patients eventually developed dementia. Although rivastigmine, a cholinesterase inhibitor, has been used to treat PDD for nearly a decade, mild PD-CI has no disease-modifying therapy yet that could block or delay its transition into dementia [8].

Several factors are thought to be correlated with cognitive decline progression, including PD duration, patients' comorbidities, and structural brain changes such as atrophy in the frontal, parietal, or temporal lobe [9, 10]. These lobe changes can substantially impact the quality of life of patients and put significant stress on caregivers because they affect several domains that interfere with daily activity, including the executive function, where the patient thinks; memory, either short or long; language, resulting in difficulties with word retrieval and visuospatial issues, which are critical for environmental perception [9–12].

Therefore, many biomarkers and imaging techniques are now used as a trial to predict this impairment [13]. For example, amyloid-beta and tau proteins, a neurodegenerative-linked cerebrospinal fluid (CSF) biomarker alongside neuroimaging brain abnormalities, have been assessed using techniques including positron emission tomography (PET) and magnetic resonance imaging (MRI) [14, 15]. In addition to that, various clinical scores have been developed to assess cognitive conditions, such as the Unified Parkinson's Disease Rating Scale, Part III (UPDRS-III), Hoehn and Yahr (H-Y) scale, and cognitive assessment scales like the Montreal Cognitive Assessment (MoCA), and Symbol Digit Modalities Test (SDMT) [16, 17]. However, their predictive ability for PD-CI remains unproven [17].

Aarsland et al. [18] reported age, H-Y score, and Mini-Mental State Examination score as predictive factors of PD-CI. Additionally, they concluded a sixfold increase in dementia in PD patients compared to controls. Chen et al. [16] built a predictive model in a 5-year cohort encompassing clinical variables and biomarkers. They achieved good accuracy when combining age, UPDRS III scores, MoCA scores, and apolipoprotein (APO) E status.

More recently, machine learning (ML) techniques have emerged as models that can enhance the prediction accuracy of cognitive decline in PD [19]. Almgren et al. [20] validated an ML model on 213 PD patients, integrating clinical scores, CSF biomarkers, and brain imaging to predict longitudinal changes in MoCA scores over four years, achieving high predictive performance. This calls for a better combination of traditional clinical assessments with advanced computational models, which could be reflected in the early identification of cognitive impairment in PD [21].

Conducting this study will enrich the literature with a new understanding of the PD-CI predictors. This could result in a better model that allows for early and timely intervention, better prognosis, and suitable stratification of PD patients in future trials.

Materials and methods

This prospective observational study was conducted over one year at Al-Azhar University Hospitals, where patients were recruited from the Neurology Outpatient Clinic and the Movement Disorders Unit. It was conducted with the institutional review board of the Al-Azhar University Faculty of Medicine's consent and in compliance with the Declaration of Helsinki [22].

Eligibility criteria

Based on the MDS Clinical Diagnostic Criteria for PD (MDS-PD), we prospectively included patients diagnosed with idiopathic PD in the previous two years. After getting the eligible patient's or their guardians' consent, we assessed each individual at baseline and at follow-ups of 3-, 6-, and 12-months. Clinically diagnosed PD patients were eligible if they met a minimum of two supporting criteria and had no absolute exclusion criteria or red flags. However, clinically probable PD patients were included with up to two red flags as long as supportive criteria counterbalanced each red flag.

On the other hand, patients who exhibited any of the following conditions were excluded: evident cerebellar abnormalities, including hypermetric saccades or gait ataxia; downward vertical supranuclear gaze palsy or selectively diminished downward vertical saccades; likely behavioral variant frontotemporal dementia or primary progressive aphasia within five years after illness onset. Over three years of lower-limb Parkinsonian symptoms. Failure to respond to levodopa at high doses despite moderately severe disease. Any evidence of another condition that may explain their Parkinsonism.

Patient management

Patients were assessed clinically, radiologically, and laboratory. A detailed clinical assessment was obtained, including a history of the disease course, its diagnosis and management, demographics such as age and gender, comorbidities like hypertension and diabetes, and drug history. Additionally, the Hamilton Anxiety Rating Scale (HAM-A) and the Beck Depression Inventory (BDI-II) were used to evaluate anxiety and depression, respectively. Motor manifestations were rated using the UPDRS-III and the H-Y Scale. In contrast, cognitive assessment was done by the MoCA and the Egyptian Arabic version of the Brief International Cognitive Assessment for MS (BICAMS).

Radiologically, 3D T1 sequence MRIs were performed at baseline and 12-month follow-up on a 1.5 Tesla machine to assess structural brain changes. A neuroradiologist at Al-Azhar University Hospitals reviewed scans of the areas of interest, such as the basal ganglia, thalami, amygdala, hippocampus, and overall brain volume.

Extensive investigations were conducted in the laboratory, including an electroencephalogram (EEG) to observe brain activity, particularly searching for indications of slowed or unusual electrical patterns in individuals lacking a previous epilepsy diagnosis. The EEG's aim was not to identify epileptiform activity, but to evaluate possible neurological changes that may be relevant to the study. Additionally, routine blood tests were performed to assess overall health, including complete blood count (CBC), erythrocyte sedimentation rate (ESR), hepatic and renal function tests, thyroid profile, lipid profile, blood glucose levels, and hemoglobin A1c (HbA1c) to monitor glucose control.

Statistical analysis

Statistical analysis was conducted using the SPSS software, version 28 (IBM, Armonk, NY, USA) [23]. The normality of quantitative data was determined using the Shapiro-Wilk test. Data that was regularly distributed were described by the mean and standard deviation (SD), and the student's *t*-test was employed for analysis, while non-normally distributed data, median, and interquartile range (IQR), and the Mann-Whitney test were used.

Chi-square or Fisher's exact test was used as appropriate to analyze the qualitative variables and describe them in frequencies and percentages. We used a multivariate logistic regression model, with a significance level of $p < 0.05$, to identify factors that could predict early cognitive impairment in PD.

Based on the previous cognitive impairment assessment scales, a score of less than 26 on the MoCA, coupled with deficits in at least one other cognitive area (such as memory or executive function), was utilized to define cognitive impairment. Additionally, the BDI and HAM-A were administered to consider mood-related factors potentially impacting cognitive performance. This classification was established at baseline and used for later statistical analyses comparing cognitively impaired and unimpaired groups.

Results

Eighty individuals with idiopathic PD were enrolled in this prospective observational study from Al-Azhar University's Neurology outpatient clinic and movement disorders center. As seen in Table 1, the mean age of participants is 60.9 ± 12.32 years. Among the patients included, 48 (60%) males and 32 (40%) females, 38 (47.5%) patients were from rural areas, and 42 (52.5%) patients were from urban. There were 31 (38.75%) literate patients and 49 (61.25%) illiterate patients. Moreover, 29 (36.25%) were smokers, and no alcohol consumption was recorded. The mean duration of illness of the studied patients was 6.6 ± 2.14 years.

Table 1. Baseline characteristics of the studied patients

Variable		Total (*n* = 80)
Age (years)		60.9 ± 12.32
Sex	Male	48 (60%)
	Female	32 (40%)
Residence	Rural	38 (47.5%)
	Urban	42 (52.5%)
Education	Literate	31 (38.75%)
	Illiterate	49 (61.25%)
Smoking		29 (36.25%)
Alcohol consumption		0 (0%)
Risk factors of the studied patients	Hypertension	27 (33.75%)
	Diabetes mellitus	18 (22.5%)
	Dyslipidaemia	21 (26.25%)
	Ischemic heart disease (IHD)	9 (11.25%)
	Atrial fibrillation	11 (13.75%)
	Arrhythmia	4 (5%)
Duration of illness (years)	IHD	6.6 ± 2.14

Laboratory investigation findings

The hematological parameters were in normal values, the mean hemoglobin (Hb) concentration 11.8 ± 0.99 g/dL ranged from 10.2 to 13.4 g/dL, the range of platelets count was 200 to 294 × 10^9/L with a mean of (245.6 ± 28.41) × 10^9/L, the white blood cells (WBCs) count ranged from 5.5 to 9.4 × 10^9/L with a mean of (7.5 ± 1.13) × 10^9/L. All metabolic parameters showed normal ranges except the fasting blood glucose (FBS), which was slightly elevated with a mean of 105.8 ± 42.24 mg/dL, the range of HbA1C was 4.5% to 7.5%, with a mean of 5.5 ± 0.86%, kidney function tests were normal, with serum creatinine levels ranging from 0.3 to 0.9 mg/dL (mean: 0.6 ± 0.18 mg/dL) and urea levels from 20 to 65 mg/dL (mean: 41.96 ± 12.52 mg/dL). Normal liver function tests, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), ranged from 25 to 63 U/L (mean 46.8 ± 12.11 U/L) and 18 to 55 U/L (mean 35.8 ± 11.92 U/L). All thyroid function tests were within normal limits, with thyroid-stimulating hormone (TSH) levels ranging from 2.5 to 4 mIU/L (mean: 3.2 ± 0.5 mIU/L), free T4 levels from 1.4 to 1.7 ng/dL (mean: 1.6 ± 0.09 ng/dL), and free T3 levels from 3.7 to 4.4 ng/dL (mean: 4.03 ± 0.21 ng/dL). The lipid profile was normal, with a mean total cholesterol of 160.9 ± 34.72 mg/dL, ranging from 100 to 220 mg/dL. The ranges for high-density lipoprotein (HDL) were 45–60 mg/dL with a mean of 52.2 ± 4.78 mg/dL, low-density lipoprotein (LDL) was 60–98 mg/dL with a mean of 76.9 ± 10.87 mg/dL, and triglycerides were 72–130 mg/dL with a mean of 102.02 ± 17.24 mg/dL. The lab investigations are detailed in Table 2.

Table 2. Laboratory investigations of the studied patients

Lap parameters	Mean ± SD	Range
Hb (g/dL)	11.8 ± 0.99	10.2–13.4
Platelets (× 10^9/L)	245.6 ± 28.41	200–294
WBCs (× 10^9/L)	7.5 ± 1.13	5.5–9.4
FBS (mg/dL)	105.8 ± 42.24	70–205
HbA1C (%)	5.5 ± 0.86	4.5–7.5
Serum creatinine (mg/dL)	0.6 ± 0.18	0.3–0.9
Urea (mg/dL)	41.96 ± 12.52	20–65
ALT (U/L)	46.8 ± 12.11	25–63
AST (U/L)	35.8 ± 11.92	18–55
TSH (mIU/L)	3.2 ± 0.5	2.5–4
Free T4 (ng/dL)	1.6 ± 0.09	1.4–1.7
Free T3 (ng/dL)	4.03 ± 0.21	3.7–4.4
Total cholesterol (mg/dL)	160.9 ± 34.72	100–220
Triglycerides (mg/dL)	102.02 ± 17.24	72–130
HDL (mg/dL)	52.2 ± 4.78	45–60
LDL (mg/dL)	76.9 ± 10.87	60–98

Hb: hemoglobin; WBCs: white blood cells; FBS: fasting blood glucose; HbA1C: hemoglobin A1c; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TSH: thyroid-stimulating hormone; HDL: high-density lipoprotein; LDL: low-density lipoprotein

Clinical criteria

With an average H-Y stage of 2.2 ± 1.14, the 80 individuals who were included in the study are mostly in the mild to moderate stage. Patients exhibited moderate motor symptoms as assessed by the UPDRS-III score, with a mean of 67.3 ± 35.45. The depressive symptoms, as assessed by BDI, were mild to moderate, with a mean of 18.3 ± 15.29. Patients exhibited mild impaired cognitive function as assessed by the California Verbal Learning Test-II (CVLT-II), MoCA, SDMT, and the Brief Visuospatial Memory Test-Revised (BVMT-R). The mean SDMT score was 40.4 ± 7.99, BVMT-R was 22.6 ± 5.42, CVLT-II was 54.0 ± 17.56, and MoCA was 25.1 ± 3.61. Additionally, the mean HAM-A was 15.02 ± 13.06, indicating a mildly elevated anxiety level, as detailed in Table 3.

Table 3. Clinical criteria of the studied patients

Parameter		Mean ± SD	Range
Hoehn and Yahr (H-Y)		2.2 ± 1.14	1–5
H-Y stages	Stage 1	26 (32.5%)	
	stage 2	30 (37.5%)	
	Stage 3	14 (17.5%)	
	Stage 4 and 5	10 (12.5%)	
UPDRS-III		67.3 ± 35.45	20–187
BDI		18.3 ± 15.29	2–50
SDMT		40.4 ± 7.99	25–55
BVMT-R		22.6 ± 5.42	14–36
CVLT-II		54.0 ± 17.56	21–79
CVLT-II delayed recall		11.5 ± 4.16	3–16
MoCA score		25.1 ± 3.61	16–29
HAM-A		15.02 ± 13.06	1–44

Quantitative data is presented in mean and standard deviation (SD), in the left column, and range in the right column, while qualitative data is presented in *n* (%). UPDRS-III: Unified Parkinson's Disease Rating Scale, Part III; BDI: Beck Depression Inventory; SDMT: Symbol Digit Modalities Test; BVMT-R: Brief Visuospatial Memory Test-Revised; CVLT-II: California Verbal Learning Test-II; MoCA: Montreal Cognitive Assessment; HAM-A: Hamilton Anxiety Rating Scale

The association between cognitive impairment and patients' variables

No significant correlation was found between the cognitive impairment and demographic characteristics, except for age, education, and illness duration, as shown in detail (Table 4). Cognitive-impaired patients had a considerably higher mean age of 71.8 years, in contrast to non-cognitive-impaired patients, whose mean age was 49.7 years. Additionally, cognitively impaired patients were significantly more illiterate compared to non-cognitively impaired patients. Sex, residency, smoking, and alcohol use did not significantly differ between the two groups; however, patients with cognitive impairment had a slightly longer disease duration (mean of 7.3 years) than those without (mean of 6.2 years).

Table 4. Correlation between baseline characteristics of the studied groups and cognitive impairment

Variable		PD with cognitive impairment (*n* = 33)	PD without cognitive impairment (*n* = 47)	*p* value
Age (years)	Mean ± SD	71.8 ± 4.58	49.7 ± 6.22	< 0.001*
Sex	Male	20 (60.61%)	28 (59.57%)	0.926
	Female	13 (39.39%)	19 (40.43%)	
Residence	Rural	17 (51.52%)	21 (44.68%)	0.547
	Urban	16 (48.48%)	26 (55.32%)	
Education	Literate	5 (15.15%)	26 (55.32%)	< 0.001*
	Illiterate	28 (84.85%)	21 (44.68%)	
Smoking		10 (30.3%)	19 (40.43%)	0.406
Duration of illness (years)		7.3 ± 2.28	6.2 ± 1.98	0.024*

* Data is significant; *p* value < 0.05. PD: Parkinson's disease

Regarding laboratory parameters, the results demonstrated significant differences in FBS and TSH among PD patients with and without cognitive impairment, as shown in detail in Table 5. FBS was significantly higher in patients with cognitive impairment, with a mean of 121.2 mg/dL, compared to those without cognitive impairment, with a mean of 95.02 mg/dL. Additionally, patients with cognitive impairment had slightly lower TSH levels, a mean of 3.1 mIU/L, compared to those without cognitive impairment, a mean of 3.3 mIU/L.

Table 5. Laboratory investigations of the studied groups regarding cognitive impairment

Variable	PD with cognitive impairment (*n* = 33)	PD without cognitive impairment (*n* = 47)	*p* value
Hb (g/dL)	11.8 ± 1.11	11.7 ± 0.9	0.614
Platelets (× 10^9/L)	242.4 ± 28.18	247.9 ± 28.65	0.4
WBCs (× 10^9/L)	7.2 ± 1.08	7.7 ± 1.13	0.075
FBS (mg/dL)	121.2 ± 49.03	95.02 ± 33.23	0.006*
HbA1C (%)	5.6 ± 1.01	5.4 ± 0.74	0.199
Serum creatinine (mg/dL)	0.6 ± 0.19	0.6 ± 0.17	0.822
Urea (mg/dL)	42.5 ± 13.62	41.6 ± 11.82	0.729
ALT (U/L)	45.3 ± 12.76	47.9 ± 11.66	0.359
AST (U/L)	35.4 ± 11.31	36.1 ± 12.45	0.806
TSH (mIU/L)	3.1 ± 0.49	3.3 ± 0.49	0.041*
Free T4 (ng/dL)	1.6 ± 0.09	1.5 ± 0.09	0.464
Free T3 (ng/dL)	4.04 ± 0.22	4.03 ± 0.21	0.892

* Data is significant; *p* value < 0.05. PD: Parkinson's disease; Hb: hemoglobin; WBCs: white blood cells; FBS: fasting blood glucose; HbA1C: hemoglobin A1c; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TSH: thyroid-stimulating hormone

PD patients with cognitive impairment exhibit a more severe clinical profile, as detailed in Table 6. Motor function was significantly worse in cognitive impairment patients than those without cognitive impairment, as evidenced by higher H-Y stage 3.4 ± 0.96 vs. 1.4 ± 0.5 and higher UPDRS-III scores 101.1 ± 34.83 vs. 47.2 ± 18.27. Additionally, their levels of anxiety were significantly greater (HAM-A 28.4 ± 11.74 vs. 7.1 ± 3.5), and their levels of depressive symptoms were significantly higher (BDI 39.4 ± 7.15 vs. 8.8 ±

3.41). Furthermore, patients with cognitive impairment exhibited significantly worse cognitive performance on various neuropsychological tests. They had significantly lower scores on the SDMT 36.5 ± 5.5 vs. 46.7 ± 8.89, BVMT-R 19.03 ± 4.86 vs. 22.7 ± 5.57, CVLT-II 39.3 ± 17.15 vs. 64.3 ± 7.8, CVLT-II delayed recall 7.9 ± 4.09 vs. 14.0 ± 1.57, and MoCA 22.4 ± 3.98 vs. 27.1 ± 1.42.

Table 6. Clinical criteria of the studied groups regarding cognitive impairment

Variable	PD with cognitive impairment (*n* = 33)	PD without cognitive impairment (*n* = 47)	*p* value
Hoehn and Yahr (H-Y)	3.4 ± 0.96	1.4 ± 0.5	< 0.001*
UPDRS	101.1 ± 34.83	47.2 ± 18.27	< 0.001*
BDI	39.4 ± 7.15	8.8 ± 3.41	< 0.001*
SDMT	36.5 ± 5.5	46.7 ± 8.89	< 0.001*
BVMT-R	19.03 ± 4.86	22.7 ± 5.57	0.008*
CVLT-II	39.3 ± 17.15	64.3 ± 7.8	< 0.001*
CVLT-II delayed recall	7.9 ± 4.09	14.0 ± 1.57	< 0.001*
MoCA score	22.4 ± 3.98	27.1 ± 1.42	< 0.001*
HAM-A	28.4 ± 11.74	7.1 ± 3.5	< 0.001*

* Data is significant, *p* value < 0.05. UPDRS: Unified Parkinson's Disease Rating Scale; BDI: Beck Depression Inventory; SDMT: Symbol Digit Modalities Test; BVMT-R: Brief Visuospatial Memory Test-Revised; CVLT-II: California Verbal Learning Test-II; MoCA: Montreal Cognitive Assessment; HAM-A: Hamilton Anxiety Rating Scale

The results indicate strong correlations between the H-Y stage and several key clinical variables, as shown in Table 7. Specifically, with the UPDRS-III score, it has a strong positive correlation ($r = 0.773$, $p < 0.001$), indicating that as disease severity increases, motor symptoms worsen. Additionally, there was a strong positive correlation between H-Y stage and BDI score ($r = 0.735$, $p < 0.001$), indicating a stronger association between disease severity and depressive symptoms.

Table 7. Correlation between Hoehn and Yahr (H-Y) stages and clinical criteria

Parameter	Hoehn and Yahr (H-Y) stages	
	r	*p*
UPDRS-III	0.773	< 0.001*
BDI	0.735	< 0.001*
SDMT	–0.509	< 0.001*
BVMT-R	–0.258	0.020*
CVLT-II	–0.421	< 0.001*
CVLT-II delayed recall	–0.548	< 0.001*
MoCA score	–0.396	< 0.001*
HAM-A	0.574	< 0.001*

* Data is significant, *p* value < 0.05. UPDRS-III: Unified Parkinson's Disease Rating Scale, Part III; BDI: Beck Depression Inventory; SDMT: Symbol Digit Modalities Test; BVMT-R: Brief Visuospatial Memory Test-Revised; CVLT-II: California Verbal Learning Test-II; MoCA: Montreal Cognitive Assessment; HAM-A: Hamilton Anxiety Rating Scale

Conversely, H-Y stage was strongly negatively correlated with cognitive function on several neuropsychological tests, including the BVMT-R ($r = –0.258$, $p = 0.020$), SDMT ($r = –0.509$, $p < 0.001$), CVLT-II ($r = –0.421$, $p < 0.001$), MoCA ($r = –0.396$, $p < 0.001$, and CVLT-II delayed recall ($r = –0.548$, $p < 0.001$), suggesting that as disease severity increases, cognitive function declines. The H-Y stage showed a stronger association between disease severity and anxiety symptoms, with a positive correlation with anxiety levels measured by the HAM-A ($r = 0.574$, $p < 0.001$).

The multivariable regression analysis aimed to identify factors associated with PD patients with cognitive impairment, as shown in Table 8. The results indicate that several variables significantly predict cognitive impairment; precisely, longer duration of illness and lower total brain tissue volume were significantly associated with cognitive impairment. Additionally, higher levels of diabetes mellitus, higher UPDRS-III scores, higher BDI scores, and lower scores on the BVMT-R, SDMT, CVLT-II, MoCA score, and CVLT-II delayed recall were all significantly associated with cognitive impairment.

Table 8. Multivariable regression analysis for the prediction of cognitive impairment

Variable	Coefficient	SE	t	*p* value
Age (years)	0.005	0.005	0.985	0.328
Sex	–0.183	0.141	–1.296	0.199
Residence	0.018	0.14	0.13	0.897
Education	–0.179	0.125	–1.428	0.157
Smoking	–0.1	0.119	–0.836	0.406
Hypertension	0.056	0.129	0.432	0.667
Diabetes mellitus	–0.381	0.177	–2.156	0.034*
Dyslipidaemia	–0.113	0.14	–0.811	0.42
IHD	0.451	0.235	1.921	0.059
Atrial fibrillation	–0.123	0.181	–0.679	0.499
Arrhythmia	0.213	0.266	0.798	0.427
Duration of illness (years)	0.024	0.01	2.344	0.022*
Hb (g/dL)	0.075	0.062	1.217	0.228
Platelets (× 10^9/L)	0	0.002	–0.172	0.864
WBCs (× 10^9/L)	–0.052	0.05	–1.039	0.303
FBS (mg/dL)	0	0.003	–0.158	0.875
HbA1C (%)	0.098	0.135	0.726	0.47
Serum creatinine (mg/dL)	–0.217	0.313	–0.692	0.492
Urea (mg/dL)	–0.019	0.005	–3.698	< 0.001*
ALT (U/L)	0.005	0.005	1.117	0.268
AST (U/L)	0.004	0.005	0.714	0.478
TSH (mIU/L)	0.046	0.116	0.4	0.691
Free T4 (ng/dL)	0.806	0.644	1.251	0.215
Free T3 (ng/dL)	0.325	0.272	1.193	0.237
Total cholesterol (mg/dL)	0	0.002	–0.008	0.993
Triglycerides (mg/dL)	–0.003	0.003	–0.911	0.365
HDL (mg/dL)	0.001	0.012	0.119	0.905
LDL (mg/dL)	0.012	0.005	2.168	0.033
Hoehn and Yahr (H-Y)	0.271	0.029	9.313	< 0.001*
UPDRS-III	0.003	0.001	3.478	0.001*
BDI	0.006	0.002	2.858	0.006*
SDMT	–0.012	0.003	–3.33	0.001*
BVMT-R	–0.016	0.008	–2.073	0.042*
CVLT-II	–0.006	0.003	–2.48	0.015*
CVLT-II delayed recall	–0.025	0.012	–2.13	0.036*
MoCA score	–0.018	0.006	–3.056	0.003*
HAM-A	0.006	0.003	2.048	0.044*

* Data is significant, *p* value < 0.05. SE: Standard Error; IBD: Ischemic heart disease; Hb: hemoglobin; WBCs: white blood cells; FBS: fasting blood glucose; HbA1C: hemoglobin A1c; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TSH: thyroid-stimulating hormone; HDL: high-density lipoprotein; LDL: low-density lipoprotein; UPDRS-III: Unified Parkinson's Disease Rating Scale, Part III; BDI: Beck Depression Inventory; SDMT: Symbol Digit Modalities Test; BVMT-R: Brief Visuospatial Memory Test-Revised; CVLT-II: California Verbal Learning Test-II; MoCA: Montreal Cognitive Assessment; HAM-A: Hamilton Anxiety Rating Scale

Discussion

This observational prospective study was conducted on 80 ambulant living patients with idiopathic PD recruited from Al-Azhar University hospitals. The results aimed to demonstrate the impact of various comorbidities and the relation of brain imaging features as predictors for cognitive impairment and disease progression in early PD patients, finding that they primarily presented with mild to moderate disease severity. Motor symptoms were moderately severe, and patients experienced mild to moderate depressive symptoms, mild cognitive impairment, and mildly elevated anxiety levels. While most laboratory parameters were normal, slightly elevated fasting blood sugar and slightly lower TSH levels were observed

in patients with cognitive impairment. Disease severity was strongly correlated with motor symptoms, depressive symptoms, anxiety, and cognitive impairment. Cognitive impairment was linked to longer illness duration, diabetes mellitus, worse motor and psychiatric symptoms, and lower brain tissue volume. This shows that PD has a complex clinical presentation and needs a comprehensive assessment.

The study supports Helmy et al. [24], who aimed to assess motor progression predictors in PD patients over 1 year in a sample of depressed patients: 64.4% using BDI, 20% were akinetic-rigid, 75.5% were tremor-dominant, 33.33% were young-onset PD, and 66.77% were late-onset. The study found significantly higher postural instability and gait disorder and New Freezing of Gait Questionnaire in females, in addition to prolonged Timed Up and Go test and higher serum lipids compared to males. Conversely, disease progression did not differ significantly between males and females. Badr et al. [25] conducted a study on 58 idiopathic PD patients. The study found that PD might be accompanied by co-morbidity, such as hypertension (33.75%), diabetes mellitus (22.5%), dyslipidemia (26.25%), IHD (11.25%), atrial fibrillation (13.75%), and arrhythmia (5%). The mean duration of illness was 6.6 ± 2.14 years. These results align with those published by Shalash et al. [26], who illustrated a mean of 2.8 ± 1.1 disease staging in the off-medication state and 38.04 ± 19.37 of motor severity. Depression was prevalent in the enrolled participants, 76.7%. Ahmed et al [27], a study of 44 PD patients, with a majority of males and urban cases, and the majority of participants aged 35 years or older. They demonstrated cognitive impairment in 41.25% of participants. No significant difference was found in study groups regarding demographics and risk factors, but illness duration was significantly longer in patients with cognitive impairment compared to those without (p = 0.024). Martínez-Horta et al. [28], a study of 901 participants, including 694 PD cases and 207 healthy controls, with a mean age of 62.5 ± 8.6 years. They demonstrated that diabetes, hypertension, and dyslipidemia were significantly higher in patients with cognitive impairment.

Brain atrophy was detected in 4 patients (5%), representing a small subset of individuals in the study. While a reduction in brain tissue volume, particularly in the frontal lobe and hippocampus, was noted in patients with cognitive impairment, this observation was not subjected to detailed statistical subgroup analysis due to the limited number of cases. Nonetheless, this finding is consistent with previous studies, such as Burton et al. [29], which have highlighted the association between regional brain atrophy and cognitive decline in PD. Although suggestive, the limited number of cases in this cohort makes it difficult to draw definitive conclusions regarding the role of brain atrophy in cognitive impairment. Therefore, while it may contribute to the broader clinical picture, these results were not emphasized in the discussion, given the small sample size and lack of detailed imaging analysis.

This study included a comprehensive assessment of clinical, neuropsychological, and laboratory parameters, as well as brain imaging, providing a robust evaluation of PD patients with serial follow-ups. The prospective design of the study allowed for the identification of potential predictors of cognitive impairment. However, we acknowledge several limitations. The low sample size, along with the single-center nature of the study, may have limited the generalizability of our findings. The lack of a control group restricts our ability to draw comparative conclusions, despite the primary focus on a homogeneous cohort of idiopathic PD patients. Additionally, the resource constraints and patient-related factors prevented us from utilizing other advanced accepted cognitive screening tools, CSF biomarkers or genetic data and imaging modalities, such as diffusion tensor imaging (DTI) or PET besides the widely available and used ones, which may have reduced the comprehensiveness of our predictive model and the mechanism behind it. Furthermore, while the one-year follow-up was chosen for detecting early predictors, extended follow-up would offer greater insight into long-term progression. In addition to that, we did not evaluate the potential effects of PD medications on cognitive function. Further multicenter, larger trials with a control group, extended follow-up, and more advanced tools are needed to validate the findings of this study. Additionally, incorporating ML models is encouraged in future studies to enhance prediction accuracy, particularly with longer durations and larger datasets.

In conclusion, the study found that H-Y, UPDRS, BDI, and HAM-A were significantly higher in cognitively impaired PD patients. However, BVMT-R, SDMT, CVLT-II, MoCA score, and CVLT-II delayed recall were significantly lower in the PD with cognitive impairment group compared to those without. To confirm these results, further prospective studies on a larger scale are needed.

Abbreviations

BDI: Beck Depression Inventory

BICAMS: Brief International Cognitive Assessment for MS

BVMT-R: Brief Visuospatial Memory Test-Revised

CVLT-II: California Verbal Learning Test-II

FBS: fasting blood glucose

HAM-A: Hamilton Anxiety Rating Scale

HbA1c: hemoglobin A1c

H-Y: Hoehn and Yahr

ML: machine learning

MoCA: Montreal Cognitive Assessment

MRI: magnetic resonance imaging

PD: Parkinson's disease

PDD: Parkinson's disease dementia

PET: positron emission tomography

SDMT: Symbol Digit Modalities Test

TSH: thyroid-stimulating hormone

UPDRS-III: Unified Parkinson's Disease Rating Scale, Part III

Declarations

Author contributions

AAG: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. NHE: Investigation, Writing—review & editing. AES: Validation, Writing—review & editing, Supervision. AE: Validation, Writing—review & editing, Supervision. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest regarding the publication of this article.

Ethical approval

This study was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Al-Azhar University, Cairo, Egypt (Approval number: Near-Med._78 Predictors Of Cognitive Impairment In Egyptian Patients With Parkinson's Disease._000078), and was conducted in accordance with the Declaration of Helsinki.

Consent to participate

Informed consent to participate in the study was obtained from all participants.

Consent to publication

Informed consent to publication was obtained from relevant participants.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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