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RESEARCH PAPER

Predictors of Parkinson's Disease Dementia Among Patients in a Tertiary Care Hospital in Bangladesh

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Abstract

Background: Parkinson's disease dementia (PDD) is a common consequence during the course of the disease. It deeply influences patients' prognosis, quality of life, caregiver burden and economic strain. However, effective treatment for PDD is currently unclear. Clinical and demographic predictors for this comorbidity are not well studied.

Objectives: To investigate putative risk factors for the development of dementia in patients with Parkinson's disease (PD) attending a tertiary care and teaching hospital in Bangladesh.

Methods: One hundred thirty-one consecutive PD cases were enrolled in this cross-sectional study; whose disease duration was more than a year. Comparison was done between demented and non-demented PD cases. Structural CNS diseases including secondary parkinsonism were excluded by clinically and MRI of brain for all cases. Dementia was evaluated based by DSM-IV and assessed using mini-mental state examination (MMSE) score and Parkinson's disease dementia short screen (PDD-SS) score. Severity of disease was evaluated by Hoehn and Yahr stage (H-Y I to V). Depression was assessed using DSM-IV. Data were analysed on a logistic regression model using SPSS v 23.

Results: The overall frequency of dementia was 38%. The mean (SD) age of the demented and non-demented PD cases was 73.32(8.86) and 63.98 (6.19) years respectively. On multivariate logistic regression model, age ≥70 years [OR=4.25, *p*=0.031], diabetes [OR=5.37, *p*=0.019], hypertension [OR=7.63, p=0.011], disease duration ≥5 years [OR=10.01, *p*<0.001], H-Y stage e" 3 [OR= 9.52, *p*<0.001] and depression [OR=8.79, p<0.001] were significantly associated with PDD.

Conclusion: In this study of PD cases, overall risks of dementia were advancing age, diabetes, hypertension, longer disease duration, higher disease stage and presence of depressive illness.

Keywords: Parkinson's disease, Dementia, Mini mental state examination, Depression

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorders with an estimated prevalence of 2–3% at 65 years and as high as 10% among those 80 years old.[1-3] It increases proportionately with age.[4] Exact aetiology and underlying mechanisms of PD are still unknown but aggregated Lewy bodies containing alpha-synuclein (αSyn) are believed to play a central role in the pathogenesis.[5] Similarly, curable treatments are not yet available.[6] Dementia is used to describe a progressive decline in a person's functioning with a loss of memory, intellect, emotional reactions, social skills and rationality.[7] Dementia is six times more prevalent in PD than general population.[8] Parkinson's disease dementia (PDD) represent the second most common cause of dementia worldwide.[9] It is the most devastating nonmotor features of PD causing severe decline in quality of life, increased family burden, economical stain, caregiver burden, mortality, and often require hospitalization.[10] PDD has a unique clinical profile and neuropathology, distinct from Alzheimer's disease (AD), with notable relative preservation of delayed memory, but severely impaired executive function, attention, and visuospatial skills.[2,9] Not all people with PD will develop dementia. It is estimated that 30-60% non-demented PD patients

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developed PDD over two to five years.[11,12] A systematic review reports the point prevalence of PDD is about 30%.[8,54] So, it should be recognised early and treated appropriately.[2] However, effective treatment is currently unclear.[13] Identifying the factors predictive of PDD is important for the high risk cases in future planning care, counseling and targeted therapeutic interventions.[10] Being able to predict PDD development accurately, would provide opportunities for intervention as well as novel treatments that might prolong survival and improve quality of life.[14] Several demographic, motor and non-motor features have been identified as predictors.[13] There may have medical comorbidities which may have modification effects.[10,15-18] Thus, information about which patients will eventually develop dementia is an important issue in public health and clinical practice.[15,19] The neurobiological basis for PDD is multifocal, multiple neurotransmitter deficits related to a synergistic effect of á-synuclein deposits.[20] There are no specific ancillary investigations for diagnosis. The main structural pathology is the degeneration in cerebral cortex, limbic structures with relative preservation of the medial temporal lobes and the hippocampus.[21] It is likely that PDD is multifactorial including genetic, demographic, environmental and medical comorbidities.[22] Vascular risk factors have been associated with cognitive deficits and dementia in general population, but their role on cognitive dysfunction in PD is still unclear.[23,24] Little researches has examined it as a potential factor that could be controlled.[10,15,17] However, most previous studies have been conducted in western countries and information for Asian PD populations, especially sub-continent are lacking.[15,22] Due to significant sociocultural differences, findings from western populations may not be directly extrapolated to this region. PDD have been shown to vary widely between different countries.[22] However, limited information on this topic, the association between PD and the risk of dementia needs to be further explored. Thus the study was designed to estimate the frequency of PPD, and to evaluate clinical, vascular, socioeconomic and demographic aspects that may contribute to PDD among the cases with PD.

Materials and Methods

This was a single centre, cross-sectional, descriptive, comparative study between demented and non-demented PD cases at the Department of Neurology, Shaheed Suhrawardy Medical College and Hospital (ShSMCH), Dhaka, Bangladesh. One hundred thirty-one consecutive PD patients were diagnosed clinically, using UK Parkinson's Disease Society Brain Bank criteria whoever agree to comply the study procedures. PD symptoms more than one year were included.[25,26] The objectives of the study were explained to the participant/legal guardian in easily understandable local language, then informed written consent was taken prior to data collection. MRI of brain was done in all cases and secondary Parkinsonism including vascular disease, traumatic brain injury, or Alzheimer's disease and age less than 40 years were excluded. Any disability or unstable disease that might prevent the patient from completing study procedure, significant aphasia affecting participation, refused to participate, other psychiatric disorders non-related to PD, abusive use of alcohol or illicit drugs and symptoms of PD durations less than a year were excluded. Diagnosis of dementia was done by a neurologist based on DSM-IV criteria using a pre-deigned structured clinical face to face interview with mini-mental state examination (MMSE) score ≤24(0–30 points) and Parkinson's disease with dementia short screen (PDD-SS) score ≤11(0–22 points).[27-29] The interview was conducted in local language and assessments were made in English by the investigators. Depression was diagnosed according to DSM-IV criteria.[27,30] Severity of PD was evaluated by the Hoehn and Yahr stage (H-Y I to V).[31] Ethical clearance was obtained from the National Research Ethics Committee of Bangladesh Medical Research Council.

Demographic and other clinical information obtained from the patient, relatives or caregiver. A subject was considered diabetes mellitus (DM) if fasting blood glucose value ≥7.0 mmol/L and/or 2-h post-load glucose concentration ≥11.1 mmol/L or currently receiving treatment for DM. Hypertension (HTN) was considered if clinically diagnosed or currently receiving medication for high blood pressure. The history of angina/infarction (ischemic heart disease-IHD) and atrial fibrillation was considered when there was evidence of a clinical diagnosis for each of these pathologies with the help of ECG, chest X-ray and echocardiography. Tobacco consumption was established according to the WHO as: non-smoker, ex-smoker and current smoker. Variables like hallucination, postural instability, sleep disturbance and family history of dementia was evaluated in a dichromats yes/no.

Data were analysed using SPSS version 23. Continuous variables were expressed as mean ± standard deviation and were evaluated by the unpaired Student's t test. Similarly, categorical variables were expressed as percentage of the total and were evaluated by the chi-square test to measure the level of significance. The relative risk of PDD was estimated as odds ratio (OR) using logistic regression models. A p-value <0.05 was considered statistically significant. We calculated adjusted odds ratio (adj. OR) between two groups, demented (Group A) and non-demented (Group B) PD cases. All significant variables from univariate analysis were entered into a linear regression model in a stepwise fashion and a final fitted model was determined.

Results

One hundred thirty-one PD cases were enrolled and 50 (38.0%) had dementia. The mean (SD) age of dementia and non-dementia was 73.32(8.86) years (range 54 to 95) and 63.98 (6.19) years (range 45 to 86) respectively. Male was slightly predominant (52%vs.68%). The mean (SD) disease duration was 8.53 (3.04) vs 3.76 (1.39) years and age at disease onset was 60.21(6.31) vs 64.79(8.64) years respectively. The frequency of residence, education, smoking status, and family history of dementia was not significance (table I). Hypertension (66% vs.12%) and depression (76% vs 27%) were detected significantly higher in group A (table II). Daily used levodopa was 596(189) and 364(200) mg which was not significant. The mean (SD) MMSE score was 18.75(4.4) vs 27(1.85) and PDD-SS core was 8.61(2.3) vs 14.75(3.26) between groups respectively.

Univariate logistic regression analysis was first performed for each hypothesized predictor (table III), age ≥70 years[OR=10.45, p<0.001)]; diabetes [OR=2.96, p=0.019]; hypertension [OR=8.54, p<0.001]; diseases duration ≥5 years [OR=18.09, p<0.001] sleep disturbance [OR=2.52, p=0.028]; postural instability [OR=3.68, p=0.021]; hallucination [OR=4.55, p=0.011]; H-Y stage ee3 [OR=16.13, p<0.001] and depression [OR=8.49, p<0.001] were significantly associated with developing PDD.

Table I: Socio-demographic characteristics of study cases

Characteristics	Group		p-value*
	Dementia(n=50)	Non-dementia(n=81)	
Age	73.32(±8.86) #	63.98(±6.19)	<0.001** s
Sex			
Male	26	55	0.095 ns
Female	24	26	
Socioeconomic condition			
Upper	13	10	1.00 ns
Middle	24	40	
Lower	13	31	
Smoking (male only)			
Smoker	14	27	0.656 ns
Non-smoker	12	28	
Education			
Illiterate	11	22	
Primary	15	16	0.271 ns
Secondary	15	19	
higher secondary and above	09	24	
Levodopa dose (mg/day)	596.50(±189.12)	364.81(±200.03)	0.430** ns
Disease duration (year)	8.53 (±3.04)	3.76 (±1.39)	< 0.001** s
PDD-SS score (0–22 points)	8.61(±2.3)	14.75(±3.26)	< 0.001** s
MMSE score (0–30 points)	18.75(±4.4)	27(±1.85)	< 0.001** s

*Chi square test was done to measure the level of significance except ** where Unpaired t test was done to measure the level of significance
#Figure within parenthesis denoted corresponding Mean (SD), s=significant; ns= non-significant

Table II: Clinical characteristics of study cases

Characteristics	Group		P value*
	Dementia (n=50)	Non-dementia (n=81)	
Diabetes	17	12	0.019 s
Hypertension	33	15	<0.001 s
Coronary heart disease	12	16	0.721 ns
(CHD)	12	17	0.852 ns
Family H/O dementia	37	43	0.028 s
Sleep disturbance			
Hallucination	27	17	0.011 s
Postural instability	27	22	0.021 s
Depression	38	22	<0.001 s
Severity of diseases (H-Y)			
stage 1	02	15	
stage 2	03	37	
stage 3	07	22	<0.001 s
stage 4	27	04	
stage 5	11	03	

*Chi square test was done to measure the level of significance except ** where Unpaired t test was done to measure the level of significance
s=significant; ns= non-significant

Table III: Unadjusted risk factor for dementia in Parkinson's disease

	Unadjusted OR	95% CI	p-value
Sex			
Female (ref)	1		
Male	0.51	0.12-4.03	0.078 ns
Age			
< 70 years (ref)	1		
≥70 years	10.45	4.58-23.83	<0.001 s
Smoking			
No(ref)	1		
Yes	0.78	0.36 - 1.68	0.523 ns
Diabetes Mellitus			
No (ref)	1		
Yes	2.96	1.27 - 6.91	0.019 s
Hypertension			
No (ref)	1		
Yes	8.54	3.69 - 18.35	<0.001 s
Coronary heart disease			
No (ref)	1		
Yes	1.28	0.55- 2.99	0.721 ns
Family H/O dementia			
No (Ref)	1		
Yes	1.19	0.51 - 2.76	0.852 ns
Diseases duration			
< 5 years (Ref)	1		
≥5 years	18.09	8.029- 38.28	<0.001 s
Sleep disturbance			
No (Ref)	1		
Yes	2.52	1.17-5.42	0.028 s
Postural instability			
No (Ref)	1		
Yes	3.68	1.21-6.38	0.021 s
Hallucination			
No (Ref)	1		
Yes	4.55	2.78- 7.22	0.011 s
H-Y stage			
< 3(ref)	1		
≥3	16.13	6.81-31.34	<0.001 s
Depression			
No (Ref)	1		
Yes	8.49	3.34-21.86	<0.001 s

When all significant variables from univariate were included in multivariate linear logistic regression mode (table IV), age ee70 years [OR=4.25, 95% CI (1.51-7.86), *p*=0.031], diabetes [OR=5.37, 95% CI (2.29-10.09); *p*=0.019], hypertension [OR=7.63, 95% CI (2.69-13.01); *p*=0.011], disease duration ee5 years [OR=10.01, 95% CI (4.81-21.65); *p*<0.001], H-Y stage ≥3 [OR= 9.52, 95% CI (4.37-19.06); *p*<0.001] and depression [OR=8.79, 95% CI (3.95-18.98); *p*<0.001] were found significantly associated with PDD.

Table IV: Logistic regression model: predictors for PDD

	Adjusted OR	95% CI	p-value
Age			
< 70 years (ref)	1		
≥70 years	4.25	1.51-7.86	0.031 s
Diabetes Mellitus			
No (ref)	1		
Yes	5.37	2.29-10.09	0.019 s
Hypertension			
No (ref)	1		
Yes	7.63	2.69-13.01	0.011 s
Diseases duration			
< 5 years (ref)	1		
≥5 years	10.01	4.81-21.65	<0.001 s
H-Y stage	1	4.37-19.06	<0.001 s
< 3(ref)	9.52	3.95-18.98	<0.001 s
≥3	1		
Depression	8.79		
No (ref)			
Yes			

Discussion

In this study of PD patients 38% was found dementia. This finding has similarity with other studies.[33,41,42] There was no sex difference. Age was a determining factor in developing PDD which was reported in many other studies.[32-35,42] As age increases, biological and psychological changes begin to occur. Dopamine levels decrease with age, allowing older individuals to be more susceptible to PDD. This is plausible given that age is the most important risk factor for dementia in the general population also.

H-Y stage was significantly correlated with PDD in our results. In agreement with this, previous studies have found a positive correlation of PDD with the

progression of PD.[13,33,38-42] The incidence of PDD was related to disease progression, greater severity of neurological and motor symptoms.[37] High severity of extrapyramidal signs with older age poses the highest risk of developing PDD.[36] H-Y stage greater than two has been proposed to be a predictor of PDD.[8] We found that longer disease duration was significantly correlated with PDD. This result is in accordance with others study.[43-47,55] Neuropsychiatric symptoms were associated with more severe dementia and advanced Parkinson's disease durations.[48]

An interesting and surprising finding was that depression, hypertension and diabetes was significantly associated with PDD in multivariate logistic regression. These factors are modifiable. Depression was important non-motor factors for PDD. Similar findings have been reported previously.[8,10,23,42,49] Indeed, the role of hypertension has been recently

highlighted as one of PDD predictors using an extensive longitudinal evaluation.[10,13,23,50] The effect of diabetes on PDD was also evaluated.[51,52] Diabetes mellitus was independently associated with more severe cognitive impairment in PD.[51] It may exacerbate brain atrophy and cognitive functions in PD with greater vulnerability in the frontal lobes.[53]

It was a single centre; cross-sectional study, making it less representative for the entire population. This study did not address clinical symptoms, subtypes and severity of dementia. The final limitation was the lack of drug information that may affect cognitive function.

Conclusion

The study shows proportion of PD patients suffer from dementia. PDD was significantly associated with a number of socio-demographic and clinical factors including advancing age, longer disease duration, higher disease stage, diabetes, hypertension and presence of depressive illness. Our overall findings in relation to frequency and PDD predictors, are in keeping what is reported in other populations also. This study showed some unique modifiable factors of PDD such as depression, hypertension and diabetes. These findings need further inquiry whether they are replicated regionally or globally. Further research is required in order to understand underlying mechanisms of dementia in Parkinson's disease.

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