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ORIGINAL RESEARCH

Assessment of cognitive impairment in patients with Parkinson's disease: prevalence and risk factors

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Background: Although Parkinson's disease (PD) is clinically characterized by motor symptoms, cognitive impairment is one of the most disabling non-motor symptoms. Despite it attracting increasing attention worldwide, less is known about its prevalence in the Chinese population. The objective of this study was to assess cognitive impairment and related risk factors in Chinese PD patients.

Methods: We collected the demographic, diagnostic, and treatment information of 901 PD patients from 42 centers throughout the People's Republic of China, then administered a battery of neuropsychological tests, to assess motor, cognitive, and neuropsychiatric symptoms.

Results: Overall, 193 of 901 (21.4%) PD patients met the criteria for dementia (PD-D), and 206 (22.8%) met the criteria for mild cognitive impairment (PD-MCI). Visuospatial dysfunction and attention/executive impairment predominated. Increased severity of cognitive impairment was associated with greater motor impairment. Patients with psychiatric symptoms, such as depression and hallucinations, were more likely to have dementia. Potentially, the younger-aged and more educated are shown less cognitive impairment, but age at onset, and levodopa equivalent dose, were not associated with the presence of cognitive dysfunction.

Conclusion: The prevalence and profile of cognitive impairment in Chinese PD patients, as well as the risk factors, are similar as those reported for other races, but the frequency of nonamnestic cognitive domains differs.

Keywords: cognitive impairment, risk factor, prevalence, Parkinson's disease

Introduction

Cognitive impairment is one of the most common and disabling non-motor symptoms in Parkinson's disease (PD), yet it is not routinely treated in clinical practice. The prevalence of PD-related cognitive impairment varies greatly across studies. Moreover, although overt dementia in PD patients (PD-D) has been extensively investigated,[1] and specific diagnostic criteria have been developed,[2] there is no established diagnosis criteria for subtler impairment in PD patients.[3]

Our understanding of cognitive impairment and dementia in the Chinese PD population is particularly limited. Two small-scale studies,[4,5] and reviews of the literature on all non-motor symptoms,[6] have revealed that Chinese PD patients suffer from non-motor symptoms, but there appear to be some differences, compared with prevalence rates and risk factors for these symptoms within Western populations.[6] Notably, there is no epidemiological data on cognitive impairment from a large sample of Chinese patients. Therefore, we recruited a series of PD patients, to investigate the frequency

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and profiles of cognitive impairment, and to assess possible predictive risk factors, within this population.

Patients and methods
Patients and study instruments
A total of 901 PD patients were recruited from 42 university-affiliated hospitals throughout seven cities in The People's Republic of China from December 2005 to January 2008. All relevant information from patients in each hospital was recorded. Patients were then examined using a standardized interview documents on demographic, diagnostic, and treatment information, along with a three-part assessment battery. This study was approved by the institutional review boards of the relevant hospitals, and written informed consent was obtained from every patient selected.

The neuropsychological examination comprised three parts. Section A consisted of patient demographics, including age, gender, education, occupation, and living situation. Section B documented diagnostic and treatment information, and data regarding the onset and symptoms of PD. Section C comprised four scales for rating symptoms. The motor and related symptoms battery contained the Hoehn and Yahr Scale (HY),[7] Part I (Mentation, Behavior, and Mood), Part II (Activities of Daily Living), and Part IV (Complications) of the Unified PD Rating Scale (UPDRS).[8] The cognitive battery contained the Chinese version of the Mini Mental State Exam (C-MMSE) (30 maximum) and the Montreal Cognitive Assessment (MoCA) (30 maximum). Additionally, all patients were assessed using standard cognitive tests: the Fuld Object Memory Evaluation (0–20 points), to assess the memory domain, the Fuld Verbal Fluency test (FVFT), to evaluate verbal ability, the revised Wechsler Intelligence Scale for Children (WISC-R) Block Design (62 maximum), to assess visuospatial function, the revised Wechsler Adult Intelligence Scale (WAIS-R) Digit Span (22 points), to evaluate attention, and the seventeen-item Hamilton Depression Rating Scale with 17 items (Hdrs-17) and Neuropsychiatric Inventory (NPI), to evaluate behavior and mood. Cut-offs for determination of cognitive impairment were based on individual education levels.

We included only cases of PD with clinical onset before the starting date of the survey. We employed a standardized diagnostic appraisal for all patients, which followed the UK Parkinson's Disease Society Brain Bank Criteria for idiopathic PD. A principal investigator reconfirmed all assessments, after regional supervisors had made diagnoses using all available information from each center. The diagnosis of probable PD with dementia (PD-D) was made using

criteria recommended by the Movement Disorder Society.[2] PD patients with mild cognitive impairment (PD-MCI) were not clinically demented, but were impaired in any one of four cognitive domains: attention, executive function, visuospatial function, and free-recall memory.

Data analyses
Data are expressed as means with standard deviations (SD) for normal distributions. We used chi-square tests for nominal variables, and Fisher's Exact tests for quantitative variables. Logistic regression analyses were performed to evaluate categorical predictor variables for PD-D and PD-MCI. Odds ratios (OR) and 95% confidence intervals (CI) were reported. Differences were considered statistically significant at $P<0.05$. Analyses were performed using SAS version 8.0 statistical software (SAS Institute Inc., Cary, NC, USA).

Results
Patient characteristics
A total of 901 consecutive patients met the UK Parkinson's Disease Society Brain Bank Criteria for idiopathic PD; a total of 18 patients were excluded because of symptoms suggesting atypical parkinsonism (n=12), and overlapping enrollment with different centers (n=6). There were 562 (62.4%) men. The average age was 65.4 ± 10.7 years (Table 1). The average duration of PD in this sample was 5.5 ± 4.5 years. According to the HY scale, 19.2%, 62.2%, and 18.6% were at Stages I, II, and III or higher, respectively.

Table 1 Patient characteristics

Characteristic	
Patients, n	901
Men, n (%)	562 (62.4)
Age (mean ± SD, years)	65.4 ± 10.7
Education (mean ± SD, years)	10.7 ± 4.6
Occupation, n (%)	
Laborers/service workers	392 (43.5)
Administrators	253 (28.1)
Professionals	256 (28.4)
Financially independent, n (%)	722 (80.1)
Age at PD onset (mean ± SD years)	60.0 ± 11.1
PD duration (mean ± SD years)	5.5 ± 4.5
Duration (onset to first visit)	
≤6 years	542 (60.2)
7–24 years	236 (26.2)
>24 years	123 (13.6)
HY stage, n (%)	
Stage I	173 (19.2)
Stage II	560 (62.2)
Stage ≥III	168 (18.6)

Abbreviations: PD, Parkinson's disease; SD, standard deviation; HY, Hoehn and Yahr scale.

Cognitive impairment prevalence in PD

Among the 901 patients, 21.4% (n=193) met the PD-D criteria recommended by the Movement Disorder Society, and 22.8% (n=206) met the criteria for PD-MCI. Overall, 44.3% of PD patients had some degree of cognitive impairment (Table 2). The cognitive assessment scores for patients with PD-D, PD-MCI, and PD with no cognitive impairment (PD-NoCI) are shown in Table 3. PD-D and PD-MCI patients performed significantly worse in nearly all the domains, compared with PD-NoCI patients. C-MMSE and MoCA global cognitive scores were significantly lower for both PD-MCI and PD-D patients. Based on the proposed cut-off value of 26 (or less) to identify cognitive impairment using both MoCA and MMSE,[10] we found that MoCA could detect 86.5% of PD-D and 84.5% of PD-MCI, whereas MMSE identified just 65.3% of PD-D and 33.6% of PD-MCI (Table 4). Our results indicate that MoCA is more sensitive than MMSE for assessing cognitive impairment in Chinese PD patients.

Cognitive deficit profiles in PD-MCI and PD-D

We employed a set of standard cognitive tests to investigate cognitive deficit profiles in PD-MCI and PD-D patients (Table 4). In PD-MCI patients, the most common cognitive deficits were visuospatial dysfunction (40.3%), executive dysfunction (27.7%), memory impairment (15.0%), and attention impairment (12.6%). Although we used different tests to assess attention and executive function, the basic cognitive processes of these two domains cannot be clearly divided, and often overlap. For this reason, we merged the two domains for analysis purposes, and found that 83 (40.3%) PD-MCI patients exhibited executive/attention dysfunction. Overall, most cognitive impairment in PD-MCI patients corresponded to visuospatial dysfunction and attention/executive impairment; only 15% of cognitive impairment in PD-MCI patients was amnestic (Table 4).

In PD-D patients, approximately 82.4% (159 patients) had visuospatial dysfunction; the frequencies of executive dysfunction, memory impairment, and attention impairment were 70.0%, 67.4%, and 53.4%, respectively (Table 4). When we merged the executive impairment and attention domains for analysis, 168 (87.0%) PD-D patients had executive and/or attention dysfunction. Overall, the attention/executive and visuospatial domains were the most commonly impaired; about one-third of PD-D patients were nonamnestic.

Predictive risk factors for PD-related cognitive impairment

Among demographic factors (Table 5), having longer education and a professional career, were potentially protective factors against cognitive impairment. Males were less likely to have PD-MCI (OR =0.63, P=0.02), but gender was not a significant predictive factor for PD-D (OR =0.97, P=0.90). Incidence of PD-MCI was much lower in patients with self-support finance independency (OR =0.44, P=0.002), but this was not the case with PD-D (OR =0.77, P=0.30). With regard to age, PD patients who were at least 75 years old were twenty-one times more likely to develop PD-D, and four times more likely to suffer from PD-MCI (P<0.001), than patients younger than 55 years. However, age at PD onset was not an influential factor.

Among clinical predictive risk factors (Table 5), cognitive impairment was associated with higher axial UPDRS impairment score, and advanced HY stages. Based on the Movement Disorder Society criteria, PD-D occurred in 12.1% of HY Stage I patients, 17.9% of Stage II patients, and 42.9% of patients at Stage III or higher. For PD-MCI, these values were 15.6%, 22.7%, and 30.9%, respectively (Stage ≥III versus Stage I PD-MCI: OR =3.97; Stage ≥III versus Stage I PD-D: OR =4.77; P=0.001). Patients with axial impairment were two times more likely to have cognitive impairment (PD-MCI: OR =2.07; PD-D: OR =2.57; P<0.05). Levodopa dosage was not a significantly influential factor. In addition, 24.4% (n=220) of all PD patients suffered from depression, and 7.0% experienced hallucinations. In this series of patients, severity of depression symptoms was positively associated with dementia risk (OR=1.98, P=0.03, the data was calculated in patients with Hdes-17 scores ≥12

Table 2 Cognitive impairment prevalence and PD duration

Duration (years)	Overall n=901	0–2 n=305	3–4 n=229	5–6 n=136	7–8 n=79	9–10 n=64	≥11 n=88
Age at admission (years)		63.9 ± 10.7	65.5 ± 10.9	65.4 ± 10.1	65.4 ± 11.6	66.5 ± 9.6	68.2 ± 10.3
HY stage ≥3 (%)		5.9	15.8	19.8	37.3	31.0	55.4
Dementia % (n=193)	21.4	20.7	15.3	22.1	19.0	35.9	30.7
MCI % (n=206)	22.8	20.7	20.5	24.3	27.8	18.7	22.7

Abbreviations: PD, Parkinson's disease; HY, Hoehn and Yahr scale; MCI, mild cognitive impairment.

Table 3 Cognitive test scores for patients with PD-D, PD-MCI, and PD-NoCI

Cognition (mean ± SD)	PD-MCI (n=206)	PD-D (n=193)	PD-NoCI (n=502)	P
MMSE (me total)	26.2 ± 2.5	21.9 ± 5.3	28.6 ± 1.5	<0.0001
MoCA (mo total)	20.0 ± 4.1	14.7 ± 5.4	24.9 ± 3.2	<0.0001
Attention (WAIS-R Digit Span Backward)	3.5 ± 1.0	2.7 ± 1.3	4.4 ± 1.2	<0.0001
Attention (WAIS-R Digit Span total)	10.8 ± 2.2	9.0 ± 2.7	12.4 ± 2.2	<0.0001
Visuospatial (Block Design)	22.8 ± 10.9	11.2 ± 10.0	37.0 ± 10.2	<0.0001
Dysexecutive (RVR total)	35.0 ± 8.6	25.6 ± 10.4	43.2 ± 9.3	<0.0001
Dysexecutive (F words)	6.0 ± 3.0	4.7 ± 2.8	7.2 ± 3.3	<0.0001
Memory impairment (FOM initial)	6.1 ± 1.5	4.3 ± 2.0	7.1 ± 1.3	<0.0001
Memory impairment (FOM total)	14.8 ± 2.6	11.0 ± 4.3	16.6 ± 1.9	<0.0001

Abbreviations: PD, Parkinson's disease; PD-D, dementia; PD-MCI, mild cognitive impairment; PD-NoCI, no cognitive impairment; MMSE, Mini Mental State Exam; MoCA, Montreal Cognitive Assessment; SD, standard deviation; WAIS, Revised Wechsler Adult Intelligence Scale; RVR, Rapid Verbal Retrieve; FOM, Fuld Object Memory Evaluation.

versus patients with Hdes-17 scores <7), and patients with hallucinations were more likely to have dementia (OR =3.15; P<0.001). Clearly, cognitive impairment is associated with the severity of PD motor and neuropsychiatric symptoms in this population.

Discussion

We thoroughly and systematically investigated the prevalence of cognitive impairment in Chinese PD patients, and found that 22.8% had PD-MCI, while 21.4% met the PD-D criteria of the Movement Disorder Society. Two large studies, from Germany and Norway, have reported similar frequencies of PD-MCI (30.6%[11] and 25.8%,[12] respectively). The prevalence of PD-D described in other large studies varies greatly; a population-based study of PD patients in the Netherlands reported 22% dementia,[13] and a study of 1,449 PD outpatients in Germany found that 29% exhibited dementia.[14] A smaller German study (605 subjects), reported that 13.1% had dementia.[11] The differences in PD-MCI and PD-D frequencies between studies are probably due to different study methods, varying criteria, and differences in disease severity. In addition, the studies mentioned above were cross-sectional, and only described point prevalence; cumulative prevalence is often

much greater, as has been shown in a Norwegian cohort,[15] and by the Sydney Multicenter Study.[16,17] For example, in the former study, the point prevalence of dementia is 26%, while the 8-year cumulative prevalence of dementia is 78.2%.[15] In the latter study, the point prevalence of dementia in patients at 20 years is 83%.[16] Although it has been reported that Asian populations may have a lower incidence of dementia overall,[18] our results indicate that the prevalence of cognitive impairment in Chinese PD patients is not significantly different from that observed in other races and areas.

With regard to cognitive impairment in PD-MCI and PD-D, the frequencies of memory impairment in our study are very close to those reported by others: 13.3%–15.1%[12,19] in PD-MCI patients, and 67.4% in PD-D patients.[20] In similarity with an earlier study,[19] we found that attention/executive impairment and visuospatial dysfunction are the predominating forms of cognitive impairment in Chinese PD-MCI and PD-D patients. Memory and executive defects had been reported to be the most common impairment profiles in PD.[21] Impaired attention was found to be an important aspect of cognitive impairment in PD; it is the most useful parameter to differentiate PD-D from Alzheimer's disease.[22] We employed the WAIS-R scale to assess attention, because it is routinely employed by the clinics involved in this study. Although WAIS-R is usually employed to measure working memory, the capacity to maintain attention is prerequisite for completing the test. Notably, the frequency of nonamnestic domain impairment was higher in our study sample than has been reported by other studies.[12,19] The different results may be due to the use of different study methods, varying degrees of disease severity, and different demographic factors. However, it may also reflect diverse patterns of neuronal degeneration associated with PD.[23] A recently published hypothesis for PD proposes two different patterns of disease evolution: ie, frontal-striatal basal ganglia circuits, and posterior cortical

Table 4 Cognitive impairment profiles in PD-D and PD-MCI patients

	PD-D n (%)	PD-MCI n (%)
Patients	193	206
MMSE <cut-off	126 (65.3)	69 (33.6)
MoCA <cut-off	167 (86.5)	174 (84.5)
Attention impairment	103 (53.4)	26 (12.6)
Visuospatial dysfunction	159 (82.4)	83 (40.3)
Executive impairment	135 (70.0)	57 (27.7)
Memory impairment	130 (67.4)	31 (15.0)

Abbreviations: PD, Parkinson's disease; PD-D, dementia; PD-MCI, mild cognitive impairment; MMSE, Mini Mental State Exam; MoCA, Montreal Cognitive Assessment.

Table 5 Predictive risk factors for PD-related cognitive impairment

	PD-D (n=193)	PD-MCI (n=206)	PD-NoCI (n=502)	Adjusted predictors for PD-D		Adjusted predictors for PD-MCI	
	n (%)	n (%)	n (%)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)
Male	118 (61.1)	113 (54.8)	331 (65.9)	0.90	0.97 (0.59–1.59)	0.02	0.63 (0.42–0.94)
Age at entry (vs <55 years)				<0.001		<0.001	
55–64 years	31 (16.1)	41 (19.9)	156 (31.1)		2.51 (1.08–5.84)		1.00 (0.55–1.84)
65–74 years	72 (37.3)	79 (38.3)	189 (37.6)		6.25 (2.23–17.50)		1.57 (0.69–3.60)
≥75 years	77 (39.9)	57 (27.7)	53 (10.5)		21.81 (6.95–68.43)		4.26 (1.69–10.70)
Education (vs 0–6 years)				<0.001		<0.001	
7–12 years	84 (43.5)	100 (48.5)	221 (44.0)		0.30 (0.17–0.54)		0.52 (0.32–0.86)
≥13 years	35 (18.1)	48 (23.3)	228 (45.4)		0.15 (0.07–0.31)		0.27 (0.15–0.49)
Occupation (vs professional)				0.02		0.004	
	27 (14.0)	41 (19.9)	118 (23.5)		0.48 (0.26–0.87)		0.49 (0.30–0.79)
Financially independent (vs not)				0.002		0.30	
Yes	124 (64.3)	164 (79.6)	434 (86.4)		0.44 (0.26–0.74)		0.77 (0.48–1.26)
Age of PD onset (vs <59 years)				0.73		0.44	
≥59 years	137 (71.0)	137 (66.5)	254 (50.6)		0.88 (0.42–1.86)		1.30 (0.67–2.53)
Hoehn and Yahr scale (vs stage I)				<0.001		<0.001	
Stage II	100 (51.8)	127 (61.6)	333 (66.3)		1.31 (0.70–2.45)		1.67 (0.99–2.82)
Stage ≥III	72 (37.3)	52 (25.2)	44 (8.8)		4.77 (2.08–10.95)		3.97 (1.92–8.18)
Levodopa dose (vs <400 mg)				0.30		0.45	
400–599 mg	32 (16.6)	36 (17.5)	102 (20.3)		0.72 (0.39–1.32)		0.77 (0.47–1.28)
≥600 mg	56 (29.0)	47 (22.8)	78 (15.5)		1.24 (0.71–2.18)		1.12 (0.68–1.83)
UPDRS axial impairment (vs not)				0.003		0.01	
Yes	70 (36.3)	50 (24.3)	38 (7.6)		2.57 (1.38–4.77)		2.07 (1.17–3.69)
Depression (vs Hrsd-17 total <9)				0.03		0.35	
(Yes: Hrsd-7 total ≥9, <12)	31 (16.1)	35 (17.0)	79 (15.7)		1.13 (0.60–2.13)		1.10 (0.66–1.84)
(Yes: Hrsd-17 total ≥12)	88 (45.6)	66 (32.0)	107 (21.3)		1.98 (1.18–3.34)		1.40 (0.89–2.20)
Hallucinations (vs not)				<0.001		0.54	
Yes	42 (21.8)	19 (9.2)	33 (6.6)		3.15 (1.62–6.15)		1.25 (0.61–2.54)

Abbreviations: PD, Parkinson's disease; PD-D, dementia; PD-MCI, mild cognitive impairment; PD-NoCI, no cognitive impairment; OR, odds ratio; CI, confidence interval; UPDRS, Unified PD Rating Scale; Hrsd-17, Hamilton Rating Scale for Depression; vs, versus.

syndromes. Executive and attention defects are more obvious when the frontal-striatal pathway is involved, whereas visuospatial and memory dysfunction are more representative of posterior cortical deficits.[24] In summary, the profile of cognitive domain impairment described here is similar to that reported in other races. Difference in the frequencies of domain impairment may be due to differences in methodology, racial composition, and disease evolution.

Understanding which factors can be used to predict cognitive impairment in PD is very important. We confirmed a previously reported series of potential risk factors for PD cognitive impairment in the current study. Patients with higher axial UPDRS impairment scores, HY stages,[25,26] and ages[26–28] are more likely to manifest cognitive impairment. Conversely, higher educational attainment,[4,26] male gender,[28] professional occupation, and financial independence are, potentially, protective factors against cognitive impairment. The latter two factors may arise because receiving education is more predominant among men during economically

difficult times, while better chronic disease management increased during better economic conditions. In our study, age was an influential factor for cognitive impairment in PD, in contrast to the findings reported by Arnaldi et al.[29] Although age at onset of motor symptom was not a significant influential factor, there are some studies which suggest that late-onset PD is predictive of cognitive impairment.[27,30] Medications used to treat PD may affect cognition. But our study, and others,[4,28] shows that the levodopa equivalent dose is not associated with the risk of cognitive impairment in PD. Hallucinations[15,30,31] and depression[26] have also been associated with cognitive impairment in PD patients, but these have different genetic explanations. With regard to hallucinations, one study reported that visual perception is more globally impaired in patients with PD-D than in PD-NoCI or healthy controls.[32] A recent publication posited that visual hallucinations are a common feature of disorders that affect temporal lobe structures and impair ascending monoaminergic pathways.[33] This provides a reasonable explanation

for how visual hallucination is linked to cognitive decline. Depression and symptom severity are associated with cognitive impairment in PD. However, it is thought that the rate and comorbidity of depression and dementia may both be driven by the severity of PD.[26,34,35] In summary, potential risk factors for cognitive impairment in the Chinese population are similar to those reported in other races.

However, there are several limitations to our study. All of our subjects were recruited consecutively from the outpatient departments of selected centers; the population may have not included some bedridden or severely disabled PD patients. With regard to the related risk factors for cognitive impairment in PD, we did not include disease comorbidity, medications other than for treatment of PD, or family history. Further studies should follow this cohort to explore cumulative prevalence and related risk factors, and focus on the progression and prognosis of cognitive impairment in PD.

In conclusion, the study aimed to explore the point prevalence and cognitive impairment profile in Chinese PD patients. Notably, it was found that MoCA is a more sensitive tool than the MMSE for identifying cognitive impairment in this population.

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Disclosure

The authors declare that they have no competing interests.

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