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Cognitive function in early Parkinson's disease: a population-based study

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Background and purpose: The study aims to describe the frequency, pattern and determinants of cognitive function in patients with newly diagnosed Parkinson's disease (PD); to compare patients with impaired cognition to patients with intact cognition; and to compare to matched healthy controls.

Methods: Patients were identified in a longitudinal population based study of idiopathic non-drug induced parkinsonism. Eighty-eight newly diagnosed patients with PD and no dementia were included during a four year period. The patients and 30 age- and sex-matched healthy control subjects underwent a comprehensive neuropsychological assessment.

Results: Patients performed significantly worse than healthy controls in a majority of neuropsychological tests. Test results in attention, psychomotor function, episodic memory (free recall), executive function and category fluency were significantly lower in the patient group. Comparison with normative data revealed that 30% of the patients had deficits in ≥1 cognitive domain (episodic memory, executive function and verbal function). Seventy per cent of the patients had normal performance. Unified Parkinson's Disease Rating Scale (UPDRS) III sub scores; speech, facial expression, rigidity and bradykinesia were significantly higher, and disease duration shorter amongst the cognitively impaired than amongst the cognitively intact patients. Tremor showed no difference. Education level was an independent predictor of dysfunction in patients with ≥2 cognitive domains affected.

Conclusion: Cognitive dysfunction is common in untreated patients in early PD, affecting attention, psychomotor function, episodic memory, executive function and category fluency. Education level was an independent predictor of severe cognitive dysfunction.

Introduction

Parkinsonism refers to a common clinical condition characterised by any combination of bradykinesia, rigidity, tremor and postural imbalance [1]. The idiopathic forms of parkinsonism are quantitatively dominated by Parkinson's disease (PD) which requires bradykinesia and at least one additional symptom of parkinsonism as well as lack of specified exclusion criteria [2]. The differential diagnosis of parkinsonism is occasionally easy, e.g. drug induced, but often difficult and up to 30% of patients are reclassified even in specialised units [3]. Cognitive impairment is common in PD; in some cases it is more disabling than the motor features. The relative risk of developing dementia in PD is nearly six times that of controls [4] but cognitive impairment is also common in nondemented PD patients [5] and sometimes classified as mild cognitive impairment (MCI) [6]. Specific parkinsonian symptoms, bradykinesia and rigidity, have been shown to be associated with decline of cognitive function [7].

The underlying neuropathological disturbance in PD involves selective deterioration of subcortical structures, e.g. dopaminergic neurons in substantia nigra which affects primarily the basal ganglia structures [8]. Hippocampal atrophy as well as prefrontal atrophy are reported in PD [9]. The executive dysfunction in PD, especially processes that involve working memory, has been shown to be related to decreased activation in the

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basal ganglia and frontal cortex [10] and suggested by us to stem from components subserved by striatum [11].

Evaluations of cognitive function in population-based cohorts with recently diagnosed idiopathic PD are rare. We performed such a study to describe the extent and character of cognitive dysfunction in patients with drug-naive newly diagnosed PD. We hypothesised that PD patients would show cognitive deficits in tests depending on primarily subcortical and prefrontal areas of the brain, i.e. attention, psychomotor function and executive function. Further, the deficits should be more obvious in processes that depend on preserved executive function, e.g. in free recall rather than in cued recall or recognition.

Patients and methods

Study sample

The study was performed on an unselected incident population with PD of unknown cause. The catchment area was the local area of Umeå University hospital (142 000 inhabitants). The local tradition is to refer patients with suspected parkinsonism to the department of Neurology at the Umeå University hospital. A letter was written twice a year to all general practitioners, geriatricians, neurosurgeons, psychiatrists, internists, private practitioners and to all company health services in the area informing them of the study and asking for referral of suspected cases. Institutions with elderly, e.g. homes for the elderly, were also surveyed.

Procedures

The study is a longitudinal prospective study with repeated examinations during 5 years following inclusion. Neuropsychological assessment is performed within 1–2 months of inclusion (baseline) and after 1, 3 and 5 years. Dopamine transporter (DAT) imaging using ^{123}I-Ioflupane ([^{123}I]FP-CIT) is also performed within 1–2 months following inclusion. The study started on January 1, 2004 and baseline data for patients included during a period of four years are presented. Altogether 139 cases with idiopathic parkinsonism were identified and 111 patients fulfilled the diagnostic criteria for PD at baseline and one-year follow-up. Neuropsychological examination was performed in 88/111 (79%) patients. Twenty-three patients (21%) declined to participate. These patients were significantly older (mean age 80 years), had various other conditions (e.g. blindness, deafness, severe cardiac disease) and scored marginally worse on the Mini Mental State Examination (MMSE) (27.5 vs. 28.7; $P = 0.04$). Patients were encouraged to participate in all neuropsychological tests and this was possible in all but nine persons where tiredness or technical issues caused problems. Depression was assessed by the Montgomery and Åsberg Depression Rating Scale (MADRS) [12].

Inclusion and exclusion criteria

Patients with previously undiagnosed parkinsonism were considered for inclusion if they had bradykinesia and at least one additional cardinal sign i.e. resting tremor, rigidity or impaired postural reflexes and no obvious explanation for the symptoms, e.g. drug-induced parkinsonism. Patients with dementia, including dementia with Lewy bodies, or cognitive dysfunction (MMSE < 24) were excluded [13]. To ensure that only idiopathic forms of parkinsonism were included, each case was checked against diagnostic criteria for PD, multisystem atrophy, progressive supranuclear palsy and corticobasal degeneration [2,14,15]. Only patients with PD were included in the analysis ($n = 88$).

Controls

Based on the first 50 patients, 30 age- and sex-matched controls were recruited via advertisement in the local newspaper. The controls had to be healthy with no known neurological disorder and a normal neurological examination.

Neuropsychological assessment

The participants were individually tested for two hours each. All patients (except two with low doses of dopaminergic treatment for a few weeks) had not received any pharmacological treatment for PD. The tests included were:

Free and Cued Selective Reminding Test (FCSRT) [16] tests verbal episodic memory with free recall and cued recall of 16 items. The procedure is repeated three times and after 20 minutes delayed recall is performed. *Logical Memory* [17] tests verbal episodic recall. Two short stories are orally presented and the examinee is asked to retell the stories from memory. *Verbal paired associate* [17] tests verbal retention and is an orally presented task that requires the examinee to learn novel word associations. *Brief Visuospatial Memory Test – revised* (BVMT) [18] tests non-verbal episodic memory with three learning trials, delayed free recall and recognition. The scoring accounts for the locations and accuracy of figure drawings. *Digit Span* [19] measures working memory. The number of digits a person can retain and recall over a brief period of time is measured. *Electronic Tapping Test* (WPS) [20] tests psychomotor speed. The examinee taps their index fingers a short period in repeated trials. Trials

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are summed and an average of each hand is calculated. *Trail Making Test* (TMT) [21] tests visual search, attention, mental flexibility and motor function. It consists of two parts, A with numbers and B with numbers and letters. *Controlled Oral Word Association* [22] evaluates spontaneous production of words beginning with a given letter (FAS) or a given category (fruit, animal and colour) within one minute. *Boston Naming Test* (BNT) [23] tests the ability to name pictured objects. *Benton Judgement of Line Orientation Test* [23] tests visuospatial function. The number of completely correct items is the final score. *Wisconsin Card Sorting Test – computer version 2* (WCST) [24] assesses the ability to form abstract concepts, to shift and maintain set; and is considered to measure aspects of executive function [22]. *Mental Control* [17] tests automatism and simple conceptual tracking (Table 1).

For a clinical evaluation, raw scores for each test were transformed to standardised scores according to the test manuals and when possible with respect to age, sex and education level. Performance was considered to be impaired if the score was < 1.5 SD below average (T 50). Lezak *et al*. [25] presented a classification system for ability levels based on a statistically defined range of scores: average performance is: ± 0.6 SD, low average -0.6 to -1.3 SD and borderline -1.3 to -2.0 SD. We used less than -1.5 SD as a cut-off level for impaired performance which is commonly accepted in clinical practice. Cognitive domains (episodic memory, working memory, visuospatial function, verbal fluency, naming and executive function) were used in the final analysis. When $> 50\%$ of single test results within a domain were below the cut off level, that domain was classified as impaired. Two individuals did not complete enough tests to make it possible to judge impairment in different domains.

Table 1 Neuropsychological functions and cognitive tests

Neuropsychological function	Test
Episodic memory, verbal	Free and cued selective reminding test (FCSRT) Logical memory and Paired associative learning from Wechsler memory scale (WMS)
Episodic memory, non-verbal	Brief visuospatial memory test (BVMT)
Working memory	Digit span from Wechsler Adult Intelligence Scale (WAIS) III
Psychomotor speed	Electronic tapping test, WPS
Attention	Trail making test (TMT) A and B
Verbal function	Controlled Oral word association (FAS and categories) and Boston naming test
Visuospatial function	The Benton Judgement of Line Orientation test
Executive function	Wisconsin card sorting test (WCST) – computer version 2 and Mental Control from WMS

Clinical and demographic correlates of cognitive impairment

Patients impaired in one or more cognitive domains were compared with the remaining patients with respect to age, gender, education, age at symptom debut, disease duration, depression (MADRS), global cognitive function (MMSE), and UPDRS motor scores for speech (item 18), facial expression (item 19), tremor (items 20,21), rigidity (item 22), bradykinesia (items 24–26,31), axial impairment (items 27–30) and total UPDRS III subscore (items 18–31) [26].

The Ethics Committee of Umeå University approved all procedures regarding patients and healthy control subjects. A written informed consent was obtained according to the Declaration of Human Rights of Helsinki 1975.

Statistical analysis

The software SPSS for Windows version 15.0 was used for all statistical analyses (SPSS Inc., Chicago, IL, USA). Differences in demographic and clinical characteristics between the patient group and controls were analysed with independent two-tailed *t*-tests. All continuous variables were approximately normally distributed.

For analysis of cognitive function several sets of analysis were conducted. We compared patients and controls, using raw test scores, with independent two-tailed *t*-tests. For adjusted *P*-value, a linear regression was performed with age, gender, education level and psychomotor function as covariates.

To examine cognitive level from a clinical perspective T-scores were derived from available normative data to determine which cognitive domains were impaired in each patient. An independent two-tailed *t*-test was performed on data with normal distribution between patients with impaired cognition and patients with intact cognition. For the variables with skewed distribution a non-parametric test was performed (Mann–Whitney).

Finally, a binary logistic regression was performed on patients with two or more cognitive domains impaired for the purpose of exploring predictors of cognitive impairment. Demographic and clinical variables that significantly differed between the groups were included as covariates in the model: education level, disease duration, bradykinesia, facial expression, rigidity and

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total UPDRS III subscore. *P*-values less than 0.05 were considered significant.

Results

Demographic and clinical characteristics

No significant difference in demographic characteristics was found between patients and controls (Table 2). Exclusion of the five patients with normal DAT-imaging had no significant effect on the results and therefore these patients were retained in the analyses.

Neuropsychological test results

Comparison of raw data between patients and controls showed differences across all cognitive domains. Patients performed at a lower level than healthy controls in all tests but not all differences were significant (Table 3).

When transforming patient raw data to normative data, domains most commonly impaired were psychomotor function ($n = 16$), attention ($n = 16$), episodic memory ($n = 12$) executive function ($n = 11$) and verbal function ($n = 11$). Psychomotor function and attention were excluded from further analysis because the tests require the use of hand or finger movements. After excluding these 30% of the patients had deficits in one or more cognitive domains, 16% had deficits in two or more cognitive domains and 70% of the patients had normal performance in all cognitive domains.

Table 2 Demographic and clinical characteristics of the population

Variable	Patients, $n = 88$	Healthy controls, $n = 30$	*P*-value
Sex, female/male	39/49	14/16	0.825
Age, years (mean, SD)	68.1 (9.3)	68.2 (6.6)	0.979
Education level, years (mean, SD)	9.9 (4.1)	11.5 (3.5)	0.055
MMSE (mean, SD, range)	28.7 (1.4, 24–30)	29.1 (0.8, 28–30)	0.074
Depression,[a] *n* (%)	14 (16)	0	< 0.001
UPDRS III (mean, SD, range)	23.8 (9.7, 5–48)	0	
Dopaminergic medication	2	0	
DAT imaging,[b] abnormal/normal	83/5	0/30	

MADRS, Montgomery and Åsberg Depression Rating Scale; DAT, dopamine transporter.

[a]MADRS score > 8.

[b]All patients and controls were examined by utilizing imaging of the DAT.

The demographic and clinical variables found to significantly differ between patients with impaired cognitive domains and cognitively intact patients were global cognitive function (MMSE) ($P = < 0.018$), duration of disease ($P = 0.019$), UPDRS III total ($P = 0.004$), facial expression ($P = 0.001$), speech ($P = 0.001$), bradykinesia ($P = 0.029$) and rigidity ($P = < 0.004$). Tremor, axial impairment, depression, age, education and age at onset did not differ significantly between the groups (Table 4).

A logistic regression analysis found education (10.3 years for < 2 vs. 7.8 years for ≥ 2 cognitive domains impaired, $P = 0.01$) to be the only independent predictor of cognitive dysfunction.

Discussion

PD patients performed significantly worse than healthy controls in attention, psychomotor function, episodic memory, category fluency, visuospatial function and in four out of nine measures of executive function. No significant differences were found in working memory, letter fluency and in five out of nine measures of executive function. After adjustment for age, gender, education and psychomotor function, significant differences remained for all domains except for visuospatial function and executive function (Table 3). As expected, the patients had more difficulty with free recall that requires an intact executive function, than with cued recall and recognition in episodic memory tests (Table 3). Notably, not all tests subserved by subcortical and prefrontal areas were affected and tests more dependent on hippocampal regions, such as episodic memory tests, were also affected [27]. This is congruent with findings of both prefrontal and hippocampal atrophy in PD [9]. The identification of specified cognitive dysfunctional domains by neuropsychological tests should alert neuroradiologists to specifically look for abnormalities in areas of the brain known to be of importance for these domains.

Speech, facial expression, rigidity and bradykinesia were significantly more affected amongst the cognitively impaired than amongst the cognitively intact patients whereas tremor showed no difference (Table 4). This suggests that the pathophysiological mechanisms for speech impairment, bradykinesia and rigidity may underlie PD-related cognitive deficits whereas tremor is influenced by other pathways. Dopaminergic cell loss in patients with tremor-dominant PD is most conspicuous in the medial substantia nigra whilst this occurs in the ventrolateral substantia nigra in patients with dominance of bradykinesia and rigidity [28]. Speech is improved by deep brain stimulation of the cholinergic pedunculopontine nucleus [29], indicating that the association between speech and cognitive impairment

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Table 3 Comparison between patients with Parkinson's disease and healthy control persons, neuropsychological raw data (mean, SD)

	Patients (88)	Controls (30)	*P*-value	Adjusted *P*-value*
Episodic memory				
BVMT-free recall immediate	17.45 (6.61)	21.87 (6.28)	0.002	0.035
BVMT-free recall delayed	7.05 (2.64)	9.10 (2.29)	< 0.001	0.008
BVMT recognition	5.37 (0.93)	5.73 (0.45)	0.006	0.507
Buschke-free recall	24.58 (7.40)	30.00 (6.10)	< 0.001	0.006
Buschke-cued recall	18.98 (5.67)	15.63 (4.30)	0.004	0.061
Buschke total	43.84 (4.24)	45.63 (3.45)	0.039	0.161
Buschke-delayed total	15.18 (1.32)	15.17 (1.08)	0.955	0.868
WMS associative easy	16.40 (1.85)	16.73 (1.36)	0.369	0.254
WMS associative hard	5.99 (3.33)	7.10 (2.87)	0.106	0.208
WMS associative total	14.29 (3.96)	15.47 (3.23)	0.146	0.162
WMS logical memory immediate	7.95 (2.81)	9.93 (2.96)	0.001	0.033
WMS logical memory delayed	6.43 (3.01)	8.23 (3.13)	0.006	0.203
Working memory				
Digit span WAIS-III forward	8.62 (1.86)	8.93 (1.87)	0.435	0.615
Backward	5.09 (2.00)	5.90 (2.31)	0.068	0.376
Total	13.72 (3.42)	14.83 (3.77)	0.135	0.430
Attention				
TMT A (s)	58.97 (26.95)	35.60 (12.37)	< 0.001	0.002
TMT B (s)	160.43 (79.95)	98.83 (41.83)	< 0.001	0.005
Psychomotor function				
WPS right	46.51 (15.31)	61.17 (6.11)	< 0.001	< 0.001**
WPS left	40.82 (15.23)	56.14 (6.09)	< 0.001	< 0.001**
Executive function				
WCST total correct (77/30)	39.04 (10.34)	43.37 (6.77)	0.013	0.053
WCST total errors	24.79 (10.03)	20.63 (6.77)	0.016	0.073
WCST perseverative responses	14.45 (8.20)	12.67 (6.18)	0.283	0.282
WCST perseverative errors	12.42 (6.16)	11.00 (4.78)	0.261	0.276
WCST nonperseverative errors	12.38 (7.30)	9.63 (3.58)	0.011	0.123
WCST conceptual level responses	31.78 (14.24)	36.57 (10.92)	0.100	0.184
WCST categories completed	2.06 (1.37)	2.53 (1.36)	0.114	0.288
WCST trials to 1st category	24.86 (18.98)	16.60 (12.03)	0.009	0.060
WMS mental control	6.16 (1.94)	6.47 (1.83)	0.449	0.665
Verbal function				
Letter fluency (FAS)	39.65 (14.43)	43.00 (12.23)	0.260	0.942
Category fluency	38.95 (9.30)	46.03 (10.98)	0.001	0.009
Boston naming test	50.44 (7.53)	51.63 (6.65)	0.442	0.872
Visuospatial function				
Line orientation test	23.41 (4.52)	25.40 (3.49)	0.031	0.348

*Adjusted for age, gender, education and psychomotor function.
**Adjusted for age, gender and education.

may be related to cholinergic function. Our findings are supported by other studies where tremor-dominant PD-patients are less cognitively affected than other subtypes [30,31]. Further, postural instability and gait disturbances motor subtype has been associated with a faster rate of cognitive decline in PD [27].

Patients with cognitive impairment had shorter disease duration and higher UPDRS III summary score. This indicates the existence of an aggressive phenotype of PD already at the time of diagnosis. Early identification of these patients is likely to be important for optimising planning of future care.

Education was the only independent significant predictor for severe cognitive impairment in our study. In a meta analysis [32], lower education level was associated with greater decline in all cognitive domains in PD and education has also been shown to be an important factor for cognitive function in other neurodegenerative diseases, i.e. dementia diseases [33]. The association between education and cognition is not fully understood but our results could support the theory of education being a buffer against effects of disease on brain function i.e. the brain reserve hypothesis [34].

In England, 79% of a population with PD, mean 70.3 years at diagnosis and mean disease duration of 30 months, was evaluated. Cognitive impairment occurred in 30% of patients with MMSE > 23 and 12% had combined temporal lobe and frontostriatal impairment [5]. In a PD population in the Netherlands, mean age 66.2 years at diagnosis and a mean disease

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Table 4 Demographic and clinical characteristics of patients with impaired cognition $n = 26$ (30%) and patients with intact cognition $n = 60$ (70%)

Variable	≥1 impaired domains[a]	Intact cognition	*P*-value
Sex, female/male ($n = 86$)	8/18	29/31	0.131
Age, years (mean, SD)	65.9 (8.4)	68.9 (9.7)	0.084
Education level (mean, SD)	9.8 (3.4)	9.9 (4.5)	0.659
Age at onset (mean, SD)	66.9 (9.7)	64.2 (8.8)	0.125
Disease duration (month)	16.3 (10.2)	25.5 (25.6)	0.019
MMSE (mean, SD)	28.0 (1.8)	29.0 (1.1)	0.018
MADRS score (mean, SD)	5.4 (4.0)	3.8 (3.7)	0.078
UPDRS III (mean, SD)	28.3 (10.4)	21.8 (8.9)	0.004
Speech	0.8 (0.7)	0.3 (0.5)	>0.001
Facial expression	1.5 (0.8)	0.8 (0.8)	0.001
Tremor	2.8 (2.7)	2.8 (2.4)	0.775
Rigidity	7.4 (4.2)	4.8 (3.6)	0.004
Bradykinesia	9.8 (4.4)	7.8 (3.8)	0.029
Axial impairment	2.6 (2.1)	2.3 (1.5)	0.507

[a]Two individuals did not complete enough tests to make it possible to judge impairment in different domains.

duration of 19 months (MMSE >24), 24% had impaired cognition compared to 4% in healthy controls. Impairments were most prominent in memory and executive function. Age at onset of disease was a predictor of cognitive dysfunction [35]. In Norway, 19% of newly diagnosed and untreated PD-patients were classified as having MCI [6]. Our study population is comparable to these populations in age at diagnosis, disease duration (mean 25 months), sex distribution and depression. Furthermore, despite differences in methods, the studies show similar proportions (12–24%) affected by deficits in multiple cognitive domains in the early phase of PD and parkinsonism. Our population was untreated by PD medication which is a great strength. In the studies above from England and the Netherlands, 50–70% of patients received such medications. Mild depression in a small subgroup (16%) is likely to have had a marginal effect on the results. No significant difference was found in occurrence of depression between patients with cognitive impairment and remaining patients.

Our study has limitations. Generalization of the results is hampered by non-participation of 21% of patients, mostly the very old. This subgroup scored significantly lower on a screening test of cognition (MMSE), and thus it is likely that their inclusion would have resulted in worse performance in tests and increased the differences. We have performed a large number of tests and some of the significances might be false. However, none of the significances are unexpected from a theoretical point of view.

The main strengths of the study are the population-based approach with a nearly complete identification of cases, extensive assessment of neuropsychological functions within a few weeks of diagnosis prior to pharmacological treatment, and functional neuroimaging to advance the evaluation of diagnosis.

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