SHORT REPORT

Predictors of cognitive impairment in advanced Parkinson's disease

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Objective: To investigate the cognitive profile of patients with idiopathic Parkinson's disease and to determine the demographic and medical variables that contribute to the cognitive outcome.
Design: Retrospective cohort analysis.
Methods: 100 patients with idiopathic Parkinson's disease were given a neuropsychological test battery investigating attention, memory, and visuospatial and executive functions. Test performance was compared against normative data, and linear regression determined significant predictors of cognitive impairment from a set of demographic and disease course variables.
Results: Frontal-type cognitive dysfunction was widespread in patients with advanced Parkinson's disease. Attention and memory were mildly to moderately impaired, whereas visuospatial function showed only subtle impairment. Older age and tremor at onset were significant predictors of poor cognitive performance.
Conclusions: The observed cognitive impairment in patients with advanced Parkinson's disease is more than expected for normal aging. Although in apparent contrast with most previous research, reporting a greater risk of cognitive dysfunction in Parkinson's disease patients with predominant akinesia/rigidity, tremor at onset may be a marker for more widespread brain pathology that contributes to an increased risk of cognitive impairment.

In the early stages of Parkinson's disease the most frequent neurocognitive abnormalities are reported in executive functioning, memory, and spatial behaviour. These cognitive dysfunctions indicate frontal lobe involvement, an observation that coincides and correlates with the nigrostriatal dopamine deficiency in this disorder.[1] In the later stages, patients with Parkinson's disease also show temporal lobe-like deficits of learning and memory. This progression of cognitive dysfunction is consistent with the biochemical findings that dopamine depletion in Parkinson's disease is most severe in the dorsal rostral portion of the head of the caudate nucleus, which is anatomically connected to the dorsolateral prefrontal cortex and the posterior parietal lobe. In a later stage, dopamine deficiency progresses to the more ventral portions of the caudate nucleus, which are thought to be connected to the ventrolateral prefrontal cortex and the temporal lobe.[2]

Our aim in this study was to evaluate the degree of cognitive impairment in a cohort of patients with advanced Parkinson's disease and to determine which demographic or medical variables contribute to the severity of general cognitive impairment.

METHODS

Patients

One hundred consecutive patients who fulfilled the diagnostic criteria of idiopathic Parkinson's disease[3] were neuropsychologically assessed as part of their treatment protocol. The sample consisted of 36 women and 64 men. Their mean (SD) age was 61.8 (10.0) years, range 29 to 81; mean years of education, 11.2 (3.1), range 4 to 20; and average estimated premorbid verbal intelligence quotient, 98.7 (13.7), range 70 to 130. Disease course characteristics were as follows:

- average disease onset by the age of 49 (10.9) years, range 15–75;
- mean disease duration 12.7 (6.1) years, range 1 to 32;
- average daily levodopa intake 758 (351) mg;
- average daily dopamine agonist intake equivalent to 3 (1.8) mg pergolide (1 mg pergolide = 1 mg pramipexole = 10 mg bromocriptine = 4 mg ropinirole);
- in 90% of the cases the first motor symptom was lateralised (in 45% on the right side of the body and in 45% on the left). By the time of the neuropsychological investigation motor symptoms appeared to be bilateral in 87% of the cases;
- in 58% the first motor symptom occurred in the upper extremities, in 28% in the lower extremities. Tremor was the initial characteristic motor symptom in 38% of the patients, akinesia and/or rigidity in 58%.

Procedure

All patients underwent neuropsychological assessment during the "on" phase of medication. We used eight standardised neuropsychological tests, from which 10 cognitive measures were selected, as follows.

Rey auditory verbal learning test

The Rey auditory verbal learning test (AVLT) assesses verbal memory.[4] The measures retained are the total number of words recalled over five acquisition trials and the delayed recall.

Benton visual retention test

The recognition form of the Benton visual retention test (BVRT) assesses non-verbal memory.[4] The number of correct answers is the measure taken.

Visual object and space perception battery

The (motor-free) subtests number location and cube analysis of the visual object and space perception battery (VOSP) were used to evaluate visuospatial localisation and spatial reasoning, respectively.[4] We recorded the number of correct responses for each subtest.

Abbreviations: AVLT, Rey auditory verbal learning test; BDI-C/A, cognitive/affective subscale of the Beck depression inventory; BVRT, Benton visual retention test; COWAT, controlled oral word association test; MRMT, Money's standardised road map test; NART, national adult reading test; PPT, Purdue pegboard test; SCWT, Stroop coloured word test; UPDRS, unified Parkinson's disease rating scale; VOSP, visual object and space perception battery; WCST, Wisconsin card sorting test

Table 1 Results of the principal component (PC) analysis and impairment scores of the total sample (n = 100)

	Factor loadings			
Cognitive variable	PC1	PC2	PC3	Impairment score*
AVLT immediate verbal recall	0.85			1.4 (1.3)
AVLT delayed recall	0.82			0.7 (0.9)
SCWT interference score	0.71			1.5 (1.6)
BVRT visual recognition	0.53			1.0 (1.2)
COWAT word fluency	0.44			1.0 (0.8)
MRMT right/left orientation		0.79		0.2 (0.4)
VOSP number location		0.75		0.8 (1.2)
VOSP cube analysis		0.62		0.6 (1.3)
WCST categories			0.84	1.4 (1.1)
PPT total placed pegs			0.68	2.7 (1.1)

*Mean (SD).
AVLT, Rey auditory verbal learning test; BVRT, Benton visual retention test; COWAT, controlled oral word association test; MRMT, Money's standardised road map test; PPT, Purdue pegboard test; SCWT, Stroop coloured word test; VOSP, visual object and space perception battery; WCST, Wisconsin card sorting test.

Money's standardised road map test
Money's standardised road map test for direction sense (MRMT) was used to assess spatial (left-right) orientation.[4] The number of correct responses was the measure taken.

Purdue pegboard test
The Purdue pegboard test (PPT) measures finger and hand dexterity.[4] The total number of pegs placed in 30 seconds with the dominant hand, non-dominant hand, and both hands simultaneously, was measured.

Stroop coloured word test
The standardised Dutch version of the Stroop coloured word test (SCWT) measures selective attention.[4] The interference score was the measure retained.

Controlled oral word association test
The controlled oral word association test (COWAT) assesses verbal fluency.[4] We measured the total number of words presented during three one-minute letter categories.

Wisconsin card sorting test
A computerised version of the Wisconsin card sorting test (WCST) was used to assess mental flexibility.[4] The measure taken was the number of categories achieved.

Other tests
In addition to the neuropsychological test battery, we administered a Dutch version of the national adult reading test (NART) to estimate premorbid verbal intelligence[4] and a Dutch version of the cognitive/affective subscale of the Beck depression inventory (BDI-C/A) to estimate the level of depression.[5]

Psychometric and statistical analysis
To evaluate the performance of each patient we compared the test results against the performance of a demographically matched normal peer group. Most normative data were stratified for age, educational level, and sex if appropriate. Specific normative data for a Flemish population are available for the AVLT, BVRT, SCWT, and COWAT.[6] For the WCST and VPOR, detailed normative data are provided in the manuals. PPT performance was evaluated against the normative data described in Spreen and Strauss.[7] The MRMT was evaluated against the cut off score published by Lezak.[4] Impairment scores were expressed in standard deviations below the normative mean, with a maximum score of 4. A performance equal to or higher than the normative group's mean score (M) minus 1 SD was considered to fall within normal limits and was attributed an impairment score of 0. Thus an impairment score of 1 reflects a test score that falls between −1 and −2 SD from the mean. Principal component analysis with varimax rotation was undertaken on the impairment scores to evaluate the factor structure of the cognitive dysfunctions.

A global impairment score that consists of the sum of the impairment scores of all tests except that of the Purdue pegboard test was calculated for each patient. The reason for excluding this test was to construct a motor-free index of global cognitive impairment. The global impairment score was used as the dependent variable in a stepwise linear regression analysis. We used the significant determinants of the global impairment score in multivariate analyses of variance to investigate possible differential effects on the individual test scores.

RESULTS
We evaluated the factor structure of cognitive dysfunction using principal component analysis. Varimax rotation (five iterations) using Kaiser normalisation yields a three factor solution (Eigen values > 1.0), shown in table 1.

We used stepwise linear regression analysis to determine significant contributors of cognitive impairment. The following demographic and medical variables entered the regression analysis using the motor-free global impairment score as the dependent variable: age, sex, education, disease duration, side of Parkinson's disease onset, location of Parkinson's disease onset, type of onset symptom that gave rise to the diagnosis of Parkinson's disease, juvenile onset (age < 40), daily dose of levodopa and daily dose of dopamine agonist, and severity of cognitive/affective depressive symptoms. The regression analysis showed that age (B = 0.26 (SE 0.06), $t = 4.50$; $p < 0.001$) and type of onset symptom (B = −2.19 (SE 1.0), $t = -2.31$; $p = 0.02$) were significant predictors that explained 23% of the variance. No other variables increased the proportion of variance of the global cognitive impairment score.

To investigate the effect of the significant determinants on the cognitive profile of the total group, we performed two multivariate analyses of variance with age ($\leqslant 60$ *v* > 60) and type of clinical onset symptom (tremor *v* akinesia/rigidity) as the between-subjects factor, respectively. As expected, age had a significant effect on the cognitive impairment profile (Hotelling's T [10,89] = 3.73, $p < 0.001$). Univariate post-hoc tests showed significant differences for verbal learning and delayed recall, visual recognition, selective attention, word fluency, left/right orientation, and fine motor coordination. The older group always performed worse than the younger group. Age did not appear to influence impairment on visuospatial perception and mental flexibility. Type of clinical

onset symptom also had a significant effect on the cognitive impairment profile (Hotelling's T [10,79] = 1.93, p = 0.05). Univariate post-hoc tests revealed significant differences for verbal learning and delayed recall, selective attention, word fluency, and spatial reasoning. The tremor group always performed worse than the akinetic/rigid group.

DISCUSSION

Principal component analysis of the impairment scores for cognitive variables reveals a first component that includes verbal and visual memory and two timed variables that require selective attention and verbal speed. A positive and significant association between (verbal) learning performance and selective attention has been reported with principal component analysis elsewhere.[8] In patients with advanced Parkinson's disease this memory/attention factor is on average mildly to moderately impaired. The second component groups all visuospatial variables that show mild to absent impairment. Fine motor control and attentional set shifting, both typical "frontal" tasks, constitute a third component. Impairment on this executive/motor component falls in the moderate to severe range. This cognitive profile is in agreement with other neuropsychological investigations of patients with Parkinson's disease.[1]

Significant predictors of cognitive dysfunction in the group overall were age and type of onset symptom. Older patients (> 60 years) performed worse on almost every cognitive measure, especially on the variables that constitute the memory/attention component. Because the impairment scores are already age corrected (by using age matched normative data for most tests), this implies that the observed cognitive impairment in older patients with Parkinson's disease is significantly greater than can be expected from a normal aging process. The detrimental effect of age on cognitive impairment (and especially memory dysfunction) in Parkinson's disease has been noted in several studies,[9 10] though others have failed to find such a relation.[11 12] In the latter cases, some of the results were based on the mini-mental state examination (MMSE). It can be argued that the use of this mental screening instrument is too insensitive a marker of cognitive impairment in this population and certainly does not assess cognitive impairment specific to Parkinson's disease. The association between older age and increased cognitive impairment does not of course necessarily reflect Parkinson's disease related deficiency per se, but can also result from the increased risk of associated neurodegenerative disorders in the elderly.

According to our results, patients with tremor at disease onset are more likely to suffer cognitive impairment in the more advanced stages of the disease than patients with akinesia or rigidity at onset. Post-hoc analyses indicate that this impairment is restricted to the memory/attention component, with visuospatial and executive/motor variables showing minimal to absent differences, respectively. How can this relation between tremor at onset and cognitive impairment be interpreted? Tremor is more resistant to dopamine treatment than other motor symptoms. The reasons for this variable response are unclear, but pathological involvement of non-dopaminergic areas of the brain is held responsible.[3] A similar effect is observed with regard to cognitive dysfunction in Parkinson's disease. The restoration of central dopaminergic transmission with levodopa treatment does not improve the cognitive changes to the same extent as the dopamine dependent motor signs.[1] In addition, prospective research showed that the decline in cognitive performance on retesting after three years was significantly greater in patients with a low percentage of motor improvement on levodopa.[11] Non-dopaminergic pathology is certainly an explanation for many of the non-motor Parkinson's disease symptoms, including cognitive decline and dementia.[11 13] In this way, tremor at onset may be a marker for more widespread brain disease, in particular for damage to non-dopaminergic neuronal systems that also contribute to an increased risk for cognitive impairment. The finding that the tremor group showed more pronounced impairment on variables of memory and attention than the akinetic/rigid group also suggests possible non-dopaminergic involvement.

Several studies have investigated the relation between motor symptoms and the risk of cognitive impairment in Parkinson's disease. Studies that specifically addressed onset symptomatology found an association between tremor at onset and impairment on specific cognitive measures (for example, memory).[14] Recently, Grossman *et al* examined the impact of lateralisation of tremor at disease onset on cognition.[15] They found that patients with left sided onset of tremor showed a significant decline in cognitive performance over a 2.5 year period, whereas patients with right sided onset remained cognitively intact. In contrast, studies that focused on (UPDRS based) "predominance" of symptom type in the early to middle stages of the disease (rather than on the actual onset symptom) reported a greater risk of cognitive impairment in akinetic than in tremor subgroups.[11 16]

The reasons for these contradictory findings are unclear. Why should tremor at onset rather than after several years, or assessed in predominance rather than in terms of onset symptom, affect cognition differently? Several hypotheses can be formulated. If tremor (and cognitive dysfunction) reflect (additional) non-dopaminergic involvement, and akinesia/rigidity reflects dopaminergic involvement, the *disease course* of both underlying mechanisms is not necessarily similar.[17] Thus initial versus later occurrence of a certain motor symptom could have a different meaning. For example, if it takes more widespread brain damage to cause tremor than it takes to cause akinesia/rigidity, but the progression of non-dopaminergic deterioration occurs at a slower rate, tremor at onset could be a predictor of more extensive brain damage (especially when supplemented with progressively predominant akinesia/rigidity). In contrast, if tremor is still predominant in the middle stages of the disease this could reflect a less aggressive decline of the dopaminergic system, thus predicting a better clinical outcome. In agreement with this hypothesis, the study of Hershey *et al* found that tremor predominance after several years was a better predictor of a benign clinical course of Parkinson's disease than tremor at onset.[18] An alternative hypothesis could be that *not all tremors are equal*. The exact pathophysiology of parkinsonian tremor remains largely unknown[17] and if laterality of tremor at onset appears to differentiate between cognitive outcome[15] this may also be the case for other characteristics of tremor. Prospective studies, using more objective criteria to describe and define the exact onset symptoms of newly diagnosed cases of Parkinson's disease, adding detailed neuropsychological documentation of the cognitive evolution during the disease course, may provide more reliable data to corroborate these hypotheses.

Finally, we should also be aware of *methodological problems* that can explain the contradictory results. First, the reliability of determinations of symptom predominance, frequently based on UPDRS motor scale scores, can be questioned. Which tremor scale items (n = 7) are compared with which akinesia/rigidity items (n = 16), or is the relative impairment on both neurological signs compared? Both options can be criticised. In addition, motor symptoms in patients with Parkinson's disease are evaluated with a so called ordinal level rating scale (from 0 to 4), indicating a relative level of neurological signs. Methodological problems could arise using the different motor scales to determine, for example, a predominant motor symptom. Second, tremor as the onset symptom (implying that akinesia/rigidity is clinically absent) and tremor as the predominant symptom (implying that akinesia/rigidity may at least be present in a certain degree) are fundamentally different observations that occur at different points in the disease

course. If these symptoms are indirect clinical markers of underlying mechanisms that are not fully understood, determination of symptom predominance might prove a poor methodological construct.

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