Paper I

Original Research Article

Neuropsychological Profile of Patients with Parkinson's Disease without Dementia

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Abstract
Cognitive deficits are often associated with Parkinson's disease (PD), although their prevalence in PD patients without dementia is still unknown. In order to describe the neuropsychological profile of PD patients without dementia, a sample of 103 PD patients was compared with a control group consisting of 38 healthy elderly subjects. Psychometric assessment consisted of the Mini Mental State Examination, the Dementia Rating Scale and a battery of neuropsychological tests. The Beck Depression Inventory was used to assess depression in PD patients. Dementia was diagnosed in 27 patients. Among non-demented subjects, 34 (45%) had no cognitive impairment and 42 (55%) had a mild cognitive impairment. Subjects with mild cognitive impairment were older, had a later onset of the disease, and more severe motor symptoms than cognitively intact subjects. Identification of mild cognitive impairment is important, since these symptoms are important for patient management and may also facilitate to determine prognosis.

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Introduction

Idiopathic Parkinson's disease (PD) is due to a nigro-striatal dopamine deficiency that results in profound basal ganglia dysfunction. The prevalence of PD is about 1/1,000 [1] and increases with advanced age. The main symptoms are rigidity, resting tremor, bradykinesia and postural abnormalities. Mild cognitive impairment or dementia may also occur.

Recent studies have shown that the frequency of dementia in PD is about 28% [2], but the prevalence of cognitive deficits in individuals with PD without dementia is still unknown. Several studies have found that most patients with PD without dementia develop mild neuropsychological deficits across a range of cognitive functions, affecting memory, visuospatial processing, executive functions and attention [3, 4]. Some of these deficits are identifiable even in the early, untreated stages of the disease [5, 6]. By contrast, an early study has suggested that the majority of PD patients have relative preservation of cognitive functions [7]. Differences in diagnostic accuracy of PD, patient selection, mental status criteria to define dementia and in the methods used to assess cognition might explain some of these contradictory findings.

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While the cognitive changes in PD patients are heterogeneous in their clinical presentation, the initial neuropsychological profile may predict the distinct evolution of cognitive decline. For example, an early frontal dysfunction can be considered one of the best predictive factors for the development of dementia in PD patients [8].

The cognitive changes in the early stages of PD are characterized by executive dysfunction, while cognitive deficits in the later stages of the disease begin to overlap with those of cortical dementias [9]. Whether patients with PD without dementia exhibit cognitive impairments and, if present, whether these impairments are global or selective is important for the management of these patients and for the determination of the patients who will eventually develop global dementia. Furthermore, recent studies have shown that cognitive impairment in parkinsonian patients predicts caregiver distress and nursing home placement [10]. Finally, such information might be useful in understanding the underlying biological mechanisms of cognitive dysfunction in PD.

The aims of this study were to evaluate the type and frequency of cognitive impairment in non-demented PD patients and to explore the relationship between cognitive deficits and the following variables: age at disease onset, presence of depression, side affected and type of parkinsonism. In order to avoid some of the methodological weaknesses of previous studies, we used a population-based sample and compared the neuropsychological performances of a non-demented PD group with the performances of a healthy elderly control group.

Patients and Methods

Subjects

Patients were recruited from an epidemiological study of PD in the country of Rogaland, Norway, conducted between 1992 and 1993 [1]. During 1996 and 1997 the survivors were invited to participate in the present study and were given a comprehensive assessment consisting of neurologic, psychiatric and neuropsychological evaluations. The evaluations were performed sequentially, within 1 month of the previous evaluation. The demographic and clinical characteristics of the study population were similar to those in the overall population of patients with PD from the evaluation in 1993.

The control group consisted of 38 healthy, elderly subjects who were either relatives of the patients or relatives of inpatients in the psychogeriatric ward at the Rogaland Psychiatric Hospital. None had a history of alcoholism, drug abuse, psychiatric illness, CNS disease, or head injury, and none were currently taking centrally active drugs. Individuals with evidence of intellectual deterioration (Mini Mental State Examination (MMSE) score ≤ 24) were not included.

The study was approved by the Regional Ethics Committee of the University of Bergen, and all subjects provided informed consent.

Methods

Diagnosis and Clinical Evaluation of PD. Information on disease history, drug therapy, response to levodopa and demographic variables was obtained in a semi-structured interview conducted by a neurologist. Diagnostic evaluation was based on clinical information obtained at the primary evaluation, including disease development and response to levodopa therapy. To achieve high diagnostic specificity as well as high sensitivity, a diagnostic clinical classification of definite, probable, and possible PD was used [11]. Definite PD required that a patient has resting tremor and at least two more cardinal signs: (1) akinesia or bradykinesia, (2) rigidity, or (3) postural abnormalities. The disease has unilateral onset and development, and response to administration of a dopaminergic agent is good to excellent. For a diagnosis of probable PD, the patient had to fulfill at least two of the four clinical criteria from the definite PD category. Resting tremor was not mandatory and a maximum of 1 of the following atypical clinical features may be present: (1) mild dementia or clinically relevant autonomic failure at disease onset, (2) symmetrical disease presentation, or (3) moderate response to administration of a dopaminergic agent. For possible PD, the patient had at least two of the four cardinal signs. The response to use of a dopaminergic agent should be at least moderate. Mild-to-moderate dementia and autonomic failure at disease onset was allowed. Patients with other neurologic diagnoses or the presence of radiologic structural brain abnormalities compatible with diagnoses other than PD were excluded.

The clinical examination of motor symptoms consisted of a complete Unified Parkinson's Disease Rating Scale (UPDRS) assessment [12], including the Hoehn & Yahr Scale [13].

Clinical Subgroups. The UPDRS motor scale was used to obtain scores for several clinical factors that might have an impact on neuropsychological deficits. We calculated a tremor score by adding scores on item 20 (tremor at rest and action) and 21 (postural tremor of hands). Rigidity was measured by the scores on item 22, and bradykinesia was measured by adding the scores on items 23–26 (finger taps, hand movements, rapid alternating movements of hand, and leg agility).

We calculated right- and left-sided motor subscores by adding the respective scores for the right and left side on UPDRS items 20–26. Patients were identified has having right or left dominance if the difference between scores for the right and left side was 3 or more.

Psychometric Assessment. A semi-structured interview based on the Diagnostic and Statistical Manual of Mental Disorders, ed 3, revised (DSM-III-R) criteria for dementia [14] was administered to the caregiver by a psychiatrist with experience in geriatric psychiatry and neuropsychiatry.

Two brief screening instruments, which are widely used in order to differentiate between cognitively impaired and cognitively unimpaired subjects, were administered to both patients and control subjects: the MMSE [15] and the Dementia Rating Scale (DRS) [16]. DRS has been used in several studies in order to describe the cognitive profile of patients with subcortical dementias [17, 18]. The DRS examines five cognitive areas (attention, initiation and perseveration, construction, categorization and memory) and provides a total score and five subscale scores. Patients with an MMSE score ≥ 16 and control subjects were given a neuropsychological battery assessing multiple cognitive domains including visual memory, visuospatial ability and executive functions. We selected neuropsychological tests to be independent of motor abilities. The tests were administered by a neuropsychologist and scored according to conventional

procedures outlined in the test manuals. The following tests were included in the neuropsychological battery: (i) The multiple choice version of the Benton Visual Retention Test (BVRT), designed to assess short-time visual memory: subjects recognize one or more designs that they have seen before [19]. (ii) The Judgment of Line Orientation (JLO) test, designed to assess visual/spatial abilities: subjects estimate angular relationships between line segments by visually matching angled line pairs to 11 numbered radii forming a semicircle [20]. (iii) The Stroop Word Test (SWT), designed to assess selective attention/executive functions. Subjects name the colors of colored patches (1st card), read printed words (2nd card), and read printed color names in which the ink used for printing is a color different from the color designated by the printed name (3rd card) [21]. In the present study we administered all the three cards, but the analysis of the results was based on the third card, which is thought to be useful in assessing executive functions. We recorded both the time the patient took to read the card and the number of errors. SWT measures for time and errors were both considered as indicators for executive dysfunction.

Cognitive impairment was considered to be present in PD patients if their scores on one or more neuropsychological tests were at least two standard deviations (SD) below the means for the control group and if the DSM-III-R criteria for dementia were not fulfilled. Dementia was diagnosed according to the DSM-III-R criteria based on the clinical interview, the cognitive screening tests and the neuropsychological tests. To qualify for a diagnosis of dementia, the interview, the rating scales (MMSE cutoff score of 24, DRS cutoff score of 123), and the neuropsychological tests had to be compatible with a diagnosis of dementia. In cases of inconsistencies among these measures, all available material was reviewed, and both raters made a diagnosis of dementia or no dementia independently, according to the DSM-III-R criteria for dementia. In cases of disagreement, a consensus diagnosis was made. Severity of depression was measured using the Beck Depression Inventory (BDI) [22], using a cutoff score of 10.

Statistics

Independent, two-tailed t tests and one-way ANOVA were used to assess the significance of mean differences in measures of cognitive performance between the PD patients and the control group on the one hand and between cognitively intact and cognitively impaired groups on the other hand. Associations between parkinsonian symptoms and cognitive performance were analyzed using two-tailed Pearson correlations. Due to multiple testing, a p value of 0.01 was considered significant. All analyses were conducted using computerized statistical software (SPSS).

Results

Clinical and Demographic Characteristics

Of the 245 patients evaluated in 1993, 7 had subsequently been diagnosed as not having PD, and 88 had died. Accordingly, 150 patients were invited to participate in the present study. Eleven patients chose not to participate. The remaining 139 PD patients completed both the neurologic and psychiatric assessments. Twenty-two patients had MMSE scores <16, 10 patients refused to perform the neuropsychological battery, and 4 patients were unable to perform any of the tests. Of the 103 patients evaluated by a neuropsychologist, 27 patients received a diagnosis of dementia. Accordingly, 76 patients were included. All patients were using antiparkinsonian medication. The mean age, years of education and sex distribution of PD patients and control subjects were similar.

Cognitive Function

PD patients without dementia did not differ significantly from the healthy elderly control subjects on MMSE and four of the DRS measures: attention, categorization, initiation/perseveration and construction. However, PD patients performed significantly poorer than the healthy elderly control subjects on BVRT, SWT (time and errors), JLO, and the DRS measure for memory. In order to determine how many of the non-demented PD patients exhibited mild cognitive impairment, we identified 42 PD patients (55%) whose scores on at least one neuropsychological test were 2 SD below the mean values for the control group. The remaining 34 PD patients showed no cognitive impairment. Demographic and clinical characteristics of PD patients and control subjects are shown in table 1.

The cognitively intact PD patients were similar to the control group in age, years of education, and gender distribution. Cognitively impaired PD patients were older and had a later onset of the disease, higher scores on bradykinesia and rigidity, and more severe motor symptoms than the cognitively intact PD patients. There were no significant differences between cognitively intact and cognitively impaired PD patients with regard to the duration of the disease, dose of levodopa, or depressive symptoms (table 1).

Within the cognitively impaired PD group, 57.1% of the patients had impaired performance (≥2 SD) on one neuropsychological test, 33.3% on two tests while the remaining 9.5% had impaired performance on all the three tests.

Within the cognitively impaired PD group, we identified three different types of cognitive profile. Eleven patients (26.1%) showed only executive dysfunction (i.e., impaired either time/errors or both on SWT), 7 patients (16.6%) had impaired visual memory and/or visuospatial abilities without executive dysfunction, and 19 patients (45.2%) showed a more widespread cognitive impairment affecting visual memory, executive and visuospatial skills. As 5 PD cognitively impaired patients did not complete

Table 1. Clinical and demographic characteristics of cognitively intact and cognitively impaired PD patients and control subjects [means (SD) except for gender]

Characteristics	PD patients		Control subjects
	cognitively intact (n = 34)	cognitively impaired (n = 42)	
Male/female ratio	13/21	21/21	11/27
Age, years	68.9 (9.5)**	73.5 (6.0)	68.7 (9.4)
Years of education	10.1 (3.6)	9.2 (3.1)	10.4 (3.6)
Age at disease onset, years	56.8 (12.0)*	61.8 (7.6)	
Hoehn & Yahr stage	2.3 (0.6)*	2.8 (0.9)	
Levodopa dose, mg	677.4 (345.6)	667.3 (310.1)	
BDI score	9.5 (6.8)	11.8 (7.6)	
MMSE score	29.5 (0.9)**	28.0 (2.1)	29.9 (1.1)
DRS score	141.5 (2.4)**	136.9 (6.6)	141.3 (3.6)

* $p < 0.01$, ** $p < 0.001$. Independent t test was used to compare cognitively intact and cognitively impaired PD patients as well as cognitively intact PD patients and control subjects.

all the neuropsychological tests they were not included in either of the three groups.

Cognitive Performance and Side and Type of Parkinsonism in Cognitively Impaired PD Patients

When PD patients with right- and left-sided dominant symptoms were compared, patients with right-sided dominant symptoms performed significantly better on BVRT than those with left-sided dominant symptoms ($p < 0.01$), with no significant differences in the other tests.

Type of Parkinsonism. SWT measures for time correlated with rigidity and bradykinesia scores ($p < 0.01$), but the other tests did not. There were no significant differences between akinetic versus tremor-dominant groups and scores on the neuropsychological tests, or between akinetic versus mixed groups regarding their performances on BVRT, JLO, and SWT. The mixed group performed significantly poorer than the tremor-dominant group on the SWT measure for time ($p < 0.01$).

Discussion

The main finding was that 55% of the non-demented PD patients were cognitively impaired. Of the total group, only 33% were cognitively intact. Mild cognitive impairment has been found to predict the development of dementia [26]. Given the relationship between cognitive impairment for patient management with regard to caregiver distress, nursing home placement [10] and develop-

ment of psychotic symptoms, these findings underline the importance of cognitive dysfunction in PD patients [23].

Within the group of cognitively impaired PD patients, we identified three neuropsychological profiles. The first subgroup had widespread cognitive impairment, affecting memory, visuospatial skills and executive functions. The second group of patients showed only executive dysfunction as revealed by poor performance on SWT. The third group of cognitively impaired PD patients had impaired performance on tests assessing visuospatial skills and visual memory, but normal performance on tests sensitive to frontal lobe dysfunction.

Cognitively impaired PD patients were older, had a later onset of PD, and had more severe motor symptoms compared to the cognitively intact PD patients. The cognitive changes found in older PD patients could not be due solely to the normal aging process since the changes were observed after correction for age. This finding might suggest that PD patients with late onset of the disease could have an additional risk of intellectual impairment as a consequence of independent age-related changes [24]. However, recent longitudinal studies have not found an association between late onset and dementia [25, 26].

Depression has been found to be associated with deficits in cognitive tasks in PD patients [27]. However, depression did not differ between cognitively intact and cognitively impaired PD patients, suggesting that cognitive deficits in PD cannot be explained only by the presence of depression.

Parkinsonism and Cognitive Functions

Based on a previous study [28], we expected that patients with left-sided parkinsonism would perform poorer than right-sided patients on a wide range of neuropsychological tests; however, left-sided PD patients performed worse than right-sided patients only on the BVRT. Furthermore, no significant differences in neuropsychological test performance were seen between akinetic versus tremor groups. This was a surprising finding, as previous research [29] showed better cognitive performance in the tremor group, compared to the akinetic group. Rigidity and bradykinesia scores correlated with the SWT measure for time, suggesting that dopaminergic mechanisms may contribute to executive dysfunction in PD. However, this finding might be an effect of motor slowness.

Strengths and Weaknesses of Our Study

One of the strengths of our study is the representative, well-characterized and relatively large sample of patients. Another strength is the diagnostic stability of our sample, with the diagnosis of PD confirmed by neurological examinations performed in the follow-up study 4 years later.

A weakness of our study is that the sample did not include patients with a disease duration of less than 4 years. There is evidence that the duration of the disease is an important determinant of the presence of cognitive deficits in parkinsonian patients [30], and our results may therefore not be generalizable to patients with a duration of PD of less than 4 years. However, a recent study had not found any correlation between cognitive changes in PD and the duration of the disease [26].

Mild cognitive changes in PD patients are common and are associated with higher age, later onset of the disease, and severity of the motor symptoms. As new drugs for ameliorating cognitive impairment in PD patients become available in the next few years, detecting mild cognitive impairment in PD patients will increase in importance. Screening instruments like MMSE and DRS are not able to detect subtle cognitive changes in PD patients, and therefore neuropsychological tests are recommended. Early treatment of cognitive impairment in parkinsonian patients might reduce caregiver burden and delay nursing home placement, as well as improve cognitive function and the quality of life of the patients themselves.

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