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# Impaired cognitive performance and hippocampal atrophy in Parkinson disease

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**Background/aim:** Dementia is common in Parkinson disease (PD). Since magnetic resonance imaging has been used, hippocampal atrophy has been shown in PD patients with or without dementia. In this study we sought the correlation of cognitive decline with bilateral hippocampal volume in PD patients.

**Materials and methods:** Thirty-three patients with diagnosis of idiopathic PD and 16 healthy subjects were included in this study. PD patients were divided into two groups as normal cognitive function and mild cognitive impairment (MCI). The Mini-Mental State Examination and detailed cognitive assessment tests were performed for all patients for cognitive analyses. Depression was excluded by the Geriatric Depression Scale.

**Results:** The mean onset age of disease was 55 years for PD patients without dementia and 59 for PD patients with MCI. According to the Hoehn–Yahr scales, 24% of patients had grade 1, 58% had grade 2, and 18% had grade 3 disease. Right and left hippocampal volumes decreased along with cognitive test scores in PD patients. Increased right hippocampal volume was correlated with forward number test in the MCI-PD group.

**Conclusion:** These findings suggest that memory deficit is associated with hippocampal atrophy in PD patients.

**Key words:** Parkinson disease, minimal cognitive impairment, neuropsychological tests, cognitive functions, hippocampal volume

## 1. Introduction

Dementia is very common in Parkinson disease (PD). Prevalence was shown as 41% of patients (1). It was shown that there was a 6-fold increased risk of developing dementia in these patients. Patient age, age of disease onset, a Hoehn and Yahr score of <2, and a Mini-Mental State Examination (MMSE) score of <29 were reported as predictive factors for developing dementia (2). Tremor-dominant PD patients have less cognitive dysfunction compared to those with postural instability and walking disorders (3,4). PD patients with dementia have more severe visual and spatial disorders compared to Alzheimer disease (AD). Because of a possible role of visual memory dysfunction, visuospatial skills and orientation are affected (5,6). Memory functions are less affected than in AD patients. In memory tests, learning new information, and especially recalling new information, was significantly impaired. Attention and vigilance is similar to Lewy body dementia and shows a fluctuating course. Reaction time is increased and attention to new signals is decreased (7).

There are no specific signs or imaging findings in the diagnosis of PD dementia. Even though some tests can differentiate between dementia of PD and AD, no specific evaluation has been reported (8). Some authors agree that a MMSE score under 24 is a guide for diagnosis of minimal cognitive dysfunction. Assessment only by MMSE may not be enough for a diagnosis of dementia. Patients with a MMSE score more of than 24 points can have dementia, especially in PD.

Since volumetric magnetic resonance imaging (MRI) analysis shows regional cerebral atrophy quantitatively, loss of hippocampal volume in PD patients was shown pathologically in postmortem studies (9,10). Since MRI has been used, hippocampal atrophy is shown in PD patients with or without dementia (11,12). Korf et al. reported that medial temporal lobe atrophy shown by MRI has a predictive value for transmission from

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minimal cognitive impairment (MCI) to dementia and it is independent of age, sex, education, MMSE score, hypertension, depression, Apo E4 allele, and white matter hypersensitivity (13).

Volumetric studies in PD are very limited compared to MCI and AD. Burton et al. showed that volume loss was in the gray matter of the temporal lobe in PD patients without cognitive dysfunction and volume loss extended to temporal, parietal, and subcortical areas in PD patients with dementia (14). Another study showed that the degree of cerebral atrophy was increased in patients with PD dementia but there was no difference between control and patient groups (15). Longitudinal studies may be useful for the evaluation of cognitive decline in PD. One study showed that PD patients had apparent loss of cerebral volume per year and it was correlated with cognitive dysfunction (16).

In this study we investigate the correlation of cognitive decline with bilateral hippocampal volume in PD patients and compare them with cognitively normal control subjects. Our hypothesis was that the volume loss of the hippocampus would be more pronounced in PD patients.

## 2. Materials and methods

Thirty-three patients with the diagnosis of idiopathic PD and 16 healthy subjects were included in this study. All of the patients were followed at our movement disorders polyclinic of the School of Medicine of Uludağ University. The MMSE was used for cognitive assessment. PD patients were divided into two groups: patients with normal cognitive functions and patients with MCI. Demographic characteristics of all groups were recorded (age, sex, and educational level). All of the subjects had graduated from at least primary school. Onset age of PD, duration of illness, grade of disease when cognitive function was scaled (according to the modified Hoehn–Yahr scale), Unified Parkinson's Disease Rating Scale (UPDRS) score, involved side, and disease onset type were recorded. Glucose, hemoglobin, thyroid-stimulating hormone, cholesterol, homocysteine, vitamin B12, and folic acid levels were checked. Patients were evaluated by Wechsler memory scale (modified by a psychologist), Luria alternating draw test, Raven's standard progressive matrices test, the Stroop test for evaluation of frontal lobe function, the RUFF shape fluency test, and the K-A-S word fluency test for speed and attention evaluation, and Trail A and B and forward and backward number repeating tests were performed. Depression was excluded using the Geriatric Depression Scale.

### 2.1. Morphometric evaluation

Images of cranial MRI were scanned to a Lenoard study station. First, anatomic segmentation was done through three dimensions (axial, coronal, and sagittal) for 3D MP-RAGE images with high resolution and, in this way, anatomical deformations because of segmentation were cleaned. Then hippocampal regions were magnified twice perpendicular to hippocampal axis. Hippocampal lines were defined by the Watson model. Separation between the hippocampal anterior line and the amygdala was made by alveus and uncal recess. The superior line was at the choroid plexus level, the external line started from where the temporal horn appeared, the internal line was on the perimesencephalic cisterna, the posterior line was where the crura of fornix appeared, and the inferior line was where the subiculum appeared. Total hippocampal volume was calculated by total hippocampal area measured through all segments. To correct individual differences, measurement of the intracranial area was calculated from the midline.

Corrected volume = (average hippocampal area of control group x hippocampal volume) / intracranial area of the patient.

Left and right hippocampal exact values and their difference were compared between patient and control groups.

### 2.2. Statistical analyses

SPSS 13.0 was used for statistical analyses. For comparison of two groups, the Mann–Whitney U test, one-dimensional variable analysis, and multiple comparison tests were done. For comparing three groups, the Kruskal–Wallis test, one-dimensional variable analysis, and ANOVA were used. For comparing categorical variables, Pearson chi-square and Fisher exact tests were performed. According to type of variables, Pearson correlation coefficient and Spearman correlation coefficient were used. Mean and standard deviation of data were presented. $P < 0.05$ was accepted as statistically significant.

## 3. Results

The mean age was 61 ± 10 years for patients with MMSE score of ≥24, 65.4 ± 10 for patients with MMSE score of <24, and 58 ± 12 for the control group. There was no statistically significant difference between groups regarding age, sex, or educational level. There was no significant difference between UPDRS scores and involvement side or disease onset type in either patient group (Table 1). The mean onset age of disease was 55 for PD patients without dementia and 59 for PD patients with MCI. According to the Hoehn–Yahr scale, 24% of patients had grade 1, 58% had grade 2, and 18% had grade 3 disease (Table 2). For all patients, mean scores were 2.3 ± 1.3 for UPDRS mental mood, 7.1 ± 4.2 for daily life activity, and 12.1 ± 6.9 for motor examination. Eighteen patients had tremor as the initial symptom and there was no statistical significant difference between disease types. In PD patients without dementia, 11 patients had right-sided symptom onset and 3 had left-sided symptom onset ($P = 0.005$).

**Table 1.** The distribution of UPDRS score, beginning side, and types of PD patients.

| | All patients with PD (n = 33) | PD without dementia (n = 14) | PD with MCI (n = 19) |
|---|---|---|---|
| Beginning age | 57 ± 10 | 55 ± 10 | 59 ± 10 |
| UPDRS MM | 2.3 ± 1.3 | 2.1 ± 1 | 2.5 ± 1.4 |
| UPDRS DLA | 7.1 ± 4.2 | 7 ± 3 | 7.1 ± 5.1 |
| UPDRS ME | 12 ± 6.9 | 1.6 ± 5.4 | 12.8 ± 7.9 |
| Beginning part (right/left) | 18/15 | 11/3 | 7/12 |
| Beginning symptom (tremor/bradykinesia) | 18/15 | 8/6 | 10/9 |

PD: Parkinson disease, MM: mental mood, DLA: daily life activity, ME: motor examination.

**Table 2.** The distribution of Hoehn–Yahr grades of PD patients.

| Hoehn–Yahr scales | All patients with PD (n = 33) | PD without dementia (n = 14) | PD with MCI (n = 19) |
|---|---|---|---|
| 1 | 8 (24%) | 3 (22%) | 5 (26%) |
| 2 | 19 (58%) | 10 (71%) | 9 (47%) |
| 3 | 6 (18%) | 1 (7%) | 5 (27%) |

PD: Parkinson disease.

Patients in the MCI-PD group had decreased right and left hippocampal volumes along with increased Trail A test scores and better performance in the forward number test. Right and left hippocampal volume was inversely correlated with verbal memory tests. In memory and thought fluency tests, there was a statistically significant increase of right hippocampal volume (Tables 3–5).

**Table 3.** The distribution of right and left hippocampal volumes of the cases.

| | PD without dementia (n = 14) | PD with MCI (n = 19) | Control (n = 14) |
|---|---|---|---|
| Right hippocampal volume | 3.4 ± 0.4 | 3.3 ± 0.4 | 3.35 ± 0.3 |
| Left hippocampal volume | 3.35 ± 0.3 | 3.2 ± 0.4 | 3.3 ± 0.4 |

PD: Parkinson disease.

**Table 4.** Correlation of hippocampal volume between control group and K-A-S word fluency test.

| | Right hippocampal volume | Left hippocampal volume |
|---|---|---|
| WFTR | –0.081 P = 0.004 | –0.83 P = 0.002 |

**Table 5.** Correlation between hippocampal volume and neuropsychological tests of MCI-PD group.

| | Right hippocampal volume | | Left hippocampal volume | |
|---|---|---|---|---|
| Trail A mistake | 0.667 | P = 0.009 | 0.608 | P = 0.021 |
| Forward number test | 0.542 | P = 0.045 | - | |
| Verbal memory | 0.669 | P = 0.009 | 0.669 | P = 0.009 |
| Logical memory | 0.549 | P = 0.042 | - | |
| Thought fluency tests | 0.537 | P = 0.048 | - | |

## 4. Discussion

Hippocampal volume loss appears with normal aging, and thus specific criteria to define pathological volume loss are needed. There is abnormal hippocampal atrophy in AD patients regardless of age at onset (17). In our study, during hippocampal volume measurements, measurement of the intracranial area was calculated from the midline to correct individual differences. There was a loss of hippocampal volume in MCI-PD patients compared to the control group and PD patients with normal cognition, but the difference did not reach statistical significance. Long-term follow-up studies show that cognitive dysfunction is correlated with changes of hippocampal volume in cases with and without dementia (18–20). A prospective MRI study showed that total cerebral, ventricular, and hippocampal atrophy was important for the prognosis in AD (21). Geroldi et al. reported that medial temporal lobe atrophy detected by volumetric MRI was predictive for progression of dementia in MCI patients (22). Bell-McGinty et al. reported that MCI patients had loss of volume of the bilateral middle temporal gyrus and hippocampus compared to a control group. Loss of volume in the left entorhinal cortex and inferior parietal lobe was more significant in MCI-amnestic patients than MCI-multiple cognitive domain patients (23). This finding suggests that different cerebral areas are affected in different MCI subtypes.

In a 3-year follow-up study in patients with MCI, left and right hippocampal volumes were 9% and 13% smaller in MCI patients developing dementia compared to MCI patients not developing dementia (24). Becker et al. showed that hippocampal atrophy was common in AD and MCI patients (25). In our study, frontal lobe deficits like attention, planning, and visuospatial function and temporal lobe deficits like verbal and visual memory were obtained. There was no significant difference between hippocampal volumes of MCI patients and control groups, confirming the results of Becker et al.

Apart from our study, hippocampal atrophy was shown in PD patients with or without dementia by two other studies (11,12). Laakso et al. (11) reported significantly decreased hippocampal volumes in AD, PD, and PD-dementia patients compared to controls. However, Camicioli et al. (12) reported a progressive hippocampal volume loss in the PD–PD-dementia spectrum. Almeida et al. (26) showed that total cerebral and caudate volumes were decreased in AD patients compared to control and PD groups.

Messina et al. (27) did volumetric MRI for PD patients and there was no significant difference between patients and the control group. Jokinen et al. (28), using similar neuropsychological tests, found that caudate F-dopa uptake in positron emission tomography was correlated with visual and verbal memory performances. Hippocampal atrophy in PD patients was associated with memory deficits in this study. Hippocampal atrophy was also related to verbal and visual memory.

Limitations of our study include the cross-sectional design and limited sample size. Absence of PD patients with dementia may also be a limitation.

In our study, frontal and temporal lobe deficits were found in PD patients. Although there was no statistically significant difference between hippocampal volumes of the groups, decreases in right and left hippocampal volumes were associated with decrease in word fluency and worse cognitive functions in PD patients with MCI. These results suggest that volumetric assessment of certain brain regions may give clinically relevant information. Longitudinal studies with larger patient groups are needed.

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