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Cognitive Impairment in Parkinson's Disease

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Abstract

Background: Parkinson's disease (PD) is a progressive neurodegenerative disorder with characteristic clinical motor features combined with non-motor symptoms. Cognitive impairment has a very significant impact on the patient's quality of life. The risk of developing dementia is six times higher in PD patients than in general population and increases with longer duration of the disease.

Objectives: The aim of this study is to assess cognitive impairment in PD patients and its characteristics and to explore the correlation between duration of the disease, its stage, and neuroimaging of the brain.

Material and methods: The study involved 64 patients with clinical diagnosis of PD established on the basis of the UKPDS BB criteria. Patients with PD were subdivided into two groups: patients with disease duration under five years and over five years. Participation in the study included taking medical history, collecting information on the course of the disease and its treatment, identification of comorbidities, and neurological examination. A neuropsychological assessment was carried out for all the patients and included: MMSE, CDT, verbal fluency test (both semantic and phonemic tasks) and, in part, the ADAS-cog test. The examination also included the BDI (Beck Depression Inventory) test. CT and MRI scans were performed of PD patients in order to assess atrophy of the brain and hippocampus.

Results: Most of the PD patients suffer from visuospatial and semantic fluency dysfunctions. The level of cognitive impairment in PD is dependent on the patient's age and the motor symptom severity assessed using the H-Y scale. We observed a clear relationship in PD between cognitive impairment and atrophy of the hippocampus, temporal and parietal lobes, and vascular lesion.

Conclusion: Cognitive function impairment appears in Parkinson's patients without diagnosed dementia. The executive functions are especially affected with the level of impairment dependent on the patient's age and the degree of movement impairment.

Keywords: Parkinson's disease; Parkinson's disease dementia; Cognitive impairment; Neuropsychological test

Introduction

Parkinson's Disease (PD) is a progressive neurodegenerative disorder, classified as a synucleinopathy, which affects 1%-2% people over 65 years of age [1-3]. PD is essentially characterized by motor symptoms, which increase with progression of the disease. Currently, we pay more attention to non-motor symptoms, which are associated with increased disability and reduced quality of life. The prevalence of non-motor symptoms in PD patients is 20% in early stages and about 88% after seven years of disease. Non-motor symptoms are an integral part of PD and they are clinical manifestations of an extensive degenerative process outside the substantia nigra area. Cognitive impairment is present at all stages of the disease with the frequency ranging from 20% to 90% [4-6]. The point prevalence of dementia in PD is close to 40% and the incidence rate is increased 4-6 times compared with the general population [7]. The typical profile of cognitive impairment is mostly described as a subcortical-type dementia. Cognitive problems such as bradyphrenia, impairment of executive and visuospatial functions, memory problems and impairment of language functions have been observed among the PD patients. In PD, dementia is a late symptom, rare in the first years of diagnosis. The cumulative prevalence is high. After ten years, dementia affects most of the patients and at least 80% of PD patients who survive for more than 20 years will develop dementia or psychotic problems [8-10]. The aim of the study was to assess the dependency between cognitive function impairment and disease duration, stage of disease and abnormalities in neuroimaging. In addition, the aim was to check if the neuropsychological tests are sufficient for assessment of the cognitive function impairment.

Materials and Methods

Subjects

The study involved 64 subjects with PD (group I) of which 29 were female and 35 were men.

Step 1 Diagnosis of Parkinsonian syndrome
Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
and at least one of the following:
muscular rigidity
4-6 Hz rest tremor
postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction
Step 2 Exclusion criteria for idiopathic Parkinson's disease
Repeated strokes with stepwise progression of parkinsonian features
Repeated head injury
History of definite encephalitis
Oculogyric crises
Neuroleptic treatment at onset of symptoms
More than one affected relative
Sustained remission
Strictly unilateral features after 3 years
Supranuclear gaze palsy
Cerebellar signs
Early severe autonomic involvement
Early severe dementia with disturbances of memory, language, and praxis
Babinski sign
Presence of cerebral tumour or communicating hydrocephalus on CT scan
Negative response to large doses of levodopa (if malabsorption excluded)
MPTP exposure
Step 3 Supportive prospective positive criteria for idiopathic Parkinson's disease (Three or more required for diagnosis of definite Parkinson's disease)
Unilateral onset
Rest tremor present
Progressive disorder
Persistent asymmetry affecting side of onset most
Excellent response (70-100%) to levodopa
Severe levodopa-induced chorea
Levodopa response for 5 years or more
Clinical course of 10 years or more

Table 1: UK Parkinson's Disease Society Brain Bank (UKPDSBB) clinical diagnostic criteria for idiopathic Parkinson's disease.

Patients were diagnosed with PD according to UK Parkinson's Disease Society Brain Bank criteria (Table 1) and did not have a diagnosis of dementia on routine clinical evaluation. The 64 PD patients was subdivided into two groups: 32 patients with disease duration under five years (IA group) and 32 patients with PD duration over five years (IB group). All the patients were treated with L-Dopa. The split into the groups was based on the end of drug holiday after 5 years of therapy. 42 patients (66%) were recruited from the Department and Clinic of Neurology at the University Hospital in Wroclaw, while the rest of the sample (22 patients) were ambulatory patients (Outpatient Clinic University Hospital). All patients provided written informed consent for participation in this study.

Exclusion criteria were the following: psychiatric disorders, administered drugs that could interfere with cognitive functions, severe internal disorders (heart, liver, or renal failure) diagnosed based on bio-chemical tests, a history of head trauma or inflammation of the brain.

Thirty healthy (15 female and 15 men) controls with normal neurological examination, without extrapyramidal syndrome or cognitive impairment were recruited from the local community. The control group was matched by sex and age with the patients.

Demographic characteristics, including gender, age, age of onset, disease duration, education level, side of onset, clinical type and levodopa equivalent daily dose were recorded for all participants. The severity of the PD was assessed according to the five-stage Hoehn and Yahr scale [11].

Patients were evaluated by the qualified neurologists

Neuropsychological assessment: A neuropsychological assessment was carried for all the patients and included: MMSE (Minimental State Examination), CDT (Clock Drawing Test) – the version by Sunderland et al., a part of the ADAS-cog test assessing the ability to remember a list of word ("word recall"), and a verbal fluency test (Controlled Oral Word Association Test -COWAT) in the alphabet-phonemic category (COWATf) and the semantic category (COWATs) consisting of "fruit and vegetables". The obtained results were referred to the standards set for each age group and gender of the studied patients. Depressive disorders were excluded in all subjects examined using the Beck Depression Inventory (BDI).

Neuroimage study: All patients with PD underwent neuroimaging studies including: CT and MR examinations. MR were assessed in 57 patients; the CT scan was performed for 7 patients with contraindications to MRI. Neuroimages were evaluated by neuroradiologist.

The analyzed MR studies included standard MR examination (T1-, T2-weighted images, FLAIR sequence, diffusion weighted imaging – DWI) without or with contrast administration.
The CT studies were performed using 64 and 16 row scanners (GE Healthcare) with a slice thickness 0.6 mm and included unenhanced and contrast enhanced CT examinations. All MR studies were performed using 1.5 T MR scanner (GE Healthcare).

Hippocampal atrophy was assessed using the 4-points Scheltens' scale (MTA medial temporal lobe atrophy). MTA scoring between 0 and 4, evaluating atrophy in the hippocampus, the parahippocampal gyrus, the entorhinal cortex and the surrounding cerebrospinal fluid on coronal reconstructions [12].

- No atrophy
- Only widening of choroid fissure

- Also widening of temporal horn of lateral ventricle
- Moderate loss of hippocampal volume (decrease in height)
- Severe volume loss of hippocampal volume

Cortical atrophy (in frontal, temporal, parietal, occipital, and brainstem areas) was assessed with a visual rating scale scoring between 0 and 3 [13].

- No cortical atrophy
- Mild atrophy
- Moderate atrophy
- Severe atrophy

Based on MR scan were also measured subcortical atrophy and vascular lesion on a scale from 0 (no lesion) to 3 (diffuse lesion).

Statistical analysis

All statistical analyses were performed with the Statistica 10 program. We first assessed the normality assumption of all variables by using the Kolmogorov-Smirnov test. Normal distribution values were expressed as means with standard deviation (SD). The significance was examined using Student's t-test and the Pearson's correlation test. Analysis of variance (ANOVA) with Scheffe's post-hoc test was used to compare more than two group means. The level of significance for all analyses was set at $p<0.05$.

Results

Demographic and clinical variables

The demographic data, duration of disease, and the Hoehn and Yahr scale rating (H-Y) are shown in Table 2.

Variables	Group I n=64	Group IA n=32	Group IB n=32	Control group n=30
Age	68.3 ± 9.8	69.0 ± 10.0	67.6 ± 9.7	64.8 ± 9.5
Female	29 (45%)	21 (66%)	8 (25%)	15 (50%)
Men	35 (55%)	11 (34%)	24 (75%)	15 (50%)
Duration	6.2 ± 4.6	2.7 ± 1.6	9.6 ± 3.9	0
H-Y	2.8 ± 0.8	2.5 ± 0.8	3.1 ± 0.8	0

Table 2: The demographic data control group.

Neuropsychological test

Table 3 shows the mean score in neuropsychological tests and the BDI. A statistically significant difference was observed in the MMSE test and its corrected value between the entire group I and the control group ($p<0.05$). In the CDT test, the mean score for the entire group I was statistically significantly lower than for the control group. The Scheffé's test also indicated a statistical significance between both groups IA and IB and the control group.

The Kruskal-Wallis test was used due to lack of normal distribution. Statistically significantly lower values were recorded for the patients and the control group in the CDT test ($p=0.004$). The results of the verbal fluency test in the semantic category were significantly lower in group I compared to the control group. Significantly higher values were obtained in the BDI scale for PD patients (group I) and in the Scheffé's test (sub-groups IA and IB).

Variables	Group I (n=64)	Group IA (n=32)	Group IB (n=32)	Control group (n=30)
MMSE	27.2 ± 2.3 p<0.05	27.2 ± 2.2	27.2 ± 2.4	28.5 ± 1.7
MMSE cor.	27.2 ± 2.1 p<0.05	27.3 ± 2.0	27.0 ± 2.2	28.2 ± 1.6
CDT	8.0 ± 2.0 p<0.05	8.1 ± 1.8 p<0.05	7.9 ± 2.1 p<0.05	9.3 ± 1.4
COWAT s	16.1 ± 5.7 p<0.05	16.8 ± 5.4 NS	15.3 ± 6.0 NS	18.6 ± 5.7
COWAT f	12.0 ± 4.7 NS	11.7 ± 4.9 NS	12.3 ± 4.5 NS	11.3 ± 4.3
ADAs-cog	16.4 ± 5.1 NS	16.8 ± 3.7 NS	16.0 ± 6.1 NS	18.1 ± 4.4
BDI	8.1 ± 2.2 p<0.05	7.9 ± 2.3 p<0.05	8.4 ± 2.1 p<0.05	5.9 ± 3.5

Values expressed as mean ± SD.

* group I vs. control group $p<0.05$ (unpaired t-test corrected according to Scheffé's test)

** group I, IA, and IB vs. control group <0.05 (unpaired t-test corrected according to Scheffé's test)

*** NS, non-significant

Table 3: Mean values of neuropsychological tests and the BDI.

A statistically significant correlation was identified between the patient's age and the mean results in MMSA, CTD, verbal fluency, and ADAS-cog tests in groups I, IA, and IB. No correlation was identified between the patient's age and the BDI test results.

The stage on the H-Y scale was significantly higher in group IB than in IA and it was correlated with the mean results of neuropsychological tests in all groups. For the BDI, a significant correlation was only identified in group I (Table 4).

Neuroimage results

The atrophy of hippocampus was assessed by the Scheltens scale (changes ≥ 1). In the majority of cases, the right side of the hippocampus was affected (46 patients). In the IA sub-group, the atrophy of the hippocampus was observed in 22 patients (69%) with the right side affected in slightly more cases. In the IB sub-group, the atrophy was observed in 25 patients (78%) with both sides affected in a similar number of patients. In most of the patients, cortical atrophy affected the temporal and frontal lobe areas. The atrophy of the cerebellum was present in 30 patients, whereas the atrophy of the brainstem was found in 12 patients. The atrophy of the occipital lobe was not reported for any of the patients. The subcortical atrophy of the first stage was present in 38 patients and of the second stage in 16 patients. Vascular lesion was observed in 31 patients with PD. Table 5 shown the results.

Age						
Variables	**Group I**		**Group IA**		**Group IB**	
	Pearson's r	**P**	**Pearson's r**	**P**	**Pearson's r**	**P**
MMSE	-0.4186	0.001	-0.4064	0.021	-0.4326	0.013
MMSE cor.	-0.3316	0.007	-0.3323	0.063	-0.343	0.055
CDT	-0.5621	0	-0.5671	0.001	-0.5717	0.001
COWAT f	-0.5266	0	-0.4707	0.007	-0.5851	0
COWAT s	-0.5806	0	-0.5537	0.001	-0.639	0
ADAS-cog	-0.4992	0	-0.436	0.013	-0.5801	0.001
BDI	0.1209	0.341	0.1899	0.298	0.0636	0.73
H-Y scale						
Variables	**Group I**		**Group IA**		**Group IB**	
	Pearson's r	**p**	**Pearson's r**	**p**	**Pearson's r**	**P**
MMSE	-0.4334	0	-0.5101	0.003	-0.4313	0.014
MMSE cor.	-0.389	0.001	-0.4325	0.013	-0.3617	0.042
CDT	-0.4601	0	-0.4996	0.004	-0.4602	0.008
COWAT f	-0.3355	0.007	-0.3784	0.033	-0.398	0.024
COWAT s	-0.5158	0	-0.5023	0.003	-0.5151	0.003
ADAS-cog	-0.3903	0.001	-0.4188	0.017	-0.3876	0.028
BDI	0.3021	0.015	0.289	0.109	0.2677	0.138

Table 4: Correlation between the mean score in neuropsychological tests, the BDI, the patient's age, and the H-Y scale.

Group IA						
Variables	**FA**	**TA**	**PA**	**BA**	**SA**	**VCh**
0	13	8	13	29	14	17
1	16	22	17	3	12	10
2	3	2	2	0	6	3
3	0	0	0	0	0	2
Group IB						
Variables	**FA**	**TA**	**PA**	**BA**	**SA**	**VCh**
0	9	4	7	23	12	16
1	14	23	21	8	10	11
2	7	4	4	1	10	4
3	2	1	0	0	0	1
Abbreviations: FA: Frontal Atrophy; TA: Temporal Atrophy; PA: Parietal Atrophy; BA: Brainstem Atrophy; SA: Subcortical Atrophy; Vch: Vascular Change.						

Table 5: Numbers of patients with all stages of the atrophy of specific lobes and vascular lesion in groups IA and IB.

The statistical analysis of correlations between the radiological image, neuropsychological tests, and the BDI confirmed significant correlation between the atrophy of the hippocampus, temporal and parietal lobes, and vascular lesion and the mean score of neuropsychological tests. The atrophy of the frontal lobe was correlated with the mean score of the BDI (Table 6). The remaining parameters were not correlated.

Variables	MMSE	MMSE cor.	CDT	COWAT F	COWAT s	ADAS cog	BDI
HL	-0.4862 (p=0.000)	-0.3981 (p=0.001)	-0.4461 (p=0.000)	-0.3388 (p=0.006)	-0.4053 (p=0.001)	-0.342 (p=0.006)	NS
HP	-0.4053 (p=0.001)	-0.3323 (p=0.007)	-0.4722 (p=0.000)	-0.3054 (p=0.014)	-0.4549 (p=0.000)	-0.3172 (p=0.011)	NS
FA	-0.294 (p=0.018)	NS	-0.4008 (p=0.001)	NS	NS	-0.2938 (p=0.018)	0.4015 (p=0.001)
TA	-0.3679 (p=0.003)	-0.3121 (p=0.012)	-0.3162 (p=0.011)	-0.387 (p=0.002)	-0.3563 (p=0.004)	-0.2757 (p=0.027)	NS
PA	-0.4154 (p=0.001)	-0.3842 (p=0.002)	-0.3254 (p=0.009)	-0.3496 (p=0.005)	-0.3059 (p=0.014)	-0.3809 (p=0.002)	NS
BA	-0.3074 (p=0.013)	NS	-0.301 (p=0.016)	-0.2951 (p=0.018)	-0.2951 (p=0.018)	-0.2673 (p=0.033)	NS
SA	-0.2939 (p=.018)	NS	-0.4644 (p=0.000)	-0.4528 (p=0.000)	-0.4528 (p=0.000)	-0.3781 (p=0.002)	NS
VCh	-0.3249 (p=0.009)	-0.2549 (p=0.042)	-0.3359 (p=0.007)	-0.3415 (p=0.006)	-0.3415 (p=0.006)	-0.3843 (p=0.002)	NS

Abbreviations: HL: Left Hippocampus; HP: Right Hippocampus; FA: Frontal Atrophy; TA: Temporal Atrophy; PA: Parietal Atrophy; BA: Brainstem Atrophy; SA: Subcortical Atrophy; Vch: Vascular Change.

Table 6: Correlation between the atrophy of specific brain areas, vascular lesion, and the results of neuropsychological tests.

Discussion

The results of neuropsychological tests were analyzed for patients with diagnosed PD and with different lengths of disease duration. None of the patients had diagnosed MCI or PD-D. A comparison of the MMSE test results between the patients and the control group shows a statistically significant difference between the groups ($p<0.05$). The usefulness of the MMSE test has been acknowledged by numerous authors. A study by Aarsland et al. showed that in a 4-year observation period the MMSE test can be used for prognosis and a reduced MMSE score in patients with advanced PD indicates an increased risk of dementia [14]. Biggins et al. stated that the lower the MMSE score, the longer the disease duration and the higher the age of disease appearance increases the risk of PD-D [15]. In an 8-year prospective study, the MMSE score decreased by 1 point per year for patients with PD but without dementia while for PD-D patients the decrease was 2.3 points per year [16]. Also, the quality of life decreased significantly for patients with the MMSE score below 25 points [17,18]. Mamikonyan et al. proved that for 1/3 of patients with the correct MMSE score the application of more sensitive neuropsychological tests revealed cognitive impairment, mostly of attention and memory [19].

The assessment of visuospatial skills using CDT shows lower scores for the PD patients compared to the control group. The difference was statistically significant and more meaningful for patients with memory impairment. The CDT is used to assess visuospatial skills, constructive praxis, planning, and abstractive thinking. A low CDT score confirms mental and visuospatial disorders among PD patients and may be used as a quick assessment of visuospatial skills. Riedel et al. proved that CDT is a useful screening tool for assessment of visuospatial disorders in the PD patients but its usefulness for assessment of depression is much lower [20].

The verbal fluency test showed a statistically significant difference between the patients and the control group. Also, the semantic fluency test showed a statistically significant difference between the PD patients with memory disorders and the control group. The verbal fluency test verifies the speech, memory, and executive functions and is an indicator of correct functioning of the frontal and temporal lobes in the dominant hemisphere. According to Pagonabarraga et al. semantic verbal fluency impairment is a bad prognosis factor, indicating progression of cognitive function impairment in the direction of dementia [21]. Also, Dujardin, Azume et al. observed a correlation between semantic verbal fluency impairment and dementia progression [22-24]. A poor result in the semantic category of the verbal fluency test characterizes the Alzheimer's disease [25]. For the PD patients, significant differences in the verbal fluency test may indicate a co-existing degeneration of the Alzheimer type.

In the working memory test (ADAS-Cog), there were no significant differences between the patients and the control group. Visibly lower scores were recorded for patients with memory impairment. The lower ADAS-Cog scores observed for patients higher on the H-Y scale may be related to advanced degenerative processes.

Depression is quite common for PD patients. It is observed in 35% of the patients [26-28]. In this study, none of the patients was diagnosed with depression despite visibly higher mean scores on the BDI scale. The results of the study indicate a correlation between cognitive impairment, the patient's age, and the H-Y level of movement impairment. No correlation was observed between the mean score in neuropsychological tests and the disease duration. The older patients with more significant movement impairment reached lower scores in MMSE, CDT, verbal fluency tests, and ADAS-cog. Similar correlations between the patient's age, disease duration, and neuropsychological test results were observed by Hobson and Meara in a study involving 86 PD patients [29]. In 2001, Aarsland et al. found a correlation between the levels of cognitive impairment and the H-Y movement impairment [14]. Similar observations were made in the GEPAD study (German Study of Epidemiology of Parkinson's Disease) testing cognitive functions on a group of 873 PD patients and in the study documented by Hughes et al. It was confirmed that the patient's age and the more advanced stage of disease on the H-Y scale translated into lower scores on neuropsychological tests [30,31].

The results of psychological examinations indicate that cognitive impairment exists in the PD patients for whom MCI and dementia were not diagnosed. Similar observations were documented in a study by Sollinger et al. the visuospatial, operational, verbal, and memory impairment appear among non-demented PD patients [32]. Cognitive function impairment not meeting the PD-D criteria may be relevant to 18% to 52% of the patients in the early disease stage [33]. An early appearance of cognitive impairment may be considered an indicator of future dementia prognosis. PD-D and Alzheimer's disease have different neuropsychological profiles of patients. In PD-D, it is subcortical and comes with deficits of attention, cognitive functions, ability to plan, and goal-directed behavior. The memory deficits in PD-D are derivative of deficits of attention and executive functions [34].

An analysis of hippocampal atrophy in PD shows symmetrical atrophy of small intensity. Cortical atrophy was mostly present in the temporal and frontal lobe areas. Neuroimages in PD-D (MR, CT) are not characteristic and can be used to rule out the derivative dementia causes. The coexistence of vascular lesion demonstrated with neuroimages correlated with the mean scores in neuropsychological tests. The radiological image may be normal in the early stages of PD. Then, in the later stages, the width of the locus niger decreases and the atrophy of certain brain areas appears [35-41] In the early stages of dementia, the atrophy may appear in the frontal lobe; then, with the progression of dementia, it extends into the temporal and occipital lobes and the subcortical areas [35].

The hippocampus is particularly important for cognitive function impairment. The hippocampus atrophy is an early indicator of dementia in AD. Camicioli et al. used voxel-based morphometry (VBM) to measure the volume of the hippocampus and confirmed that it atrophies not only in AD patients but also in PD and PD-D patients [42,43]. Similar conclusions were drawn by Apostolova et al., who proved that the hippocampus atrophy and the dilation of the ventricular system appear more often in PD and PD-MCI compared to the control group [44]. Another examination showed that the changes intensify with co-existence of visual hallucinations [45]. Apart from hippocampal atrophy, atrophies of the thalamus, anterior cingulate cortex, and other subcortical structures (like caudate nucleus, corpus amygdaloideum, or putamen) may also appear in PD-D patients [35,41,46]. The findings of this study confirm those of previous medical studies that brain atrophy with the accompanying hippocampus atrophy are frequent pathologies in PD.

Conclusion

Cognitive function impairment appears in Parkinson's patients without diagnosed dementia. The executive functions are especially affected with the level of impairment dependent on the patient' age and the degree of movement impairment. A clear correlation was identified between cognitive function impairment and atrophies of the hippocampus, temporal and parietal lobes, and vascular lesion.

Neuropsychological tests with clinical and radiological evaluations may be a very practical method of screening for cognitive function impairment. Such evaluations may allow to identify patients at risk of dementia for whom pharmacotherapy should be started.

Compliance with Ethical Standards

Conflict of interest

The authors have no conflicts of interest to disclose.

I declare that all the authors of the manuscript "Cognitive Impairment in Parkinson's Disease" have not got any financial agreement with any organization and other financial relationships (stock ownership in medically-related fields, intellectual property rights, consultancies, advisory boards, expert testimony, employment partnerships contracts, honoraria, royalties grant and other) in the past year, related and unrelated to the current research.

Ethical approval

All procedures performed in this study were in accordance with the ethical standards. Approval of the Medical University Wrocław Commission of Medical Ethics was obtained.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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