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Short communication

Cognitive impairment in carriers of glucocerebrosidase gene mutation in Parkinson disease patients

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ABSTRACT

Aim: Parkinson disease (PD) is the common neurodegenerative disease with motor and numerous non-motor symptoms, including cognitive impairment. Mutation of glucocerebrosidase (GBA) gene is the most common genetic risk factor of sporadic PD. The aim of this study was to assess clinical features of PD associated with GBA mutation.

Methods: One hundred and thirty-eight PD patients were involved and examined by the movement disorder specialist using several scales including Unified Parkinson Disease Rating Scale (UPDRS) part II and III, Hoehn and Yahr (H&Y) staging, Mini-Mental State Examination (MMSE) and Hamilton Depression Scale (HDS). The exons 8 and 9 of GBA was sequenced and screened for variants.

Results: The GBA variants were found in 16 (11.6%) PD patients: N370S mutation in 5 (3.6%) and T369M variant in 11 (7.9%). No significant differences between the group of mutation carriers and non-carriers were found in relation to clinical features except for dementia (MMSE score < 26) occurring more often in N370S mutation carriers (60.0% vs 19.6%, $p = 0.03$).

Conclusion: The N370S GBA mutation is the risk factor for cognitive impairment in PD patients.

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1. Introduction

Parkinson disease (PD) is a common neurodegenerative disease affecting 1% of population aged over 65 years. PD patients differ markedly on the onset of disease, and on severity of motor (bradykinesia, tremor, rigidity, postural instability) and non-motor (cognitive impairment, autonomic dysfunction, REM sleep behavior disorder, etc.) symptoms. Two clinically different subtypes of disease, tremor dominant (TD) and postural instability–gait difficulty (PIGD), are well recognized.

Cognitive impairment is one of the most important non-motor symptoms in PD patients. Cognitive disturbances can start early, but in the majority of cases appear in advanced PD and increase in the course of disease. Up to 20–40% of PD patients are demented. In the study of 100 Polish PD patients dementia was revealed in 19%. [1] Many authors believe PD with dementia is a separate clinical entity named PD dementia (PDD). The motor symptoms are usually more severe and the survival is shorter in PDD compared to non-demented PD patients.

Glucocerebrosidase (GBA) gene mutation is the most common genetic risk factor for sporadic PD [2]. The prevalence of the *GBA* mutation in PD patients, similarly to general population, differs in relation to ethnicity. The highest prevalence of *GBA* mutation was found in Jewish; 19% in PD patients and 3% in general population. The study of French population showed *GBA* mutation in 4% of PD patients and 1% in general population. The PD phenotype of *GBA* mutation carriers differs from non-carriers [2,4–7], most notably for the more common and more severe cognitive impairment [4–6], while the data concerning other putative features (earlier onset, symptoms severity, prevalence of rigidity, postural instability or orthostatic hypotension) are controversial.

The aim of this study was to assess the clinical characteristics of *GBA* mutation carriers in Polish PD patients.

2. Materials and methods

All PD patients hospitalized in the Department of Neurology, University Hospital, in Krakow between 2007 and 2011 year were invited to participate in this study. The diagnosis of PD was made by movement disorder specialist (MR) according to the UK Parkinson's Disease Brain Bank Clinical Diagnostic Criteria [8]. Patients with history of other neurologic, psychiatric or severe systemic disorders, as well as heavy metals intoxication or exposure to the toxic substances, were excluded from the study. Each subject signed the consent form. The study was approved by the Local Ethics Committee (KBET/54/B/2007).

The severity of parkinsonism was assessed using the Unified Parkinson Disease Rating Scale (UPDRS), including Hoehn and Yahr (H&Y) staging. TD and PIGD subtypes of PD were differentiated according to the method proposed by Jankovic et al. [9] using coefficients calculated from the scores of parts II and III of UPDRS. Cognitive functions were assessed using Mini Mental State Examination (MMSE). Patients scored < 26 were recognized as cognitively impaired. Hamilton Depression Scale (HDS) to assess the severity of depressive symptoms and tilt test to detect orthostatic hypotension was performed in all patients.

Blood sample (5 ml) for genetic testing was collected. *GBA* exons 8 and 9 were tested with direct sequencing, using methods that prevent amplification of the *GBA* pseudogene [7]. The sequencing was performed in the Laboratory of Molecular Genetics, Department of Medical Genetics, Polish-American Institute of Pediatrics, Jagiellonian University.

Statistical analyses included Student *t*-test, Mann–Whitney *U*-test for non-parametric statistic and χ^2 test.

3. Results

One hundred and thirty-eight PD patients (mean age: 57.8 years, 70 females) were recruited for the study. The clinical characteristics of PD patients are summarized in the Table 1.

The polymorphisms of *GBA* gene were detected in 16 (11.6%) patients. Genetic variants included N370S mutation in 5 (3.6%) and SNP c.1223C>T (rs75548401, T369M) in 11 patients (7.9%). L444P mutation was not found in any patient. Patients with N370S mutation did not differ from others in relation to sex (male/female: 2/3 vs. 60/61, respectively) or mean age (70.3 vs. 72.0 years, respectively).

N370S carriers did not differ from others in the mean age of disease onset and in the majority of clinical findings including mean MMSE score, except the number of patients with cognitive impairment (Table 2). The number of patients with MMSE score < 26 was statistically higher in the carriers of the N370S mutation (3/5 vs. 23/117, $p = 0.03$). No difference in the number of cognitively impaired PD patients was found in subjects with T368M variant and non-carriers (36.4% vs. 19.7%, $p = 0.19$). The number of patients with the depressive disorder (>7 HDS score) was not higher in the group of mutation carriers. Depression and cognitive impairment were independent from each other in the carriers ($p = 0.71$) and non-carriers ($p = 0.099$).

4. Discussion

The study reveals relatively high frequency of N370S mutation in *GBA* gene in our cohort of PD patients (3.6%). Additionally,

Table 1 – Clinical characteristics of studied Parkinson disease patients.

Clinical findings	Mean ± SD	Range
Disease onset (year)	57.8 ± 10.8	30–89
UPDRS, part II (score)	10.7 ± 6.6	1–36
UPDRS, part III (score)	24.2 ± 12.4	3–66
UPDRS, part IV (score)	2.6 ± 2.7	0–11
H&Y (score)	2.2 ± 0.8	1–5
Levodopa daily dose (mg)	597.9 ± 416.6	0–1600
MMSE (score)	28 ± 4[a]	26–30
HDS (score)	8.2 ± 5.8	0–30

SD – standard deviation; UPDRS – Unified Parkinson Disease Rating Scale; H&Y – Hoehn and Yahr; MMSE – Mini Mental State Examination; HDS – Hamilton Depression Scale.
[a] Median ± inter-quartile range.