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BDNF G196A (Val66Met) polymorphism associated with cognitive impairment in Parkinson's disease

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HIGHLIGHTS

- A total of 244 Parkinson disease patients (69 with dementia, 166 without dementia) and 242 controls were evaluated.
- *BDNF* Val66Met (rs6265, G196A) polymorphism was not associated with cognitive status in PD patients, as well as PD risk and onset.
- Age and disease stage were found to be independent risk factors predisposing to PD dementia.

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) is a neurotrophin widely expressed in the mammalian brain, regulating neuronal survival and known to influence dopaminergic neurons and cognitive processes. The present study investigated the *BDNF* Val66Met polymorphism associations with PD risk, and cognitive impairment in PD. A total of 486 study subjects (244 PD and 242 age and sex matched controls) were included in the study. UPDRS score, Hoehn–Yahr staging and the Schwab–England scale were used to assess motor abilities and activity during daily life. The patients were classified into groups with dementia (PDD, $n = 69$) and without it (nPDD, $n = 166$) on the basis of neuropsychological assessment. The most common functional polymorphism in *BDNF* Val66Met (rs6265, G196A) gene was determined using TaqMan real-time PCR assay. Frequencies of evaluated *BDNF* alleles and genotypes were similar in PD and the controls. The mean age of disease onset among *BDNF* Met/Met carriers was later (65.00 ± 6.13) in comparison to Val/Val (57.45 ± 10.68) and Val/Met (56.33 ± 10.91) subjects ($p = 0.077$). The studied *BDNF* polymorphism was not associated with cognitive status in PD patients. However, patients with Met/Met alleles demonstrated better delayed recall of information than patients with Val/Val alleles. The results of multivariate logistic regression analysis revealed age ($p = 0.0003$) and the disease stage ($p = 0.002$) as independent risk factors predisposing to PD dementia.

1. Introduction

Cognitive impairment is one the most common neuropsychiatric manifestations of Parkinson's disease (PD), especially in the late stage. Several epidemiological studies have revealed 30% prevalence of dementia in PD (PDD). Interestingly, cognitive impairment may affect newly diagnosed PD patients, 20–60% of nondemented PD (nPDD) patients develop dementia in the first 2–5 years of the disease, whereas the cumulative prevalence of dementia is at least 75% in patients surviving more than 10 years.

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The risk factors contributing to cognitive impairment in PD are not well established. Pathophysiology of PD-related cognitive impairment and dementia is complex and may be different in the early and late stage of the disease. The role of dopaminergic deficiency as the main factor of cognitive dysfunction remains controversial [1,17,33]. Frontostriatal cognitive profile is supposed to be more closely linked to dopaminergic deficits, while posterior cognitive profile predisposes to earlier dementia and is related with PD characterized by postural instability and gait impairment (PIGD). Studies with PD-related dementia suggest the critical role of Lewy body pathology. However some authors pointed out on concurrent Alzheimer's-type pathology in PDD as a more significant factor [12]. Recently, some studies evaluated the role of vascular pathology in cognitive abnormalities accompanying early PD. Kim et al. showed that cognitive dysfunction is related to neurocirculatory abnormalities, especially orthostatic hypotension and supine hypertension in early PD [21]. Currently, only general features such as severity of PD, in particular gait and postural disturbances, mild cognitive impairment (MCI), and age have been found to be associated with a shorter time to dementia [5]. Published studies have suggested a genetic contribution to PDD predisposition, evidenced in a family history of the disease [20].

Despite conclusive evidence for the importance of genetic factors in pathogenesis of PD, the reports on associations between gene mutations or polymorphisms and PDD are conflicting. Recently, scientists who studied the mechanisms of neurodegenerations, have indicated that brain-derived neurotrophic factor (BDNF) deficit may contribute significantly to PD pathogenesis and dementia development in the course of the disease. BDNF belongs to the neurotrophin family of growth factors, and is involved in survival, differentiation, and maintenance of neurons in nervous system, especially in hippocampus, cortex and forebrain, which are implicated in a wide range of cognitive functions. The results of experimental studies indicate that BDNF is essential for maintaining the corticostriatal pathway, as well as that cortical BDNF is required for survival and differentiation of striatal neurons, both in physiological and pathological conditions [2,24,35].

The expression of BDNF is genetically inherited. Reductions of BDNF have been observed in patients with Alzheimer's disease (AD), and this model may be useful for understanding the role of BDNF in AD [4]. *BDNF* gene polymorphisms are associated with an increased risk for late onset PD, however studies showed inconsistent results [19,24]. The most explored polymorphism in *BDNF* gene is a G to A change resulting in a valine to methionine substitution at codon 66 (Val66Met) in the terminal exon of the gene (rs6265). Functional consequences of the *BDNF* polymorphism involve decreased protein secretion in carriers of Met allelic variants. Based on the aforementioned findings the present study was aimed at evaluation of the most common functional *BDNF* gene polymorphism associations with PD and cognitive impairment in its course.

2. Materials and methods

2.1. Subjects

Consecutive 244 PD patients of Caucasian origin (120 males and 124 females), aged from 35 to 87 years (64.23 ± 9.42 years) diagnosed, and confirmed during follow-up visits, according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [16] were recruited in Outpatient Movement Disorder Clinics at two Polish centers (Gdansk, Szczecin) from January 2008 to December 2010. Clinical stage of the disease was rated according to Hoehn and Yahr and the severity of motor symptoms was assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) (parts II–IV) [14]. All patients with clinical symptoms suggesting secondary causes of parkinsonian syndrome (vascular, drug-induced), with features suggestive of atypical parkinsonian syndromes (multiple system atrophy, progressive supranuclear palsy and corticobasal syndrome) were excluded from final data analysis.

Control samples were obtained from 242 randomly selected healthy individuals (113 males and 129 females), aged 25–88 years (64.95 ± 9.41 years) from the same geographical region as the patients, matched by sex, age and ethnicity (all of Caucasian origin) to avoid the influence of population stratification.

All demographic and clinical data were collected according to a semi-structured interview and medical documentation (age, gender and for PD patients age at disease onset, levodopa dose, concomitant medications).

All participants were assessed with Mini-Mental State Examination (MMSE) [7] and Beck Depression Inventory (BDI) [3] to screen for dementia and depression. Control subjects were included if they were not depressed and not demented (≥25 in MMSE), did not demonstrate any parkinsonian symptoms on neurological examination, had no history of stroke and did not suffer from any liver and kidney dysfunction. Neuropsychological assessment was performed only in the PD group.

The protocol of the study was approved by the relevant local ethics committees, and study participants provided written informed consent.

2.2. Neuropsychological assessment

All patients who met inclusion criteria underwent detailed neuropsychological examination described previously [32], and were classified as non-demented (nPDD) and demented (PDD) according to Emre et al. criteria [6]. All patients who met inclusion criteria underwent detailed neuropsychological examination, which is general characteristics of nPDD and PDD patients is shown in Table 1.

Table 1
Demographic and clinical characteristics of non-demented (nPD) and demented (PDD) patients (mean ± SD).

Demographic and clinical data	nPD (n = 166)	PDD (n = 69)	p value
Females/males	84/82	34/35	n.s.*
Mean age and range (years)	62.1 ± 8.9 39–80	68.1 ± 9.2 35–79	$p = 10^{-5}$**
Age at disease onset and range (years)	55.9 ± 10.2 28–80	59.6 ± 11.1 29–75	$p = 0.014$**
Disease duration (years)	6.2 ± 4.9	8.4 ± 5.9	$p = 0.003$**
Hoehn–Yahr disease stage	2.06 ± 0.74	2.54 ± 0.94	$p = 0.0002$***
Daily levodopa dosage (mg)	698 ± 496	835 ± 471	$p = 0.011$***
MMSE score	28.1 ± 1.80	23.7 ± 4.3	$p = 10^{-14}$***
Education (years)	12.80 ± 3.4	11.8 ± 3.7	$p = 0.044$**

ns – not significant.
* Fisher test.
** Student t-test.
*** p values were calculated according to the Mann–Whitney U test.