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Original research article

The impact of Apolipoprotein E alleles on cognitive performance in patients with Parkinson's disease

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ABSTRACT

Apolipoprotein E (ApoE) is a vital component of several lipoproteins and plays a major role in lipid metabolism. *APOE* gene comprises of three alleles determined by two single nucleotide polymorphisms (rs429358 and rs7412) resulting in the protein isoforms, among which ApoE4 is a confirmed risk factor for Alzheimer's Disease. However, the impact of *APOE* genotypes on Parkinson's Disease Dementia (PDD) is still inconclusive. The PDD diagnostic criteria are very inconsistent, and could be complemented with genetic factors. Our study covers a total of 237 patients diagnosed with Parkinson's Disease (PD) according to UK PD Brain Bank criteria, who were classified as subjects with (PDD, n equals 73) and without (nPDD, n equals 164) dementia, using neuropsychological assessment tests. TaqMan real-time PCR assays were used to determine *APOE* allele. No statistically significant differences in *APOE* alleles frequencies between nPDD and PDD patients have been observed. The study results revealed that the *APOE* polymorphism is not associated with cognitive status in PD patients.

1. Introduction

Dementia occurs in up to 40% of Parkinson's Disease patients, which is estimated to be six times more often than among healthy individuals [1]. The cumulative prevalence is even higher as at least 80% of PD patients who survive more than 12 years from the diagnosis will develop dementia [2].

Apolipoprotein E (ApoE) is a vital component of several lipoproteins and plays a major role in lipid metabolism. The *APOE* gene is mapped to chromosome 19 and comprises of three

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alleles determined by two single nucleotide polymorphisms located in exon 4 at position 3937 (T/C; rs429358) and 4075 (C/T; rs7412). ApoE3 is the most common isoform, while ApoE2 and ApoE4 differ from ApoE3 by single amino acid substitution at position 112 or 158 [3,4]. It has been observed that *APOE4* allele is overrepresented among patients affected with late-onset familial Alzheimer's Disease (AD). Moreover, *APOE4* has a dosage effect on the risk and age at the onset of sporadic AD [5]. Several similarities have been found between AD and PD, namely both are characterized by neuronal loss and pathological aggregation of proteins (β-amyloid and tau in AD and α-synuclein in PD) which presumably have the common fibrillization pathway [6,7]. Furthermore, the clinical symptoms of AD and PD may overlap in some patients [8]. The pathogenesis of dementia in PD is not clear and it may be a mixture of Lewy Bodies as well as Alzheimer's and vascular pathologies [9]. Therefore, *APOE2* and *APOE4* genotypes have been proposed and tested as possible PDD susceptibility factors [10]. Although data from genome wide association studies do not support this hypothesis, the role of *APOE4* in PDD development is still inconclusive [4,11]. The purpose of this study was to determine the impact of *APOE* genotypes on the risk of dementia among PD patients. The present analysis would be the first to be carried out on the Polish population with the use of a wide range of neuropsychological tests and Emre et al. criteria [12] to assess the cognitive impairment in PD patients.

2. Materials and methods

2.1. Subjects

The study population comprised of 237 patients of Caucasian origin (123 males and 114 females), aged from 35 to 89 years (64.23 ± 9.97), diagnosed with PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [13]. Diagnosis was confirmed during follow-up visits (at least two with levodopa response assessment). The subjects were enrolled between January 2008 and December 2010 at two Polish centers (Gdansk, Szczecin). Further investigations, including the assessment of the severity of motor symptoms determined by means of the Unified Parkinson's Disease Rating Scale (UPDRS) (parts II–IV), were also undertaken. The exclusion criteria consisted of clinical symptoms suggesting secondary causes of Parkinson's Disease (drug-induced, vascular) or atypical Parkinsonian syndromes (multiple system atrophy, corticobasal syndrome and progressive supranuclear palsy). Brain MRI was performed to exclude any vascular cause of PD. The study was approved by the relevant local ethics committees and written informed consent obtained from the participants. Based on the neuropsychological assessment described below, the group was divided into two subgroups of non-demented PD (nPDD, $n = 164$) and demented PD (PDD, $n = 73$). Demographic and clinical data were collected according to a semi-structured interview and medical documentation and are presented in Table 1.

2.2. Neurological examination

Neurological examination was performed to confirm the PD diagnosis and exclude other symptoms suggesting atypical or symptomatic cases. It consisted of the Unified Parkinson's Disease Rating Scale (UPDRS; part II–IV), Hoehn–Yahr staging and the Schwab-England activities of daily living scale.

2.3. Neuropsychological assessment

All assessments were conducted by experienced psychologists, who established examination procedures and their standards before the onset of the study. Patients were examined in the 'on state'. The Mini Mental State Examination (MMSE) test with the age and education correction was used as a screening tool. Patients had undergone a detailed neuropsychological examination, including the Wechsler Adult Intelligence Scale-Revised (WAIS-R), the Rey Auditory Verbal Learning Test (RAVLT), the Benton Visual Retention Test (BVRT), the Trail Making Test (TMT), the Rey-Osterrieth Complex Figure Test (ROCF), the Verbal Fluency Test and

Table 1 – Demographic and clinical characteristics of non-demented (nPDD) and demented (PDD) Parkinson's Disease patients.

Demographic and clinical data	Parkinson's Disease patients ($n = 237$)	nPDD ($n = 164$)	PDD ($n = 73$)	p-value
M/F	123/114	86/78	37/36	0.888*
Mean age ± SD and range (years)	64.23 ± 9.97 35–89	61.9 ± 9.6 39–89	69.4 ± 8.9 35–85	0.000004**
Age at disease onset and range (years)	57.42 ± 11.07 28–87	55.8 ± 10.9 28–87	61.1 ± 10.5 29–80	0.0005**
Disease duration and range (years)	6.8 ± 5.3 0.5–25	6.1 ± 4.9 0.5–24	8.2 ± 5.9 0.5–25	0.004**
Daily levodopa dosage (mg)	724 ± 441 ($n = 228$)	697 ± 442 ($n = 157$)	782 ± 435 ($n = 71$)	0.034***
UPDRS (part II–IV)	35.0 ± 18.6 ($n = 215$)	30.2 ± 15.5 ($n = 148$)	45.6 ± 20.5 ($n = 67$)	0.00000001***
MMSE score	26.8 ± 3.5 ($n = 235$)	28.1 ± 1.9 ($n = 163$)	23.6 ± 4.2 ($n = 72$)	0.00000001***

Statistical analyses performed with:
* Fisher's test.
** Student's t-test.
*** Mann–Whitney's test.

the Wisconsin Card Sorting Test (WCST). The Beck Depression Inventory Test (BDI) was performed to assess the severity of depression. In addition, all the patients were examined by means of Parkinson's Disease – Cognitive Rating Scale (PD-CRS). The diagnosis of dementia was established in accordance with the Emre et al.'s [12] criteria. Among 73 PDD patients, there were 51 individuals with probable PDD and 22 patients with possible PDD.

2.4. *Genetic study*

Peripheral venous blood samples were collected from each subject into tubes containing EDTA. It was followed by an extraction of genomic DNA using a Genomic Mini AX Blood SPIN (A&A Biotechnology, Poland). The concentration of every sample of DNA was measured spectrophotometrically by Nanodrop ND-1000 (Thermo Scientific, USA) and diluted to 20 ng/μl. To determine *APOE* polymorphisms (rs429358 and rs7412) real-time PCR using pre-validated allelic discrimination TaqMan assays (rs429358 assay ID: C_3084793_20, rs7412 assay ID: C_904973_10; Life Technologies, USA) was carried out.

2.5. *Statistical analysis*

The distribution of samples was evaluated using the Shapiro–Wilk test. According to data alignment with normal distribution, Student's *t*-test or Mann–Whitney's test was performed to estimate the statistical differences between the groups. Categorical variables' frequencies between the groups (genotypes, alleles, sex etc.) were analyzed by the means of Fisher's test. All *p*-values of less than 0.05 were considered statistically significant.

3. Results

As shown in Table 1, several statistically significant differences have been found between nPDD and PDD patients. The mean age in PDD group was significantly higher (69.4 ± 8.9) than in nPDD group (61.9 ± 9.6, $p = 0.000004$). Moreover, PDD patients were statistically 5 years older at the onset of the disease compared to non-demented patients ($p = 0.0005$). The disease duration was also longer among PDD patients ($p = 0.004$), which supports the observation on the cumulative prevalence of dementia in PD. Along with the progression of the disease, the daily levodopa dosage has increased as well (782 ± 435 mg vs. 697 ± 442 mg). This tendency is commonly seen in everyday clinical practice. Both MMSE and UPDRS (part II–IV) scores did show significant differences among demented- and non-demented patients.

3.1. APOE *gene rs429358 polymorphism*

Among 237 patients, 187 were wild type TT homozygous (78.9%), 48 persons were CT heterozygous (20.3%), while 2 subjects were CC homozygous (0.8%). Among non-demented Parkinson's Disease patients the most frequent genotype was TT (132 patients – 80.5%), 31 were CT heterozygous (18.9%) and one person was CC homozygous (0.6%). Demented patients were mostly TT homozygous (55 patients – 75.3%) as well, whereas 17 persons were heterozygous (23.3%) and one was CC homozygous (1.4%). No statistically significant differences in rs429358 genotype frequencies between patients with and without dementia have been found.

3.2. APOE *gene rs7412 polymorphism*

The frequency of the rs7412 genotypes among Parkinson's Disease patients was as follows: wild type CC homozygous – 212 subjects (89.5%), CT heterozygous – 25 subjects (10.5%). However, no TT homozygous was determined during the analysis. Among the 164 non-demented subjects 145 cases were CC homozygous (88.4%), whilst the rest (11.6%) were CT heterozygous. Among PDD patients 67 persons were CC homozygous (91.8%). CT genotype was confirmed among 6 patients (8.2%). No statistically significant differences in rs7412 genotype frequencies between patients with and without dementia have been found.

3.3. APOE *alleles*

Based on rs429358 and rs7412 polymorphisms *APOE* alleles frequencies were assessed and are presented in Table 2. According to the performed analysis, *APOE*3* was described as the most frequent allele in both nPDD and PDD groups. No significant correlation in the frequencies of *APOE* alleles between Parkinson's Disease patients with or without dementia was found.

4. Discussion

Several genetic risk factors of Parkinson's Disease have been proposed, including a confirmed Alzheimer's Disease risk factor: *APOE4*, as well as *APOE2*. The aim of this study was to investigate whether PDD and nPDD patients differ significantly in terms of *APOE* genotypes.

This study demonstrates no statistically significant correlation between *APOE* genotypes and dementia in Parkinson's Disease. These results are consistent with Ezquerra et al., who did not find any correlation between *APOE4* and PDD ($p = 0.36$)

Table 2 – *APOE* alleles' frequencies among Parkinson's Disease patients.

APOE allele	Parkinson's disease patients ($n = 237$)	nPDD patients ($n = 164$)	PDD patients ($n = 73$)	*p*-value
*APOE*2*	25 (0.0527)	19 (0.0579)	6 (0.0411)	0.653
*APOE*3*	397 (0.8376)	276 (0.8415)	121 (0.8288)	0.785
*APOE*4*	52 (0.1097)	33 (0.1006)	19 (0.1301)	0.426

P-value according to Fisher's test.

Table 3 – Review of the published studies on the impact of *APOE* genotypes on PDD.

Year	Authors	Number of the subjects	Criteria for dementia	Main findings
1996	Helisalmi et al. [17]	nPDD = 15 PDD = 8	not defined	The *APOE4* allele frequency for PDD higher than for nPDD patients [*p*-value unknown].
2000	Harhangi et al. [10]	nPDD = 81 PDD = 26	DSM III	*APOE2* allele strongly increased the risk of dementia in patients with PD ($p < 0.007$).
2004	Jasinska-Myga et al. [18]	nPDD = 51 PDD = 53	MMSE	*APOE* genotype and allele frequencies did not differ between nPDD and PDD groups.
2005	Camicioli et al. [19]	nPDD = 19 PDD = 28	Based on global impression of history and, where available, MMSE consideration. [post-mortem study]	Of 12 subjects with an *APOE4* allele, 9 (75%) became demented compared with 19 of the 35 (54%) subjects without an *APOE4* allele ($p = 0.31$).
2006	Mollenhauer et al. [20]	nPDD = 23 PDD = 73	MMSE < 25	The distribution of the *APOE* genotypes in PDD and nPDD groups was similar to that of controls.
2006	Pankratz [8]	nPDD = 274 PDD = 50	MMSE	A significant increase in the risk for dementia given the presence of an *APOE4* allele (OR = 3.38; $p = 0.002$) The presence of an *APOE2* allele did not have a significant effect on the risk for dementia. [Study with the exclusive focus on familial PD.]
2007	Papapetropoulos et al. [21]	nPDD = 33 PDD = 39	Diagnosis made by a psychiatrist, formal psychometric testing and/or MMSE < 24.	An association between PDD and *APOE4* (OR 1.7; 95% confidence interval: 1.02–2.9; $p = 0.04$).
2007	Jasinska-Myga et al. [16]	nPDD = 100 PDD = 98	ICD-10 and DSM-IV criteria, with MMSE < 24 and cognitively related disability determined by the Physical Self-Maintenance Scale score. Neuropsychological battery of tests to assess verbal and nonverbal memory, orientation, language, attention, abstract reasoning, and visuospatial ability.	Frequency of *APOE* alleles did not differ between the groups with PDD and nPDD ($p = 0.84$)
2008	Ezquera et al. [11]	nPDD = 138 PDD = 86	Emre et al.	No statistical significant difference was detected comparing the *APOE4* genotypes frequency in PDD with nPDD patients ($p = 0.36$). No difference was detected comparing the *APOE* 2 genotype frequencies PDD with nPDD patients ($p = 0.38$).
2009	Williams-Gray et al. [6]	nPDD = 88 PDD = 19	MMSE ≤ 24 and fulfillment of the DSM-IV criteria at follow-up.	Eight of 31 individuals (26%) carrying the *APOE4* allele developed dementia, vs. 11 of 76 (14%) non-carriers; OR 2.06 (0.74–5.74, $p = 0.16$).
2010	Choi et al. [22]	nPDD = 20 PDD = 23	DSM IV	No significant association between the *APOE4* genotype and dementia.
2014	Monsell et al. [23]	nPDD & PDD = 232	Clinical Dementia Rating Sum of Boxes score (CDR-SB)	In subjects seen within 5 years of their PD diagnosis, the odds of dementia were higher in *APOE4* carriers: OR = 5.15 (1.52–17.40, $p = 0.008$). For those seen 5 + years after their diagnosis: OR 3.54 (1.27–9.92, $p = 0.02$).
2017	Huertas et al. [24]	nPDD = 239 PDD = 59	Emre et al.	The development of dementia was influenced by the *APOE4* allele (HR = 1.90; $p = 0.03$). No association was found for the *APOE2* allele.

or *APOE2* and PDD ($p = 0.38$) [11]. Furthermore, Ezquerra et al., reported no influence of *APOE4* genotype on age at the onset of the disease ($p = 0.32$). Although our own study made use of similar diagnostic criteria methodology (to that of the aforementioned study) in order to evaluate dementia in PD, methodological differences need to be indicated. The Ezquerra et al. study differs from our own in so far that RFLP genotyping was performed, which is known to be less sensitive and specific method than real-time PCR.

However, our results are inconsistent with Williams-Gray et al., study [6]. Although no influence of *APOE4* genotype on Parkinson's Disease incidence rate was determined in the abovementioned analysis, a statistically significant correlation between *APOE4* genotype and Parkinson's Disease Dementia was found [OR 1.74 (1.36–2.23), $p = 1 \times 10^{-4}$]. In spite of a large study population (4198 cases and 10066 controls), several factors may impact the validity of the results, in particular the heterogeneity of odds ratios between the analyzed studies. Moreover, PDD cases in each analysis were limited (average 39, min.8–max.98). Additionally, the discrepancy between the meta-analysis and our results may be explained by a different methodology, particularly by the diagnostic criteria for dementia. The research presented in the meta-analysis was performed for 13 years (from 1994 to 2007); consequently,

differences are unavoidable (Emre et al., criteria were published in 2007). Dementia in Williams-Gray's own study was diagnosed according to MMSE score and DSM-IV criteria. MMSE is a screening method and is not recommended as a PDD diagnostic criterion. The lack of adequate power of dementia diagnostics by the means of MMSE has also been noted by Mata et al. [14]. Therefore, a range of psychometric tests has been used in his research, including Trail Making Test (TMT) and Hopkins Verbal Learning Test-Revised (HVLT-R). As a result, the impact of *APOE4* allele on lower performance across multiple cognitive domains has been found. According to the diagnostic criteria published in 2007, MMSE cannot be the only test for dementia in Parkinson's Disease [13].

The *APOE* polymorphisms in the Polish population were analyzed, among others, by Bednarska-Makaruk et al. [15]. Though the research comprised of randomly selected subjects, the frequency of *APOE* alleles was similar to our study. However, the distribution of *APOE* alleles among PDD and nPDD in other studies on the Polish population was significantly different than in the presented research, both in PDD and nPDD groups [16]. We do not know what was the exact genotyping method in Jasińska-Myga et al.'s analysis.

The previous studies on the impact of *APOE* genotypes on PDD have been presented in Table 3. The discrepancy in the published studies may be attributed to several factors: namely sample size limitations, the heterogeneity of the study populations and different diagnostics criteria for PDD. In our study a detailed neuropsychological testing and Emre et al. criteria was used in order to assess cognitive impairment in PD patients. Thus, it has enabled a higher sensitivity in dementia diagnostics.

The impact of *APOE4* genotype on dementia in pure synucleinopathies including Parkinson's Disease was explored by Tsuang et al., who enrolled 640 demented cases to their study [4]. Within the case group 81 patients were diagnosed with PDD according to UK PD SBB and Emre et al., criteria. Real-time PCR using TaqMan assays was carried out to determine *APOE* alleles The control subjects were autopsied and a clinical evaluation was made within 3 years of their death to exclude neuropathological changes. Statistically significant impact of the *APOE4* genotype on PDD was evaluated ($p = 1.94 \times 10^{-5}$). Additionally, the results show an association between *APOE4* allele and Alzheimer Disease, Lewy Body Disease with Alzheimer Disease neuropathologic changes (LBD-AD) and pure DLB (p-DLB) as well. Although, *APOE4* is a well-established risk factor for AD and DLB-AD, the impact of *APOE4* on PDD and p-DLB suggests other than amyloidogenic mechanisms [4]. Nevertheless, *APOE4* allele frequency was lower in PDD group (19.1%) than in other synucleinopathies, for instance in the group with dementia with Lewy bodies (31.9%, $p = 0.01$).

Several studies have established a significant correlation between Alzheimer's Disease and *APOE4* [25–27]. Up to 65% of all pathologically confirmed AD cases carry at least one *APOE4* allele and 12–15% are homozygous for *APOE4* compared to 1–3% of healthy individuals [28]. However, the research on the impact of *APOE2* genotype on AD are inconclusive [29,30]. The similarity between PD and AD pathogenesis, involving *APOE* polymorphisms as well, may not be as clear as it has been assumed. Although the conclusions drawn that the frequent co-occurrence of α-synuclein, amyloid, and tau protein suggest common pathomechanisms for PD and AD, it is elusive to determine whether these lesions emerge from the same background mechanisms [10,31,32]. The outcome possibly represents a collision of two or more processes. Furthermore, the unclear situation is further impeded by the overlapping symptoms of AD and PD/DLB, all of them causing movement disorders and dementia [33]. Similarly, several studies have examined *APOE* in DLB based only on clinical criteria, thus no distinction between LBD-AD and pDLB have been made [4]. Therefore, well-established diagnostics criteria, especially concerning dementia in respective neurodegenerative diseases, are vital.

In summary, we have shown no statistically significant interaction between *APOE* genotypes (based on rs429358 and rs7412 polymorphisms) and the onset of Parkinson's Disease Dementia. The study population was enrolled at more than one clinic center and distinguishes by its sample size. The limitation of our study could be the lack of a pathologic confirmation of the diagnosis. Nevertheless, our study is one of the few that has used a full battery of neuropsychological tests and the first one on the Polish population which has assessed cognitive decline in Parkinson's Disease patients according to PDD criteria proposed by Emre et al. In our view these unified criteria allow for the diagnosis of dementia in Parkinson's Disease patients in more reliable way than before.

Conflict of interest

None declared.

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