

# Apolipoprotein E Gene Polymorphism, Total Plasma Cholesterol Level, and Parkinson Disease Dementia

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**Background:** Apolipoprotein E gene (*APOE*) polymorphism is an important determinant for the development of various cardiovascular and neurodegenerative disorders. There have been conflicting reports of association of *APOE* polymorphism with dementia in Parkinson disease (PD).

**Objective:** To determine the relationship between *APOE* polymorphisms and plasma cholesterol concentration, and PD with dementia (PDD).

**Design:** Four-year (1999-2002) case-control study.

**Setting:** Academic medical center with inpatient and outpatient movement disorders services.

**Patients:** Consecutive white patients of the same ethnic background with PD.

**Interventions:** Strict clinical, neuropsychological, and neuroimaging criteria were used to exclude dementia with Lewy bodies, Alzheimer disease, and vascular dementia. Findings were compared in 2 clinical groups, including 98 patients (47 men and 51 women; mean age, 71 years) with PDD and 100 patients (52 men and 48 women; mean age, 62 years) with PD without dementia.

**Main Outcome Measures:** Analysis of *APOE* genotypes and allelic frequency (polymerase chain reaction) and plasma cholesterol concentration (enzymatic assay) were evaluated by a clinician blinded to the clinical diagnosis, and findings were compared between the groups with PDD or PD without dementia. Multiple stepwise regression analysis and the Spearman rank correlation coefficient were used to evaluate relationships between dementia and both *APOE* polymorphism and cholesterol concentration. Statistical significance was set at  $P < .05$ .

**Results:**  $\epsilon 4$  Allele frequencies were similar in PDD and PD without dementia (16.8% vs 19%, respectively). Cholesterol concentration, *APOE* genotypes, and allelic frequencies did not relate to PDD.

**Conclusions:** In contrast to Alzheimer disease, when PDD is carefully defined, it is clearly not associated with *APOE* polymorphisms or with a distinctive plasma cholesterol profile. Ongoing longitudinal follow-up with emphasis on autopsy recruitment will enable further analyses of biochemical alterations underlying PDD.

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**D**EMENTIA OCCURS IN 30% of patients with Parkinson disease (PD). The prototypic form of PD with dementia (PDD) is often termed “subcortical dementia” or “executive dementia,” with dysfunction in frontal subcortical circuits, especially in dorsolateral prefrontal networks.<sup>1</sup> Dementia also occurs with superimposed pathologic features of Alzheimer disease (AD), with early and progressive memory impairment accompanied by the disorder of other cortical functions that contrast with prominent impairment of executive functions associated with slowing of thought processes of PDD. In addition, patients with PD can develop vascular dementia

from bilateral subcortical or cortical strokes. Neuropsychological testing and neuroimaging can be used to exclude clinical AD or vascular dementia and to identify PDD. Apolipoprotein E (Apo E) is a major protein constituent of lipoproteins in the central nervous system, and is responsible for lipid metabolism and participates in the transport of cholesterol. The human apolipoprotein gene (*APOE*), on chromosome 19q13.2, is polymorphic with 3 common alleles:  $\epsilon 2$ ,  $\epsilon 3$ , and  $\epsilon 4$ .<sup>2</sup> *APOE* polymorphism is an important determinant for the development of various neurodegenerative and cardiovascular disorders. The *APOE*  $\epsilon 4$  allele is a risk factor for sporadic and familial late-onset AD, and a high prevalence of the *APOE*  $\epsilon 4$  allele has

also been found in vascular dementia and dementia with Lewy bodies (DLB).<sup>3-5</sup> The *APOE*- $\epsilon$ 4 allele is associated with higher plasma levels of total cholesterol and low-density lipoprotein cholesterol, which are considered risk factors for the development of atherosclerosis. It is probable that *APOE* gene polymorphisms influence the development of dementia directly through neurodegenerative processes and by promoting atherogenesis. Little is known about the genetic or biochemical risk factors for PDD. Studies investigating the relationship between plasma lipid and lipoprotein concentrations, and cognitive impairment relative to *APOE* gene polymorphisms have produced conflicting findings.<sup>6-10</sup> Similarly, the role of *APOE* in PDD has been investigated in several studies, but results have been inconsistent.<sup>11-17</sup>

To examine the association between *APOE* polymorphisms and PDD as a specific clinical entity, we used clinical, neuropsychological, and neuroimaging criteria to exclude AD, DLB, and vascular dementia. With this method, we defined 2 prototypic patient cohorts: those with PDD and those with PD without dementia. We compared these groups relative to *APOE* genotypes and alleles, especially the frequency of the *APOE*  $\epsilon$ 4 allele. Further, we studied plasma cholesterol concentrations to examine relationships with PDD.

## METHODS

### SUBJECT POOL

Consecutive patients with PD were recruited from both inpatient and outpatient movement disorders services (Department of Neurology, Ageing, Degenerative and Cerebrovascular Diseases, Medical University of Silesia, Katowice, Poland) during the 4 years from April 1999 to December 2002. The study was approved by the local ethics committee. Signed informed consent was obtained for all patients. The clinical diagnosis of idiopathic PD was based on criteria from the UK Parkinson's Disease Society Brain Bank. If cognitive problems preceded or began within the first year of the presence of signs of parkinsonism, cases were excluded as likely being DLB or AD. The 1996 Consensus Guidelines for DLB and National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria were operational during this study. We did not recruit subjects with medical conditions known to be associated with secondary hyperlipidemia and dementia, specifically, significant thyroid, liver, or renal diseases. We did not recruit subjects with dementia treated with drugs that could have caused or exacerbated cognitive impairment, specifically, anticholinergic agents, tricyclic antidepressant drugs, or benzodiazepines.

### INCLUSION AND EXCLUSION CRITERIA AND GROUP ASSIGNMENT

All patients with PD underwent the Mini-Mental State Examination (MMSE) as a general cognitive screen. Cognitively related functional disability was assessed with the Physical Self-Maintenance Scale. Patients were categorized as having dementia according to *ICD-10* (*International Statistical Classification of Diseases, 10th Revision*) and *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria, with MMSE score less than 24 and cognitively related disability determined by the Physical Self-Maintenance Scale score. Patients

underwent computed tomography (CT) and magnetic resonance imaging (MRI) to exclude those with vascular lesions. The remaining patients without vascular lesions underwent more detailed cognitive testing that included a neuropsychological battery of tests to assess verbal and nonverbal memory, orientation, language, attention, abstract reasoning, and visuospatial ability. These tests included the Stroop Interference Test, Rey Auditory Verbal Learning Test, Benton Visual Retention Test, Verbal Fluency Tests (Controlled Oral Word Association, and Category Naming), Reitan Trail Making Test (parts A and B), verbal subtests of the Wechsler Adult Intelligence Scale, and the Clock Drawing Test. The composite scores were summarized by a neuropsychologist (A.G.) and compared with series of our previously established cutoff scores for age and level of educational achievement. Dementia was classified as subcortical if patients had predominant frontal lobe deficits, memory retrieval that improved on cueing, global slowing during cognitive tasks with scores that improved by allowing additional time, absence of aphasia, apraxia, and prominent agnosia. Patients were grouped according to type of dementia (subcortical vs cortical), and those with profiles of cortical dementia and fulfilling *DSM-IV* and NINCDS/ADRDA criteria for AD were excluded, leaving a cohort defined as having PDD. The control group, those with PD without dementia, fulfilled neither *ICD-10* nor *DSM-IV* criteria for dementia, had MMSE scores of 24 or greater, and scored above all cutoff scores. The *APOE* genotype was determined by polymerase chain reaction, and total fasting plasma cholesterol concentration was measured with standardized enzymatic procedures.

### MAIN OUTCOME MEASURES

The primary outcome measures were the distribution of *APOE* polymorphisms and allelic frequencies, and total plasma cholesterol concentrations, as well as by comparison of the PDD and PD without dementia groups for *APOE* genotypes and allelic frequencies, and plasma cholesterol concentration. Differences between groups were compared with the *t* test,  $\chi^2$  analysis, and the Mann-Whitney test. Secondary analyses tested relationships between severity of dementia and both *APOE* gene polymorphisms and cholesterol levels as well as relationships between the total plasma cholesterol level and *APOE* gene polymorphisms, using multiple stepwise regression analysis, the Spearman rank correlation coefficient, 1-way analysis of variance, and the Kruskal-Wallis test with post hoc test. Two multiple stepwise regression analyses were performed, one with the MMSE score as the dependent variable and *APOE* genotypes and alleles (in separate models), cholesterol level, Montgomery Asberg Depression Rating Scale, current age, and duration of PD as independent variables, and the other with cholesterol level as the dependent variable and *APOE* genotypes and alleles (in separate models), sex, current age, and duration of PD as independent variables. Significance was set at  $P < .05$ . Statistica software (version 5.1, StatSoft Inc, Tulsa, Okla) was used for the analyses.

## RESULTS

Three hundred ninety patients with PD were screened, and 350 met diagnostic criteria for PD (**Figure**). Of the 40 excluded subjects, 12 had symptoms suggestive of DLB and 28 had clinical signs of atypical parkinsonism syndrome. All patients with PD were white and of Eastern European descent, and none had a positive family history of parkinsonism. Of 350 patients with PD, 109 met criteria for dementia and 210 had no dementia; the re-

maining 31 patients met some but not all required criteria for dementia and were not further studied. In the 109 patients with dementia, CT was performed in 79, and MRI in 30. Two patients were excluded because of vascular lesions revealed at CT or MRI, and 9 additional patients were excluded because results of neuropsychological testing suggested the presence of AD. The final 98 patients in the PDD group underwent genetic and cholesterol testing. To achieve a similar sample size of patients without dementia, the first 105 consecutive control patients with PD underwent CT ( $n=80$ ) or MRI ( $n=25$ ). Five patients were excluded because of abnormal findings at CT or MRI, leaving 100 patients who underwent genetic and cholesterol testing. Patients with PDD were older and had later onset of PD and more severe motor impairment compared with control patients without dementia, but sex, disease duration, levodopa dosage, and depression ratings were similar in the 2 groups (**Table**).

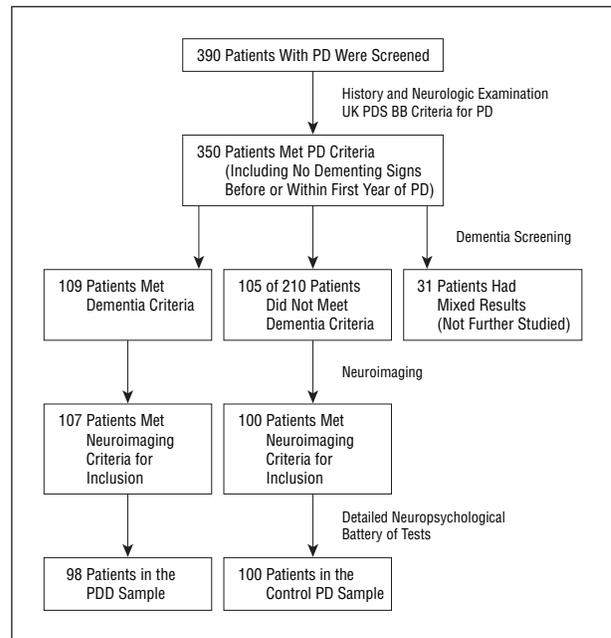
Frequency of *APOE* alleles did not differ between the groups with PDD and PD without dementia ( $P = .84$ ):  $\epsilon 2$ , 8.2% vs 8.5%;  $\epsilon 3$ , 75.0% vs 72.5%; and  $\epsilon 4$ , 16.8% vs 19.0%. Frequency of *APOE* genotypes likewise did not differ between the 2 groups ( $P = .83$ ):  $\epsilon 2/\epsilon 2$ , 1.0% vs 1.0%;  $\epsilon 2/\epsilon 3$ , 11.2% vs 8.0%;  $\epsilon 3/\epsilon 3$ , 57.1% vs 56.0%;  $\epsilon 4/\epsilon 2$ , 3.1% vs 7.0%;  $\epsilon 4/\epsilon 3$ , 24.5% vs 25.0%; and  $\epsilon 4/\epsilon 4$ , 3.1% vs 3.0%. Genotypes including *APOE*  $\epsilon 4$  alleles were represented in 31% of patients with PDD and 35% of patients without dementia ( $P = .51$ ). Most patients in both groups carried the *APOE*  $\epsilon 3$  allele; the *APOE*  $\epsilon 2$  allele was rarely represented.

There was no relation between *APOE* polymorphisms and MMSE score, and although MMSE scores were negatively associated with the *APOE*  $\epsilon 4$  allele ( $\beta = -.01$ ;  $P = .84$ ) and positively associated with the *APOE*  $\epsilon 2$  allele ( $\beta = .01$ ;  $P = .83$ ), neither was statistically significant.

Patients in the PD without dementia group were significantly younger than those in the PDD group; however, the relation between MMSE and age in the PD without dementia group had no statistical significance (Spearman rank correlation coefficient,  $P = .37$ ). At regression analysis, with MMSE as the dependent variable and age as the independent variable, the regression coefficient had negative value ( $-0.02$ ), with no statistical significance ( $P = .26$ ).

No significant differences were found in total plasma cholesterol levels between the PDD group and the PD without dementia group, both in general and with reference to *APOE* genotypes ( $P = .52$ ). Further, although MMSE scores and cholesterol levels were positively associated, the relationship was not significant ( $\beta = .02$ ;  $P = .70$ ).

*APOE* polymorphisms correlated with total plasma cholesterol levels (1-way analysis of variance and Kruskal-Wallis test). Cholesterol levels in patients with PD with  $\epsilon 4/\epsilon 4$  or  $\epsilon 4/\epsilon 3$  genotypes were higher than in patients with PD with the  $\epsilon 3/\epsilon 3$  genotype ( $P < .001$ ). In contrast, cholesterol levels in patients with the  $\epsilon 3/\epsilon 2$  genotype were significantly lower than in patients with the  $\epsilon 3/\epsilon 3$  genotype ( $P < .001$ ). Cholesterol levels in the  $\epsilon 4$  allele carriers were higher than in the  $\epsilon 3$  allele carriers ( $P < .001$ ). In contrast, cholesterol levels in the  $\epsilon 2$  allele carriers were significantly lower than in the  $\epsilon 3$  allele carriers ( $F = 15.80$ ;  $P < .001$ ). Total plasma cholesterol levels were related to



**Figure.** Flow chart showing patient recruitment. PD indicates Parkinson disease; PDD, Parkinson disease with dementia; and UK PDS BB, United Kingdom Parkinson's Disease Society Brain Bank.

both *APOE* genotypes ( $r=0.53$ ;  $P < .001$ ) and *APOE* alleles ( $r=0.48$ ;  $P < .001$ ).

## COMMENT

In addressing the controversial area of PDD and linkage to *APOE* gene polymorphisms, we focused our clinical selection criteria specifically to include patients with the prescribed subcortical or executive dementia typical of PD-related cognitive deficits. We used neuropsychological tests and neuroimaging measurements to exclude subjects with cortically based signs or neuroimaging evidence of diffuse cortical atrophy or vascular disease. With this stringency, we excluded 11 patients with dementia from our study cohort so that we could focus specifically on identifying genetic associations with prototypic PDD. Whether PDD and DLB are distinct conditions or types of the same entity is not known, but to maximize the purity of our clinical sample, we additionally excluded patients in whom symptoms of dementia preceded or began within the first year of signs of parkinsonism. We considered this exclusion especially important because there are reports of a high representation of the *APOE*  $\epsilon 4$  allele in patients with DLB. The distribution of *APOE* alleles and genotypes was similar to findings in another study of the Polish population and to population-based studies of white people.<sup>18,19</sup> Our observations of no association between *APOE* polymorphisms or allelic frequencies and PDD are supported by other studies, including one meta-analysis<sup>11,12</sup> and one recent study in autopsy-confirmed PD.<sup>13</sup> Like our findings, these studies found no differences between patients with PD with or without dementia insofar as *APOE* alleles and *APOE* genotypes. In addition, we found no association between genetic polymorphisms and MMSE score, a finding simi-

**Table. Demographic, Clinical, Psychological, and Genetic Characteristics of Patients With PD With and Without Dementia\***

Characteristic	Patients With PD With Dementia (n = 98)	Patients With PD Without Dementia (n = 100)	P Value
Sex, F/M	51/47	48/52	.57†
Age, y (range)	71.4 ± 5.2 (58-85)	61.7 ± 7.7 (40-81)	.001‡
Age at onset of PD, y (range)	63.6 ± 7.6 (47-83)	54.6 ± 8.1 (32-77)	.001§; <i>df</i> =20; <i>t</i> =8.1
Duration of PD, y	8.1 ± 4.9	7.1 ± 3.5	.26‡
MMSE score	20.1 ± 3.0	28.6 ± 1.4	.001‡
PSMS score	18.6 ± 4.0	8.2 ± 1.8	.001§; <i>df</i> =20; <i>t</i> =10.6
Hoehn-Yahr stage	2.8 ± 0.5	2.4 ± 0.5	.001‡
UPDRS score, parts I-IV	61.6 ± 16.2	40.8 ± 14.5	.001§; <i>df</i> =20; <i>t</i> =9.6
UPDRS score, part III	37.6 ± 9.0	27.3 ± 8.7	.001‡
Levodopa dosage, mg/d	599.2 ± 247.0	565.00 ± 275.9	.27‡
GDS score	13.0 ± 5.4	12.8 ± 6.9	.23‡
MADRS score	16.3 ± 8.0	15.8 ± 10.7	.13‡
Total cholesterol level, mg/dL	200.9 ± 32.9	204.0 ± 34.1	.52§; <i>df</i> =20
Frequency of <i>APOE</i> genotypes, %¶			
ε4/ε4	3.1	3.0	
ε4/ε3	24.5	25.0	
ε4/ε2	3.1	7.0	
ε3/ε3	57.1	56.0	
ε2/ε3	11.2	8.0	
ε2/ε2	1.0	1.0	
No. of <i>APOE</i> alleles  ¶			
ε4	33	38	
ε3	147	145	
ε2	16	17	

Abbreviations: GDS, Geriatric Dementia Scale; MADRS, Montgomery Asberg Depression Rating Scale; MMSE, Mini-Mental State Examination; NS, not significant; PD, Parkinson disease; PSMS, Physical Self-Maintenance Scale; UPDRS, Unified Parkinson Disease Rating Scale.

SI conversion factor: To convert total cholesterol to millimoles per liter, multiply by 0.0259.

\*Data are given as mean ± SD unless otherwise indicated.

†Pearson  $\chi^2$  test.

‡Mann-Whitney test.

§*t* Test.

||We tested for overall differences in genotypes (*P* = .83) and alleles (*P* = .84) using the  $\chi^2$  test with highest credibility.

¶ $\chi^2$  Test with highest credibility.

lar to that in another study that observed no relationship between *APOE* genotypes and Dementia Rating Scale scores.<sup>11</sup> Other authors have reported a significantly higher frequency of the *APOE* ε4 allele in patients with PDD, showing a similar allelic distribution as in patients with AD.<sup>14-16</sup> These studies, however, did not specifically exclude patients with PD with neuropsychological signs suggestive of cortically based dementia or those with evidence of vascular dementia. Likewise, findings of a recent meta-analysis suggest that the *APOE* ε4 allele could be associated with PDD, but that may be confounded by marked heterogeneity of source data.<sup>17</sup> Our careful selection criteria were designed to eliminate such diagnostic confounds.

Our findings of a significant association between *APOE* polymorphisms and total plasma cholesterol level in patients with PD are similar to reports for the general population<sup>10,20,21</sup> and contrast with findings reported for the patients with AD.<sup>10</sup> Further, there was no distinction in cholesterol levels between patients with PDD and those with PD without dementia. These analyses amplify the distinctions in genetic profiles, plasma cholesterol level, and neurocognitive patterns between patients with PDD and those with AD, suggesting that cholesterol is not pathophysiologically linked to PDD.

Although we attempted to define our patients with PDD with strict criteria, we acknowledge that we do not have pathologic confirmation to exclude AD, DLB, or vascular lesions. Long-term follow-up in these patients and efforts to recruit autopsy consent are ongoing. Because no single consensus statement has been developed for defining PDD, our enrollment criteria may need to be altered for future studies. We recognize that the MMSE is a relatively crude measure and classifier of the presence or absence of dementia in PD. Other limitations include technical issues and the timing of our evaluations. Previous studies have documented that plasma cholesterol levels decrease before the onset of AD, and our assays were obtained after PDD was diagnosed. We acknowledge that an association between premorbid cholesterol levels and the eventual diagnosis of PDD could not be detected using our study design. A prospective study of patients with PD followed up longitudinally with repeated lipid studies would better clarify potential relationships between PDD and cholesterol levels or related plasma constituents.

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