SHORT REPORT

Apolipoprotein E genotype in familial Parkinson's disease

The French Parkinson's Disease Genetics Study Group (see appendix)

Abstract

APOE genotypes were compared in 57 cases of familial Parkinson's disease, 46 cases of sporadic Parkinson's disease, and 387 controls. The frequency of the APOE allele ε4 was similar in patients with Parkinson's disease and controls, but the APOE allele ε2, thought to be protective for dementia, was significantly more frequent in patients with sporadic Parkinson's disease than in controls. This is the first study of Parkinson's disease to include familial cases. It confirms the absence of association between the APOE allele ε4 and this disease.

(*J Neurol Neurosurg Psychiatry* 1997;**63**:394–395)

Keywords: apolipoprotein E gene; Parkinson's disease;

The ε4 allele of apolipoprotein E gene (APOE) is associated with early and late onset Alzheimer's disease.[1] Because patients with Parkinson's disease occasionally become demented and the neuropathological hallmarks of Alzheimer's disease—neurofibrillary tangles and senile plaques—are found at postmortem in the brains of patients with Parkinson's disease, several studies of the APOE genotype in Parkinson's disease, with or without dementia, have been undertaken.[2–7] Except in a small series of demented patients,[4] no association was found between APOE allele ε4 and Parkinson's disease. There have been, however, no studies of patients with familial Parkinson's disease, the pathogenesis of which may differ from that of the "sporadic" form of the disease. We have, therefore, compared APOE genotype distributions in 57 index cases with familial Parkinson's disease with those from 46 patients with isolated Parkinson's disease and 387 age and sex matched subjects randomly selected from a control sample of non-demented subjects.

Patients and methods

All patients and controls were of French origin. The criteria for a definite diagnosis of Parkinson's disease were the presence of a pronounced response to levodopa and at least two of the following: bradykinesia, rigidity, rest tremor, or asymmetric onset. Exclusion criteria were the presence of at least one of the following: ophthalmoplegia, pyramidal or cerebellar syndrome, apraxia, prominent and early postural instability, urinary incontinence, or dementia within the first two years of evolution. Familial cases, defined by the presence of definite Parkinson's disease in at least two examined first degree relatives, were selected through a French clinical network (The French Parkinson's Disease Genetics Study Group). Isolated cases with no family history of Parkinson's disease among first and second degree relatives, verified by structured interviews of the patient and spouse, were recruited successively at the Fédération de Neurologie of the Hôpital de la Salpêtrière in Paris, France. Controls were age and sex matched selected subjects from a non-demented control sample.[8]

APOE genotypes were determined by polymerase chain reaction/restriction on DNA extracted from the blood of consenting patients.[9] APOE allele and genotype frequencies were compared by χ^2 test, with the Yates' correction when appropriate.

Results

Mean age at onset and at examination were similar in isolated and familial Parkinson's disease (table). The most frequent genotype in all groups was ε3/ε3. Only three patients were demented; they belonged to the familial Parkinson's disease group and had the ε3/ε3 APOE genotype. No ε4 homozygotes were found. The allele distribution was significantly different in patients with familial and sporadic Parkinson's disease compared with controls (χ^2=8.16, P=0.017). The comparison was not significant between familial and sporadic Parkinson's disease groups. The ε2 allele was significantly more frequent in sporadic Parkinson's disease than in controls (odds ratio 2.45, 95% confidence interval 1.15–5.21), but did not differ between familial and sporadic patients.

Discussion

Thus in familial Parkinson's disease, as in sporadic cases, there is no association with the APOE ε4 allele. The lack of association between APOE ε4 allele and Parkinson's disease was already reported in previous studies that did not distinguish between sporadic and familial cases.[2 3 6 7] Our data suggest that the APOE ε2 allele may be associated

Correspondence to:
Dr Alexandra Dürr, INSERM U289, Hôpital de la Salpêtrière, 47 Bd de l'Hôpital, 75651 Paris Cedex 13, France.

Received 17 December 1996
Accepted 12 February 1997

Table 1 General characteristics, APOE genotypes, and allele frequencies in patients with Parkinson's disease (PD) and controls

	Familial PD	*Sporadic PD*	*Controls*
Number	57	46	387
Mean(SD) age at onset (y)	57 (13)	56 (10)	
Mean (SD) age at examination (y)	65 (12)	65 (9)	67 (9)
Sex M/F	29/28	27/19	215/172
APOE genotype % (n):			
2/2	2 (1)	0	0.5 (2)
2/3	14 (8)	26 (12)	11 (43)
3/3	70 (40)	57 (26)	62 (239)
4/2	0	0	1.5 (6)
4/3	14 (8)	17 (8)	24 (92)
4/4	0	0	1 (5)
APOE allele frequency %:			
ε2	9	13	7
ε3	84	78	79
ε4	7	9	14

with patients with sporadic Parkinson's disease. The association cannot be explained by the exclusion of patients with early dementia, possibly related to APOE ε4 allele, as demented subjects were also excluded from the controls.

Although no conclusion can be drawn concerning the relation between familial and isolated Parkinson's disease, it is clear that an important risk factor for Alzheimer's disease, the APOE ε4 allele, is less frequent in Parkinson's disease, whether sporadic or familial.

We are grateful to the families for their participation. We thank the Association France Parkinson and the French Health Ministry (PHRC) for financial support. Our special thanks to Merle Ruberg for critical reading of the manuscript.

Appendix: The French Parkinson's Disease Genetics Study Group

A Dürr, S Medjbeur, O Didierjean, M Vidailhet, A-M Bonnet, D Grid, C Penet, A Brice, Y Agid, INSERM U289 and Fédération de Neurologie, Hôpital de la Salpêtrière; M Martinez, INSERM U358; J Feingold, INSERM U155, Paris; P Amouyel, INSERM CJF 95–05, Lille; M Borg, Hôpital Pasteur Nice; E Broussolle, Hôpital Neurologique Lyon; A Destée, CHR Lille; F Durif, Hôpital Fontmaure Chamalière; G Fénelon, Hôpital Tenon Paris; J-R Fève, Hôpital Laënnec Nantes; P Pollak, CHU Grenoble; O Rascol, Hôpital Purpan Toulouse; F Tison, Hôpital Pellegrin-Tripode Bordeaux, C Tranchant, J-M Warter, CHR Strasbourg; M Vérin, Hôpital de Pontchaillou Rennes; F Viallet, CHU Aix en Provence; France.

1 Pericak-Vance M, Haines J. Genetic susceptibility to Alzheimer disease. *Trends Genet* 1995;**11**:504–8.
2 Marder K, Maestre G, Cote L, *et al.* The apolipoprotein ε4 allele in Parkinson's disease with and without dementia. *Neurology* 1994;**44**:1330–1.
3 Benjamin R, Leake A, Edwardson JA, *et al.* Apolipoprotein E genes in Lewy body and Parkinson's disease. *Lancet* 1994;**343**:1565.
4 Arai H, Muramatsu T, Higuchi S, Sasaki H, Trojanowski JQ. Apolipoprotein E gene in Parkinson's disease with or without dementia. *Lancet* 1994;**344**:889.
5 Koller WC, Glatt SL, Hubble JP, *et al.* Apolipoprotein E genotype in Parkinson's disease with and without dementia. *Ann Neurol* 1995;**37**:242–5.
6 Poduslo SE, Riggs D, Rolan T, Schwankhaus J. Apolipoprotein E and B alleles in Parkinson's patients. *Neurosci Lett* 1995;**194**:145–7.
7 Whitehead AS, Bertrandy S, Finnan F, Butler A, Smith GD, Ben-Shlomo Y. Frequency of the apolipoprotein E ε4 allele in a case-control study of early onset Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1996;**61**:347–51.
8 Amouyel P, Cottel D, Berr C, Vidal O, Brousseau T. ε4 Allele of the apoliprotein E gene is a potent risk factor for cognitive impairment. *Neurobiol Aging* 1994,**15**:S43.
9 Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *J Lipid Res* 1990;**31**:545–8.