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Short communication

Apolipoprotein E-4 gene dose in clinically diagnosed Alzheimer's disease: prevalence, plasma cholesterol levels and cerebrovascular change

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Summary. The prevalence of the apolipoprotein E-4 allele (ApoE-4) was significantly higher in a referral population of 40 patients with clinically diagnosed Alzheimer's disease than in a sample of non-demented elderly controls ($P < 0.01$). The highest plasma cholesterol levels were found in demented patients homozygotic for Apo E-4, but no significant increases of glucose, triglycerides and thyroxine or of leuko-araiosis and brain infarcts were verified in this preliminary study.

Key words: Alzheimer's disease – Apolipoprotein E-4 – Cholesterol – Leuko-araiosis cerebral infarct

Introduction

Recent evidence suggests that the allele type 4 of apolipoprotein E (ApoE-4) encoded on the long arm of chromosome 19 represents an important risk marker for the development of Alzheimer's disease (AD) [1, 10]. Of the normal population, 25% are carriers of this allele [11] which is associated with increased plasma cholesterol levels [3] and atherosclerosis [4].

This preliminary report examines the following hypotheses:

1. Patients satisfying NINCDS-ADRDA criteria for 'probable' or 'possible' AD have a higher frequency of the ApoE-4 allele than non-demented elderly controls [2].
2. Patients hetero- or homozygotic for ApoE-4 have higher plasma cholesterol levels and
3. they have more severe cerebrovascular changes (leuko-araiosis, infarcts) than patients without this allele.

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Samples and methods

Patients and non-demented controls were recruited during an ongoing longitudinal study on AD. The mean age of the control sample (19 men, 18 women) was 66.1 years (SD 7.2 years). Twenty-four demented patients satisfied NINCDS-ADRDA criteria for 'probable' and 16 for 'possible' AD [9]. Nineteen patients had a presenile onset of illness. Patients and controls underwent extensive clinical testing including cranial computed tomography (CT) and quantitative EEG [5]. The CT scans were rated blindly for the severity of leuko-araiosis and brain infarcts according to standardised criteria (Hentschel et al., in preparation).

ApoE-4 genotyping was carried out with a technique modified after Hixon et al. [8] and Wenham et al. [13] using 4% Metaphor (FMC) agarose gels to resolve the restriction fragments generated by polymerase chain reaction [2].

Results

Of 40 patients with AD, 17 were heterozygotic and 6 were homozygotic for ApoE-4 compared to only 7 and 1 of 37 non-demented controls ($\chi^2 = 10.8$ [$df = 2$] $P < 0.01$). There were no significant differences regarding the distribution of male versus female, 'probable' versus 'possible' AD, and presenile versus senile onset of illness between the groups of demented patients with different ApoE genotypes (Table 1).

The cholesterol level was increased in patients homozygotic for ApoE-4 (Table 1). The plasma triglyceride, glucose, thyroxine and thyrotropin concentrations were nearly identical in the different groups.

No association was found between the ApoE-4 genotype and the intensity and extension of leuko-araiosis or the number and severity of brain infarcts in our patient group, but relevant vascular changes were observed in only 6 patients.

Table 1. Clinical features and the ApoE-4 genotype

ApoE-4 genotype		Heterozygotic	Homozygotic	
Male:female	7:10	7:10	3:3	$\chi^2 = 0.2$ [2] n.s.
Probable/ possible AD	11/6	9/8	4/2	$\chi^2 = 0.6$ [2] n.s.
Presenile/ senile onset	9/8	6/11	4/2	$\chi^2 = 2.1$ [2] n.s.
Age (mean ± SD; years)	70.6 ± 8.8	73.1 ± 9.7	66.7 ± 6.9	$F = 1.2$ [2,37] n.s.
Plasma cholesterol (mean ± SD; mg/l)	223.3 ± 43.4	222.8 ± 37.5	274.0 ± 41.0	$F = 2.2$ [2,31] $P < 0.10$*

n.s. = not significant, * one-tailed test (hypothesis 2)

Discussion

We confirmed a significantly increased prevalence of the ApoE-4 allele in patients with AD (hypothesis 1) [2] and found mildly increased plasma cholesterol levels in patients homozygotic for ApoE-4 (hypothesis 2). We were not able to obtain any evidence for an association between the ApoE-4 dosis and the severity of vascular brain changes (hypothesis 3).

It is presently unclear whether ApoE-4 has to be considered as a mere risk marker due to a genetic linkage disequilibrium on chromosome 19 or as a biological factor involved in the pathogenesis of plaques, neurofibrillary tangles – and possibly cerebrovascular changes in AD [1, 11, 12]. AD is an illness presenting with a large variety of clinical and neuropathological features, even within the boundaries of the NINCDS-ADRDA criteria [7]. However, these strict clinical exclusion criteria may have led to the elimination of demented patients with 'mixed' pathology and accompanying medical illness from our study [6]. Thus, these narrow criteria represent a limiting factor for our evaluation of hypothesis 3. It may not be of advantage to exclude patients with mixed degenerative and vascular changes from future clinical dementia studies, as both forms of disease may share important pathogenetic mechanisms.

Prospective studies on larger patient samples are needed to investigate the relationship between APO-E, lipid metabolism and cerebrovascular disease in dementia. A risk marker as potent and prevalent in the general population as ApoE-4 will represent an important tool in future research; it will probably influence diagnostic considerations; it may perhaps open new prophylactic and therapeutic strategies, and it will pose serious ethical and political problems.

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References

1. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late-onset families. Science 261:921–923
2. Czech C, Mönning U, Tienari P, Masters C, Beyreuther K, Förstl H (1993) ApoE-4 allele frequency in clinically diagnosed Alzheimer's disease, frontal lobe degeneration and non-demented controls. Lancet 342:1309–1310
3. Dallongeville J, Lussier-Cacan S, Davignon J (1992) Modulation of plasma triglyceride levels by apoE phenotype: a meta-analysis. J Lipid Res 33:447–454
4. Davignon J, Gregg RE, Sing CF (1988) Apolipoprotein E polymorphism and atherosclerosis. Arteriosclerosis 8:1–21
5. Förstl H, Besthorn C, Geiger-Kabisch C, Sattel H, Schreiter-Gasser U (1993) Psychotic features and the course of Alzheimer's disease: relationship to cognitive, electroencephalographic and computerized tomography findings. Acta Psychiatr Scand 87:395–399
6. Förstl H, Hewer W (1993) Medical morbidity in Alzheimer's disease. In: Ageing and Dementia, a Methodological Approach (Ed. Burns A). Edward Arnold, London, pp 275–284.
7. Förstl H, Sattel H, Bahro M (1993) Clinical features of Alzheimer's disease: diagnosis and non-cognitive disturbances. Int Rev Psychiatry 5:327–350
8. Hixon JE, Vernier DT (1990) Restriction of isotyping of human apolipoprotein E by gene amplification and cleavage with Hhal. J Lipid Res 31:545–548
9. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 34:939–944
10. Poirier J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthier S (1993) Apolipoprotein E polymorphism and Alzheimer's disease. Lancet 342:697–699
11. Scott J (1993) Apolipoprotein E and Alzheimer's disease. Lancet 342:696
12. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD (1993) Apolipoprotein E: high avidity binding to β-amyloid and increased frequency of type-4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci USA 90:1977–1981
13. Wenham PR, Price WH, Blundell G (1991) Apolipoprotein E genotyping by one stage PCR. Lancet 337:1158–1159