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Serum Total Cholesterol, Apolipoprotein E ε4 Allele, and Alzheimer's Disease

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Abstract

The ε4 allele of the apolipoprotein E (apoE) is associated with Alzheimer's disease (AD) and also with elevated serum total cholesterol and low-density lipoprotein levels. However, the interrelationships between apoE genotype, plasma cholesterol levels and AD risk have been studied very little. We examined the possible role of serum total cholesterol in the pathogenesis of AD in a population-based sample of 444 men, aged 70–89 years, who were survivors of the Finnish cohorts of the Seven Countries Study. Previous high serum cholesterol level (mean level ≥6.5 mmol/l) was a significant predictor of the prevalence of AD (odds ratio = 3.1; 95% confidence interval = 1.2, 8.5) after controlling for age and the presence of apoE ε4 allele. In men who subsequently developed AD the cholesterol level decreased before the clinical manifestations of AD. We conclude that high serum total cholesterol may be an independent risk factor for AD and some of the effect of the apoE ε4 allele on risk of AD might be mediated through high serum cholesterol.

Introduction

Apolipoprotein E (apoE) is a cholesterol transport protein which also takes part in the repair of injured nerves [1]. ApoE is polymorphic and exists as three major isoforms referred to as apolipoprotein E2, E3 and E4. These are products of three alleles (ε2, ε3 and ε4) at a single gene locus on chromosome 19. The expression of any two of these three codominant alleles results in three homozygous phenotypes (E2/E2, E3/E3, E4/E4) and three heterozygous phenotypes (E2/E3, E2/E4, E3/E4) [1].

The ε4 allele is an important genetic risk factor for both sporadic and familial late-onset (age >60 years) Alzheimer's disease (AD) [2, 3]. The mechanism through which

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the ε4 allele increases the risk of AD is unknown. Accumulation of β-amyloid in association with apoE polymorphism may play a central role. There is evidence that suggests that the amount of β-amyloid in the brains of AD cases and in subjects without AD is related to the ε4 allele [4, 5]. However, the causative role of β-amyloid in the pathogenesis of AD is debatable [6].

The presence of the ε4 allele is also correlated with the risk of coronary heart disease [7]. This may be due to the impact of the apoE polymorphism on cholesterol metabolism. In relation to the ε3 allele, the ε4 allele elevates plasma total and low-density lipoprotein cholesterol levels while the ε2 allele has an opposite effect [7].

The association of apoE ε4 allele with both elevated serum cholesterol and an increased risk of AD raises a question about the relationship between serum cholesterol level and AD risk. To our knowledge, there has been only one study, by Jarvik et al. [8], in which the interrelationships between the apoE genotype, serum cholesterol level and the risk of AD have been examined. This case-control study found that in most apoE genotype groups in both sexes AD cases had lower total cholesterol than controls. However, there was no difference between the AD cases and the controls for the genotype ε3ε4, and the AD cases had higher cholesterol than the controls for the genotype ε2ε3 in women. We investigated the association of serum cholesterol and the apoE genotype with AD risk in a population-based longitudinal study where serum total cholesterol measurement was available for three decades prior to the diagnosis of AD.

Materials and Methods

The subjects for this study are from the Finnish cohorts of the Seven Countries Study of coronary heart disease and other atherosclerotic diseases [9]. In 1959, all 1,711 men aged 40–59 years living in two rural areas in eastern and southwestern Finland were invited to participate in this prospective study. Follow-up examinations were carried out in 1964, 1969, 1974, 1984 and 1989. A total of 524 men, 31% of the original cohort, survived until 1989 and 470 (90%) of these men were examined. The apoE genotype was available for 444 of these men and they were included in this study. These men represent the entire surviving cohort with respect to cholesterol measurement. No significant difference in total cholesterol level was found at any follow-up examination between the 444 participants and the 80 surviving nonparticipants.

Diagnosis of dementia was made using a two-stage procedure. First, the Mini-Mental State Examination [10] (score greater than 27) and the Clinical Rating of Dementia Scale [11] (0, or 0.5 if memory score 0) were used to exclude men without dementia. These criteria yielded 116/444 cases of suspected dementia. Second, to identify the patients with dementia fulfilling the DSM-III-R criteria [12] (problems in memory and other mental functions which interfere with work and social activities) and to determine the type of dementia, data from the Blessed Dementia Scale [13], the physician's clinical examination, clinical history, and patient records from the health center and hospitals were used. In most cases no brain imaging was available. In brief, AD was diagnosed, if there was a gradual onset and progressive cognitive decline without other conditions known to cause irreversible dementia. In vascular dementia, there were focal neurological signs or symptoms indicative of cerebrovascular disease that were judged to be etiologically related to the mental disturbance. Of the 47 patients fulfilling the criteria for dementia, 27 had AD, 13 vascular dementia and 7 dementia due to other conditions (6 cases of Parkinson's disease and 1 case with progressive dementia in a man with previous mild mental retardation). In an earlier study, using criteria similar to these without neuroradiological investigations there was an accuracy of 82% in the diagnosis of AD when compared to neuropathological diagnosis [14]. The duration of AD could not be determined, but the results of the memory test conducted for the subjects in 1984 indicated that most of the men with AD had developed dementia between 1984 and 1989. In the 1984 examination, of the 27 men diagnosed in 1989 as AD subjects, 9 had given more than one wrong answer, and only 4 of them three or more wrong answers, on the 10-item Short Portable Mental Status Questionnaire [15].

Serum total cholesterol was analyzed during 1959–1974 by the method of Abell et al. [16] as modified by

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Table 1. ApoE genotype according to dementia status

ApoE genotype	Subjects with AD		Subjects with other types of dementia		Subjects with no dementia	
	n	%	n	%	n	%
2/3	1	4	1	5	27	7
3/3	14	52	12	60	266	67
2/4	1	4	1	5	9	2
3/4	11	41	6	30	94	24
4/4	0	0	0	0	1	0
Total	27	100	20	100	397	100

Table 2. Association of apoE ε4 allele and serum cholesterol concentration in 1959–1974 with AD in 1989

Characteristic	All subjects		Subjects with AD		Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
	n	%	n	%		
ApoE ε4 allele						
No	321	72	15	56	1	1
Present	123	28	12	44	2.2 (1.0–4.9)[a]	1.7 (0.7–3.9)[c]
Cholesterol						
<6.5 mmol/l	184	41	6	22	1	1
≥6.5 mmol/l	260	59	21	78	2.6 (1.0–6.6)[b]	3.1 (1.2–8.5)[d]

Odds ratios were adjusted for age and cholesterol when the effect of apoE ε4 allele was examined, and for age and apolipoprotein E ε4 allele when the effect of cholesterol was examined.

[a] p = 0.049; [b] p = 0.043; [c] p = 0.236; [d] p = 0.024.

Anderson and Keys [17], and in 1984 and 1989 with an automated analyzer [18]. When we examined the predictive power of cholesterol level on the prevalence of AD we used the average of the first four cholesterol measurements (1959, 1964, 1969 and 1974) since our focus was on time before the onset of the dementing disorder. The average of the measurements is a more reliable measure of the general level of cholesterol in earlier life than any of the single measurements alone [19]. There were 35 subjects whose cholesterol value was missing in one measurement and 2 subjects whose cholesterol value was missing in two measurements between 1959 and 1974. For these subjects the average of the three or two valid measurements, respectively, was used in the analyses.

We determined apoE phenotypes from serum using a modification of the method of Ehnholm et al. [20] and Havekes et al. [21] which is based on isoelectric focusing of delipidated serum followed by immunoblotting using rabbit anti-human apoE antiserum. ApoE genotypes were inferred from the isoform phenotypes. A recent study by Lahoz et al. [22] has demonstrated that apoE phenotyping and genotyping have a high concordance in the apoE allele assignment (91% after first assignment and 97% after reassessing), and that both methods result in similar allele frequencies at the population level.

Statistical analyses were conducted with the SPSS program. The association of apoE genotype and serum cholesterol concentration with AD was examined by logistic regression analysis. The changes in serum total cholesterol levels during the 30 years follow-up and differences by dementia status were analyzed using repeated measures analysis of variance.

ApoE genotype was entered in the logistic regression analyses as a dichotomous variable, i.e. men with

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and without the ε4 allele. There was only 1 man with two ε4 alleles. We also chose to use serum cholesterol as a dichotomous variable because of the small number of subjects with AD. Men were classified into two groups according to the average cholesterol level during 1959–1974 using an a priori value of 6.5 mmol/l as the cutoff point. This value was chosen based on previous studies on coronary heart disease [23]. This cutoff point was defined before any analyses were performed. Age was entered in the analyses as a continuous variable.

Results

Table 1 presents the distribution of apoE genotypes for the 444 men according to dementia status. The allele frequencies were 4.5% for ε2, 81.5% for ε3, and 14.0% for ε4. In the entire data only 1 78-year-old man had the genotype ε4/ε4 and he was not demented.

Of the 123 men with the ε4 allele 12 (10%) and of the 321 men without the ε4 allele 15 (5%) had AD (odds ratio 2.2; 95% confidence interval 1.0–4.9; table 2). The prevalence of AD was 8% (21/260) in men who had previously had average serum cholesterol ≥6.5 mmol/l and 3% (6/184) in men with previous serum cholesterol averaging <6.5 mmol/l (odds ratio 2.6; 1.0–6.6). Adjustment for age and the presence of apoE ε4 allele strengthened slightly the association between serum cholesterol and AD. In contrast, the association between the presence of the ε4 allele and the prevalence of AD became slightly weaker after controlling for age and serum cholesterol and was no longer statistically significant.

The mean serum cholesterol concentration of all men increased from 6.6 mmol/l in 1959 to 7.0 mmol/l in 1969 and thereafter decreased to 5.7 mmol/l in 1989. The mean cholesterol level in men with AD in 1989 was higher in the first four measurements (1959, 1964, 1969, 1974) but declined more rapidly after 1974 ($p < 0.008$) than that in men without dementia (fig. 1). In 1984 and 1989 the AD cases had slightly lower cholesterol concentrations than the non-demented subjects. To clarify the specificity of serum cholesterol level and changes to AD, we also examined the time course of mean serum total cholesterol among the men having vascular dementia in 1989. These men did not have an elevated total cholesterol level for longer periods at any time but the decrease from 1954–1984 to 1989 was also more rapid ($p < 0.001$) than among the nondemented men.

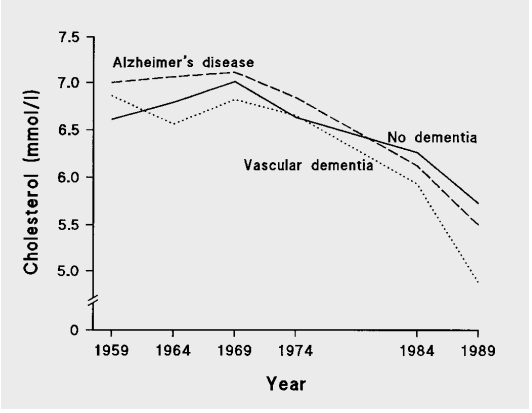

Fig. 1. Age adjusted mean serum total cholesterol concentration during 1959–1989 according to dementia status in 1989.

Discussion

Our results suggest that men who have a history of high serum total cholesterol level during middle age or early old age have an elevated risk of developing AD in older ages. Several other studies are concordant with our observation. For example, in China and Japan, where the cholesterol level is lower than in Western Europe [24], the prevalence of AD is lower [25]. Since high serum total cholesterol is also a risk factor of coronary heart disease, the results of a large population-based prevalence study from

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Rotterdam [26], which showed an increased risk of AD among persons having atherosclerosis, are concordant with our results. In addition, cerebral β-amyloid deposition similar to that found in AD is 3–10 times more common in subjects with coronary artery disease than in controls without heart disease [27]. Also, experimental evidence coincides with these findings. In rabbits with experimentally induced hypercholesterolemia, accumulation of intracellular immunolabeled β-amyloid protein in brain has been demonstrated [28].

The distribution of apoE alleles in our elderly sample was similar to that found in other elderly populations [29]. In accordance with earlier studies, we observed a significant association between the prevalence of AD and the apoE ε4 allele. However, this association weakened after controlling for age and for the serum total cholesterol concentration measured during 15–30 years before the determination of AD status. Thus, it seems possible that elevated cholesterol concentration is an intermediate factor through which the apoE ε4 allele is associated with the risk of AD [30]. This kind of causal link could be the explanation for the unexpected findings concerning the prevalence of AD and the association between apoE genotype and AD in African populations. In Nigeria, where the frequency of apoE ε4 allele is high [31] but there are low cholesterol levels [32], AD seems to be rare [33]. However, African Americans have as high a prevalence of AD as other Americans and Western peoples [25, 33]. The association between apoE genotype and cholesterol concentration may be the result of a Western lifestyle since no association was found in an African Bushmen population with low plasma cholesterol [34]. Similarly, there seems to be no association between the ε4 allele and AD in native Africans [35] although this association was substantial in elderly African Americans [36].

Although the ε4 allele frequency among AD cases in Western populations is higher than in the general population, the majority of AD cases are, as it has often been emphasized [5, 33], not carrying this allele. Little is known about the risk factors among these people. Our findings suggest that a high cholesterol level is a strong predictor in this group.

At present we can only speculate about possible pathophysiological mechanisms. One possibility is that hypercholesterolemia might lead to intima thickening or weakening of endothelial functions [37] in cerebrovascular arterioles and capillaries and these changes might have disastrous effects on brain metabolism. It was also recently reported that β-amyloid interacts with endothelial cells on blood vessels [38]. Another possible mechanism is the effect of cholesterol on amyloid precursor protein (APP) metabolism. Elevated solubilized cholesterol concentration in cell culture medium reduces the level of APP_{sol}, the nonamyloidogenic soluble N-terminal derivative of the alpha-secretase pathway [39]. APP_{sol} has a neurotrophic and neuroprotective effect on neurons in cell culture [40, 41]. The reduction of the level of APP_{sol} may exacerbate the nerve cell death and decrease the regenerative capacity of injured neurons.

Among men who subsequently developed AD, serum cholesterol declined after 1974 more rapidly than among surviving men who did not develop AD. As a result of this, the mean cholesterol level of AD cases, which at the beginning of the follow-up was higher than that of the others, was lower in the last two measurements. The crossover of serum cholesterol levels between the groups took place during 1974–1984, i.e. during the early stages of AD pathogenesis, before the clinical manifestations of dementia in the majority of cases was evident. This is in accord with findings regarding many other chronic diseases in

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which several risk factors such as body mass index, blood pressure and serum cholesterol decrease in the subclinical phase [42]. In AD, Skoog et al. [43] have reported similar trends in blood pressure.

Many prior studies of AD have used a case-control design in which all measurements are clustered around the time of the study. This is probably why the associations between high serum cholesterol and AD have been missed. With respect to the serum total cholesterol level among manifest cases of AD and vascular dementia, our results replicate earlier findings [8, 26, 44].

Our findings, which show an association between serum total cholesterol level and AD, are based on an unselected but small sample, and therefore require confirmation by other longitudinal studies. Our results also raise several questions about the pathogenesis of AD. In particular, attention should be given to cerebrovascular changes in AD, to the cholesterol metabolism in brain, and to the role of cholesterol and apoE in nerve damage and regeneration. If high serum total cholesterol level in the middle age and early old age is an important risk factor for late-onset AD, it offers the possibility for the prevention of the disease.

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