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Association of apolipoprotein E genotypes, blood pressure, blood lipids and ECG abnormalities in a general population aged 85+

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Abstract

Background: Several studies have linked apolipoprotein E (ApoE) ε4 allele with elevated cholesterol and blood pressure levels. Data on the association of APOE genotypes with blood pressure, lipids, atrial fibrillation and ECG abnormalities in individuals aged 85 years and over is sparse.

Methods: This cross sectional study consisted of all residents of the city of Vantaa (N = 601) aged 85 years or over of whom 505 participated in the study. Blood pressure was measured by using mercury sphygmomanometer. 12-Lead ECG, short ambulatory ECG, or both were taken from all study subjects to diagnose atrial fibrillation (AF). Ambulatory ECG was carried out home or in the institute. APOE genotyping was performed using a combination of the polymerase chain reaction (PCR) and solid-phase minisequencing technique. Statistical analysis was made by using Kruskall-Wallis-test (continuous data) and χ^2-test (rates and proportions).

Results: In these very elderly individuals, APOE 4 allele was significantly associated with elevated cholesterol and low-density lipoprotein (LDL) levels. Blood pressure or cardiac arrhythmias did not differ between APOE genotypes.

Conclusions: These observations suggest that the important role of APOE genotype still influences cardiovascular risk profile even among the very elderly people.

Background

Apolipoprotein E (ApoE) has an important role in the regulation of plasma cholesterol concentration. It also mediates the receptor uptake of triglyceride rich lipoproteins and may participate in reverse cholesterol transport [1,2]. ApoE is polymorphic and exists in three protein isoforms designated E2, E3, and E4, [1,2] encoded by three alleles ε2, ε3 and ε4 [3]. Genotypes ε4/ε4 and ε4/ε3 are associated with a high cholesterol concentration [4,5]. Thus ApoE polymorphism may influence the risk of atherosclerosis [4]. An association between the APOE ε4 and ε2 alleles with high blood pressure, and especially, with high

systolic blood pressure has been observed [6,7]. However, lack of association with high blood pressure has also been reported [8-10].

Methods

The Vantaa 85+ Study is a longitudinal population based study examining all residents of Vantaa, a city in Southern Finland, aged 85 years or over (N = 601) on April the first 1991. All persons whether living home or in institutions was asked to participate in the study. Altogether 553 (92%) consented in the study, 36 persons had died, 11 persons refused to participated and one could not be reached. Of these 553 clinically examined subjects, APOE genotyping was available from 531 (88.4%) subjects blood pressure measurement from 521 (86.7%) and both from 505 (84.0%). The Ethics Committee of the Helsinki University Central Hospital approved the study. An informed consent was obtained from all participants or from a close relative if a participant was demented.

A physician performed structured interviews including a history of cardiovascular symptoms and treatment. The data was also collected from a computerised primary health care record database. Physical examination of the subjects included cardiac auscultation and measurement of blood pressure and pulse rate. Blood pressure (systolic Korotkoff phase I and diastolic phase V) was measured with a calibrated mercury sphygmomanometer with the cuff on the right arm, the subject sitting after having rested for five minutes. The blood pressure of bedridden patients was measured in a recumbent position.

The analysis of ECG recordings included evaluation of arrhythmias and conduction abnormalities. Evaluation of the signs of coronary heart disease (CHD) was not performed. ECG recordings were performed with two methods. An ambulatory ECG monitoring technique with three exploring electrodes corresponding to leads V1 and V5 was used in 301 subjects and it was carried out at home or in the institute. The recording period ranged from 30 minutes to two hours with an average monitoring time of one hour. All the recordings were further analysed by the Reynolds TR1-Holter analysing equipment. Accuracy of reading was evaluated by analysing 10 registrations twice, there were no differences between these two analyses. Routine twelve lead resting ECGs were available from 204 subjects. One specialist performed all analyses.

Total serum cholesterol, high density lipoproteins (HDL), low density lipoproteins (LDL) and triglycerides were quantified by enzymatic techniques. APOE genotyping was performed using a combination of the polymerase chain reaction (PCR) and solid-phase minisequencing technique [11].

Statistical analysis was made by using Kruskall-Wallis-test (continuous data) and χ^2-test (rates and proportions), with 7 SPSS for Windows program. No adjustment for multiple comparisons was made.

Results

The mean age of the study population (N = 505) was 88.3 years (range 85–104 years). 107 (21.2%) were males and 398 (78.8%) females. The distribution of APOE allele frequencies were ε4 15.3%, ε3 76.9%, and ε2 7,8%. These frequencies follow Hardy-Weinberg equilibrium, and agree with the previously reported allele frequencies in the elderly Finnish population [12].

The mean systolic and diastolic blood pressures were 149 mmHg (range 90–230 mmHg) and 82 mmHg (range 45–120 mmHg), respectively. There was no association between systolic or diastolic blood pressure level and APOE genotypes (Table 1). As previously shown [13] total serum cholesterol levels differed significantly between different APOE genotypes, with ε3/ε4 and ε4/ε4 being associated with the highest levels (Table 2, P = 0.02). Also high LDL cholesterol level associated with ε3/ε4 and ε4/ε4 (P = 0.001). The levels of triglycerides, or HDL cholesterol showed no association with APOE genotypes.

Table 1: Systolic and diastolic blood pressures, and APOE genotypes in the study population (N = 505). MmHg ± SD.

APOE genotype	N(%) in study population	Mean systolic BP	Mean diastolic BP
ε2/ε2	2 (0.4)	150 ± 14.1	85 ± 7.1
ε2/ε3	62 (12.3)	149 ± 25.5	81 ± 12.0
ε2/ε4	14 (2.8)	141 ± 32.1	76 ± 13.4
ε3/ε3	294 (58.2)	150 ± 28.1	81 ± 13.2
ε3/ε4	126 (24.9)	147 ± 27.3	82 ± 12.3
ε4/ε4	7 (1.4)	132 ± 27.3	82 ± 8.1
P		0.5	0.7
Total	505 (100)		

Table 2: Blood lipids and APOE genotypes in the study population (N = 505). Mmol ± SD.

APOE Genotype	Mean serum cholesterol	Mean serum triglycerides	Mean serum HDL	Mean serum LDL
ε**2**/ε**2**	4.1 ± 1.2	1.7 ± 0.5	1.1 ± 0.4	2.2 ± 0.9
ε**2**/ε**3**	5.1 ± 1.2	1.9 ± 0.8	1.0 ± 0.3	3.2 ± 1.1
ε**2**/ε**4**	4.9 ± 0.9	1.4 ± 0.5	1.2 ± 0.3	3.1± 0.9
ε**3**/ε**3**	5.4 ± 1.3	2.0 ± 1.2	1.0 ± 0.3	3.6 ± 1.1
ε**3**/ε**4**	5.6 ± 1.2	2.0 ± 1.2	1.0 ± 0.3	3.8 ± 1.1
ε**4**/ε**4**	6.0 ± 2.1	1.4 ± 0.8	1.0 ± 0.2	4.3 ± 1.9
P	0.02	0.5	0.1	0.001

APOE genotypes and ECG abnormalities are shown in table 3. The genotype ε3/ε3 seemed to be associated with the highest frequencies of chronic atrial fibrillation (AF) but the difference was of borderline statistical significance only. Extrasystolias or conduction disturbances were not associated with the APOE genotypes. There were also no differences between males and females regarding APOE and AF, blood pressure or lipids.

Discussion

The association of various APOE genotypes with some prevalent diseases such as atherosclerosis and Alzheimer's disease has drawn a lot of attention during the last decade. Previous studies have consistently shown that APOE genotype contributes to cholesterol levels [3,5]. The present study shows that APOE genotype affects serum cholesterol and LDL-levels in the very elderly. However, there was no association between APOE genotype and some other cardiovascular risk factors such as systolic or diastolic blood pressure, and serum triglycerides. Although the occurrence of AF was higher in individuals with allele ε3, there were no statistically significant relationships between APOE genotype and the presence of arrhythmias or conduction abnormalities.

It is well known that the ε4 allele of APOE is associated with the increased prevalence of atherosclerosis and CHD [4,13,14]. However, there are controversial results concerning the association between apoE genotype and some cardiovascular risk factors. Previous studies have suggested that high blood pressure may be associated with the presence of the ε4 allele [6,15,16], others have found an association with ε2 allele and hypertension [7], and no association were found in some studies [8-10]. ApoE may interfere with smooth muscle cell proliferation [17] and thus participate in smooth muscle cell hypertrophy in the arterial wall. These mechanisms may explain the association in young or middle-aged populations that were mainly included in the previous studies. However, other mechanisms such as increased rigidity and decreased elasticity of the aorta and other large vessels [18] may contribute to the development of high blood pressure, and thus explain the lack of association in the very elderly.

Table 3: APOE genotypes, atrial fibrillation and ECG abnormalities in the study population. Total number and percentages of total (N = 505).

APOE Genotype	Atrial fibrillation	No atrial fibrillation	VPB*or SVPB	No VPB or SVPB	Conduction disturbances	No conduction disturbances
ε**2**/ε**2**	1(0.2)	1(0.2)	0(0)	2(0.4)	0(0)	2(0.4)
ε**2**/ε**3**	7(1.4)	53(10.5)	35(6.9)	26(5.1)	9(1.8)	52(10.3)
ε**2**/ε**4**	1(0.2)	13(2.6)	8(1.6)	6(1.2)	4(0.8)	10(2.0)
ε**3**/ε**3**	54(10.7)	240(47.5)	122(24.2)	173(34.3)	25(4.9)	269(53.3)
ε**3**/ε**4**	20(4.0)	107(21.2)	55(10.9)	70(13.9)	10(1.9)	116(23.0)
ε**4**/ε**4**	3(0.6)	5(0.9)	2(0.4)	6(1.1)	0(0)	8(1.6)
Total	86(17.0)	419(81.7)	222(43.7)	283(56.3)	48(9.4)	457(90.6)
P		0.06		0.1		0.1

* Abbreviations: VPB = ventricular premature beats SVPB = supraventricular premature beats Conduction disturbances include first and second degree atrioventricular block, left bundle branch block, right bundle branch block

In the present study, there was no relationship between APOE genotype and blood pressure. Because CHD is a well-known etiological factor for AF [19], we examined the relationship between APOE genotype and ECG changes. There were no statistically significant associations between ECG changes and APOE genotype. Previous population-based studies have suggested that the ε4 allele frequency is smaller in the elderly [20], possibly due to increased mortality of the ε4 allele carriers [21]. The frequency of the ε4 allele in the very elderly in the present study was, however only slightly lower (15.3%) than previously shown frequency in the young Finnish subjects (19.4%) [22]. The signs of CHD were not analysed on the recordings, as resting ECG is not reliable for detection of CHD. Thus the association between APOE genotypes and the extent atherosclerotic process in the arteries cannot be measured on the basis of our material. There are several possible aetiologies for AF in this age group, some of which are not associated with APOE polymorphism. There were no statistically significant association between other ECG changes and APOE genotypes.

These observations show that APOE genotype still influences cholesterol levels but not other cardiovascular risk factors such as blood pressure among the very elderly.

Competing interests

None declared.

Authors' contributions

SR participated in the design of the study, planning and reviewing of statistics and writing and editing the manuscript. KM participated in the study design, planning statistics and editing the manuscript. AV participated in the design of the study, collecting the data and editing the manuscript. LN participated to the co-ordinate and design the study. KJ participated in editing the manuscript. RS participated to co-ordinate the study and design and edit the manuscript. EL participated in planning the study and editing the manuscript.

All authors read and approved the final manuscript.

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References

1. Davignon J, Gregg RE, Sing SF: **Apolipoprotein E polymorphism and atherosclerosis.** *Arteriosclerosis* 1988, **8:**1-21.
2. Mahley RW: **Apolipoprotein E: cholesterol transport protein with expanding role in cell biology.** *Science* 1988, **240:**622-630.
3. Uterman G, Kindermann I, Kaffarnik H *et al.*: **Apolipoprotein E phenotypes and hyperlipidemia.** *Hum Genet* 1984, **65:**232-6.
4. Uterman G: **Apolipoprotein E polymorphism in health and diseased.** *Am Heart J* 1987, **113:**433-440.
5. Assman G, Schmitz G, Menzel H-J *et al.*: **Apolipoprotein E polymorphism and hyperlipidemia.** *Clin Chem* 1984, **30:**641-3.
6. Uusitupa M, Sarkkinen E, Kervinen K *et al.*: **Apolipoprotein E phenotype and blood pressure.** *The Lancet* 1994, **343:**57.
7. Couderc R, Mahieux F, Bailleul S *et al.*: **Prevalence of Apolipoprotein E phenotypes in Ischemic Cerebrovascular Disease.** *Stroke* 1993, **24:**661-664.
8. Lilja MK, Kervinen K, Jounela AJ *et al.*: **Apolipoprotein E Polymorphism in hypertensive patients: gene frequencies, plasma lipids and relation to antihypertensive drugs.** *Circulation* 1989, **80:**II-285.
9. Eto M, Watabane K, Makino I: **Increased frequencies of apolipoprotein ε2 and ε4 alleles in patients with ischemic heart disease.** *Clinical genetics* 1989, **36:**183-188.
10. de Knijff P, Boomsma D, Feskens E *et al.*: **Apolipoprotein E phenotype and blood pressure.** *The Lancet* 1994, **342:**1234.
11. Syvänen A-C, Sajantila A, Lukka M: **Identification of individuals by analysis of biallelic DNA markers using PCR and solid-phase minisequencing.** *Am J Hum Genet* 1993, **52:**46-59.
12. Kuusisto J, Koivisto K, Kervinen K, Mykkänen L, Helkala E-L, Vanhanen M, Hänninen T *et al.*: **Association of apolipoprotein E phenotypes with late onset Alzheimer's disease: population based study.** *BMJ* 1994, **309:**636-8.
13. Lehtinen S, Lehtimäki T, Sisto T, Salenius JP, Nikkilä M, Jokela H, koivula T, Ebeling F, Enholm C: **Apolipoprotein E polymorphism, serum lipids, myocardial infarction and severity of angiographically verified coronary artery disease in men and women.** *Atherosclerosis* 1995, **114:**83-91.
14. Ilveskoski E, Perola M, Lehtimäki T, Laippala P, Savolainen V, Pajarinen J, Penttilä A, Lalu K, Koivula T, Karhunen PH, Mannikko A, Liesto KK: **Age-dependent association of apolipoprotein E genotype with coronary and aortic atherosclerosis in middle-aged men: an autopsy study.** *Circulation* 1999, **100:**608-613.
15. Rantala M, Savolainen MJ, Kervinen K, Kesaniemi YA: **Apolipoprotein E phenotype and diet-induced alteration in blood pressure.** *Am J Clin Nutr* 1997, **65:**543-50.
16. Uusitupa M, Karhunen L, Rissanen A *et al.*: **Apolipoprotein E phenotype modifies metabolic and hemodynamic abnormalities related to central obesity in women.** *Am J Clin Nutr* 1996, **64:**131-6.
17. Mahley RW: **Apolipoprotein E: cholesterol transport protein with expanding role in cell biology.** *Science* 1988, **240:**622-40.
18. Sowers JR: **Hypertension in the elderly.** *Am J Med* 1987, **82(1B):**1-8.
19. Camm AJ, Obel OA: **Epidemiology and mechanism of atrial fibrillation and atrial flutter.** *Am J Cardiol* 1996, **78(8A):**3-11.
20. Louhija J, Miettinen HE, Kontula K *et al.*: **Aging and genetic variation of plasma apolipoproteins. Relative loss of the apolipoprotein ε4 phenotype in centenarias.** *Arterioscler Thromb* 1994, **14(7):**1084-9.
21. Corder E, Lannfelt L, Viitanen M, Corder L, Manton K, Winblad B, Basun H: **Apolipoprotein E Genotype determines Survival in the Oldest Old (85 Years or Older) Who Have Good Cognition.** *Arch Neurol* 1996, **53:**418-422.
22. Lehtimäki T, Moilanen T, Viikari J, Åkerblom HK, Enholm C, Rönnemaa T, Marniemi J, Dahlen G, Nikkari T: **Apolipoprotein E phenotypes in Finnish youths: a cross-sectional and six-year follow-up study.** *J Lipid res* 1990, **31:**487-495.

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