Print ISSN 1738-1495 / On-line ISSN 2384-0757
Dement Neurocogn Disord 2015;14(2):70-75 / http://dx.doi.org/10.12779/dnd.2015.14.2.70

ORIGINAL ARTICLE

A Comparison of Apolipoprotein E Polymorphism in Alzheimer's Disease and Subcortical Vascular Dementia in Koreans

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Background and Purpose The apolipoprotein E (Apo E) ε4 allele is known to be a risk factor for Alzheimer's disease (AD). However, there are debates about the relationship between Apo E ε4 frequency and subcortical vascular dementia (SVaD). We compared the frequency of the Apo E ε4 allele in AD and SVaD in Koreans.

Methods The study was comprised of 400 subjects who visited the Dementia Clinic at Daegu Catholic University from July 2007 to December 2011. Neuropsychological tests, a brain MRI, and blood laboratory tests were performed on all subjects. Two hundred and ninety subjects were AD, 32 subjects were SVaD and 78 subjects were normal. The diagnosis for SVaD was based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and Erkinjuntti criteria, and the diagnosis for AD was based on the DSM-IV and National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's disease and Related Disorders Association criteria. Apo E polymorphism was genotyped in all subjects.

Results The Apo E ε4 allele frequency was 17.4% in AD, 10.9% in SVaD and 8.3% in the normal group (p=0.03). The odds ratio (OR) after age adjustment for AD conferred to the Apo E ε4 was 2.04 (p=0.04). But, the OR for SVaD conferred to the Apo E ε4 allele was 1.34 (p=0.62), indicating that the Apo E ε4 allele does not significantly confer the risk of SVaD.

Conclusions Apo E ε4 is a reliable predictor of AD but has modest efficacy for predicting SVaD in Koreans.

Key Words apolipoprotein E, Alzheimer's disease, subcortical vascular dementia.

Received: February 18, 2015 **Revised:** June 8, 2015 **Accepted:** June 8, 2015

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INTRODUCTION

The apolipoprotein E gene (Apo E) is located on the 19th chromosome and has 3 alleles, which are ε2, ε3, and ε4.[1] Previous studies showed that the Apo E ε4 allele is a risk factor that increases the risk of sporadic Alzheimer's disease (AD) and late-onset AD in addition to decreasing the age of onset. Although disputable, some studies have suggested that Apo E ε4 is related to a high level of low density lipoprotein and may affect nervous system diseases associated with vascular injuries.[2,3] Also, vascular pathology has been repeatedly reported in late-stage AD patients. It is also reported that cerebrovascular and cardiovascular risk factors can enhance the progress of AD. In this way, many recent studies have suggested that vascular factors may be common etiologic factors of both AD and vascular dementia (VaD).[4]

Subcortical vascular dementia (SVaD) is known to be caused by microangiopathy within the deep brain. SVaD can be divided into arteriosclerotic leukoencephalopathy (Binswanger type), which contains the etiologic factor in the white matter, and multiple subcortical lacunar lesion (lacunar type), which is caused by multiple infarction of deep brain gray matter.

Likewise, considering the effect of Apo E ε4 lipid metabolism and the common vascular etiologic factor found in AD

and SVaD, it has been suggested that the expression of Apo E ε4 may affect the development of AD and SVaD. However, the topic is still under dispute, and no large study of Korean subjects has been conducted. Therefore, the author compared the frequency of the Apo E ε4 genotype in a community population in Korea to assess Apo E ε4 as a predictor of AD and SVaD.

METHODS

Subjects

The subjects were recruited from Koreans over 55 years old who had visited the Dementia Clinic at the Department of Neurology, Catholic University Hospital in Daegu from July 2007 to December 2011. The AD group and SVaD group were selected from all subjects who visited the dementia clinic and met the diagnostic criteria. General demographic information (age, sex, etc.) and medical history (year of occurrence, history of high blood pressure/diabetes/cardiovascular disease/hyperlipidemia/smoking/drinking/medication) were collected for all three groups. Blood laboratory tests including complete blood count, kidney function, liver function, cholesterol, thyroid function, vitamin B12, folate and syphilis tests were conducted. The Seoul Neuropsychological Screening Battery and Brain MRI were also administered. The normal group consisted of patients who had no medical history except for hypertension or diabetes mellitus and visited the dementia clinic to receive a medical checkup. This group of patients also scored more than 27 points in the Korean-Mini Mental State Examination (K-MMSE) and showed normal results in brain MRI and blood tests. The AD group was diagnosed according to the criteria specified by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) as well as the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's disease and Related Disorders Association. The SVaD group was diagnosed according to the criteria from both DSM-IV and Erkinjuntti and included both the Binswanger and lacunar types. Multi-infarct dementia, which shows ischemic lesions on the cerebral cortex, strategic infarct dementia, genetic VaD and dementia caused by hemorrhagic lesion were excluded from the study.

Apo E genotype

The genetic diversity of Apo E 358 (rs423958) and Apo E 4112 (rs7412) was analyzed for three alleles. 200 uL of blood was used, and DNA was extracted by using a 200 uL elution solution. Using DNA (10 ng/uL), the Apo E genotype was amplified by polymerase chain reaction (PCR) in 384-well plates. A LightCycler 480 system (LightCycler 480, Roche Diagnostic, Mannheim, Germany) was used for the PCR. The genotype was confirmed using two fluorescent pairs of probes. After PCR, melting-curve analysis was performed by following the LightCycler 480 manual, and different genotypes were classified by analyzing the melting-curve based on different melting temperatures. In order to secure the credibility of the experimental results, the Hardy-Weinberg equilibrium test was performed.

Statistical analysis

Differences in normal traits based on each group were analyzed with a chi-square test. One-way analysis of variance, a parametric approach, and the Kristal-Wallis test, a non-parametric approach, were employed for analysis depending on the regularity. If the differences were statistically significant, a post hoc test was performed using the Scheffe test. In addition, in AD, SVaD, and the normal group, the differences in the Apo E ε4 allele frequencies, carrier frequency and consistency rate based on sex were analyzed using the chi-square test. For the odds ratio (OR) based on Apo E ε4 possession, multivariable logistic regression analysis was conducted by setting the normal group as the reference group after age adjustment. A 95% confidence interval for the risk ratio was suggested as well. The program used for statistical analysis in this research was the IBM SPSS Win ver. 19.0 (Chicago, IL, USA), and the values were considered to be statistically significant when the *p*-value was below 0.05.

RESULTS

The general demographics of the AD group, SVaD group, and normal group

The total number of subjects was 400, with 290 in the AD group, 32 in the SVaD group, and 78 in the normal group. The male ratio was 27.6%, 34.4%, and 32%, respectively, and showed no statistical significance (p=0.58). The mean age (years) was 74.1, 73.8, and 65.1. The subjects in the AD group and SVaD group were older than those in the normal group. The mean K-MMSE score was 18.9 in the AD group and 19.2 in the SVaD group, which showed no difference. The Clinical Dementia Rating (CDR), CDR-sum of box, Barthel activities of daily living (ADL), and Geriatric Depression Scale (GDS) showed no statistically significant differences between the AD and SVaD groups (Table 1).

The Apo E ε4 allele frequency and carrier frequency in the AD group, SVaD group, and normal group

The Apo E ε4 allele frequency and carrier frequency in the

normal group were 8.3% and 16.7%, while those of the AD group were 17.4% and 31.7%, respectively, which showed statistical significance when compared with the normal group. In the SVaD group, the respective frequencies were 10.9% and 21.9%, which showed a statistically significant difference but not as much as the difference between the AD group and the normal group (p=0.03, 0.02) (Table 2).

In the normal and SVaD groups, there were no Apo E ε4 homozygotes, and only 9 patients (3.1%) were homozygotes in the AD group. Most were heterozygotes.

OR for AD and SVaD conferred to Apo E ε4 after age adjustment

The OR of AD conferred to the Apo E ε4 allele was 2.03, which was high enough to show statistical significance when compared to the normal group (p=0.04). In the SVaD group, the OR was 1.34, but showed no statistical significance (p=0.62) (Table 3).

The Apo E ε4 allele frequency and carrier frequency based on sex in the AD, SVaD and normal groups

In the AD group, the Apo E ε4 frequency and carrier fre-

Table 1. General characteristics of subjects

	Group			p-value
	AD[a] (n=290)	SVaD[b] (n=32)	Normal[c] (n=78)	
Sex, n (%)				0.58
Male	80 (27.6)	11 (34.4)	25 (32.0)	
Female	210 (72.4)	21 (65.6)	53 (69.0)	
Age (years)	74.1±6.3	73.8±6.0	65.1±8.3	0.00*, a, b>c†
Hachinski Ischemic Score	3.04±2.38	3.56±2.95	2.74±1.46	0.23
Cholesterol (mg/dL)	187.36±43.11	188.99±41.57	186.43±34.65	0.96
LDL (mg/dL)	121.93±36.15	130.96±39.29	127.83±31.67	0.25
K-MMSE	18.81±5.10	19.16±4.68	28.46±1.84	0.00*, a, b<c†
CDR	0.92±0.49	0.91±0.53	0.31±0.25	0.00*, a, b>c†
CDR-SB	5.31±2.92	4.67±2.58	0.65±0.58	0.00*, a, b>c†
B-ADL	18.44±2.71	18.59±2.55	19.85±0.65	0.00*, a, b<c†
GDS	17.67±7.30	20±6.68	13.85±6.69	0.00*, a, b>c†

Values are presented as mean±standard deviation or number (%).
*Statistically significant with p<0.05, †Multiple comparison result by Scheffe.
AD: Alzheimer's disease, B-ADL: Barthel-activities of daily living, CDR: Clinical Dementia Rating, CDR-SB: CDR-sum of boxes, GDS: Geriatric Depression Scale, K-MMSE: Korean version of the Mini-Mental State Examination, LDL: low density lipoprotein, SVaD: subcortical vascular dementia.

Table 2. Apolipoprotein E genotype, allele and carrier frequency in each group

	Group			p-value
	AD (n=290)	SVaD (n=32)	Normal (n=78)	
Genotype frequency, n (%)				0.23
ε2/2	1 (0.34)	0 (0.0)	0 (0.0)	
ε2/3	19 (6.55)	3 (9.38)	10 (12.82)	
ε2/4	5 (1.72)	0 (0.0)	2 (2.56)	
ε3/3	178 (61.38)	22 (68.75)	55 (70.51)	
ε3/4	78 (26.9)	7 (21.88)	11 (14.1)	
ε4/4	9 (3.1)	0 (0.0)	0 (0.0)	
Allele frequency, n (%)				0.03*
ε2	26 (4.48)	3 (4.69)	12 (7.69)	
ε3	453 (78.1)	54 (84.38)	131 (83.97)	
ε4	101 (17.41)	7 (10.94)	13 (8.33)	
Carrier frequency, n (%)				0.02*
ε4=0	198 (68.28)	25 (78.13)	65 (83.33)	
ε4≥1	92 (31.72)	7 (21.88)	13 (16.67)	

*Statistically significant with p<0.05.
AD: Alzheimer's disease, SVaD: subcortical vascular dementia.

Table 3. Odds ratio for AD and SVaD conferred to the apolipoprotein E polymorphism after age adjustment

	AD			SVaD		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Genotype						
ε3/3		Reference group			Reference group	
ε2/2	0.07	0.01–1.21	0.07		-	
ε2/3	0.52	0.19–1.38	0.19	0.97	0.27–3.51	0.96
ε2/4	0.84	0.12–6.01	0.86	1.43	0.08–25.63	0.81
ε3/4	1.89	0.87–4.11	0.11	1.82	0.64–5.20	0.26
ε4/4	3.32	0.32–34.38	0.32		-	
ε4 allele						
Absent		Reference group			Reference group	
Present	2.03	1.01–4.09	0.04*	1.34	0.42–4.32	0.62

*Statistically significant with $p<0.05$.
AD: Alzheimer's disease, CI: confidence interval, OR: odds ratio, SVaD: subcortical vascular dementia.

Table 4. Apolipoprotein E genotypes, allele and carrier frequency by sex

	Group								
	AD			SVaD			Normal		
	M (*n*=80)	F (*n*=210)	*p*-value	M (*n*=11)	F (*n*=21)	*p*-value	M (*n*=25)	F (*n*=53)	*p*-value
Genotype frequency, *n* (%)			0.26			0.20			0.75
ε2/2	0 (0)	1 (0.48)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
ε2/3	8 (10)	11 (5.24)		0 (0)	3 (14.29)		3 (12)	7 (13.21)	
ε2/4	1 (1.25)	4 (1.9)		0 (0.0)	0 (0.0)		0 (0)	2 (3.77)	
ε3/3	46 (57.5)	132 (62.86)		7 (63.64)	15 (71.43)		19 (76)	36 (67.92)	
ε3/4	20 (25)	58 (27.62)		4 (36.36)	3 (14.29)		3 (12)	8 (15.09)	
ε4/4	5 (6.25)	4 (1.9)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Allele frequency, *n* (%)			0.50			0.20			0.64
ε2	9 (5.63)	17 (4.05)		0 (0)	3 (7.14)		3 (6)	9 (8.49)	
ε3	120 (75)	333 (79.29)		18 (81.82)	36 (85.71)		44 (88)	87 (82.08)	
ε4	31 (19.38)	70 (16.67)		4 (18.18)	3 (7.14)		3 (6)	10 (9.43)	
Carrier frequency, *n* (%)			0.86			0.15			0.45
ε4=0	54 (67.5)	144 (68.57)		7 (63.64)	18 (85.71)		22 (88)	43 (81.13)	
ε4≥1	26 (32.5)	66 (31.43)		4 (36.36)	3 (14.29)		3 (12)	10 (18.87)	

*Statistically significant with $p<0.05$.
AD: Alzheimer's disease, F: female, M: male, SVaD: subcortical vascular dementia.

quency in males were 19.4% and 32.5%, while those in the females were 16.7% and 31.4%, respectively, which showed no statistically significant difference (p=0.496, 0.861). In the SVaD group, the Apo E ε4 frequency and carrier frequency in both the male and female groups were 18.8%, 36.4% and 7.1%, 14.3%, respectively. The male group showed higher allele frequency and carrier frequency, but showed no statistically significant difference (p=0.201, 0.151) (Table 4).

DISCUSSION

A correlation between Apo E ε4 and AD has been suggested in many previous studies, which has not been disputed. Yet the correlation between SVaD and Apo E ε4 is still highly controversial. In this study, the frequency and OR of Apo E ε4 after age adjustment in the AD group was higher than in the normal group, compatible with previous studies. In contrast, the frequency of Apo E ε4 in the SVaD group was higher than in the normal group but only by a small amount compared with the AD group. The OR after age adjustment for Apo E ε4 in SVaD was not statistically significant.

Despite the controversy regarding the roles of Apo E, it is known to be associated with lipid metabolism in the peripheral system. And in the central nervous system, it has been suggested that Apo E handles the accumulation of amyloid beta-peptide, phosphorylation of the tau protein, and stability and regeneration of nerve cells.[5-7] Among the three Apo E genotypes, the Apo E ε4 genotype is known to independently in-

crease low density lipid protein generation in the peripheral system. It is also known to be related to the production of peroxide radicals, accumulation of amyloid beta-peptide, and eruption of cerebral amyloid angiopathy in the central nervous system.[8-10] Additionally, Apo E ε4 is known to be associated with the deterioration of the recovery function after nerve cell injury as well as the change in choline acetyl-transferase activity that affects the development of AD.[11-15]

In Asians, compared to Caucasian, the frequency of the Apo E ε4 allele is known to be low.[16,17] Furthermore, in VaD cases, it has been reported that the frequency of the Apo E ε4 allele differs among races.[18-21] Therefore, examining the frequency of the Apo E ε4 allele between individuals with AD and SVaD group in Koreans may be useful in the differential diagnosis of dementia.

In most previous large studies on Apo E ε4 frequency in VaD, VaD diagnosis was made according to the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseigement en Neurosciences criteria.[22] This criteria has an advantage in that it emphasizes the temporal relationship between ischemic or hemorrhagic events and cognitive decline but it also has an disadvantage in that it includes many types of VaD with different pathogenesis. So this study additionally incorporated the Erkinjuntti criteria to exclusively compare SVaD, which is caused by a relatively similar pathogenesis, excluding dementia caused by hemorrhagic lesions, genetic VaD, and multi-infarct dementia, which shows ischemic lesions on the cerebral cortex. Considering that Apo E ε4 affects ischemia in the capillary vessels, and that the main cause of SVaD is microangiopathy, this comparison method may better reflect the effect of Apo E ε4 on the development of VaD. In addition, this study has a larger sample size than previous studies with Korean populations associated with AD and SVaD, which could be more statistically significant.[23]

The study showed similar general demographic and neuropsychological test results, including for MMSE, CDR, GDS, and B-ADL, between the AD and SVaD groups. Consequently, we were able to compare the Apo E ε4 frequency between the two groups without static adjustment. Interestingly, the difference in the hachinski ischemic score (HIS) was not statistically significant, even though the HIS of SVaD was slightly higher than that of AD. Unlike other types of VaD, cognitive decline in SVaD does not follow a stepwise pattern but rather, a slow and progressive course. We think this cognitive decline pattern for SVaD could affect the relatively low HIS compared with other VaD groups.

The study results indicated that the AD group showed higher Apo E ε4 allele frequency and carrier frequency than the normal group. Yet the SVaD group showed less of a difference when compared to the normal group. After age adjustment, the OR of the AD group conferred to Apo E ε4 was high, and showed statistical significance. But in the SVaD group, OR after age adjustment was lower than in the AD group and did not show statistical significance. This could be because cerebrovascular arteriosclerosis and ischemia, both of which are known to cause SVaD, are affected not only by lipid metabolism associated with Apo E ε4 but also by other factors including high blood pressure, diabetes, drinking, smoking, and ethnic diversity.

Some studies have suggested that the Apo E ε2 allele has a protective effect against AD.[24,25] Similar to previous studies, this study showed that the Apo E ε2 allele frequency in both the AD and SVaD groups was lower than in the normal group. But the effect of Apo E ε2 on AD has been more controversial than that of Apo E ε4 until now. And the association between Apo E ε2 and SVaD was not well known. In cases of mixed type dementia in the SVaD group, the protective effect of Apo E ε2 on AD could also be observed.

In addition, previous studies with Caucasian patients showed that females had a higher frequency of Apo E ε4 than males, which was considered to be correlated to the increase of AD risk and early onset of AD.[26] However, this study did not show any statistically significant gender difference among the three groups, suggesting that Apo E ε4 frequency does not differ by gender in Korean dementia patients.

In summary, regardless of gender, Apo E ε4 in Koreans may be an important factor in the development of AD, but it cannot be considered a predictive factor for SVaD. Despite having an effect, the effect is small.

A limitation of this study is that, when compared to the AD group, the number of subjects in the SVaD and normal groups was relatively small. In addition, the study was performed in a retrospective manner, and the risk factors for SVaD, such as hypertension, diabetes, and cardiovascular diseases were not controlled in either group. In the future, large prospective studies of patients with dementia to evaluate the role of Apo E ε4, controlling for vascular risk factors, could provide more confirmatory knowledge for differential diagnosis of dementia in Koreans.

Conflicts of Interest

The authors have no financial conflicts of interest.

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