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Age, hypertension, and genetic polymorphisms and their relative associations with white matter hyperintensities in Korean patients with Alzheimer's disease

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Abstract

Objectives: White matter hyperintensities are known to influence dementia in Alzheimer's disease. Genetic components are suggested as putative risk factors for vascular pathology and cognitive decline. This study aimed to determine whether there is an association between candidate genetic polymorphisms and the severity of white matter hyperintensities in patients with Alzheimer's disease. *Methods*: Seventy-five patients diagnosed with Alzheimer's disease underwent genetic tests for specific alleles of apolipoprotein E, angiotensin-converting enzyme, and methylenetetrahydrofolate reductase. All patients underwent brain magnetic resonance imaging scans and neuropsychological tests. The severity of white matter hyperintensities was semiquantified using the CREDOS rating scale, and patients were divided into three groups according to their rating. *Results*:The severity of white matter hyperintensities was related to age and hypertension. However, none of the gene polymorphisms we tested was found to be associated with the severity of white matter hyperintensities.
Conclusion:The genetic polymorphisms found in apolipoprotein E, angiotensin-converting enzyme and methylenetetrahydrofolate reductase did not contribute to white matter hyperintensities in Alzheimer's disease.Only age and hypertension factors were found to be contributory to white matter hyperintensities.

INTRODUCTION

Alzheimer's disease (AD), the most common cause of dementia, is characterized by amyloid plaques and neurofibrillary tangles. Several pathological studies have revealed the coexistence of vascular lesions in AD.[1] Vascular lesions are known to influence the development and progression of dementia in AD.[2] Some researchers have suggested that AD could be divided into two radiological subtypes: AD with and without small vessel disease.[3] Small-vessel pathologies of cerebral white matter include micro-ischemia (or micro-hemorrhages), gliosis, and demyelination. These pathologies are observed on T2-weighted, and fluid-attenuated inversion recovery (FLAIR) images as white matter hyperintensities (WMHs). WMHs are more common in the patients with dementia when compared to healthy elderly individuals.[4] A recent meta-analysis reported that the presence of WMHs predicted an increased risk of dementia, and that the severity of WMHs significantly correlated with the risk of developing AD.[5] The pathogenesis and clinical significance of WMHs in AD, however, are not fully understood.

WMHs are known to be influenced by multiple environmental and genetic factors. Advanced age and predictors of vascular disease (especially hypertension) are well-known risk factors for developing WMHs.[6] Several studies also report that WMHs are potentially heritable.[7]

Many genes, including apolipoprotein E (ApoE), angiotensin-converting enzyme (ACE), and methylenetetrahydrofolate reductase (MTHFR) are considered putative risk factors for vascular pathology in dementia. ApoE plays a role in lipid metabolism[8] and has been identified as an important gene implicated in the risk for AD.[9,10] It has also been implicated as a gene associated

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with cardiovascular disease and stroke.[11] A pathological study of AD brains showed that the ApoEε4 allele is associated with small-vessel arteriosclerosis.[12] However, other reports found that the ApoEε4 allele is not associated with WMHs.[13,14] ACE is involved in blood pressure regulation and degradation of the amyloid β peptide*in vitro*. It was subsequently predicted to be agene associated with the risk of developing AD and WMHs.[15] Polymorphisms in the MTHFR gene were also assumed risk factorsof vascular or degenerative dementia.[16] MTHFR is a key enzyme in the remethylation of homocysteine. A polymorphism at position 677 of the MTHFR gene (C677T) produces a thermolabile form of the enzyme with low activity; this mutation results in hyperhomocysteinemia, a known risk factor forclinical stroke, cardiovascular disease, and white-matter lesions as identified by MRI.[17,18] However, the results regarding a potential correlation between these polymorphisms and either dementia or WMHs have been divergent among studies.[19-21] These inconsistencies may be attributed to large genetic differences resulting from the use of clinically and ethnically diversestudy populations (i.e., healthy elderly individuals and patients with AD, vascular dementia, or mixed dementia).

Defining the genetic polymorphisms that influence the vascular pathology in AD is critical to identifying its underlying genetic background. We therefore examined whether polymorphisms in the genes ApoE, ACE, or MTHFR influence the presence and severity of WMHs in patients with AD.

METHODS

Subjects

The diagnosis of probable AD was made according to the NINCDS-ADRDA criteria.[22] A total of 148 patients with AD were screened from October 2010 to March 2013at the Neurology Department at Gyeongsang National University Hospital (GNUH).We evaluated the detailed medical history, laboratory tests, cognitive assessment, and brain MRI scans of the patients. Patients with a history of alcohol or drug abuse,major depression or other psychiatric disorders, severe head trauma, cerebrovascular disease, other neurodegenerative disorders, and vascular dementia were excluded. In addition, patients with severe medical conditions affecting their cognitive function, e.g., severe renal or hepatic dysfunction, hearing loss, visual problems, or malignancies were also excluded from this study. After screening, 75 consecutive patients with probable AD were included in this study. Clinical and demographical data were retrospectively analyzed with approvalof the Institutional Review Board (IRB) of GNUH.

Laboratory tests

Blood samples (3mL) from each patient were collected into tubes containing EDTA. The ApoEε2/ε3/ε4, ACE I/D, MTHFR C677T polymorphisms were determined using polymerase chain reaction (PCR) performed by the Green Cross Reference Laboratory (Youngin-si, South Korea). Based on the gene polymorphisms, patients with AD were divided into two groups: a 'carrier' group with ε4 allele of ApoE, D allele of ACE, T allele of MTHFR and a 'non-carrier' group without the abovementioned alleles for each gene.

Assessment of cerebral ischemia

All participants underwent brain imaging using a 1.5-T MRI system (Siemens, Magnetom Avanto, Erlangen, Germany) at baseline. Axial T1-, T2-weighted and FLAIR imageswere obtained at a slice thickness of 5 mm for all subjects. The severity of WMHs on T2-weighted and FLAIR axial images was evaluated based on the CREDOS (Clinical Research for Dementia of South Korea) WMH scaleby two neurologists, blinded to patients' clinical information. All patients were divided into three groups based on the CREDOS WMH scale: AD with 'mild'WMHs, 'moderate' WMHs, and 'severe' WMHs. The CREDOS WMH rating scales[23] were developed by the CREDOS study group, with modifications from Fazekas[24], and Scheltens' scales.[25] In this scale, periventricular white matter changes (P) and deep white matter changes (D) were divided into 3 groups. Periventricular white matter changes (P) were identified by measuring capping or banding length vertical to the lateral ventricle in an axial view:P1(<5mm), P2(≥5mm, <10mm), P3(≥10mm). Deep white matter changes (D) were identified by measuring the longest length of deep white matter variationin axial and coronal views: D1(<5mm), D2(≥5mm, <10mm), D3(≥10mm). Based on a periventricular and deep white matter evaluation, the scores were classified into groups as follows: the combination of D1 and P1 (D1P1), or D1 and P2 (D1P2) were categorized as the 'mild' WMHs group, D3P3 was classified as the 'severe' WMHs group, and all remaining scores were classified as the 'moderate' WMHs group.

Statistical analysis

All statistical analyses were performed using Statistical Package for Social Science program (SPSS version 19; SPSS, Chicago, IL, USA) at a significance level of ≤ 0.05. Normal distributions of continuous variables were evaluated using the Kolmogorov-Smirnov test. The clinical data were presented as means± SD. Demographic subject data were compared using either a χ^2 test or one-way analysis of variance. We conducted the Pearson Chi-square test to evaluate the relationship between genetic polymorphisms of interest and the severity of WMHs.

RESULTS

Of the 75 patients included, 46 were categorized into the 'mild' WMHs group, 21into the 'moderate' WMHs group, and 8 were classified as having 'severe' WMHs. Their age and K-MMSE scores were normally distributed. Other continuous variables used to describe patients were not normally distributed. Baseline characteristics are described in Table 1. The age of the 'moderate' and 'severe' WMHs group was significantly higher than that of the 'mild' WMHs group (p <0.001). There was no significant difference in gender, disease duration, or education among three groups. Patients in the 'moderate' and 'severe' WMHs groups exhibited lower cognitive performance compared to the 'mild' WMHs group, as measured by the K-MMSE and CDR-sum-of-the-box (SOB) tests. The significant difference remained after K-MMSE scores were adjusted for age (p=0.002, measured by ANCOVA). Hypertension correlated with the severity of WMHs (p=0.005). The other vascular risk factors we investigated (including diabetes, dyslipidemia, and smoking) also showed no significant differences among the three groups (Table1). Allele frequencies observed among the patients are summarized in Table 2. All genotype frequencies met the Hardy-Weinberg equilibrium, except for the ACE polymorphism.

Table 1: Baseline characteristics of the study population

	Total (N=75)	'Mild' WMHs (N=46)	'Moderate' WMHs (N=21)	'Severe' WMHs (N=8)	p-value
Demographics					
Age (year)	71.89 ± 6.50	69.65 ± 6.99	75.29 ± 3.59	75.88 ± 3.22	<0.001*†
Female (%)	55 (73.3%)	32 (69.6%)	17 (80.9%)	6 (75%)	0.620
Education (year)	4.35 ± 3.65	4.79 ± 3.67	3.81 ± 3.74	3.19 ± 3.24	0.382
Disease duration (year)	1.71 ± 1.89	1.76 ± 1.89	1.52 ± 1.81	1.88 ± 0.99	0.843
K-MMSE	16.26 ± 6.27	18.15 ± 5.28	14.00 ± 6.84	10.29 ± 5.28	0.001*†
CDR	0.69 ± 0.45	0.63 ± 0.34	0.78 ± 0.53	0.93 ± 0.79	0.185
CDR_SOB	4.60 ± 3.04	3.95 ± 2.18	5.42 ± 3.59	6.83 ± 5.10	0.037
Vascular risk factors					
Diabetes (%)	11 (14.7%)	6 (13%)	4 (19%)	1 (12.5%)	0.8
Hypertension (%)	39 (52%)	17 (37%)	16 (76%)	6 (75%)	0.005
Dyslipidemia (%)	26 (34.7%)	13 (28.3%)	8 (38.1%)	5 (62.5%)	0.16
Smoking (%)	3 (4%)	3 (6.52%)	0 (0%)	0 (0%)	0.37

WMHs: White matter hyperintensities, K-MMSE: Korean version-Mini-Mental State Examination, CDR_SOB: Clinical Dementia Rating_sum of box

Values represent the mean ± standard deviation. P-values were calculated by χ^2 test or ANOVA.

P values < 0.05 obtained by ANOVA were analyzed by Turkey post hoc test: *between mild and moderate WMHs, †between mild and severe WMHs, ‡ between moderate and severe WMHs.

Table 2: Allele frequencies observed among the study group

Gene	Polymorphism	Alleles		Genotype frequencies			Hardy-Weinberg P
		a	b	aa	ab	bb	
ApoE	ApoE112	Cys	Arg	28	30	3	>0.05
	ApoE158	Arg	Cys	55	6	0	>0.05
ACE	ACE	I	D	25	19	17	<0.05
MTHFR	MTHFR677	C	T	23	28	10	>0.05

ApoE: Apolipoprotein E, ACE: Angiotensin-converting enzyme, MTHFR: Methylenetetrahydrofolate reductase

ApoE, ACE, MTHFR polymorphism, and white matter changes

The correlation values between the genetic polymorphisms we tested and WMHs are shown in Table 3. There was no association among any of the genetic polymorphisms (the ApoEε4 allele, ACE I/D, or the MTHFR C677T polymorphism) and the WMHs groups.

DISCUSSION

AD can be divided into subtypes according to clinical onset, specific neuropsychological results, or the presence of WMHs.[3,26] WMHs are known as risk factors of dementia and are associated with the severity and type of clinical symptoms in AD. Therefore, there is a need to understand the pathophysiology of WMHs in AD. However, few studies have evaluated the correlation between genetic polymorphisms and WMHs specifically in the context of AD. The present study included three groups of patients with AD categorized according to the severity of small-vessel pathology. We aimed to determine whether an association exists between WMHs and multiple gene polymorphisms (the ApoE ε4, ACE D, and MTHFR T alleles). Our results suggest that genetic polymorphisms of the ApoE, ACE and MTHFR genes show no significant association with WMHs in patients with AD. In addition, our findings indicate that patient age and hypertension are the robust risk factors correlated with the severity of WMHs. In addition, we show that the severity of WMHs is a predicting factor of lower cognitive performance in AD.

The Rotterdam Scan study indicated that ApoE ε4 allele carriers had a higher severity of subcortical WMHs than ApoE ε3/ε3 carriers.[27] Another study reported that the ACE D/D polymorphism was associated with the severity of deep WMHs, but not with periventricular hyperintensities (PVH) in patients with dementia.[19] A pathological study of patients with AD found an association between the ACE D/D genotype and white matter myelin loss.[28] However, a meta-analysis study reported that genetic polymorphisms (including ApoE ε4, MTHFR C677T and the ACE I/D polymorphism) showed

Table 3: Severity of WMHs according to genetic polymorphism

			WMHs group			
		N=75	Mild (N=46)	Moderate (N=21)	Severe (N=8)	p-value
ApoEe4 allele	non-carrier	37	23	10	4	0.98
	carrier	38	23	11	4	
ACE D allele	non-carrier	33	18	10	5	0.44
	carrier	42	28	11	3	
MTHFR T allele	non-carrier	28	15	10	3	0.5
	carrier	47	31	11	5	

ApoE: Apolipoprotein E, ACE: Angiotensin-converting enzyme, MTHFR: Methylenetetrahydrofolate reductase, WMHs: white matter hyperintensities
P-values were calculated by χ^2 test.

no significant effect on the severity of WMHs.[29] Another meta-analysis has shown that ACE I/D polymorphisms have no effect on the vascular dementia.[30] A study of 50 gene polymorphisms (including those in the ApoE, MTHFR and ACE genes) showed negative results in an attempt to find a relationship between the polymorphisms and WMHs in patients with subjective memory complaints.[31] A population-based study has shown that the ApoE ε4, ACE I/D, and MTHFR C677T polymorphisms had no significant effect on WMH volumes.[32] Hypertension and lacunar infarcts were significantly associated with WMHs, indicating that the origin of WMHs might be ischemia.[33]These inconsistencies in findings may be attributed todifferences in study populations, cardiovascular risk factors, and the severity of ischemic changes.

Another factor that should be considered when interpreting the published results is the ethnic variation among study populations. Many studies on the association between genetic polymorphisms and either dementia or WMHs have been conducted among Caucasian populations; however, it is not known whether these genetic polymorphisms are likely to have the same influence in Korean populations (or Asian populations in general). Several Korean studies have been performed to investigate a potential association between genetic polymorphisms and either dementia or WMHs. A study was conducted to evaluate the association of gene polymorphisms with dementia among 55 centenarians with dementia, 34 centenarians without dementia, and controls groups (n=7231 for the ACE genotype and n=6435 for the ApoE genotype).[34] The study showed that the ACE D allele had no association with dementia, but that ApoE ε4 allele was associated with dementia, even inindividuals over 100 years of age. A study to identify a putative association between MTHFR gene polymorphisms and AD in Koreans was performed in 2008.[35] This study found that the MTHFR TT genotype was linked to AD. The abovementioned two studies examined polymorphisms of ApoE, ACE, MTHFR as risk factors for developing AD; however, they did not evaluate ischemic changes in AD. Until now, only one Korean study has characterized the association between ApoE gene polymorphisms and WMHs in dementia (including AD); this study showed that the ApoE 4 allele was more prevalent in the AD group than subcortical vascular dementia.[13] However, there was no difference in the ApoE genotype in patients having AD with or without WMHs in the study. This result is therefore consistent with our findings.

The clinical significance of WMHs in patients with AD is unclear. Some authors reported that WMHs influence cognitive functioning and drug response in patients with AD.[36] In our study, the severity of WMHs did not influence the response of cholinesterase inhibitors (data is not shown). However, the‘moderate’and ‘severe’ WMHs groups showed lower performance in general cognitive functions compared to the‘mild’ WMHs group. This result is consistent with the findings of previous reports.[37,38] One study composed of 1472 patients with amnestic MCI suggested a negative association between the severity of WMHs and cognitive performance, especially that involving frontal executive tasks. In addition, an interaction was found linking the presence of ApoE 4 with the severity of WMHs and frontal executive functioning.[38] In an investigation of the response of patients with AD to cholinesterase inhibitors, the concurrence of WMHs and hypertension adversely affected the response to drug therapy.[39] These results suggest that management of WMHs and hypertension could reduce the progression of cognitive decline in patients with AD.

This study has several limitations. First, the sample size was small, and the ACE polymorphism did not meet Hardy-Weinberg equilibrium, presumably due to the sample size. Second, although we used a semi-quantitative rating system evaluated by two specialists, a visual rating scale has its limitations in accuracy. Third, we collected no data on thevitamin B12 levels of patients. A mutation in the MTHFR gene is associated withdecreased vitamin B12 levels, which could potentially affect patient cognition. Fourth, control subjects with normal cognitive status were not included in this study. Polymorphisms in the ApoE, ACE and MTHFR genes are putative risk factors for AD as well as WMHs. For example, the ACE I allele increased the risk of late-onset AD and ACE D allele increased the risk of WMHs.[40] As each allele could play a different role, more accurate results maybe obtained by comparing patient allele frequencies with those of a control group. Therefore, a large-sample, case-controlled study is needed to thoroughly test and carefully investigate the correlation between genetic polymorphisms and WMHs.

In conclusion, age and hypertension were associated with the severity of WMHs in patients with AD. However, our results showed no correlation between the genetic polymorphisms ApoE ε4, ACE I/D, or MTHFR C677T and white matter changes in patients with AD.

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DISCLOSURE

Conflicts of interest: None

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