Relationship between the diagnostic components of metabolic syndrome (MS) and cognition by ApoE genotype in the elderly

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ABSTRACT

The purpose of this study was to find out the effect of the ApoE genotype on the relationship between metabolic syndrome (MS) and its diagnostic components and cognitive impairment in the elderly. A total of 2944 subjects aged over 60 years were analyzed from the data of Gwangju Dementia and Mild Cognitive Impairment Study. We examined demographic characteristics, current and past illness history, drug history, Korean version-mini-mental state examination (K-MMSE). We also examined ApoE genotype and analyzed associated factors with MS. The MS was present in 53.8% of the subjects (36.8% of men and 61.1% of women). On multiple logistic regression analysis, MS was not associated with the cognitive impairment (K-MMSE score <18) adjusted for age, sex, and educational level. The interactive effect between systolic and diastolic blood pressure (SBP, and DBP, respectively) and ApoE on cognition was not significant (all $p > 0.3$), but the interactive effect between triglyceride (TG), high-density-lipoprotein-cholesterol (HDLc) and ApoE on cognition was significant after adjustment for age, sex, and education ($B = -0.285$, Wald = 4.194, $p = 0.041$; $B = 0.372$, Wald = 4.134, $p = 0.042$). These results suggest that blood TG and HDLc may affect cognitive function in the elderly in the presence of ApoE ε4 allele.

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1. Introduction

In elderly populations, the effect of MS on cognitive function may vary depending on the ApoE genotype. Until recently, certain studies reported that cognitive impairment in the elderly was more severe for those with MS (Kalmijn et al., 2000; Yaffe et al., 2004). Individual diagnostic components for MS including hypertension (Haan et al., 1999; Hebert et al., 2004; Qiu et al., 2005; Waldstein et al., 2005), diabetes (Elias et al., 1997; Stewart and Liolitsa, 1999), dyslipidemia (Isbir et al., 2001; Yaffe et al., 2002), and obesity (Jeong et al., 2005) have been shown to increase the risk of dementia or cognitive impairment. Furthermore, the respective effects of each component on cognitive function reportedly differ according to the ApoE genotype (Haan et al., 1999; Stewart and Liolitsa, 1999; Isbir et al., 2001; Yaffe et al.,

2002). However, our review of the academic literature has revealed few studies discussing the influence of the ApoE genotype on the relationship between the MS, its component and cognition simultaneously in a community resident elderly population on a large scale. As such, we initiated this study to investigate whether MS and its components are associated with cognitive impairment and modified by the ApoE genotype. Our hypothesis was that the presence of MS or its diagnostic components would be associated with a greater risk of cognitive impairment and that this association would be modified by the ApoE genotype.

2. Subjects and methods

2.1. Study participants

This study is a part of a large, longitudinal study of people with men aged 60 years or older in the Korean community. Methods are detailed elsewhere (Lee et al., 2009). Briefly, we excluded 341 subjects who fulfilled the exclusion criteria (any difficulty with regard to activities of daily living (ADL); inability to communicate with the interviewer; undergoing active treatment for cancer in

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the last 5 years; intake of antidepressants, sedatives, or other psychiatric drugs; and suffering from epilepsy or other psychiatric disorders), and 293 subjects who had incomplete data. A total of 2944 subjects were included the analysis; Informed consent was obtained after providing a complete description of the study to the subjects and their relatives. This study has been approved by the Severance Mental Health Hospital Institutional Review Board.

2.2. Assessment and measurements

Considering the difficulties faced by the elderly in answering self-report questions, all surveys were conducted through the assistance of investigators. The investigators, who had experience in epidemiologic studies, were trained by senior psychiatrists and neuropsychologists to be familiar with the administration of the questionnaires to the study subjects. Information was gathered on the participant's age, sex, educational level, literacy, marital status, living arrangements (i.e., the number of family members living together), medical history, and history of drug, alcohol and tobacco use. The information was verified from at least one close family member or reliable informants closely acquainted with the subject. Physical measurements were taken with the assistance of two nurses. For waist circumference, the narrowest area between the upper end of the ileac crest and the lower end of the scapula was measured while the subject stood upright. Fasting blood samples were obtained in the morning.

2.3. Definition of cognitive impairment

Assessing cognitive function with the K-MMSE (Kang et al., 1997), we defined cognitive impairment by a K-MMSE score lower than 18. A Korean study in the community defined the cut-off point of K-MMSE score for screening of dementia as 17/18 points; the sensitivity and specificity of the findings were 91% and 86%, respectively (Kim et al., 2003).

2.4. Definition of MS

In the present study, MS was defined according to the modified NCEP-ATP III standard. Cases satisfying three or more of the five following diagnostic criteria were deemed to constitute MS: (a) abdominal obesity: waist circumference in excess of 90 cm (male) or 80 cm (female); (b) hypertension: systolic blood pressure higher than 130 mm/Hg or diastolic blood pressure higher than 85 mm/Hg or currently using an antihypertensive medication; (c) hyperglycemia: fasting blood glucose level higher than 110 mg/dl or currently using antidiabetic medication (e.g., insulin or oral agents); (d) hypertriglyceridemia: TG level higher than 150 mg/dl; and (e) hypo-HDLc-emia: HDLc level less than 40 mg/dl (male) or 50 mg/dl (female).

2.5. Statistical analysis

The data were analyzed as follows. Categorical variables were compared by the χ^2-test and continuous variables by the Student t-test for MS. After adjusting for age, gender, and education level multiple logistic regression analysis was performed for cognitive impairment (K-MMSE score <18) with MS by the ApoE genotype. To test the influence of the ApoE genotype on the relationship between MS and diagnostic components of MS and cognition, point biserial correlation between cognitive impairment and the diagnostic components of MS was performed according to the ApoE genotype. To verify the interactive effects between each diagnostic component and the ApoE genotype on cognitive impairment, we performed a multiple logistic regression analysis after adjusting for age, gender and education level. The ApoE genotype was transformed by contrast coding, while each diagnostic component was transformed to a standardized score. Interaction term was included in the multiple logistic regression model by multiplying the ApoE genotype by each diagnostic component as an independent variable. In all statistical analyses, the significant level was $p < 0.05$. As a statistical program, the SPSS 12.0 version was used.

3. Results

3.1. Demographic characteristics of subjects

The baseline demographic characteristics of the subjects according are described in Table 1. One thousand five hundred

Table 1
Demographic characteristics of the subject population by presence of MS, mean ± S.D. or n (%).

Variables	Total (n = 2944)	Without MS (n = 1359)	With MS (n = 1585)	p
Sex				
Males	883 (30.0)	558 (63.2)	325 (36.8)	<0.0001[b]
Females	2061 (70.0)	801 (38.9)	1260 (61.1)	
Age (years)	72.1 ± 6.7	71.9 ± 6.9	72.3 ± 6.4	0.09[a]
60–69	1095 (37.2)	530 (48.4)	565 (51.6)	0.14[b]
70–79	1413 (48.0)	628 (44.5)	785 (55.5)	
80–	436 (14.8)	201 (46.1)	235 (53.9)	
Education (years)	4.8 ± 4.5	5.5 ± 4.8	4.2 ± 4.3	<0.0001[a]
Literacy				
No	548 (18.6)	206 (37.6)	342 (62.4)	<0.0001[b]
Yes	2396 (81.4)	1153 (48.1)	1243 (51.9)	
Marital status				
Married/remarried	1784 (60.6)	892 (50.0)	892 (50.0)	<0.0001[b]
Unmarried/widowed/separated	1160 (39.4)	467 (40.3)	693 (59.7)	
Number of family members living together	2.5 ± 1.8	2.4 ± 1.8	2.6 ± 1.8	0.01[a]
ApoE (n = 1516)				
ε4 (−)	1271 (83.3)	576 (45.3)	695 (54.7)	0.44[b]
ε4 (+)	245 (16.2)	104 (42.4)	141 (57.6)	
K-MMSE	22.0 ± 4.7	22.4 ± 4.7	21.6 ± 4.6	<0.0001[a]

[a] Student t-test.
[b] χ^2-test.

Table 2
Point biserial correlation between cognitive impairment (K-MMSE <18) and the diagnostic components of MS.

	ApoE ε4 (−)	ApoE ε4 (+)
Waist circumference	−0.009	0.111
SBP	0.087[*]	0.190[**]
DBP	0.061	0.164[**]
FBG	−0.008	−0.071
HDLc	−0.004	−0.171[**]
TG	−0.035	0.188[*]

[*] $p < 0.01$.
[**] $p < 0.05$.

eighty-five subjects (53.8%) had MS. According to the presence of MS, there were significant differences in sex ($\chi^2 = 147.2$, d.f. = 1, $p < 0.0001$), educational level ($t = 7.3$, d.f. = 2762, $p < 0.0001$), literacy ($\chi^2 = 19.9$, d.f. = 1, $p < 0.0001$), marital status ($\chi^2 = 26.8$, d.f. = 1, $p < 0.0001$), and the number of family members living together ($t = -2.45$, d.f. = 2941, $p = 0.01$).

3.2. Relationship between MS and cognitive impairment

According to the multiple logistic regression analysis, MS was not associated with cognitive impairment after adjusting for age, sex, and educational level. Despite the presence of the ApoE ε4 allele, MS was not associated with cognitive impairment (K-MMSE score <18) after adjusting for age, sex, and educational level.

3.3. Relationship between the diagnostic components of MS and cognitive impairment according to the ApoE genotype

As indicated in Table 2, point biserial correlation showed that the correlation coefficient between SBP, DBP, HDLc, TG, and cognitive impairment was less than 0.10 in the ApoE e4(−) group but more than 0.10 in the ApoE e4(+) group. Accordingly, for these four variables in the latter group, we performed additional analyses that showed that the interactive effect between SBP, DBP and ApoE on cognition was not significant (all $p > 0.3$); however, the interactive effect between TG, HDLC and ApoE on cognition was significant after adjusting for age, sex, and education

($B = -0.285$, Wald = 4.194, $p = 0.041$; $B = 0.372$, Wald = 4.134, $p = 0.042$). The results are described in Tables 3 and 4.

4. Discussion

Our study showed that among the elderly over 60 years old in a community, there was no significant association between MS and cognitive impairment (K-MMSE score <18) after adjustment for age, sex, and educational level. And this non-association remained regardless of the presence of ApoE ε4 allele. However, previous studies reported that there was a significant association between MS and cognitive decline in the elderly (Dik et al., 2007; Komulainen et al., 2007; Van den Berg et al., 2007; Yaffe et al., 2007). It is possible that due to difference of the research design, different results may be obtained. The former studies were longitudinal studies, on the other hand, our study was a cross-sectional study and thus it was difficult to compare them directly with our results. The former studies used different assessments of cognitive function such as 3MS and other neuropsychological test. MS was associated with memory impairment, but not with the MMSE score (Komulainen et al., 2007). Another possibility is that there was a significant interaction between the MS and inflammation on cognition. The MS was negatively associated with cognition in subjects with high inflammation whereas an association was absent in subjects with low inflammation (Dik et al., 2007).

In the present study, the higher blood TG or lower blood HDLc was, the more cognitive impairment (K-MMSE score <18) was after adjusting for age, sex, and educational level, in the presence of ApoE ε4 allele. In animal model, hypertriglyceridemia, the main dyslipidemia of MS, is in part responsible for the leptin resistance seen in obesity. So TGs are likely a major cause of the cognitive disturbances in diet-induced obesity (Farr et al., 2008). In human, poorer cognitive performances of individuals with hypertriglyceridemia has been reported in centenarians (Atzmon et al., 2002). Our result is consistent with a previous study reporting that higher TG levels were associated with a decline in memory function. The authors insisted that lipid levels moderated the influence of ApoE on episodic memory, such that decline in recognition was noted for ApoE ε4 allele carriers with higher cholesterol levels (De Frias et al., 2007).

Table 3
Interactive effect on cognition between ApoE e4 and TG after adjusting for age, sex, and education.

	B	±S.E.	Wald	d.f.	p	OR =	95% CI for OR
Intercept	−9.850	1.402	49.342	1	<0.0001	0.000	
Sex	0.447	0.262	2.921	1	<0.087	1.564	0.936–2.612
Age	0.111	0.016	46.464	1	<0.000	1.117	1.082–1.153
Education level	−1.030	0.111	86.116	1	<0.000	0.357	0.287–0.444
ApoE e4	−0.305	0.151	4.067	1	<0.044	0.737	0.548–0.991
TG	0.269	0.140	3.686	1	<0.055	1.308	0.994–1.721
ApoE e4 × TG	0.285	0.139	4.194	1	<0.041	1.329	1.012–1.746

Nagelkerke $R^2 = 0.393$.

Table 4
Interactive effect on cognition between ApoE e4 and HDLc after adjusting for age, sex, and education.

	B	±S.E.	Wald	d.f.	p	OR =	95% CI for OR
Intercept	9.854	1.403	49.337	1	<0.0001	0.000	
Sex	0.428	0.262	2.677	1	<0.102	1.534	0.919–2.561
Age	0.111	0.016	46.312	1	<0.0001	1.117	1.082–1.153
Education level	1.036	0.111	87.397	1	<0.0000	0.355	0.286–0.441
ApoE e4	−0.358	0.166	4.632	1	<0.031	0.699	0.505–0.969
HDLc	−0.416	0.183	5.170	1	<0.023	0.660	0.461–0.944
ApoE e4 × HDLc	−0.372	0.183	4.134	1	<0.042	0.690	0.482–0.987

Nagelkerke $R^2 = 0.394$.

The ApoE genotype that plays an important role for the metabolism and distribution of cholesterol has been shown to be a genetic risk factor for non-familiar sporadic Alzheimer disease (Corder et al., 1993). Until now, the relationship between HDLc in the cerebro-spinal fluid and HDLc in the blood has not been elucidated yet. However, a study reported that lipoprotein which plays a role in transporting cholesterol is present only as the HDLc type in the cerebro-spinal fluid. And in the brain, the ability of astrocytes that support and protect neurons to secrete cholesterol varies according to the ApoE genotype (Dietschy and Turley, 2001). This may be an example of the mechanism explaining the relationship of HDLc and cognitive function. According to this study, it has been reported that in the cases with the ApoE ε4 allele, the ability of astrocytes to secrete cholesterol was decreased by 2.4 times than the cases with ApoE ε3 allele and thus it influenced the metabolism of cholesterol in the brain and the distribution, hence, it may induce the vulnerability of the regeneration of cell membrane of neurons and the neural plasticity, which suggests the necessity of studies on this field in future. Furthermore HDLc play a key role in the protection of LDLc from oxidation. Such activity depends on the presence of apolipoproteins and enzymes such as paraoxonase 1, platelet activating factor-acetylhydrolase. The impairment of HDLc antioxidative activity in MS is partly related to an enrichment of small HDLc in TGs and their depletion in cholesteryl esters, to the replacement of apoA-I by serum amyloid A, and to glycation and oxidation of apoA-I (Hansel et al., 2006).

Our study had the following strengths. First, it was the first large-scale study on the effect of the ApoE genotype on the relationship between cognitive impairment in the elderly and MS and its diagnostic components. Second, by characterizing the association of MS and its diagnostic components with cognitive impairment according to the ApoE genotype, the study may provide some basic information for the strategy to prevent dementia by the ApoE genotype. The risk factors for dementia and cognitive function, such as hypertension, diabetes, hyperlipidemia, and obesity, could be readily assessed by regular examinations and controlled by, inter-alia, the correction of lifestyles and drug treatments. Therefore, treatment and control of MS and its diagnostic components may play key roles in the overall strategy to prevent dementia.

Our study had the following limitations. First, because our subjects were not recruited randomly, the possibility of a selection bias may preclude the study population from being an accurate representation of the elderly over 60 years old in a community. Hence, the 53.8% incidence rate of MS in our study should be interpreted as the positive rate of the study population rather than the prevalence rate representing all the elderly in a community. Second, because the K-MMSE is the most base-level screening test to assess cognitive function, its ability to measure cognitive function impairment clinically is limited. Thus, the results of our study, which were based on data from subjects who had completed the K-MMSE, may be limited. However, subsequent data obtained in the future from neuropsychological tests and diagnostic procedures conducted by psychiatrists will continue to be reported. Third, because there is yet to be definitive diagnostic criteria for MS, the standards, including the NCEP-ATP III standard used in the present study, continue to change. Finally, because this was a cross-sectional study, the general applicability of our results may be limited. We anticipate that these limitations will be adjusted for in future prospective cohort studies.

Conflict of interest statement

None.

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