Relationship between Diagnostic Components of Metabolic Syndrome or Head Circumference and Cognition by ApoE genotype in the Elderly

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감사의 글

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노인정신의학의 길을 밝혀주시고 이끌어주신 오병훈 교수님, 저를 믿고 연세대학교 노화과학연구소로 보내주신 이홍식 교수님, 북한이탈주민 연구를 통해 연구자의 길을 열어주신 전우택 교수님을 비롯하여 한 명의 정신과 전문의가 될 수 있도록 많은 관심과 가르침을 주셨던 연세대학교 의과대학 정신과 교수님들께 진심으로 감사 말씀드립니다.

부족하고 느린 저에게 기회를 주시고 또, 가족처럼 따뜻하게 대해주시는 정영기, 임기영, 노재성, 이영문, 신윤미, 조선미 교수님께도 감사 말씀드립니다.

전공의 시절 정신과 교육분석을 통해 인간이 얼마나 나약한 존재인지 알게 해주시고, 또 그런 모습을 솔직하게 받아들일 수 있는 용기를 통해 변화 가능하다는 것을 깨닫게 해주신 이재승 선생님께도 감사드립니다.

연구는 항상 정직하고 투명하게 해야한다는 가르침을 주신 나덕렬 교수님, 수많은 데이터속에 여러 가지 질서가 존재함을 깨닫게 해주신 정해관 교수님, 항상 큰 형님처럼 넉넉하고 따뜻하게 배려해주신 이동우 교수님, 지역사회 노인정신의학에 대해 눈뜨게 해주신 조성진 교수님, 이준영 교수님께 감사드립니다. 그리고 GDEMCIS를 도와주시는 여러 CRCD 연구자 여러분들께도 감사드립니다. CRCD 연구 모임을 통해 많은 것을 배울 수 있었고 더욱 더 분발할 수 있는 힘이 되었습

니다.

천재적인 재능으로 상상 이상의 것을 보여주는 차경렬 선생님, 항상 말없이 묵묵히 많은 일을 해내면서 어느덧 동반자로서의 길을 가고 있는 이강수 선생에게도 특별히 감사드립니다. 다재다능한 김경란 선생에게도 감사드리고 항상 듬직하고 믿음직한 정해선 팀장님께도 감사드립니다. 그리고, 모든 면에서 항상 모범이 되셨던 노화과학대학원의 1호 박사이신 신경균 교수님 이하 노화과학 대학원 동문 선후배 선생님들께도 감사드립니다.

이렇게 감사드릴 분이 많은 저는 복 받은 사람인 것 같습니다.

매사에 정이 많고 강직하신 아버님, 사랑이 많고 따뜻한 어머님. 감사합니다. 그리고 사랑합니다. 저를 믿음으로 지켜봐주시는 장인어른과 장모님께도 감사드립니다. 너무나 멋지고 부러운 형님과 형수님, 사랑이 넘치는 누나와 매형, 재능이 많은 큰 처남 식구들과 처형에게도 감사를 드립니다.

더 이상 말이 필요없는 진정한 후원자 사랑하는 아내 지현과 항상 건강하고 바르게 자랄 것으로 기대되는 든든한 아들 재우, 태우에게 사랑과 감사를 전하며 이 논문을 바칩니다.

2008년 1월

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Relationship between Diagnostic Components of Metabolic Syndrome and Cognition by ApoE genotype in the Elderly

ABSTRACT

Relationship between Diagnostic Components of Metabolic Syndrome and Cognition by ApoE genotype in the Elderly

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Objective : The purpose of this study was to find out the effect of the ApoE genotype on the relationship between metabolic syndrome and its diagnostic components and cognitive impairment in the elderly.

Methods : A total of 2944 subjects (883 men and 2061 women) aged over 60 years were analyzed from the data of GDEMCIS (Gwangju Dementia and Mild Cognitive Impairment Study). The metabolic syndrome was assessed as defined by the modified NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III). We examined demographic characteristics, current and past illness history, drug history, K-MMSE (Korean version-Mini Mental State Examination). We also examined ApoE genotype and analyzed associated factors with metabolic syndrome. This study was approved by the institutional review board.

Results : Metabolic syndrome was present in 53.8% of the subjects (36.8% of men and 61.1% of women). On multiple logistic regression analysis,

metabolic syndrome was not associated with cognitive impairment (K-MMSE score < 18) adjusted for age, sex, educational level, current smoking status. On multiple logistic regression analysis with the 5 diagnostic components of metabolic syndrome, as systolic blood pressure or the level of blood triglyceride was higher (OR = 1.03, 95% CI = 1.00-1.06; OR = 1.006 , 95% CI = 1.00-1.01), or the level of blood high density lipoprotein (HDL) cholesterol was lower (OR = 0.96, 95% CI = 0.92-1.00), the risk of cognitive impairment increased after adjusting for age, sex, educational level, current smoking status in the presence of ApoE ε4 allele.

Conclusion : These results suggest that systolic blood pressure, blood triglyceride and HDL cholesterol may affect cognitive function in the elderly in the presence of ApoE ε4 allele.

Key words: metabolic syndrome, cognitive impairment, K-MMSE, elderly, ApoE genotype

1. Introduction

There are various diagnostic criteria for metabolic syndrome (Table 1). In 1998, the WHO (World Health Organization) suggested an unified definition of metabolic syndrome (1). According to the criteria of the WHO, metabolic syndrome is defined as the case with diabetes or insulin resistance and having more than 2 symptoms among hypertension, hypertriglyceridemia, hypoHDL (high density lipoprotein) cholestrerolemia, obesity, and microalbuminuria. However, due to the limitation of the diagnostic procedure that serum insulin and 24-hour urine microalbumin have to be evaluated, it has not been used widely in practice.

In 2001, the National Cholesterol Education Program Third Adult Treatment Panel (NCEP-ATP III) released new diagnostic criteria for metabolic syndrome (2). It emphasized intensive intervention on the patients with cardiovascular diseases and the primary prevention of the cases with several risk factors. According to the new criteria, hyperglycemia and insulin resistance are not emphasized, but criteria of risk factors for cardiovascular diseases becomes strict, and the importance of abdominal obesity was emphasized by designating the waist circumference as a single category. In most studies, as far as we know, metabolic syndrome is defined using the NCEP-ATP III criteria.

In USA as well as Korea, the prevalence of metabolic syndrome is increasing according to the age groups (Figure1, 2). Individual NCEP-ATP III diagnostic components of metabolic syndrome such as hypertension (3-6), diabetes (7,8), dyslipidemia (9,10), and obesity (11) are known to be a

factor respectively that increases the risk of dementia or cognitive impairment. And it has been reported that the effect of each diagnostic component on cognitive function is different depending on ApoE genotype (4, 7, 9, 10). Therefore, it is anticipated that the effect of metabolic syndrome on cognitive function may vary depending on the ApoE genotype in the elderly.

Until recently, some studies reported that the cognitive impairment was more severe in the group with metabolic syndrome than in the group without it in the elderly (12, 13), however, to our knowledge, there are no study of the effects of ApoE genotype on the relationship between metabolic syndrome and diagnostic components of metabolic syndrome and cognition for the community resident elderly population in a large scale.

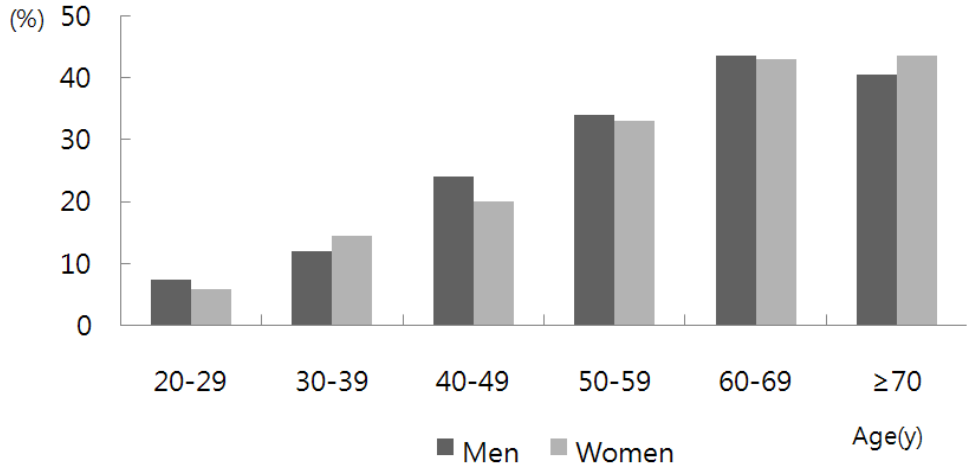
Thus, we conducted this study to investigate whether the metabolic syndrome and its components are associated with cognitive impairment and modified by ApoE genotype. Our hypothesis was that presence of the metabolic syndrome or its diagnostic components would be associated with greater risk of cognitive impairment and that this association would be modified by ApoE genotype.

Table 1. Various diagnostic criteria of metabolic syndrome

	WHO (1998)	ATP III (2001)	EGIR (2002)	IDF (2004)
Required	Insulin R or Glucose↑	No	Insulin R	WCr (Ethnicity)
At least , of the following:	2	3	2	2
Obesity	O	O	O	
HTN	O	O	O	O
DM		O	O	O
HyperTG	O	O	O	O
HypoHDLc		O		O
Albuminuria	O			

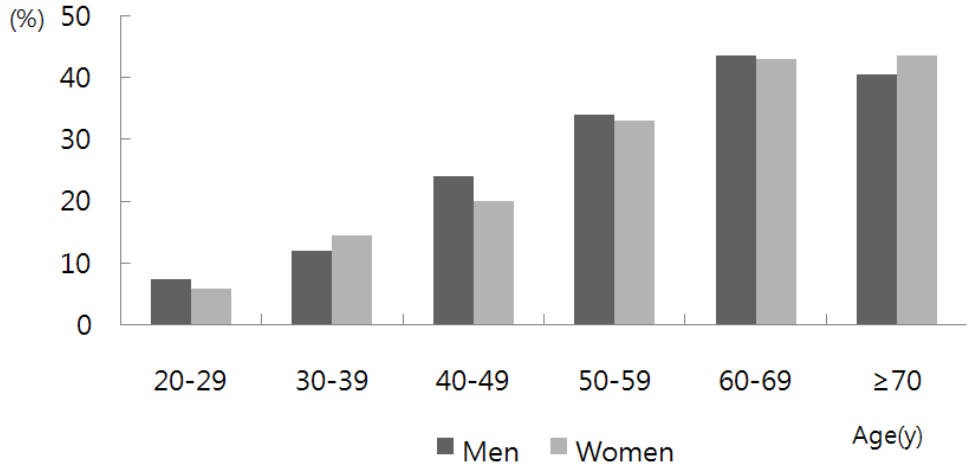
WHO = World Health Organization, ATPIII = National Cholesterol Education Program Third Adult Treatment Panel, EGIR = European Group for the Study of Insulin Resistance, IDF = International Diabetes Federation, HTN = hypertension, DM = diabetes, TG = triglyceride, HDLc = high density lipoprotein cholesterol, Insulin R = Insulin resistance, WCr = waist circumference

Figure 1. Prevalence of metabolic syndrome according to age groups in USA*



*Data from NHANES (National Health and Nutrition Examination Survey), ATP III diagnostic criteria. (1988-1994)

Figure 2. Prevalence of metabolic syndrome according to age groups in Korea*



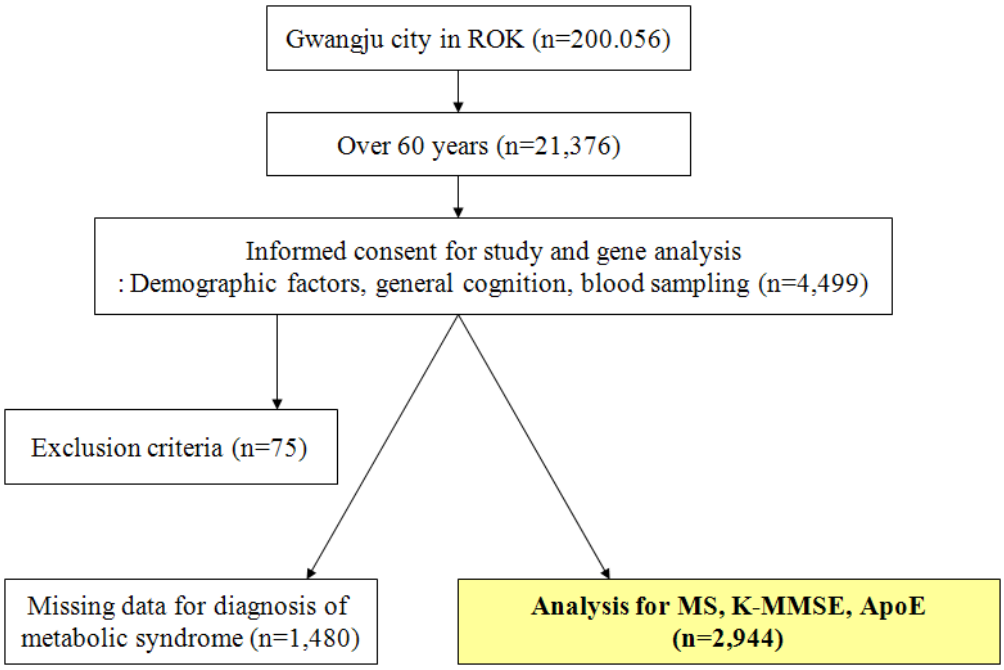
*Data from KNHANES (Korean National Health and Nutrition Examination Survey), modified ATP III diagnostic criteria (2005)

2. Subjects and Methods

2.1. Study Participants

This study was based on data derived from a large prospective study called the Gwangju Dementia and Mild Cognitive Impairment Study (GDEMCIS). The baseline study of GDEMCIS termed 1st wave was conducted in 2005.10-2007.3. According to biannual follow-up, in 2nd wave (2007.10-2009.3) and 3rd wave (2009.10-2011.3), changes in cognitive function and clinical measurements will be assessed by re-examination using the same procedures of baseline study. The GDEMCIS cohort comprises nonrandom convenience samples of elderly people, all of whom are ethnic Koreans aged over 60 years who have participated in a long-term follow-up. We recruited our subjects through advertisements about comprehensive evaluation of cognitive function, neurological examination, careful diagnosis, and, if needed, regular case management at no charge. Informed consent was obtained after providing a complete description of the study to the subjects and their relatives. Figure 3 shows flow chart of study participants. This study was approved by the Severance Mental Health Hospital Institutional Review Board.

Figure 3. Flow chart of study participants



2.2. Assessment and measurement

Informed consent was obtained after complete description of the study to the subjects and their relatives. Considering the difficulties faced by the elderly in answering the self-report questions, all surveys were conducted by the investigators. The information for each subject was verified from at least one close family member or reliable informants who were closely acquainted

with the subject. The field investigators had prior experiences with epidemiologic investigations. They were trained by senior psychiatrists and neuropsychologists so that they were adequately familiar with the administration of the questionnaires to the study subjects.

Information was gathered on participants' age, sex, educational level, literacy, marital status, number of family members living together, present and past illness history, drug history, smoking history and physical measurement by two nurses. Concerning the measurement of the waist circumference, the principle was to stand straight and measure the narrowest area between the upper end of the ileac crest and the lower end of the scapula. And fasting blood samples were obtained in the morning.

For ApoE genotyping, the collected blood was added to a vacutainer (BD, Franklin Lakes, NJ) containing acid citrate dextrose (ACD) and stored in a −80°C freezer. DNA was extracted from the stored frozen peripheral blood, and the single nucleotide polymorphism (SNP) of the ApoE gene was analyzed using the GeneScan analysis software (ABI, FosterCity, CA).

After the initial interview, the following subjects were excluded: those with a history of significant hearing or visual impairment that rendered participation in the interview difficult, those with a history of neurological disorders (stroke, Parkinson’s disease, or active epilepsy), those with psychiatric illness (schizophrenia, mental retardation, severe depression, or mania), those taking psychotropic medications, or those with significant alcohol and other substance abuse. Individuals living alone were also excluded because their complaints could not be corroborated by another responsible person.

In this study, 4499 subjects participated in the present study. Of these, 75 were excluded on the basis of the above mentioned criteria, and 1480 were excluded because their data was incomplete. Thus, the sample consisted of 2944 subjects who agreed to participate in the study.

2.3. Definition of cognitive impairment

Cognitive function was assessed with the Korean version-Mini Mental State Examination (14). 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 (15). Based on these results, we defined cognitive impairment as lower than 18 in K-MMSE score.

2.4. Definition of metabolic syndrome

In the present study, metabolic syndrome was defined according to the standard of the 2001 NCEP-ATP III (2). Among them, the standard of abdominal obesity was defined according to the standard suggested by the WHO Western Pacific Region and the International Association for the Study of Obesity, and the ATP III that modified the standard of Asian abdominal obesity.

Among the following 5 categories, the cases satisfy more 3 categories were diagnosed as metabolic syndrome.

(1)Abdominal obesity: the waist circumference bigger than 90 cm(male), 80 cm(female)

(2)Hypertension: Systolic blood pressure higher than 130 mmHg or diastolic blood pressure higher than 85 mmHg or currently using an antihypertensive medication

(3)Hyperglycemia: fasting blood glucose higher than 110 mg/dL or currently using antidiabetic (insulin or oral agents) medication

(4)Hypertriglyceridemia: triglyceride higher than 150 mg/dL

(5)HypoHDLcholesterolemia: HDL cholesterol less than 40 mg/dL(male), 50 mg/dL(female)

2.5. Statistical analysis

Categorical variables were compared by Chi square test and continuous variables were by Student t-test for metabolic syndrome. Multiple logistic regression analysis for cognitive impairment (K-MMSE < 18) with metabolic syndrome and its diagnostic components was performed after the adjustment of the age, gender, the education level, and current smoking by ApoE genotype. In all statistical analysis, the significant level was $p < 0.05$, and 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 to the metabolic syndrome was described in Table 2. 1585 subjects had metabolic syndrome (53.8%). According to the presence of metabolic syndrome, there were significant differences in sex ($\chi 2 = 147.2$, df = 1, $p < 0.0001$), educational level (t = 7.3, df = 2762, $p < 0.0001$), literacy ($\chi 2 = 19.9$, df = 1, $p < 0.0001$), marital stutus ($\chi 2 = 26.8$, df = 1, $p < 0.0001$), and number of family living together (t = -2.45, df = 2941, $p = 0.01$).

Table 2. Demographic characteristics of the 2944 participants by presence of the metabolic syndrome

VARIABLE		Total n=2944 (%)	Without MS n=1359 (%)	With MS n=1585 (%)	*p*
Sex	Male	883(30.0)	558 (63.2)	325 (36.8)	<.0001‡
	Female	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†
	60-69	1094(37.2)	530(48.4)	564(51.6)	
	70-79	1410(47.9)	627(44.5)	783(55.5)	0.14‡
	80-	436(14.8)	201(46.1)	235(53.9)	
Education (years)*		4.8±4.5	5.5±4.8	4.2±4.3	<.0001†
Literacy	No	548(18.6)	206 (37.6)	342 (62.4)	<.0001‡
	Yes	2396(81.4)	1153 (48.1)	1243 (51.9)	
Marital status	Married/Remarried	1784(60.6)	467 (40.3)	693 (59.7)	<.0001‡
	Unmarried/Widowed /Separated	1160(39.4)	892 (50.0)	892 (50.0)	
No. of family living together*		2.5±1.8	2.4±1.8	2.6±1.8	0.01†
ApoE(N=1516)	ε4 (-)	1271(83.3)	576(45.3)	695(54.7)	0. 44‡
	ε4 (+)	245(16.2)	104(42.4)	141(57.6)	

MS = Metabolic syndrome, *Mean±SD, † Student t-test, ‡ Chi-square test.

3.2. The relationship between metabolic syndrome and cognition (K-MMSE score)

The subjects with metabolic syndrome had significantly lower K-MMSE score than those without (t = 4.2, df = 2616, $p < 0.0001$) (Table 3). Among subjects with metabolic syndrome, the subjects with abdominal obesity or hypoHDL cholesterolemia had significantly lower K-MMSE score. The K-MMSE score was significantly lower than the group without abdominal obesity or hypoHDL cholesterolemia (t = 5.3, df = 2086, $p < 0.0001$; t = 4.8, df = 1636, $p < 0.0001$).

Table 3. Relationship between metabolic syndrome / the diagnostic components of metabolic syndrome and K-MMSE score

Total, n=2618			
VARIABLE(N)		K-MMSE Mean±SD	*p*
MS1	no(1008)	22.6±4.7	<0.0001
	yes(1610)	21.6±4.6	
MS2	no(605)	22.3±4.5	0.07
	yes(2013)	21.9±4.7	
MS3	no(1221)	22.0±4.7	0.92
	yes(1397)	22.0±4.6	
MS4	no(1567)	22.0±4.8	0.92
	yes(1051)	22.0±4.5	
MS5	no(1758)	22.3±4.8	<0.0001
	yes(860)	21.3±4.8	
MS	no(1215)	22.4±4.7	<0.0001
	yes(1403)	21.6±4.6	

MS1 = Abdominal obesity as defined by Asian-Pacific guideline: waist circumference ≥ 90 cm for men and ≥ 80 cm for women; MS2 = Hypertension as defined by blood pressure ≥ 130/85 mmHg or currently antihypertensive medication; MS3 = Diabetes mellitus as defined by fasting blood glucose ≥ 110 mg/dL or currently antidiabetic medication; MS4 =Triglyceride ≥ 150 mg/dL; MS5 = HDL cholesterol < 40 mg/dL for men and < 50 mg/dL for women; MS = Metabolic syndrome. Student's t-test was performed.

3.3. The relationship between metabolic syndrome and cognitive impairment (K-MMSE score < 18)

On multiple logistic regression analysis, metabolic syndrome was not associated with cognitive impairment after adjusting for age, sex, educational level, and current smoking. Regardless of presence of ApoE ε4 allele, metabolic syndrome was not associated with cognitive impairment (K-MMSE score < 18) after adjusting for age, sex, educational level, and current smoking (Table 4).

Table 4. Multiple logistic regression analysis for cognitive impairment (K-MMSE score < 18) with metabolic syndrome after adjustment for age, sex, educational level, smoking

	n=2944 (R square=0.42, p <0.0001)	
	β (SE)	OR (95% CI)
Intercept	-8.61(1.33)	-
Age	0.11(0.02)	1.12(1.08-1.15)
Sex (Female vs. male)	0.51(0.32)	1.66(0.90-3.08)
Education level	-0.38(0.04)	0.68(0.63-0.75)
Smoking (Current vs. Ex or Non)	0.46(0.33)	1.59(0.83-3.05)
Metabolic syndrome	-0.14(0.21)	1.07(0.71-1.61)

3.4. Relationship between the diagnostic components of metabolic syndrome and cognitive impairment (K-MMSE score < 18) according to the ApoE genotype

Multiple logistic regression analysis with the five diagnostic components of metabolic syndrome revealed that the higher systolic blood pressure or the level of blood triglyceride (OR = 1.03, 95% CI = 1.00-1.06; OR = 1.006 , 95% CI = 1.00-1.01), or the lower level of blood HDL cholesterol (OR = 0.96, 95% CI = 0.92-1.00) increased the risk of cognitive impairment after adjusting for age, sex, educational level, current smoking in the presence of ApoE ε4 allele (Table 5-7)

Table 5. Multiple logistic regression analysis for cognitive impairment (K-MMSE score < 18) with systolic blood pressure after adjustment for age, sex, educational level, smoking

	Apo E4 (-) (R square=0.399, p <0.0001)		Apo E4 (+) (R square=0.378, p <0.0001)	
	β (SE)	OR (95% CI)	β (SE)	OR (95% CI)
Intercept	-9.30(1.47)		-14.8(4.19)	-
Age	0.10(0.02)	1.11(1.07-1.15)	0.13(0.05)	1.14(1.04-1.25)
Sex (Female vs. male)	0.51(0.31)	1.67(0.91-3.05)	3.59(1.68)	36.2(1.36-966.9)
Education level	-0.38(0.04)	0.69(0.63-0.75)	-0.16(0.09)	0.85(0.71-1.02)
Smoking (Current vs. Ex or Non)	0.47(0.33)	1.61(0.84-3.07)	3.58(1.63)	36.0(1.49-872.9)
Systolic blood pressure	0.009(0.005)	1.009(0.99-1.02)	0.03(0.01)	1.03(1.00-1.06)

Table 6. Multiple logistic regression analysis for cognitive impairment (K-MMSE score < 18) with triglyceride after adjustment for age, sex, educational level, smoking

	Apo E4 (-) (R square=0.404, p <0.0001)		Apo E4 (+) (R square=0.396, p <0.0001)	
	β (SE)	OR (95% CI)	β (SE)	OR (95% CI)
Intercept	-8.59(1.36)		-13.0(3.83)	-
Age	0.11(0.02)	1.12(1.08-1.15)	0.15(0.05)	1.16(1.05-1.27)
Sex (Female vs. male)	0.53(0.31)	1.70(0.93-3.11)	3.06(1.61)	21.4(0.90-504.2)
Education level	-0.38(0.04)	0.68(0.63-0.75)	-0.17(0.09)	0.84(0.70-1.02)
Smoking (Current vs. Ex or Non)	0.42(0.33)	1.59(0.83-3.04)	3.46(1.51)	31.8(1.64-618.4)
Triglyceride	0.000(0.001)	1.00(0.99-1.003)	0.006(0.003)	1.006(1.00-1.01)

Table 7. Multiple logistic regression analysis for cognitive impairment (K-MMSE score < 18) with high density lipoprotein cholestrol after adjustment for age, sex, educational level, smoking

	Apo E4 (-) (R square=0.404, p <0.0001)		Apo E4 (+) (R square=0.395, p <0.0001)	
	β (SE)	OR (95% CI)	β (SE)	OR (95% CI)
Intercept	-8.46(1.37)		-9.29(3.78)	-
Age	0.12(0.12)	1.12(1.08-1.15)	0.14(0.05)	1.15(1.05-1.26)
Sex (Female vs. male)	0.53(0.31)	1.69(0.93-3.09)	2.49(1.43)	12.0(0.73-199.5)
Education level	-0.38(0.04)	0.68(0.63-0.75)	-0.18(0.09)	0.84(0.70-1.005)
Smoking (Current vs. Ex or Non)	0.46(0.33)	1.58(0.82-3.04)	3.12(1.33)	22.7(1.66-310.9)
High density lipoprotein cholesterol	-0.003(0.007)	0.99(0.98-1.01)	-0.04(0.02)	0.96(0.92-1.00)

4. Discussion

Our study showed that among the elderly over 60 years old in a community, there was no significant association between metabolic syndrome and cognitive impairment (K-MMSE score < 18) after adjustment for age, sex, educational level, and current smoking. And this non-association remained regardless of the presence of ApoE ε4 allele. However, Previous studies reported that there was a significant association between metabolic syndrome and cognitive decline in the elderly (16-19). It is possible that due to difference of the research design, different results may be obtained. The former studies were all 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.

In our study, it was found that the higher systolic blood pressure was associated with cognitive impairment (K-MMSE score < 18) was after adjusting for age, sex, educational level, current smoking in the presence of ApoE ε4 allele.

This result was consistent with a previous study that reported 10 times greater risk of poor cognitive function in those with both ApoE ε4 allele and midlife high systolic blood pressure ($\geq$160 mmHg) compared with those without ApoE ε4 allele and normal systolic blood pressure after adjusting for age, education, smoking, alcohol use, and BMI in community-dwelling elderly men (20). Systolic blood pressure and ApoE ε4 allele may also interact through the amyloid processing pathways. In an autopsy study high systolic blood pressure was associated with the presence of neurofibrillary tangles and neuritic plaques (21). ApoE ε4 allele is

associated with a greater amyloid deposition and neuritic plaque formation in demented and nondemented individuals (22). In vitro and in vivo data suggest that amyloid has a vasoconstrictive effect on the cerebral microcirculation (23,24). This could increase blood pressure and exacerbate the insult to the brain created by high systolic blood pressure.

In the present study, the higher blood triglyceride or lower blood HDL cholesterol was, the more cognitive impairment (K-MMSE score < 18) was after adjusting for age, sex, educational level, current smoking in the presence of ApoE ε4 allele. This result is consistent with a previous study reporting that higher triglyceride 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 (25).

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 (26). Until now, the relationship between HDL cholesterol in the cerebro-spinal fluid and HDL cholesterol 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 HDL 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 (27). This may be an example of the mechanism explaining the relationship of HDL cholesterol 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.

Our study has the following strengths. First, it is the first large scale study on the effect of the ApoE genotype on the relationship between metabolic syndrome and each diagnostic components of metabolic syndrome and cognitive impairment in the elderly. Second, by characterizing the association of metabolic syndrome and the diagnostic components of metabolic syndrome with cognitive impairment according to ApoE genotype, it may provide some basic information for the strategy to prevent dementia by 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 they could be controlled by the correction of life styles, drug treatments, etc., so treatment and control of metabolic syndrome and its component may be an important meaning for the strategy to prevent dementia.

Our study has the following limitations. First, the study population participated in our study does not represent the elderly over 60 years old in a community. The subjects were not recruited randomly, hence, a selection bias may be present, hence, 53.8% shown in our study should be considered as the positive rate of metabolic syndrome of the study population rather than the prevalence rate of metabolic syndrome representing the elderly in a community. Second, K-MMSE used in our

study is the most base level screening test to assess cognitive function, and thus to measure the cognitive function impairment clinically, it has a substantial limit. The result of our study was the analysis of only the subjects who completed the screening test, and in future, based on the data obtained from the neuropsychological test and the diagnostic procedure by psychiatrists, continuing results will be reported. Third, the diagnostic criteria of metabolic syndrome itself is still controversial and it is still on the change. Fourth, it was a cross-sectional study, hence, it has a great limitation in the interpretation of results. This limitation is anticipated to be adjusted by future prospective cohort study.

PART II

Relationship between Head Circumference and Cognition by ApoE genotype in the Elderly

ABSTRACT

Relationship between Head Circumference and Cognition by ApoE genotype in the Elderly

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Objectives: The purpose of this study was to find out the effect of the ApoE genotype on the relationship between head circumference and cognition in the elderly.

Methods : A total of 1902 subjects (599 men and 1303 women) aged over 60 years were analyzed from the data of GDEMCIS (Gwangju Dementia and Mild Cognitive Impairment Study). We assessed K-MMSE (Korean version-Mini Mental State Examination), head circumference, and ApoE genotype in all subject This study was approved by the institutional review board.

Results: The head circumference was correlated with the K-MMSE scores ($r = 0.22$, $p < 0.01$), age ($r = -0.11$, $p<0.01$), educational level ($r = 0.30$, $p<0.01$), height ($r = 0.50$, $p<0.01$), and weight ($r = 0.49$, $p<0.01$). On analysis of covariance, the interaction of ApoE with head circumference on K-MMSE was observed. ($F = 2.527$, $df = 4$, $p = 0.039$) A test of simple

main effect according to ApoE ε4 status showed that, in the ApoE ε4(-) group, the mean of K-MMSE between HC quintile was not different. (F = 0.517, df = 41,148, p = 0.723) But in the ApoE ε4(+) group, the mean of K-MMSE between HC quintile was significantly different (F = 4.163, df = 4,211, p = 0.003).

Conclusion: These findings suggest the possibility that the presence of ApoE ε4 affects cognitive function only when the brain reserve is low in the elderly population.

Key words: head circumference, cognition, K-MMSE, elderly, ApoE genotype, brain reserve

1. Introduction

Alzheimer's disease (AD) has been proposed to occur as neuropathological changes accumulate in key regions of the brain and "brain reserve" descends beyond a critical level where normal cognitive function can no longer be maintained (28). The concept of brain reserve was introduced by Katzman et al., who speculated that the clinical expression of AD was related to brain size and showed that persons with heavier brains and larger neurons were more likely to remain nondemented despite having a similar number of Alzheimer lesions as did persons with dementia (29). Indeed, one population-based autopsy series found that more than 30% of individuals with mild and severe AD pathology remained nondemented until death (30,31). In a retrospective computerized tomography (CT) study, investigators demonstrated that the onset of AD symptoms was delayed in proportion to premorbid brain size and hypothesized that premorbid brain volume is a determinant of cognitive reserve in AD patients (32).

Brain volume is possibly an important variable associated with brain reserve. At birth, the volume of the human brain is approximately 25% that of an adult. This increases to 75% by the end of the first postnatal year, with the remaining 25% achieved over the next few years of life. During this time, brain growth is the principal determinant of cranial vault growth, which normally ceases at about 7 years of age. Later in life, however, changes in brain size caused by aging or degenerative disease do not affect head circumference (HC), which reflects not the present brain volume but rather the maximal brain volume attained in youth (33). The

brain reserve hypothesis is supported by several studies, which used HC as an index of brain size and showed that HC was significantly correlated with cognitive function (34-36) and AD (37,38).

A previous study (39) suggested that the ApoE genotype is a strong risk factor for AD and accounts for as much as 50% of AD in many populations. This is evidenced in autopsy study showing that the presence of one or more ε4 alleles of ApoE is generally associated with an increase in the severity of neuropathological findings (38). In the Nun Study, the authors found that the presence of ApoE ε4 genotypes was associated with a six-fold increase in the probability of meeting the neuropathological criteria for AD at autopsy but only a two-fold increase in dementia (40). Therefore, subjects possessing the ApoE ε4 allele in combination with small HC would be at a particularly high risk for earlier onset and severe manifestation of AD.

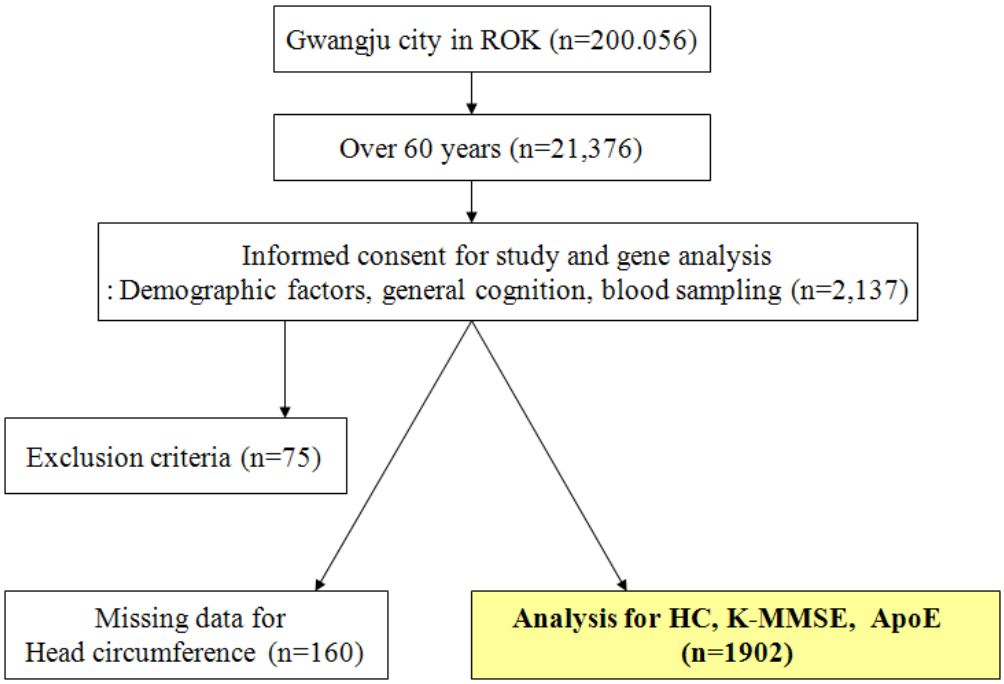
The effect of the ApoE genotype on the association between HC and cognitive function in the elderly has not yet been examined in Korea. We assessed the relationship between HC and cognitive function and also examined the effect of the ApoE genotype on this relationship in the elderly people aged over 60 years.

2. Subjects and Methods

2.1. Study Participants

This study was based on data derived from a large prospective study called the Gwangju Dementia and Mild Cognitive Impairment Study (GDEMCIS). The baseline study of GDEMCIS termed 1st wave was conducted in 2005.10-2007.3. According to biannual follow-up, in 2nd wave (2007.10-2009.3) and 3rd wave (2009.10-2011.3), changes in cognitive function and clinical measurements will be assessed by re-examination using the same procedures of baseline study. The GDEMCIS cohort comprises nonrandom convenience samples of elderly people, all of whom are ethnic Koreans aged over 60 years who have participated in a long-term follow-up. We recruited our subjects through advertisements about comprehensive evaluation of cognitive function, neurological examination, careful diagnosis, and, if needed, regular case management at no charge. Informed consent was obtained after providing a complete description of the study to the subjects and their relatives. Figure 4 shows flow chart of study participants. This study was approved by the Severance Mental Health Hospital Institutional Review Board.

Figure 4. Flow chart of study participants



2.2. Assessment and measurement

The study protocol included cognitive screening through the Korean version of the Mini-Mental State Examination (K-MMSE), which has been validated for Korean-speaking populations, 14 recording of the subject's medical history, and a detailed physical examination with an emphasis on neurological signs and symptoms. A registered nurse and clinical psychologist conducted the physical measurements and cognitive screening. Considering the difficulties faced by the elderly in answering the self-report

questions, all surveys including a self-report questionnaire were conducted by interview through field investigators with prior experience in epidemiologic investigations. Trained by senior psychiatrists and neuropsychologists, the investigators were adequately familiar with the administration of the questionnaires to the study subjects. The information obtained was verified from at least one close family member or reliable informants closely acquainted with the subject.

Starting with a clinical sample of 2137 persons, the study sample consisted of 1902 subjects who agreed to undergo ApoE genotyping. Following the initial interview, 160 were excluded because their data was incomplete. Another 75 subjects were excluded due to the following criteria: those with a history of significant hearing or visual impairment that rendered participation in the interview difficult, those with a history of neurological disorders (e.g., stroke, Parkinson's disease, or active epilepsy), those with psychiatric illness (e.g., schizophrenia, mental retardation, severe depression, or mania), those taking psychotropic medications, or those with significant alcohol and other substance abuse. Individuals living alone were also excluded because their complaints could not be corroborated by another responsible person.

HC was measured by registered nurses using a linear tape measure calibrated in units of 0.1 cm. The circumference was measured from the glabella to the occipital protuberance by pulling the tape around the scalp. Special care was taken to minimize the inclusion of scalp hair and to exclude the ear pinna and other possible measurement interferences. For ApoE genotyping, the collected blood was contained to a vacutainer (BD,

Franklin Lakes,NJ) containing acid citrate dextrose (ACD) and stored in a −80°C freezer. DNA was extracted from the stored frozen peripheral blood, and the single nucleotide polymorphism (SNP) of the ApoE gene was analyzed using the GeneScan analysis software (ABI, FosterCity,CA).

Informed consent was obtained after a complete description of the study to the subjects and their relatives. Considering the difficulties faced by the elderly in answering the self-report questions, all surveys were conducted by interviewing the investigators, and the information was verified from at least one close family member or reliable informant who was closely acquainted with the subject. The field investigators had prior experience with epidemiologic investigations. They were trained by senior psychiatrists and neuropsychologists so that they were adequately familiar with the administration of the questionnaires to the study subjects.

2.3. Statistical analysis

Categorical variables were compared by the $\chi 2$ test, and continuous variables were compared by ANCOVA for each of the HC quintile groups. HC was treated both as a categorical variable based on quintiles and as a continuous variable. We conducted ANCOVA by regressing head circumference on K-MMSE and including ApoE status, as well as the interaction of ApoE with head circumference after adjusting for the age, sex, educational level, height and weight. After ANCOVA, a simple main effect analysis according to ApoE status was done. In the ApoE4(+) group, pairwise comparisons by the LSD (Least Significant Difference) method was

used to find the mean difference according to HC quintile. In the end, a difference with $p< 0.05$ was considered statistically significant, and SPSS version 12.0 was used for all analyses.

3. Results

3.1. Demographic characteristics of the participants (Table 8)

The demographic characteristics of the subjects in each of the HC quintile groups are shown in Table 8. The following groups were delineated based on HC: smaller than 53 cm was referred to as Q1 (N=334), larger than 53 cm and smaller than 54 cm was Q2 (N=368), larger than 54 cm and smaller than 54.6 cm was Q3 (N=451), larger than 54.6 cm and smaller than 56 cm was Q4 (N=357), and larger than 56 cm was Q5 (N=392). The mean age of the participants was 72.2 years (standard deviation[SD]: 6.6, range: 61–98). The mean HC was 54.3 cm ([SD]: 1.7, range: 47.8–63). Of the 1902 responders, 599 were males (31.5%), and 1303 were females (68.5%); the male to female ratio was approximately 1:2. The mean K-MMSE score was 22 ([SD]: 4.7). And 304 (16%) subjects carried ε4 gene. There were significant differences among five quintile groups with respect to all variables tested except the ApoE ε4 genotype.

Table 8. Demographic characteristics of 1902 participants grouped on the basis of the quintile of the head circumference

Variables	Total (N = 1902)	Q1 (N = 334)	Q2 (N = 368)	Q3 (N = 451)	Q4 (N = 357)	Q5 (N = 392)	χ^2 or F	df	p value
Sex Male (%)*	599 (31.5)	32 (9.6)	57 (15.5)	116 (25.7)	136 (38.1)	258 (65.8)	346.25	4	0.000‡
Age (y)	72.2 ± 6.6	73.3 ± 7.1	72.4 ± 7.1	72.3 ± 6.5	71.7 ± 6.3	71.6 ± 5.8	3.738	41892	0.008†
Education (y)	4.9 ± 4.6	3.3 ± 3.7	3.9 ± 4.1	4.6 ± 4.4	5.3 ± 4.6	7.2 ± 5.0	43.480	41897	0.000†
Literacy Yes (%)*	1585 (83.3)	251 (75.1)	281 (76.4)	385 (85.4)	302 (84.6)	366 (93.4)	59.161	4	0.000‡
HC (cm)	54.3 ± 1.7	51.9 ± 0.7	53.2 ± 0.3	54.1 ± 0.2	55.1 ± 0.2	56.8 ± 1.0	3753.261	41897	0.000†
Height (cm)	155.0 ± 8.9	148.8 ± 7.0	151.8 ± 7.4	154.6 ± 7.7	157.0 ± 8.0	162.2 ± 8.4	137.751	41615	0.000†
Weight (kg)	58.3 ± 9.8	52.1 ± 8.7	55.7 ± 8.4	57.5 ± 8.2	60.6 ± 8.0	65.0 ± 10.5	107.21	41759	0.000†
BMI(kg/m^2)	24.4 ± 3.3	23.6 ± 3.5	24.3 ± 3.1	24.3 ± 3.6	24.7 ± 3.1	25.0 ± 3.1	8.088	41606	0.000†
K-MMSE	22.0 ± 4.7	20.5 ± 4.6	21.2 ± 4.9	21.7 ± 5.0	22.3 ± 4.8	23.6 ± 3.8	18.844	41522	0.000†
ApoE $\varepsilon 4$(+) (%)*	304 (16)	64 (19.2)	56 (15.2)	78 (17.3)	50 (14.0)	56 (14.3)	5.132	4	0.171‡

Q1: first quintile (47.8 cm ≤ HC < 53 cm), Q2: second quintile (53 cm ≤ HC < 54 cm), Q3: third quintile (54 cm ≤ HC < 54.6 cm), Q4: fourth quintile (54.6 cm ≤ HC < 56 cm), and Q5: fifth quintile (HC ≥ 56 cm)

†ANOVA test, ‡Chi-square test for trend, *N (%), other values: mean ± SD

HC: head circumference, BMI: body mass index, K-MMSE: Korean version-Mini Mental State Examination

3.2. Correlation between HC and the K-MMSE score and other variables (Table 9)

The K-MMSE score showed a positive correlation with HC (r = 0.22, p<0.001), educational level (r = 0.57, p<0.001), height (r = 0.28, p<0.001), and weight (r = 0.37, p< 0.001), and showed a negative correlation with age (r = −0.43, p<0.001) (Table 9). Regardless of the presence of ApoE ε4, HC was positively correlated with the K-MMSE scores.

Table 9. Correlation analysis of the K-MMSE score with other variables

	K-MMSE	HC (cm)	ApoE4	Weight (kg)	Height (cm)	Education (y)	Age (y)
K-MMSE	1	0.216**	0.003	0.366**	0.275**	0.567**	–0.431**
HC		1	-0.021	0.49**	0.50**	0.30**	–0.11**
ApoE ε4				-0.043	-0.018	-0.014	-0.009
Weight				1	0.58**	0.30**	–0.29**
Height					1	0.49**	–0.24**
Education						1	–0.34**
Age							1

K-MMSE = Korean version-Mini Mental State Examination; HC = head circumference, **: p <0.01

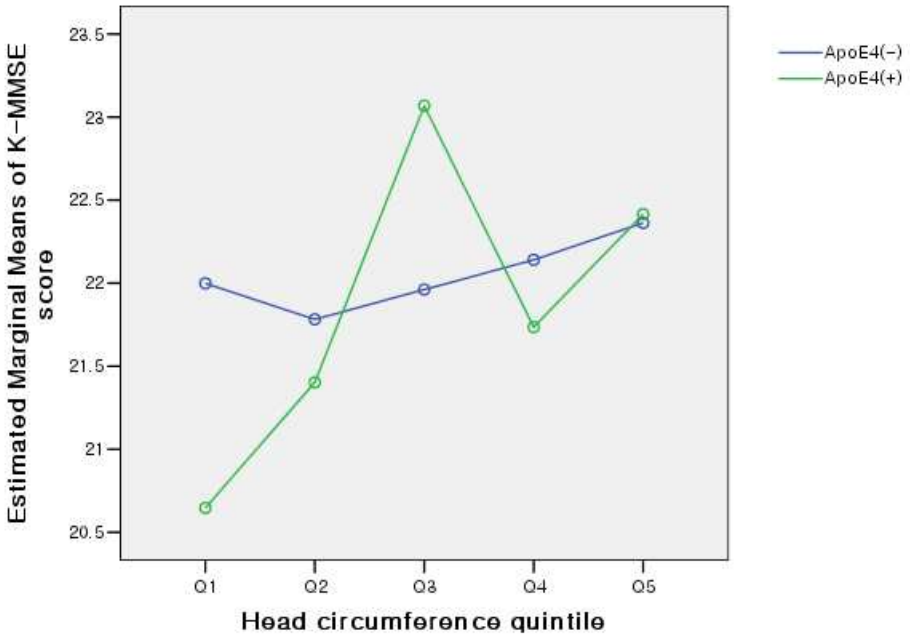
3.3. Effect of the ApoE genotype on the relationship between HC and K-MMSE scores after adjusting for the age, sex, educational level, height, and weight (Table 10)

Using ANCOVA, we tested HC, ApoE status and the interaction of ApoE with HC on K-MMSE after adjusting for the age, sex, educational level, height and weight. Results are shown in Table 10. After ANCOVA, we conducted a test of simple main effect according to ApoE status. In the ApoE4(-) group, the mean of K-MMSE between HC quintile was not different. ($F=0.517$, $df=41,148$, $p=0.723$) But in the ApoE4(+) group, the mean of K-MMSE between HC quintile was significantly different. ($F=4.163$, $df=4,211$, $p=0.003$). In the ApoE4(+) group, pairwise comparisons by the LSD (Least Significant Difference) method showed a significant mean difference between Q1 and Q3, Q5, and also between Q2 and Q3 (Figure 5).

Table 10. Differences of the K-MMSE according to head circumference quintile and ApoE4 status by ANCOVA

source	Sum of squares	df	Mean of squares	F	p
Sex (female vs male)	1.868	1	1.868	0.141	0.708
Age (years)	1641.723	1	1641.723	123.789	0.000
Education level (years)	4125.963	1	4125.963	311.105	0.000
Height (cm)	57.657	1	57.657	4.347	0.037
Weight (kg)	5.952	1	5.952	0.449	0.503
HC quintile	150.967	4	37.742	2.846	0.023
ApoE ε4 (positive vs negative)	6.770	1	6.770	0.510	0.475
HC quintile * ApoE ε4 interaction	134.054	4	33.513	2.527	0.039
Error	18089.784	1364	13.262		
Total	30168.596	1378			

Figure 5. Regression model illustrating the estimated marginal means of K-MMSE for each head circumference quintile group*



* Analysis of covariance (ANCOVA)

Q1: first quintile (47.8 cm ≤ HC < 53 cm), Q2: second quintile (53 cm ≤ HC < 54 cm), Q3: third quintile (54 cm ≤ HC <54.6 cm), Q4: fourth quintile (54.6 cm ≤ HC < 56 cm), and Q5: fifth quintile (HC ≥ 56 cm)

4. Discussion

The results from our study of community-dwelling elderly people aged over 60 years showed that HC was associated with decreased general cognitive function only in individuals with ApoE ε4. This association was present even after adjustment for all other confounding factors, such as age, sex, educational level, height, and weight. Our investigation supports previous studies in which it was shown that a combination of the ApoE genotype and small HC could be an indicator of cognitive impairment. In a study of 1985 Japanese-Americans, Graves et al found that HC could predict the severity of cognitive impairment, with the smallest HC predicting the greatest impairment (37). Another study (38) reported an increased risk for AD (OR = 2.9, 95% CI: 1.4 to 6.1) associated with the lowest 20th percentile of HC in women in a population-based sample even after adjustment for the age, education level, and ethnicity; the OR for men was 2.3 (95% CI: 0.6 to 9.8). However, the results of brain imaging studies in which MRI or CT was used to examine the relationship between brain volume and the age of onset of AD gave contradictory results (32,41,42).

The use of HC as an index of maximal brain size was motivated by the ease of measurement, and it was also shown to have a high correlation with the brain volume. Brain volume decreases with age as atrophy increases, and the brain becomes more susceptible to alcohol abuse and degenerative brain diseases such as AD. Unlike brain volume, HC is largely determined by the external size of the skull and is unaffected by brain atrophy (33). In vivo measurements of brain size can be obtained from

brain imaging techniques such as MRI. These procedures are highly accurate but expensive and therefore cannot be readily applied to large samples. Measurement of HC is simpler, more economical, and more widely accessible than imaging, and it has been validated as a predictor of brain volume in other studies. Previous studies on the correlation of HC with intracranial volume have shown that, in general, there is a positive correlation of 0.5–0.8 (43,44). It has been reported that HC by itself could predict cognitive function. However, HC is one of many brain reserves such as the intracranial volume, and total brain volume and final brain growth are at least partly genetically controlled and associated with deprivation during early life such as nutrition, educational attainment, or a combination of these. Therefore, when assessing the association between HC and cognitive function, we must correct for potential confounders such as age, education, gender, height, and weight (45). Apart from HC, some anthropometric measurements such as limb length and body height were also associated with cognitive impairment (46,47). Among the various physical measurements, HC has shown consistent correlation with cognitive function.

Our results also suggest that HC, which is an index of brain reserve, may mediate a relatively large effect on cognition in individuals with the ApoE ε4 genotype who are genetically predisposed to AD. Mirroring previous findings, the presence of the ApoE ε4 allele shifts the onset of AD toward an earlier age (48,49) and leads to faster pathologic progression of AD lesions (42,50,51). Borenstein-Graves et al showed that HC was related to the incidence of AD in initially nondemented older persons followed longitudinally who carried one or more ε4 alleles but was

unrelated in people who did not carry this allele (39). Further, more than one ApoE ε4 allele acted as a strong risk factor that hastened the age of onset (52), and the risk of AD in first degree relatives is increased in proportion to the number of ApoE ε4 alleles (53).

These findings collectively suggest that cognitive function is influenced not only by brain neuropathology but also by other factors such as the brain reserve. Therefore, despite the presence of similar pathological lesions in the brain, the clinical manifestations differ from one individual to another, and this can be understood on the basis of the brain reserve hypothesis.

Our study had the following limitations. First, the subjects who participated in this study may not be representative of the elderly aged over 60 years in Korea. As this was a non-random convenience sample cohort, a selection bias might be present. Second, because the K-MMSE used in this study is a screening tool for assessing cognitive function, it has substantial restrictions when the cognitive function is assessed clinically. However, this is a preliminary result of the GDEMCIS, and these subjects underwent comprehensive neuropsychological testing. Third, in this study, brain volume was not measured by brain imaging techniques but by measuring HC, an indirect indicator of brain volume; therefore, it would be unreasonable to generalize HC as being the precise brain reserve or the intracranial volume of the subjects. Fourth, since this was across-sectional study, a regular follow-up that examines the effects of HC and ApoE genotype on the development of dementia and the deterioration of cognitive function would be required.

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IV. ABSTRACTS IN KOREAN

Part I

노인에서 ApoE 유전자형에 따른 대사증후군의 하부진단요소들과 인지기능과의 관계

목적 : 이 연구는 노인 인구에서 ApoE 유전자형이 대사증후군 및 대사증후군의 하부진단요소들과 인지장애와의 관계에 미치는 영향을 알아보기 위해 이루어졌다.

방법 : GDEMCIS (Gwangju Dementia and Mild Cognitive Impairment Study) 자료 중 60세 이상 2944명 (남자 883명 여자 2061명)이 분석에 이용되었다. 대사증후군은 modified NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III)의 진단기준에 의해 평가되었다. 인구사회학적 요인, 현재 및 과거 질환력, 약물력, K-MMSE (Korean version-Mini Mental State Examination)를 조사하였다. ApoE 유전자형을 조사하여 대사증후군과 관련된 요인들을 분석하였다. 이 연구는 연구윤리심의위원회의 승인을 받았다.

결과 : 대사증후군은 전체 대상자 중에서 53.8%였으며, 남자 중에서 36.8%, 여자 중에서 61.1%였다. 다중로지스틱회귀분석에서 대사증후군은 나이, 성별, 교육수준, 현재 흡연력을 보정하였을 때 인지장애 (K-MMSE score < 18)와 통계적으로 유의한 관련이 없었다. 다중로지스틱회귀분석에서 대사증후군의 5개 하부진단요인 중 ApoE ε4 대립유전자가 존재할 경우에만 나이, 성별, 교육수준, 현재 흡연력을 보정하였을 때 수축기혈압 또는 혈중 중성지방이 높을수록 (OR = 1.03, 95% CI

= 1.00-1.06; OR = 1.006 , 95% CI = 1.00-1.01) 또는 혈중 고밀도지단백 콜레스테롤이 낮을수록 (OR = 0.96, 95% CI = 0.92-1.00) 인지저하 (K-MMSE score < 18)의 위험도를 높였다.

결론 : 이는 노인 인구에서 ApoE ε4 대립유전자가 존재할 경우 수축기 혈압과 혈중 중성지방 및 고밀도지단백 콜레스테롤이 인지기능과 관련이 있음을 의미한다.

핵심어구: 대사증후군, 인지장애, K-MMSE, 노인, ApoE 유전자형

Part II

노인에서 ApoE 유전자형에 따른 머리둘레와 인지기능과의 관계

목적: 이 연구는 노인 인구에서 ApoE 유전자형이 머리둘레와 인지기능의 관계에 미치는 영향을 알아보기 위해 이루어졌다.

방법 : GDEMCIS (Gwangju Dementia and Mild Cognitive Impairment Study) 자료 중 60세 이상 1902명 (남자 599명 여자 1303명)이 분석에 이용되었다. 모든 대상자는 한국형 간이정신상태검사(K-MMSE)를 평가받았고, 머리둘레 및 ApoE 유전자형을 검사하였다. 이 연구는 연구윤리심의위원회의 승인을 받았다.

결과 : 머리둘레는 K-MMSE 점수 (r = 0.24, p < 0.01), 나이 (r = -0.46, p < 0.01), 교육수준 (r = 0.57, p < 0.01), 키 (r = 0.40, p < 0.01), 몸무게 (r = 0.30, p < 0.01)와 양의 상관관계를 나타내었다. 공분산에서 나이, 성별, 교육수준, 키, 몸무게를 보정한 후 머리둘레와 K-MMSE의 관계에 대한 ApoE ε4 대립유전자의 상호작용을 확인하였다. ApoE ε4 대립유전자의 상태에 따른 단순 주효과 분석에 의하면, ApoE ε4 (-) 집단에서는 머리둘레 5분위간 K-MMSE의 평균이 차이가 나지 않지만 (F = 0.517, df = 41,148, p = 0.723), ApoE ε4 (+) 집단에서는 머리둘레 5분위간 K-MMSE의 평균이 차이가 났다 (F = 4.163, df = 4,211, p = 0.003).

결론: 이는 노인 인구에서 ApoE ε4 대립유전자가 뇌예비력이 낮을 경우에만 인지기능에 영향을 줄 가능성을 시사한다.

핵심어구: 머리둘레, 인지기능, K-MMSE, 노인, ApoE 유전자형, 뇌예비력