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Relationship between Metabolic Syndrome and Intracranial Atherosclerosis According to Age

Eun Joo Chung, MD[1], Xuexiu Li, MD[2], Jung Hwa Seo, MD[1], and Eung-Gyu Kim, MD, PhD[1]

[1]Department of Neurology, Inje University College of Medicine, Busan Paik Hospital, Busan, Korea
[2]Department of Neurology, Beijing Capital Medical University, Sanbo Brain Hospital, Beijing, China

Background: Although metabolic syndrome (MetS) is associated with intracranial large artery disease (IC-LAD), no systematic study has been conducted according to patient age. Thus, we evaluated the association between MetS and IC-LAD according to age. **Methods:** Acute ischemic stroke patients over 40 years of age with IC-LAD confirmed by CT angiography were enrolled. The patients were divided into 2 groups according to age, with 65 as the cut-off point. Vascular risk factors and laboratory results were compared between the two groups, and multivariate analysis was performed to verify the independent factors associated with IC-LAD. **Results:** One hundred and sixty-one patients had IC-LAD. The older patients (>65 years) had higher systolic blood pressure (SBP) (*P*=0.041) and triglyceride (TG) (*P*=0.0146). In the older group, there was a high prevalence of women (*P*=0.0006), nonsmokers (*P*=0.0001) and multiple (≥2) numbers of IC-LADs (*P*=0.0094). In the multiple logistic regression analysis for each component of MetS as a risk factor of IC-LAD, diabetes mellitus (DM) (*P*=0.0407) and high TG (≥150) (*P*=0.018) were significantly correlated with IC-LAD in the older group. **Conclusion:** High SBP and TG are predominantly observed in elderly patients. In particular, the older group has a high prevalence of women, nonsmoker and multiple IC-LADs (≥2). Among the components of MetS, DM and high TG are important risk factor for IC-LAD in the older group.

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KEY WORDS: Metabolic syndrome · Intracranial large artery · Atherosclerosis.

Introduction

Metabolic syndrome (MetS) plays an important role in the development of carotid intima-media thickness (IMT).[1] A greater number of components of MetS corresponds to higher risk of cardiovascular disease (CVD).[2] According to the National Cholesterol Education Program-Adult Treatment Panel III criteria, MetS is particularly associated with CVD in men aged ≥45 years and women aged ≥55.[3] Based on these results, an association between MetS and intracranial atherosclerotic stroke was reported.[4-7] Moreover, the incidence of stroke increases with age.[8] Intracranial atherosclerosis is known to be more prevalent than extracranial atherosclerosis in the Korean population.[9] In addition, both the components of MetS and the number of MetSs are associated with intracranial large artery disease (IC-LAD).[9] However, most studies of MetSs have focused on the stroke subtype or individual components of MetS.[7,9,10] No systematic study has analyzed each component of MetS according to the ages of patients with IC-LAD. In addition, hypertension, diabetes, MetS, abdominal obesity, and hypertriglyceridemia are predictors of CV risk in elderly individuals.[11]

Therefore, we studied the clinical risk factors of IC-LAD, including each component of MetS, in the patients with IC-LAD, grouped according to age. We analyzed abnormal risk factors of MetS and the number of IC-LADs according to age. Finally, we investigated the risk factors of MetS associated with IC-LAD according to age.

Methods

We collected consecutive patients with acute first ischemic strokes who had diffusion-weighted MRI abnormalities. Patients over 40 years old were registered. We included only large artery atherosclerosis, which we defined according to the Trial of Org 10172 in Acute Stroke Treatment.[12] For the diagnosis of IC-LAD, we enrolled 161 patients with intracranial disease, and their CT angiography (CTA) was reviewed by

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Address for correspondence: Eung-Gyu Kim, MD, PhD
Department of Neurology, Inje University College of Medicine, Busan Paik Hospital, 75 Bokji-ro, Busanjin-gu, Busan 614-110, Korea
Tel: +82-51-890-8641, Fax: +82-51-895-6367
E-mail: kgstroke@korea.com

two neurologists (JHS, EGK) who were blinded to the clinical data (P>0.05). First, we measured the abdominal circumference, weight and height; then, we calculated the body mass index (BMI). We measured the C-reactive protein (CRP), lipid profile (low density lipoprotein-cholesterol, LDL-C; triglyceride, TG; total cholesterol; and high density lipoprotein-cholesterol, HDL-C), fasting glucose, and hemoglobin $A1_C$ ($HbA1_C$) and performed echocardiography, electrocardiogram, and CTA. Patients with cardiac problems, such as atrial fibrillation, were excluded after the echocardiogram. Stroke in more than one vascular territory or systemic embolism supports a clinical diagnosis of cardiogenic stroke.[12] Subjects who had a medical history of transient ischemic attack, previous stroke or coronary heart disease were excluded. Patients who had traditional clinical lacunar syndromes and no evidence of cortical dysfunction were also excluded because strokes in these patients are often labeled as lacunar infarcts.[12] The diagnosis of MetS essentially followed the ATP-III guidelines and was defined as the presence of three or more of the following risk factors:[9] 1) abdominal obesity (≥90 cm for men and ≥80 cm for women);[13] 2) elevated TG (≥150 mg/dL); 3) HDL <40 mg/dL for men and HDL <50 mg/dL for women; 4) elevated blood pressure [systolic blood pressure (SBP) ≥130 mm Hg and diastolic blood pressure (DBP) ≥85 mm Hg] or use of antihypertensive medication; and 5) impaired fasting glucose ≥110 mg/dL or use of antidiabetic medication due to diabetes mellitus (DM). In addition, subjects who had a medical history of transient ischemic attack, stroke or coronary heart disease were excluded. Patients who had traditional clinical lacunar syndromes and no evidence of cortical dysfunction were also excluded because strokes in these patients are often labeled as lacunar infarcts.

Because the mean age of the total patients was 62.68±12.11 (median; 65), we divided the patients into the following two subgroups according to age: ≤65 and >65. This study was approved by the local ethics committee, and informed consent was obtained from all participants.

Statistical analyses

The descriptive statistics of the continuous variables in the two groups, divided by age, are expressed as means±standard deviation (SD). The descriptive statistics for categorical variables are also expressed as means±SD. To analyze the difference between two groups, we used the t-test for continuous variables and the chi-square test for categorical variables. In the multiple logistic regression analysis, we investigated the risk factors associated with IC-LAD according to age and using each component of MetS. For the multiple logistic regression analysis, we analyzed factors selected by the backward selection. Statistical analyses were performed using the R language, ver. 3.01 (R Foundation for Statistical Computing, Vienna, Austria). A P value<0.05 was considered statistically significant.

Results

One hundred and sixty-one patients were classified as having IC-LAD. There were no statistically significant differences between groups (≤65 years and >65 years) in abdominal circumference, BMI, DBP, fasting blood sugar (FBS), HbA1c, CRP, HDL and LDL. SBP (P=0.041) and TG (P=0.0146) in patients over the age of 65 were higher than in patients 65 and under (Table 1).

Women (P=0.0006), nonsmokers (P=0.0001) and patients with multiple IC-LADs (≥2) (P=0.0094) were more prevalent in patients over the age of 65 (Table 2).

TABLE 1. Demographic characteristics of patients according to age (for continuous variables)

	Age ≤65 (n=82)		Age >65 (n=79)		*P*-value
	Mean	SD	Mean	SD	
Age (year)	53.7	9.92	72.1	4.89	<0.0001*
Abdominal circumference (cm)	89.5	9.11	89.2	8.88	0.8555
BMI (kg/m^2)	24.0	3.45	23.4	2.85	0.2486
SBP (mm Hg)	136.7	25.14	144.7	23.96	0.0410*
DBP (mm Hg)	82.7	14.33	86.1	13.05	0.1192
FBS (mg/dL)	121.7	38.06	122.1	40.03	0.9538
HbA1c	6.2	1.46	6.3	1.48	0.6793
CRP (mg/dL)	0.6	1.24	0.8	2.00	0.3944
TG (mg/dL)	112.0	61.94	143.6	61.94	0.0146*
HDL-C (mg/dL)	45.3	12.02	46.5	10.83	0.5019
LDL-C (mg/dL)	119.5	35.02	116.0	36.37	0.5362

*P-value<0.05. SD: standard deviation, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FBS: fasting blood sugar, HbA1c: hemoglobin A1C, CRP: C-reactive protein, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol

Multiple logistic regression analysis showed that, of the MetS components, DM (*P*=0.0407) and abnormal TG (≥150) (*P*=0.018) were significant risk factors for IC-LAD in patients over 65 (Table 3). However, there was no association between the clinical components of MetS and IC-LAD in patients 65 and younger.

TABLE 2. Demographic characteristics of patients according to age (for categorical variables)

	Age ≤65 (n=82)		Age >65 (n=79)		*P*-value
	n	%	n	%	
Sex					
Men	61	37.89	37	22.98	
Women	21	13.04	42	26.09	0.0006*
Abdominal obesity					
<90 for men, <80 for women	25	18.38	24	17.65	
≥90 for men, ≥80 for women	47	34.56	40	29.41	0.8746
Abnormal BMI					
<25	52	35.14	54	36.49	
≥25	24	16.22	18	12.16	0.4809
Smoke					
Non-smoker	38	23.60	62	38.51	
Smoker	44	27.33	17	10.56	0.0001*
Abnormal blood pressure					
SBP <130 and DBP <85	48	30.57	40	25.48	
SBP ≥130 and DBP ≥85	30	19.11	39	24.84	0.2241
Abnormal FBS					
<110	41	25.47	41	25.47	
≥110	41	25.47	38	23.60	0.9337
DM					
No DM	56	34.78	50	31.06	
DM	26	16.15	29	18.01	0.6151
Abnormal HbA1c					
<6.5	54	36.24	56	37.58	
≥6.5	20	13.42	19	12.75	0.9611
Abnormal CRP					
≤0.3	55	34.59	44	27.67	
>0.3	27	16.98	33	20.75	0.2596
Abnormal TG					
<150	57	35.40	63	39.13	
≥150	25	15.53	16	9.94	0.1905
Abnormal HDL-C					
<40 for men, <50 for women	46	28.57	43	26.71	
≥40 for men, ≥50 for women	36	22.36	36	22.36	0.9568
Abnormal LDL-C					
≥100 for men, ≥100 for women	24	14.91	26	16.15	
<100 for men, <100 for women	58	36.02	53	32.92	0.7421
Number of LAS					
1	56	34.78	37	22.98	
≥2	26	16.15	42	26.09	0.0094*
MetS					
No	52	32.30	52	32.30	
Yes	30	18.63	27	16.77	0.8771

*P-value<0.05. BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FBS: fasting blood sugar, DM: diabetes mellitus, HbA1c: hemoglobin A1C, CRP: C-reactive protein, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, LAS: large artery stenosis, MetS: metabolic syndrome

TABLE 3. Multiple logistic regression analysis of risk factors associated with intracranial large artery stenosis according to age (using the components of metabolic syndrome)

	Age ≤65 (n=82)			Age >65 (n=79)		
	Coefficient	SE	*P*-value	Coefficient	SE	*P*-value
Intercept	-1.275	1.077	0.2365	-0.863	0.576	0.1343
Sex	1.056	0.565	0.0616	-0.288	0.634	0.6495
Abdominal obesity				1.198	0.643	0.0625
Abnormal BMI						
Smoker						
Abnormal blood pressure						
Abnormal FBS						
DM				1.247	0.609	0.0407*
Abnormal HbA1c						
Abnormal CRP						
Abnormal TG	-1.196	0.648	0.0649	1.804	0.763	0.0180*
Abnormal HDL-C						
Abnormal LDL-C	-1.099	0.757	0.1469	1.005	0.614	0.1017

**P*-value<0.05. BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FBS: fasting blood sugar, HbA1c: hemoglobin A1c, CRP: C-reactive protein, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol

Discussion

In this study, patients over 65 had higher SBP and TG than patients 65 and younger. Elevated blood pressure is known to be one of the most important risk factors of MetS.[4,14] SBP in persons over 50 years of age is a more predictive risk factor of CVD than DBP.[14] Hypertriglyceridemia is a predictor of CV risk in elderly individuals.[11] Interestingly, in our study, patients over the age of 65 had relatively higher TG levels, despite exhibiting no differences in overweight and obesity measures from the 65 and under group. This result suggests that high TG is a risk factor for MetS and that this risk factor is independent of overweight and obesity measures in elderly patients.

Men and smokers are relatively common among the IC-LAD patients 65 and under, and women and nonsmokers are more common in patients over 65 years. We suggest that one of the reasons for these results is that elderly Korean women have low rates of smoking. In addition, life expectancy is higher among women and non-smokers. The higher prevalence of women and non-smokers in the elderly group could be a result of these factors.

Despite these demographic characteristics, multiple numbers of IC-LADs (≥2) were observed in the older patients. Thus, this study suggests that old age, and not demographic characteristics, is the largest contributor to IC-LAD.

The incidence of MetS increases steeply with age,[15,16] and MetS is more prevalent in men than women.[17] However, our results do not show a higher prevalence of MetS in the older age group. These results suggest that IC-LAD in elderly patients is related to other factors, such as sex hormones-despite these being a controversial risk factor.[18] A positive correlation between carotid IMT and follicular stimulating hormone may reflect an association between low estrogen and IMT.[19]

Multiple logistic regression analysis showed that DM is a contributing risk factor for IC-LAD among elderly patients (especially those over 65). In the general population, despite good control of DM, patients with DM have a greatly increased risk of stroke at all ages.[20] In particular, DM increases large artery diseases.[21] Although there was no difference in the FBS, HbA1c and DM measures between the two groups in this study, the presence of DM was a risk factor for IC-LAD in patients older than 65 years. In addition, high TG is one of the risk factors of MetS and is associated with an increased risk of CVD.[4,22] The independent association of DM and high TG with IC-LAD only in the elderly group suggests that IC-LAD in the younger age group may be related to other pathologies (i.e., aortic dissection, vasculitis, moyamoya disease, atherosclerosis, etc.).[23,24] Thus, these results suggest that the management of DM and high TG is an important strategy for reducing IC-LAD in elderly patients.

One limitation of our study is the high prevalence of women and nonsmokers, which may have led to results that differ from general IC-LAD patients. In summary, our results suggest that the control of elevated BP, DM and high TG in elderly patients is an important step to reduce IC-LAD.

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REFERENCES

1. Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid intimal-medial

thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. *Circulation* 2001;104:2815-9.
2. Klein BE, Klein R, Lee KE. Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in Beaver Dam. *Diabetes Care* 2002;25:1790-4.
3. Lorenzo C, Williams K, Hunt KJ, Haffner SM. The National Cholesterol Education Program - Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. *Diabetes Care* 2007;30:8-13.
4. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;112:2735-52.
5. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005;365:1415-28.
6. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. *Lancet* 2005;366:1059-62.
7. Bang OY, Kim JW, Lee JH, Lee MA, Lee PH, Joo IS, et al. Association of the metabolic syndrome with intracranial atherosclerotic stroke. *Neurology* 2005;65:296-8.
8. Marini C, Triggiani L, Cimini N, Ciancarelli I, De Santis F, Russo T, et al. Proportion of older people in the community as a predictor of increasing stroke incidence. *Neuroepidemiology* 2001;20:91-5.
9. Park JH, Kwon HM, Roh JK. Metabolic syndrome is more associated with intracranial atherosclerosis than extracranial atherosclerosis. *Eur J Neurol* 2007;14:379-86.
10. Imamura T, Doi Y, Arima H, Yonemoto K, Hata J, Kubo M, et al. LDL cholesterol and the development of stroke subtypes and coronary heart disease in a general Japanese population: the Hisayama study. *Stroke* 2009;40:382-8.
11. Cabrera MA, de Andrade SM, Mesas AE. A prospective study of risk factors for cardiovascular events among the elderly. *Clin Interv Aging* 2012;7:463-8.
12. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;24:35-41.
13. WHO/IASO/IOTF. *The Asia-Pacific perspective: redefining obesity and its treatment.* Melbourne: Health Communications Australia. 2000.
14. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560-72.
15. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 2002;287:356-9.
16. Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988-1994. *Arch Intern Med* 2003;163:427-36.
17. Novak M, Björck L, Welin L, Welin C, Manhem K, Rosengren A. Gender differences in the prevalence of metabolic syndrome in 50-year-old Swedish men and women with hypertension born in 1953. *J Hum Hypertens* 2013;27:56-61.
18. Canderelli R, Leccesse LA, Miller NL, Unruh Davidson J. Benefits of hormone replacement therapy in postmenopausal women. *J Am Acad Nurse Pract* 2007;19:635-41.
19. Celestino Catão Da Silva D, Nogueira De Almeida Vasconcelos A, Cleto Maria Cerqueira J, De Oliveira Cipriano Torres D, Oliveira Dos Santos AC, De Lima Ferreira Fernandes Costa H, et al. Endogenous sex hormones are not associated with subclinical atherosclerosis in menopausal women. *Minerva Ginecol* 2013;65:297-302.
20. Khoury JC, Kleindorfer D, Alwell K, Moomaw CJ, Woo D, Adeoye O, et al. Diabetes mellitus: a risk factor for ischemic stroke in a large biracial population. *Stroke* 2013;44:1500-4.
21. Kim BJ, Lee SH, Kang BS, Yoon BW, Roh JK. Diabetes increases large artery diseases, but not small artery diseases in the brain. *J Neurol* 2008;255:1176-81.
22. Lemieux I, Pascot A, Couillard C, Lamarche B, Tchernof A, Alméras N, et al. Hypertriglyceridemic waist: A marker of the atherogenic metabolic triad (hyperinsulinemia; hyperapolipoprotein B; small, dense LDL) in men? *Cirulation* 2000;102:179-84.
23. Sato S, Toyoda K, Matsuoka H, Okatsu H, Kasuya J, Takada T, et al. Isolated anterior cerebral artery territory infarction: dissection as an etiological mechanism. *Cerebrovasc Dis* 2010;29:170-7.
24. Miyawaki S, Imai H, Shimizu M, Yagi S, Ono H, Mukasa A, et al. Genetic variant RNF213 c.14576G>A in various phenotypes of intracranial major artery stenosis/occlusion. *Stroke* 2013;44:2894-7.