

Significant associations of metabolic syndrome and its components with silent lacunar infarction in middle aged subjects

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ABSTRACT

Background: Metabolic syndrome (MetS) is associated with an increased risk of ischaemic stroke, including silent brain infarction. No study has examined its association with the lacunar subtype. The present cross sectional study examined the relationship between MetS, its components and silent lacunar infarction (SLI) in middle aged subjects.

Methods: We studied 2076 subjects aged 40–59 years with no history of stroke or clinical symptoms, who visited a health care facility for a routine health checkup and underwent brain MRI. MetS was defined according to the National Cholesterol Education Programme Adult Treatment Panel III report. A multiple logistic regression model was used to examine the associations between MetS and SLI while adjusting for age, gender, a past history of ischaemic heart disease and current smoking.

Results: MetS was strongly associated with the presence of SLI (adjusted OR 6.52; 95% CI 4.30 to 9.90). Regarding MetS components, elevated blood pressure, impaired fasting glucose, hypertriglyceridaemia and large waist circumference were significantly associated with SLI, independent of an interrelationship between the components, while low high density lipoprotein cholesterol was not significantly associated.

Conclusions: MetS was significantly associated with the prevalence of SLI in middle aged persons. Independent risk factors for SLI not only included elevated blood pressure and impaired fasting glucose, which are well known risk factors, but also hypertriglyceridaemia and large waist circumference.

Silent brain infarction is found incidentally by brain imaging in individuals who have not yet demonstrated any symptoms or neurological deficits. It is considered the precursor of clinical strokes and cognitive impairment.¹ Several studies have consistently found that advanced age and hypertension are risk factors for silent brain infarction.² A recent cross sectional study has reported that clustering of risk factors for ischaemic heart disease (IHD) (ie, metabolic syndrome (MetS)),³ is associated with ischaemic stroke, including silent brain infarction.⁴

Silent brain infarction is composed of two subtypes: the lacunar type resulting from occlusion of a single small perforating artery⁵ and the non-lacunar type resulting from embolism⁶ and atherosclerotic stenosis.⁷ The advancement of MRI technology enables neurologists and neurosurgeons to distinguish the lacunar subtype from the non-lacunar subtype of silent brain infarction.⁸ Because the lacunar and non-lacunar infarcts of ischaemic

stroke have different vascular pathologies,⁹ differences in risk factors should be examined between the two subtypes, even in the case of silent brain infarction. If there are treatable risk factors that are distinctively associated with silent lacunar infarction (SLI), a specific strategy for preventing lacunar infarcts may be developed, especially in middle aged individuals who have not had cerebrovascular events

In the present cross sectional study, we examined the associations of MetS and its components with SLI in middle aged subjects.

SUBJECTS AND METHODS

Study subjects

A total of 2076 subjects, aged 40–59 years, replied to an invitation by their health insurance for a routine health checkup and voluntarily visited the Kochi Healthcare Centre, which is affiliated with the Kochi Medical School Hospital, Kochi prefecture, Japan. Participants completed a questionnaire survey on lifestyle characteristics and medical history, blood analysis and brain MRI from September 2005 to December 2006. The present analysis included 2076 persons with no history of stroke who had effective values for all study variables. All persons gave informed consent and the study was approved by the institutional review board at Kochi Healthcare Centre.

Definition of MetS

We used the definition of MetS proposed by the National Cholesterol Education Programme Adult Treatment Panel III (NCEP-ATP III) report.³ Persons were diagnosed with MetS when three or more of the following conditions were present: elevated blood pressure (BP), impaired fasting glucose (IFG), hypertriglyceridaemia (hyper-TG), low high density lipoprotein cholesterol (low HDL-C) and abdominal obesity defined by a large waist circumference (WC). Specifically, IFG was defined as fasting glucose levels ≥ 110 mg/dl. Elevated BP was defined as systolic BP levels ≥ 130 mm Hg or diastolic BP levels ≥ 85 mm Hg. Hyper-TG was determined based on serum triglyceride levels ≥ 150 mg/dl. Low HDL-C was identified by serum HDL-C levels < 40 mg/dl in men or < 50 mg/dl in women. Each condition was also considered to be present in subjects who reported current medication for the condition. Measurements for the four components were conducted in the laboratory of the centre. A large WC was defined as ≥ 102 cm in men or ≥ 88 cm in women. In the present study, we also used an

ethnic specific value for large WC that was proposed by the new International Diabetes Federation (IDF) definition¹⁰ (ie, ≥ 90 cm in men or ≥ 80 cm in women). Trained nurses measured the WC of the examinee with a light expiration at the midpoint between the iliac crest and the lower margin of the rib. The measured value was rounded down to the nearest centimetre.

SLI diagnosis

MRI examinations were performed using 0.4 T open MRI (APERTO, Hitachi Medical Corporation, Tokyo, Japan). The imaging protocol consisted of: T2 weighted images (repetition time/echo time (TR/TE) 5800/105 ms), T1 weighted images (TR/TE 350/13.6 ms) and fluid attenuated inversion recovery (FLAIR; TR/TE 9000/105 ms; inversion time 2200 ms) images. SLI was defined as a focal lesion of ≥ 3 mm in diameter, with signal intensity corresponding to liquor (such as hyperintense on T2 weighted images and hypointense on T1 weighted and FLAIR images). Dilated perivascular spaces were distinguished from SLI based on their location (along perforating or medullary arteries, often bilaterally symmetrical, usually in the lower third of the basal ganglia) and by the absence of gliosis. Two of the three trained neurosurgeons (KP, ST and HN), who were blinded to the subject history and diagnosis, assessed independently the presence of SLI on MR images. If the decision of two investigators was discrepant, SLI was determined by consensus of the three neurosurgeons.

Statistical analyses

Multiple logistic regression models were fitted to determine the associations of MetS and its components with SLI while controlling for age, gender, a past history of IHD and current smoking. In the models that examined the associations between MetS components and SLI, five components were entered simultaneously. All p values were two tailed, and values of $p < 0.05$ were considered significant. All statistical analyses were

performed using SPSS15.0 J for Windows (SPSS Japan, Inc., Tokyo, Japan).

RESULTS

Mean age of the subjects was 50.9 (SD 5.5) years. There were 1093 men and 983 women. The number of subjects with MetS was 188 (9.1%). A total of 118 (5.7%) were diagnosed with SLI. Subjects with SLI were older (52.5 vs 50.9 years), male dominant (72.0% vs 51.5%) and more likely to have MetS (37.3% vs 7.4%) in comparison with those without SLI. There was no difference between the two groups for the prevalence of a past history of IHD (0.8% vs 0.9%) or current smokers (28.8% vs 25.7%).

The presence of MetS was significantly associated with the prevalence of SLI, regardless of cut-offs for WC (table 1). The shift in cut-offs for WC to the lower range strengthened the association.

In terms of MetS components (table 1), elevated BP, IFG, hyper-TG and large WC were significantly associated with SLI, independent of the inter-relationship between the components. On the other hand, low HDL-C was not significantly associated with SLI. When we grouped WC into three categories with two cut-offs (one used in the new IDF definition and the other used in the NCEP-ATP III definition), a large WC ≥ 102 cm for men and ≥ 88 cm in women was significantly associated with SLI compared with a normal waist circumference (< 90 cm in men, < 80 cm in women). An intermediate waist circumference (≥ 90 and < 102 cm for men, ≥ 80 and < 88 cm for women) also increased the risk of SLI.

DISCUSSION

The present study demonstrated a strong association between MetS defined by NCEP-ATP III criteria and SLI in middle aged subjects. Kwon *et al* reported an association between MetS, defined by a modified version of the NCEP-ATP III criteria, and silent brain infarctions composed of lacunar, atherosclerotic and

Table 1 Adjusted odds ratios* of SLI for the presence of metabolic syndrome and its components in middle aged subjects (n = 2076)

Criteria or components	Metabolic syndrome	n	% of SLI	Adjusted OR (95% CI)	p Value
When waist circumference was dichotomised at 101/102 cm for men and 87/88 cm for women	Present	188	23.4	6.52 (4.30–9.90)	<0.001
	Absent	1888	3.9	1 (Reference)	
When waist circumference was dichotomized at 89/90 cm for men and 79/80 cm for women	Present	362	21.8	8.35 (5.59–12.5)	<0.001
	Absent	1714	2.3	1 (Reference)	
Components of metabolic syndrome†					
Elevated blood pressure	Present	738	11.5	2.94 (1.90–4.56)	<0.001
	Absent	1338	2.5	1 (Reference)	
Impaired fasting glucose	Present	376	16.0	2.68 (1.77–4.05)	<0.001
	Absent	1700	3.4	1 (Reference)	
Hypertriglyceridaemia	Present	532	12.4	2.82 (1.83–4.33)	<0.001
	Absent	1544	3.4	1 (Reference)	
Low high density lipoprotein cholesterol	Present	101	10.9	0.71 (0.34–1.47)	0.352
	Absent	1975	5.4	1 (Reference)	
Large waist circumference	≥ 102 cm for men, ≥ 88 cm for women	248	12.9	4.30 (2.40–7.71)	<0.001
	$90 \leq$ and < 102 cm for men, $80 \leq$ and < 88 cm for women	539	8.0	1.95 (1.23–3.09)	0.004
	< 90 cm for men, < 80 cm for women	1289	3.3	1 (Reference)	

*Adjustment was made by fitting a logistic regression model for age in years, gender, a past history of ischaemic heart disease and current smoking.

†All of the five components were included simultaneously in a logistic regression model with adjustment for the covariates.

SLI, silent lacunar infarction.

embolic infarctions in Korean subjects (aged 20–86 years).⁴ They used the same ethnic and gender specific values as us, based on the new IDF definition of MetS. When age, gender, a history of coronary artery disease and high sensitivity C reactive protein were adjusted for, the association between MetS and silent brain infarction that they presented was weaker (adjusted odds ratio (OR) 2.18; 95% confidence interval (CI) 1.38 to 3.44) than what we found. In Kwon *et al's* study, two components (elevated BP and IFG) significantly raised the risk of silent brain infarction, while four of five components were significantly associated with SLI in the present study. The differences in the strength of the association across studies could be accounted for by the differences in the age and gender distributions of the study subjects, the potential confounding factors adjusted for, component specific associations and types of silent brain infarction examined.

Elevated BP and IFG were independent risk factors for SLI after adjusting for inter-relationships among each MetS component. The finding is plausible because hypertension and diabetes mellitus have been regarded as risk factors associated with lipohyalinosis in small perforating arteries and the subsequent lacunar infarction.^{11 12} The unique finding of the present study is that hyper-TG and large WC were also significant risk factors for SLI, independent of the other components. Hyper-TG should attract attention as a modifiable factor that may contribute to the vascular pathology of lacunar infarction, irrespective of elevated BP and IFG. When defining MetS, body mass index (BMI) can be used in place of WC. When we chose BMI as a component of MetS, we obtained similar adjusted ORs showing the association between MetS and SLI: 8.55 (95% CI 5.68 to 12.9) when using BMI dichotomised at 24/25 and 5.71 (95% CI 3.68 to 8.87) with BMI was dichotomised at 29/30. In evaluating the association between MetS and SLI, it seems to be appropriate to use BMI in place of WC.

Although the strength of the association between MetS and SLI might be inflated because of selection biases, the present

study provides information for neurologists and neurosurgeons about the elevated prevalence of lacunar infarction in apparently healthy individuals with MetS. With regard to MetS components, practitioners need to recognise the importance of exploring not only elevated BP and IFG, which are well known risk factors for SLI, but also hyper-TG and large WC in middle aged subjects.

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Ethics approval: The study protocol was approved by the Institutional Review Board at Kochi Healthcare Centre, Kochi, Japan

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