Significant Association between Leukoaraiosis and Metabolic Syndrome in Healthy

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Article abstract

Objective: To investigate the relationship between leukoaraiosis (LA), which has

been considered as an intermediate substitute of ischemic brain damages, and

metabolic syndrome (MetS) that attracts attention as a risk factor for cerebrovascular

diseases, in healthy subjects derived from various age groups.

Methods: We studied 1,030 healthy persons at ages between 28 and 78 years (mean,

52.7 years) with no past history of stroke who visited a health care facility for routine

health checkups. MetS was defined using the criteria of the National Cholesterol

Education Program Adult Treatment Panel III. LA was assessed using the rating scale

of the Atherosclerosis Risk in Communities study on MRI. Logistic regression

analysis was performed to examine associations between LA and MetS.

Results: A total of 296 (28.8%) subjects had LA on MRI. MetS was significantly

associated with the presence of LA〔adjusted odds ratio (OR), 3.33; 95% confidence

interval (CI), 2.30-4.84〕. The association was constant across grades of LA; the

adjusted OR was 3.41 (95%CI, 2.30-5.06) for minimal LA and 3.07 (95%CI,

1.75-5.38) for LA combining mild, moderate, and severe grades. As for MetS

components, elevated blood pressure (BP) (adjusted OR,2.16; 95%CI, 1.57 -2.99),

impaired fasting glucose (IFG) (adjusted OR,1.64; 95%CI, 1.13-2.39), and

hypertriglyceridemia (hyper-TG) (adjusted OR,1.56; 95%CI, 1.08-2.28)〕 were independently associated with all grades of LA.

Conclusions: MetS was significantly associated with every grade of LA, including the minimal LA. IFG and hyper-TG were associated with LA independently of elevated BP. MetS can play an important role in identifying healthy subjects who have an increased risk of LA.

Key words: cross-sectional study, leukoaraiosis, metabolic syndrome, MRI

Introduction

The term leukoaraiosis (LA) is derived from the Greek *leuko* (white) and *araiosis* (rarefaction), and refers to lesions of altered signal intensities on CT scans and MRIs in the periventricular and subcortical white matter of elderly people.[1-4] Traditionally, the finding of LA has been considered to have no clinical significance because many individuals with LA are asymptomatic[1, 2]. However, there is accumulating evidence from population-based studies that LA is associated with an increased risk of stroke and recurrent stroke, depending on the grade of LA that is present.[5-7] Furthermore, the progression of LA is also significantly associated with cognitive impairments and dementia of Alzheimer type.[8-12] Thus, LA could be considered as an intermediate surrogate of brain dysfunctions including cerebrovascular damages. Prevention of occurrence and progress of LA may contribute to avoiding these serious diseases. It has been shown that the risk factors for LA are advanced age and elevated blood pressure (BP) as well as smoking, alcohol, diabetes, and dyslipidemia.[7, 12, 13] These risk factors are comparable to those of ischemic heart disease (IHD). A set of metabolic and physiological risk factors of IHD, specifically, hypertriglyceridemia (hyper-TG), low high-density lipoprotein cholesterol (HDL-C), elevated BP, abdominal obesity, and impaired fasting glucose (IFG), has been defined as

metabolic syndrome (MetS).[14-17] In recent years, MetS has attracted much attention

as a modifiable condition that increases risks of cerebrovascular events including

stroke[18,19] and silent brain infarction[20]. However, relationship between MetS and LA

has been never studied. It is important to elucidate whether MetS increases the risk of

LA, especially in individuals at middle ages who have not experienced

cerebrovascular events yet. Most previous studies of LA were targeted on

populations composed of the older subjects. [2, 4, 6-9] In the present cross-sectional

study, we examined associations of MetS and its components with LA in healthy

people at ages from 28 to 78 years.

Methods

Study Population.   We studied 1,033 healthy consecutive subjects who, from April

2005 through March 2006, visited Kochi Healthcare Center (KHC), which is

affiliated with Kochi Medical School Hospital (KMSH), Kochi prefecture, Japan,

and underwent a questionnaire survey on medical history and lifestyle, blood

analysis, and brain MRI as part of their routine health checkup. Three subjects who

reported that they had a past history of stroke were excluded from this analysis. No

subject had symptoms or neurological deficits in the physical examination. All

subjects lived in Kochi prefecture. A total of 1,030 subjects who satisfied this

criterion and provided informed consent were included in the study, which was

approved by the institutional review board at KHC.

Vascular Risk Factors.   The evaluation of present history of IHD and MetS

involved data from a questionnaire survey and laboratory results. We used the same

condition-specific cut points for MetS as those proposed in a recent National

Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) report,

with minor modifications. MetS was considered to be present when $\geqq$ 3 of following

were met: IFG, elevated BP, hyper-TG, low HDL-C, and abdominal obesity defined

by a large waist circumference (WC). Specifically, IFG was defined as a fasting

glucose $\geqq$ 110 mg/dL and was also considered to be present in persons reporting

current use of insulin or oral hypoglycemic agents. Elevated BP was defined as a

systolic BP $\geqq$ 130 mm Hg or a diastolic BP $\geqq$ 85 mm Hg; hypertension was also

considered to be present in persons who reported current use of antihypertensive

medication. Hyper-TG was determined based on serum triglyceride levels $\geqq$ 150

mg/dL. Low HDL-C was identified by a serum HDL-C of <40 mg/dL in men or <50

mg/dL in women. Hyper-TG or low HDL-C was also considered to be present in

persons who reported current use of antihyperlipidemia agents. The NCEP-ATP III

report defines a large WC as >102 cm in men or >88 cm in women.[16] However, these

cutoff points are not applicable in an Asian population.[21] Thus, based on

recommendations of the Japan Obesity Association, we adopted the definition of a

large WC as $\geqq$ 85 cm in men and $\geqq$ 90 cm in women.[22]

LA diagnosis and grading. MR imaging 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.

Images were obtained as 27 transaxial slices per scan. The slice thickness was 5 mm,

with no interslice gap. LA was defined as a focal lesion of $\geqq$ 3 mm in diameter, with

hyperintensity on T2-weighted and FLAIR images and without prominent

hypointensity on TI-weighted images. LA grading was done according to the

Atherosclerosis Risk in Communities Study (ARIC) as follows.[3, 6] no white matter

signal abnormalities (grade 0); discontinuous periventricular rim or minimal "dots" of

subcortical white matter (grade 1); thin continuous periventricular rim or few patches

of subcortical white matter hyperintensity (WMH) (grade 2); thicker continuous

periventricular rim with scattered patches of subcortical WMH (grade 3); thicker,

shaggier periventricular rim with mild subcortical WMH—may have minimal

confluent PVH (grade 4); mild periventricular confluence surrounding the frontal and

occipital horns (grade 5); moderate periventricular confluence surrounding the frontal

and occipital horns (grade 6); periventricular confluence with moderate involvement

of the centrum semiovale (grade 7); periventricular confluence involving most of the

centrum semiovale (grade 8); and all white matter involved (grade 9). The ARIC

MRI standard images were graded 1 through 8: anything less than grade 1 was

considered grade 0, and anything more than grade 8 was considered grade 9. Finally,

LA was classified as:none, grade=0; minimal, grades=1-3; mild, grades=4 and 5;

moderate, grades=6 and 7; and severe, grades=8 and 9. Five trained neurosurgeons

(KP, ST, SY, HN, and MN) blinded to subject data and diagnosis assessed the

presence of LA on magnetic resonance images. When the 5 investigators had

differing opinions, LA classification was determined by consensus.

Statistical Analysis.   In order to analyze the relationship between study variables

and LA, we used the chi-square test for categorical data and the Student t-test for

continuous data that were logarithmically transformed. Multiple logistic regression

models were fit to determine the associations of MetS and its components with LA

while controlling for age, gender, present history of IHD, and current smoking as

possible confounders. MetS component conditions were included as dichotomous variables based on the NCEP-ATP III–defined cut points. Two kinds of regression model were fit: model 1 and model 2. In model 1, the component conditions of MetS were entered into a model separately; in model 2, five components of MetS were entered into a model simultaneously. The model 2 was constructed to examine an association between each component and LA when considering interrelationship between five components. In particular, because elevated BP is a condition whose association with LA has already been established, we thought that it was necessary to perform an analysis which addressed confounding effects of elevated BP on the associations between other MetS components and LA. A multinomial logistic regression model was fit to describe the associations between MetS and different categories of LA grades. This single model produced separate odds ratios showing associations between MetS and each category of LA grade when none was designated as the reference category of LA. Each of the other categories of LA was compared with this reference. Three categories of LA greater than or equal to mild, i.e., severe, moderate, and mild, were combined due to small numbers of subjects with those grades of LA. Age, gender and current smoking were included as covariates in the multinomial regression. All P values were 2-tailed, and values of

P<0.05 were considered significant. All statistical analyses were performed using

SPSS14.0 J for Windows (SPSS Japan, Inc., Tokyo).

Results

The subjects' ages ranged from 28 to 78 years; their mean age was 52.7 years. There

were 534 men and 496 women. As shown in Table 1, on MR imaging of the 1,030

individuals, minimal LA was found in 205 (19.4%), mild LA in 52 (5.6%), moderate

LA in 37 (3.6%), and severe LA in 2 (0.2%). LA prevalence increased with ages,

irrespective of LA grades. Table 2 shows comparisons of elementary statistics of

study variables between subjects with LA and those without LA. Mean age and the

proportion of male gender were higher in subjects with LA than in those without LA.

However, the LA and non-LA groups did not differ with respect to smoking status.

The prevalence of MetS was significantly higher in the LA group (34.0%) than in the

non-LA group (13.6%). All MetS components were significantly associated with LA.

When MetS components were examined individually with adjustment for age, gender,

present history of IHD, and current smoking (Table 3; model 1), four conditions

satisfying the NCEP-ATP III–criteria i.e., elevated BP, IFG, hyper-TG, and large WC,

were associated with increased risks of LA. However, when the five components

were entered simultaneously into the model, with adjustment for four covariates

included in model 1, significant ORs were observed for elevated BP (adjusted OR,

2.16; 95% CI, 1.57 -2.99), IFG (adjusted OR, 1.64; 95% CI, 1.13-2.39), and

hyper-TG (adjusted OR, 1.56; 95% CI, 1.08-2.28) (Table 3; model 2). Large WC and

low HDL-C were not associated with LA in the model 2.

We examined whether ORs showing the association between LA and MetS increased

with advancing grades of LA. Mild through severe LA grades were combined into

one category in this analysis. The proportional odds assumption was checked for the

relationship between MetS and ordinal categories of LA grades with the test of

parallel lines under the ordered logistic regression model of LA on dichotomized

MetS (the location component only model with a logit link function). The null

hypothesis was rejected that the slope coefficients are the same across categories of

LA grades (P=0.037). This finding indicates that the proportional odds assumption is

not reasonable in terms of the relationship between MetS and different categories of

LA grades. Therefore, a multinomial logistic regression model was used to assess the

relationship[24]. As shown in Table 4, the increase in the odds of LA in individuals

with MetS compared with those without MetS was constant across grades of LA; the

adjusted ORs were 3.41 (95%CI, 2.30-5.06) for minimal LA, 3.07 (95%CI,

1.75-5.38) for mild, moderate, and severe LA, and 3.33 (95%CI, 2.30-4.84) for all grades of LA. The adjusted OR for all grades of LA was derived from a multiple logistic regression of presence or absence of any grade of LA on presence or absence of MetS while considering a set of covariates.

Discussion

Several studies have examined the prevalence of LA. The ARIC study reported a 24.6% prevalence of LA among individuals aged 55-72 years, 49% of whom were hypertensives.[3] The Cardiovascular Health study found a prevalence of 33% in individuals aged 65 years or older, 44% of whom were hypertensives.[25] The prevalence of LA was 27% in the Rotterdam Study, which included individuals aged 65-84 years, 39% of whom were hypertensives.[9] These prevalence figures were obtained without FLAIR images. The prevalence of LA in our study was 28.8% in persons aged 28-78 years (Table 1), 37.4% of whom were hypertensives. Given the young average age of our study subjects compared with the average ages of other study populations, the relatively high prevalence of LA may be due to the accurate assessment of minimal LA with FLAIR image of MRI.

To the best of our knowledge, the present study provides the information on the

association between MetS, its components, and LA in healthy people. As shown with

the model 2 in Table 3, elevated BP was the strongest risk factor of MetS

components after adjusting for interrelationships among MetS components.

Furthermore, IFG and hyper-TG were also independent risk factors for LA. The

association of Hyper-TG with LA has been for the first time described in our study.

Hyper-TG may be additionally worth exploring as a modifiable factor that may

contribute to occurrence and development of LA independently of elevated BP.

LA is a neuroimaging finding that is caused by pathological changes such as

demyelinization, gliosis, vessel lipohyalinosis, and disturbed blood-brain exchanges.[1, 2, 8] Postmortem studies have indicated that LA seen on MRI are associated with

degenerative changes in arterioles that are related to atherosclerosis and with

lipohyalinosis of white matter perforating small arteries.[2, 8] Development of ischemic

injury in white matter substances associated with MetS, whether the pathogenesis is

atherosclerosis, lipohyalinosis, or both, may be responsible for occurrence and

development of LA. In the present study, MetS was significantly associated with

both minimal and advanced LA. This indicates that MetS might be attributable to

occurrence of LA, but not progression of LA. Specialists and family physicians

should note that MetS may be an important factor for occurrence of LA that is

associated with the development of brain damages such as stroke and dementia.

When an individual satisfies the criteria on MetS, especially the component

conditions of elevated BP, IFG or hyper-TG, physicians should also notice the

possible presence of LA on MRI in spite of the grades.

The present study was cross-sectional and the causality of the association between

MetS and LA could not be determined. A longitudinal study that follows the study

population will provide an opportunity to clarify attributes of MetS and its

components to occurrence of LA in individuals without LA finding at baseline.

Acknowledgments

Table 1. Prevalence of leukoaraiosis by age group

Age group	Number	Prevalence of grade-specific leukoaraiosis (%)					
		None	Minimal	Mild	Moderate	Severe	All grades
<40	83	96.4	3.6	0	0	0	3.6
40-49	289	87.5	11.8	0.7	0	0	12.5
50-59	417	70.3	22.8	3.6	3.1	0.2	29.7
60-69	193	50.8	27.5	13.0	8.3	0.5	49.2
70<=	48	18.8	31.3	33.3	16.7	0	81.2
Total	1,030	71.2	19.4	5.6	3.6	0.2	28.8

Table 2. Vascular risk factors, metabolic syndrome and its components of subjects with/without leukoaraiosis(LA), Part 1

		All (N=1,030)	Without LA (N=733)	With LA (N=297)	*P* value
Age	Mean (SD), years	52.7(9.6)	50.2(8.8)	59.1(8.7)	<0.001
Gender	Male, Number (%)	534(51.8)	358(48.8)	176(59.3)	0.003
Present history of ischemic heart disease	Present, Number (%)	8(0.8)	6(0.8)	2(0.7)	>0.900
Current smoking	Yes, Number (%)	257(25.0)	174(23.7)	83(27.9)	0.182

(Table 2 continues to the next page.)

Table 2. Vascular risk factors, metabolic syndrome and its components of subjects with/without leukoaraiosis(LA), Part 2

		All (N=1,030)	Without LA (N=733)	With LA (N=297)	*P* value
Metabolic syndrome	Present, Number (%)	201(19.5)	100(13.6)	101(34.0)	<0.001
Components of metabolic syndrome					
Systolic blood pressure	Mean (SD), mmHg	123.1(18.2)	120.1(17.3)	130.5(18.3)	<0.001
Diastolic blood pressure	Mean (SD), mmHg	72.6(11.8)	71.3(11.8)	75.6(11.0)	<0.001
Elevated blood pressure	Number (%)	385(37.4)	216(29.5)	169(56.9)	<0.001
Fasting blood glucose	Mean (SD), mg/dL	103.6(18.7)	102.2(18.6)	107.0(18.4)	<0.001
Impaired fasting glucose	Number (%)	228(22.1)	127(17.3)	101(34.0)	<0.001
Triglyceride	Mean (SD), mg/dL	119.6(86.0)	113.7(83.1)	133.9(91.4)	<0.001
High-density lipoprotein cholesterol (HDL-C)	Mean (SD), mg/dL	67.7(17.8)	68.4(18.1)	65.8(16.8)	0.039
Hypertriglyceridemia	Number (%)	258(25.0)	158(21.6)	100(33.7)	<0.001
Low HDL-C	Number (%)	49(4.8)	28(3.8)	21(7.1)	0.040
Waist circumference	Mean (SD), cm	83.0(10.1)	81.9(9.9)	85.7(10.1)	<0.001
Large waist circumference	Number (%)	399(38.7)	256(34.9)	143(48.1)	<0.001

P values were obtained using the chi square test for categorical data, and the t-test for continuous data transformed by logarithm.

Table 3. Adjusted odds ratios (ORs) of leukoaraiosis for components of metabolic syndrome

Components of metabolic syndrome	Model 1		Model 2	
	Adjusted OR(95% CI)	*P* value	Adjusted OR(95% CI)	*P* value
Elevated blood pressure, present/absent	2.55 (1.87 - 3.48)	<0.001	2.16 (1.57 - 2.99)	<0.001
Impaired fasting glucose, present/absent	2.23 (1.57 - 3.17)	<0.001	1.64 (1.13 - 2.39)	0.010
Hypertriglyceridemia, present/absent	1.94 (1.37 - 2.73)	<0.001	1.56 (1.08 - 2.28)	0.019
Low high-density lipoprotein cholesterol, present/absent	1.75 (0.93 - 3.30)	0.085	1.07 (0.54 - 2.15)	0.843
Large waist circumference, present/absent	1.61 (1.16 - 2.23)	0.005	1.17 (0.83 - 1.67)	0.370

In model 1, separate logistic regression models were fitted for each component, with adjustment for age in years, gender,

present history of ischemic heart disease, and current smoking.

In model 2, five components were entered into a logistic regression model simultaneously, with adjustment for four covariates

included in model 1.

Table 4. Adjusted odds ratios (ORs) of grade-specific leukoaraiosis for metabolic syndrome

Grades of leukoaraiosis	Adjusted OR(95% CI)	*P* value
None	1.00 (Reference)	-
Minimal	3.41 (2.30 - 5.06)	<0.001
Mild, moderate and severe	3.07 (1.75 - 5.38)	<0.001
All grades	3.33 (2.30 - 4.84)	<0.001

Grade-specific ORs were obtained by a multinomial logistic regression model with none as reference.

The OR for all grades was obtained by a binary logistic regression model with none as reference.

Both models included age, gender, and current smoking as covariates.

References

1. Awad IA, Johnson PC, Spetzler RF, Hodak JA. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly. II. Postmortem pathological correlations. Stroke 1986;17:1090-1097.

2. Hachinski VC, Potter P, Merskey H. Leuko-araiosis. Arch Neurol 1987;44:21-23.

3. Liao D, Cooper L, Cai J, Toole JF et al. Presence and severity of cerebral white matter lesions and hypertension, its treatment, and its control. The ARIC Study. Stroke 1996;27:2262-2270.

4. Goldstein IB, Bartzokis G, Hance DB, Shapiro D. Relationship between blood pressure and subcortical lesions in healthy elderly people. Stroke 1998;29:765-772.

5. Inzitari D, Giordano GP, Ancona AL, Pracucci G, Mascalchi M, Amaducci L. Leukoaraiosis, intracerebral hemorrhage, and arterial hypertension. Stroke 1990; 10:1419-1423.

6. Wong TY, Klein R, Sharrett AR et al. Cerebral white matter lesions, retinopathy, and incident clinical stroke. JAMA 2002;288:67-74.

7. Jeerakathil T, Wolf PA, Beiser A et al. Stroke risk profile predicts white matter hyperintensity volume: the Framingham Study. Stroke 2004;35:1857-1861.

8. Brun A, Englund E. A white matter disorder in dementia of the Alzheimer type: a pathoanatomical study. Ann Neurol 1986;19:253-262.

9. Breteler MMB, van Swieten JC, Bots ML et al. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: The Rotterdam Study. Neurology 1994;44:1246-1252.

10. De Groot JC, de Leeuw FE, Oudkerk M et al. Periventricular cerebral white matter lesions predict rate of cognitive decline. Ann Neurol 2002;52:335-341.

11. Prins ND, van Dijk EJ, den Heijer T et al. Cerebral white matter lesions and the risk of dementia. Arch Neurol 2004;61:1531-1534.

12. van Dijk EJ, Breteler MM, Schmidt R et al. The association between blood pressure, hypertension, and cerebral white matter lesions: cardiovascular determinants of dementia study. Hypertension 2004;44:625-630.

13. den Heijer T, Vermeer SE, van Dijk EJ et al. Alcohol intake in relation to brain magnetic resonance imaging findings in older persons without dementia. Am J Clin Nutr 2004;80:992-997.

14. Reaven GM. Role of insulin resistance in human disease. Diabetes 1988; 37:1595–1607.

15. Deedwania PC. The deadly quartet revisited. Am J Med 1998;105(suppl 1A): 1S–3S.

16. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001; 285:2486–2497.

17. McNeill AM, Rosamond WD, Girman CJ et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. Diabetes Care 2005;28:385–390.

18. Koren-Morag N, Goldbourt U, Tanne D. Relation between the metabolic syndrome and ischemic stroke or transient ischemic attack: a prospective cohort study in patients with atherosclerotic cardiovascular disease. Stroke 2005;36(7):1366-71.

19. Bang OY, Kim JW, Lee JH et al. Association of the metabolic syndrome with intracranial atherosclerotic stroke.   Neurology. 2005 Jul 26;65(2):296-298.

20. Kwon HM, Kim BJ, Lee SH, Choi SH, Oh BH, Yoon BW. Metabolic syndrome as an independent risk factor of silent brain infarction in healthy people. Stroke 2006;37:466-470.

21. Western Pacific Regional Office of the World Health Organization, The International Obesity Task Force. The Asia-Pacific perspective: redefining obesity and its treatment. Sydney: Health Communications Australia; 2000.

22. Oda E, Watanabe K. Japanese criteria of metabolic syndrome. Circ J 2006;70: 364.

23. Pico F, Dufouil C, Lévy C et al. Longitudinal study of carotid atherosclerosis and white matter hyperintensities: The EVA-MRI Cohort. Cerebrovasc Dis 2002;14:109-115.

24. Kleinbaum DG, Klein M. Logistic Regression: A Self-Learning Text, 2nd ed. New York: Springer-Verlag; 2002.

25. Longstreth WT, Manolio TA, Arnold A et al., Clinical correlates of white matter

findings on cranial magnetic resonance imaging of 3301 elderly people. The

Cardiovascular Health Study. Stroke 1996;27:1274-1282.