Significant Association between Leukoaraiosis and Metabolic Syndrome in Healthy Subjects

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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 \textit{leuko} (white) and \textit{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.\textsuperscript{1-4} Traditionally, the finding of LA has been considered to have no clinical significance because many individuals with LA are asymptomatic\textsuperscript{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.\textsuperscript{5-7} Furthermore, the progression of LA is also significantly associated with cognitive impairments and dementia of Alzheimer type.\textsuperscript{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.\textsuperscript{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).\textsuperscript{14-17} In recent years, MetS has attracted much attention as a modifiable condition that increases risks of cerebrovascular events including stroke\textsuperscript{18,19} and silent brain infarction\textsuperscript{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.\textsuperscript{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 $\geq 3$ 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 $\geq 110$ 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 $\geq 130$ mm Hg or a diastolic BP $\geq 85$ 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 $\geq 150$
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. However, these
cutoff points are not applicable in an Asian population. Thus, based on
recommendations of the Japan Obesity Association, we adopted the definition of a
large WC as $\geq 85$ cm in men and $\geq 90$ cm in women.

*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 $\geq 3$ 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: 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
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. 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. The Cardiovascular Health study found a prevalence of 33% in individuals aged 65 years or older, 44% of whom were hypertensives. The prevalence of LA was 27% in the Rotterdam Study, which included individuals aged 65-84 years, 39% of whom were hypertensives. 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 demyelination, 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

We would like to thank Mr. Shouei Yamamoto for preparation of data, and Mr. Masashi Takechi for MRI manipulation.
Table 1. Prevalence of leukoaraiosis by age group

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number</th>
<th>None</th>
<th>Minimal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>All grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>83</td>
<td>96.4</td>
<td>3.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3.6</td>
</tr>
<tr>
<td>40-49</td>
<td>289</td>
<td>87.5</td>
<td>11.8</td>
<td>0.7</td>
<td>0</td>
<td>0</td>
<td>12.5</td>
</tr>
<tr>
<td>50-59</td>
<td>417</td>
<td>70.3</td>
<td>22.8</td>
<td>3.6</td>
<td>3.1</td>
<td>0.2</td>
<td>29.7</td>
</tr>
<tr>
<td>60-69</td>
<td>193</td>
<td>50.8</td>
<td>27.5</td>
<td>13.0</td>
<td>8.3</td>
<td>0.5</td>
<td>49.2</td>
</tr>
<tr>
<td>70&lt;=</td>
<td>48</td>
<td>18.8</td>
<td>31.3</td>
<td>33.3</td>
<td>16.7</td>
<td>0</td>
<td>81.2</td>
</tr>
<tr>
<td>Total</td>
<td>1,030</td>
<td>71.2</td>
<td>19.4</td>
<td>5.6</td>
<td>3.6</td>
<td>0.2</td>
<td>28.8</td>
</tr>
</tbody>
</table>
Table 2. Vascular risk factors, metabolic syndrome and its components of subjects with/without leukoaraiosis (LA), Part 1

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

(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

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

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

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

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

<table>
<thead>
<tr>
<th>Grades of leukoaraiosis</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.00 ( Reference )</td>
<td>-</td>
</tr>
<tr>
<td>Minimal</td>
<td>3.41 ( 2.30 - 5.06 )</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mild, moderate and severe</td>
<td>3.07 ( 1.75 - 5.38 )</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All grades</td>
<td>3.33 ( 2.30 - 4.84 )</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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.


