Relationship Between Asymptomatic Intracranial Stenosis and Extracranial Arteriosclerotic Findings in Workplace Health Checkups: A Pilot Study

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Background: Intracranial arteriosclerotic disease (ICAD) is common in Asians and has been presumed to be largely associated with metabolic syndrome (MetS), but the risks for asymptomatic ICAD detectable in examinations of the brain, among other tests, are not well known. The present study is aimed at identifying the risks for asymptomatic ICAD using data on risk factors obtained in health checkups, including data from magnetic resonance imaging (MRI), chest computed tomography (CT), and neck echography. *Methods:* Subjects comprised 103 examinees more than equal to 40 years old (56.9 ± 4.7 years, 93 men) who underwent head MRI, chest CT, and carotid echography in the same period in a workplace health checkup between April and September 2014. Subjects were evaluated for ICAD based on stenosis of bilateral middle cerebral arteries and the basilar artery on previously reported scores from magnetic resonance angiography. Evaluations for extracranial arteriosclerotic disease (ECAD) were based on findings from carotid echography, and total calcium scores were calculated based on the number, areas, and peak Hounsfield computed tomographic numbers of the aortic arch calcified lesion detected. *Results:* ICAD, including mild cases with stenosis less than 50%, was seen in 21 subjects (20.3%); and MetS was evident in 12 subjects (11.7%). Logistic regression analysis with multivariate adjustment for major vascular risk factor demonstrated that echogenic of plaque was significantly associated with the ICAD (OR 3.69, 95%CI 1.02-13.3), however age was significant predictor of the risk profile in patients with ECAD. *Conclusions:* Carotid atherosclerosis could predict intracranial atherosclerosis in middle-aged people. However, further study with large sample size is warranted.

Key Words: Intracranial atherosclerotic disease—extracranial atherosclerotic disease—carotid—ultrasound sonography—calcium volume—aortic lesion

Introduction

Intracranial cerebral arterial stenosis, which is a risk factor for ischemic stroke,[1-3] is prevalent in Asian regions.[4-6] Carotid echography is widely used to detect extracranial arteriosclerotic lesions. Carotid plaque area has been considered a risk factor for acute myocardial infarction and stroke.[7,8] In evaluations of plaques, plaque volume has overtaken carotid intima-media thickness (IMT) as a strong risk factor.[7] Nevertheless, the current status on early detection of intra- and extracranial arteriosclerotic lesions in Japanese people with risk factors has remained unknown. In Japan, an epidemiological study at Hisayamacho showed that the incidence of hypertension and prevalence of dyslipidemia increase with age; both of which are risk factors for atherothrombotic cerebral

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infarction due to arteriosclerosis.[9] There are evidences of intracranial stenosis and carotid atherosclerosis as stroke risk,[10-12] while evidences of aortic atherosclerosis for stroke are lacking. In the United States, despite the availability of many prophylactic agents to prevent risks, risk management has yet to take hold as a widely practiced preventive measure against ischemic stroke.[13] Thus, approaches that lead to decreased prevalence of such diseases and for indicators that allow early and easy detection of risk factors are needed. In the present study, we hypothesized that in addition to carotid and intracranial arterial lesions, aortic arteriosclerotic foci, in particular, can also represent an indicator. Vascular assessments using CT have shown that intracranial arterial stenosis tends to occur at multiple sites,[14] therefore, it is important to assess of arteriosclerotic lesions in the central to peripheral direction.

The present study assessed aortic calcification findings, carotid sclerotic lesions, and intracranial arteriosclerotic lesions in an objective manner using MRI, CT, and carotid echography performed in workplace health checkups. Through such assessments, we conducted an exploratory study intended to elucidate the current status of intra- and extracranial arteriosclerotic foci in workplace health checkups, in which traditional vascular risks are evaluated extensively, and risk factors for developing intracranial arteriosclerotic foci.

Subject and Methods

Subjects were selected, taking into consideration the age makeup of the study population (≥40 years old), from among those who underwent head MRI, carotid echography, and chest CT in the same period in a workplace health checkup between April and September 2014. The present study was conducted at a single study site with the protocol approved by the Clinical Study Committee at Fujitsu Limited Health Promotion Unit.

Measurements of clinical characteristics that are risk factors and laboratory parameters were taken during the study period. Risk factors were defined as follows: hypertension, blood pressure more than equal to 140/90 mmHg and/or current use of antihypertensive agents; dyslipidemia, total cholesterol level more than equal to 220 mg/dL, triglyceride level more than equal to 150 mg/dL, high-density lipoprotein level less than 40 mg/dL, or ongoing treatment with a lipid-modifying drug; and diabetes, fasting blood glucose level more than equal to 126 mg/dL, hemoglobin (Hb)A1c more than equal to 6.5%, or ongoing treatment with an antidiabetic agent. Whether a subject was a smoker was determined based on information recorded in the medical chart. Subjects with chronic kidney disease (CKD) were defined as those with an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2, history of chronic kidney disease, or presence of albumin or proteinuria for more than equal to 3 months.

Subjects were evaluated for extracranial arteriosclerotic foci based on carotid lesions detected by carotid echography and the aortic arch calcification volume measured on chest CT (SOMATOM Emotion16, Siemens Japan, Tokyo, Japan). Extracranial arteriosclerotic disease (ECAD) were defined as plaque size more than equal to 1.1 mm in carotid artery, presence or absence of plaque lesions with IMT more than equal to 1.1 mm, plaque echogenicity, and surface properties were investigated in the assessment using carotid echography.

Atherosclerotic lesions of aortic arch were measured by the calcification volumes on chest CT (CT density >130 Housfield units having an area ≥ 1 mm^2 for the aortic arch wall) were measured by grading calcification lesions on the Agatston scale.[15] This calcification volumes were analyzed using measurement simulation software (Zed-View, LEXI Co., Ltd. Tokyo, Japna)

MRI and magnetic resonance angiography (MRA) were performed on Excelart (1.5 T; Toshiba Medical Systems, Tokyo, Japan) or Achieva Nova Dual (1.5 T; Philips, Tokyo, Japan). MRA was obtained using a 3-dimensional time-of-flight gradient-echo technique to assess intracranial stenosis. MRA data were read by a 3-person team of stroke and radiology specialists under blinded conditions for patient information. Intracranial arteriosclerotic disease (ICAD) was measured by categorizing bilateral middle cerebral arteries and basilar artery (BA) on the global stenosis score to assess the extent of stenosis. Extent of stenosis in the 3 arteries of bilateral middle cerebral arteries and BA was graded on a 5-level scale, as follows: grade 0, normal, no signal reduction; 1, mild, less than 50% signal reduction; 2, moderate, more than 50% signal reduction; 3, severe, loss of local signals, but presence of distal signals; and 4, occlusion.[16] The degree of stenosis was confirmed on the consensus agreement of at least 2 neurologists. If no agreement was reached, the degree of stenosis was assessed through an additional consultation. Total score of the 3 blood vessels on MRA was calculated as the global stenosis score.

Fluid attenuation inversion recovery images were used to assess the severity of white matter changes according to the Fazekas classification sytem,[17] which grades deep and periventricular white-matter lesions on separate 4-level scales from 0 (absent) to 3 (marked abnormality). These assessments were performed based on clinical data by 2 trained neurologists under blinded conditions.

Patient attributes are expressed as mean and standard deviation, and categorical data are expressed in absolute and relative frequencies. Univariate analyses were performed using the chi-squared test, Fisher's exact test, or Mann-Whitney *U* test, as appropriate. Relationships to the number of ICAD-related metabolic syndrome (MetS) factors (hypertension, hypertriglyceridemia, obesity, diabetes) were analyzed using multivariate logistic regression modeling. Risk factors for ICAD and ECAD were analyzed using univariate logistic regression models and by determining odds ratios (ORs) and 95% confidence

Table 1. *Patient's characteristics*

	N (%)
Age, y	56.8 ± 4.7
Male	93 (90.3)
BMI	24.4 ± 5.1
Smoking	25 (24.3)
HTN	35 (36.4)
DL	38 (37.6)
DM	9 (8.7)
Mets	12 (11.7)

Abbreviations: BMI, body mass index, HTN, hypertension, DL, dyslipidemia, DM, diabetes mellitus, Mets, metabolic syndrome.

intervals (CIs) through the stepwise procedure, with factors identified as insignificant in univariate analysis removed from the multivariate logistic regression model. Furthermore, to diagnose ICAD, minimum area under the curve, sensitivity, and specificity were determined. All statistical analyses were performed using the IBM SPSS for Windows version 19.0 software program (IBM Inc. Japan, Tokyo, Japan)in all statistical analyses.

Results

Patient attributes were shown in Table 1. A total of 103 patients (56.9 ± 4.7 years, 93 men) were classified into the following categories: ICAD, 21 (20.4 %); ECAD, 22 (21.3%). Table 2 presents data on carotid echography and findings from head MRI. Data showed no relationship to ICAD corresponding to the number of factors applicable to MetS, as determined in the multivariate logistic model. Table 3 shows results related to the risk factors for ICAD

Table 2. *Imaging characteristics*

Max IMT, mm	1.52 ± 0.89
Echogenecity, %	Iso 64.1, hyper 18.4, hypo 0
Echo surface, %	Regular 81.6, irregular 1.9
PVH, %	0: 55.7, Ⅰ: 40.2, Ⅱ 4.1
DWM, %	0: 50.5, Ⅰ: 36.9, Ⅱ 5.8
MCA stenosis, %	18.5
GSS = 0	81.5
GSS = 1	13.6
GSS = 2	2.9
GSS = 3	1.0
GSS = 4	1.0
BA stenosis, %	6.9
GSS = 0	93.1
GSS = 1	4.9
GSS = 2	1.0
GSS = 3	1.0
GSS = 4	0

Abbreviations: BA, basilar artery; DSWMH, deep white matter hyperintensity; GSS, global stenosis scale; IMT, intima-media thickness; MCA, middle cerebral artery; PVH, periventricular hyperintensity.

obtained using the logistic regression model. Analyses using univariate logistic regression models showed that age, echogenicity, and plaque size were related to intracranial atherosclerotic foci. In a multivariate logistic regression model with these relevant factors adjusted for age and sex, plaque echogenicity was identified as an independent relevant factor (OR, 3.69; 95%CI, 1.02-13.3). Table 4 provides a logistic regression model of the risk factors for ECAD (lesions with carotid plaque ≥1.1 mm). In the univariate logistic regression model, age, deep white-matter foci, and lateral ventricular white-matter foci were found to be factors related to carotid atherosclerotic lesions ECAD. In a multivariate logistic regression model with these factors adjusted by age and sex, age was the only independent factor related to ECAD (OR, 1.25; 95%CI, 1.08-1.45). Area under the curve for diagnosing ICAD was .655 with IMT; sensitivity was 85.7%, and specificity was 51.9% at an IMT cut-off of more than 1.35 mm.

Discussion

Prospective assessment of examinees who underwent a workplace health checkup in the present study revealed that: (1) ICAD is related more to carotid plaque size and plaque echogenicity than to the number of factors for MetS and traditional risk factors; and (2) while hypertension and aging are factors associated with severe aortic calcification, presence of aortic calcification foci showed no correlation with ICAD.

IMT is widely known as a surrogate marker for arteriosclerotic findings,[18-21] but the data indicated a relationship between intracranial arteriosclerotic findings and carotid echographic findings. Meanwhile, the data showed no relationship between aortic calcification findings and presence of intracranial arteriosclerotic foci. The dissociation among these findings may be attributable to the difference between aortic calcification and the process of arteriosclerosis formation in plaque formation observed in carotid echography. In other words, the onset and progression of aortic sclerosis and carotid or intracranial main trunk arterial sclerosis do not always manifest as systemic arteriosclerotic findings; phenomena that occur independently within the environment of each individual blood vessel are reflected in the early clinical condition of arterial sclerosis.

ICAD is known to be associated with MetS.[22] Nevertheless, few investigations have examined Japanese populations, particularly the working-age generation, and even fewer have determined risk factors for asymptomatic ICAD detected in examinations of the brain. The prevalence of asymptomatic intracranial stenosis has been reported to be as high as 8.6%[23] or 12.6%,[24] our finding shown in 20.4% was higher than previous studies. The reasons for this dissociation include that the evaluation for ICAS was performed using MRA, which is superior to transcranial color Doppler sonography as had been

Table 3. *Risk profile of the ICAD (95%CI)*

	Unadjusted regression			Multivariate regression		
	OR	95%CI	P valuie	OR	95%CI	*P* value
Age	1.04	.94-1.15	.05	.99	.88-1.11	.81
Sex	.34	.09-1.34	.12	.25	.05-1.16	.08
BMI	1.10	.98-1.23	.33			
Smoking	.75	.22-2.51	.64			
HT	1.64	.60-4.44	.33			
DL	1.96	.73-5.29	.18			
DM	.00	.00	1.00			
Echogenicity	3.37	1.38-8.20	.008	3.69	1.02-13.36	.046
Echo surface	.11	.002-1.93	.06			
Plaque size	1.84	1.002-3.33	.04	.95	.37-2.44	.91
Calcium score	1.00	1.00-1.00	.64			

Abbreviations: BMI, body mass index; DM, diabetes mellitus; DL, dyslipidemia; HTN, hypertension; ICAD, intracranial atherosclerotic disease.

Table 4. *Risk profile of the ECAD (95%CI)*

	Unadjusted regression			Multivariate regression		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Age	1.14	1.03-1.26	.014	1.16	1.02-1.31	.025
Sex	3.18	.38-26.40	.29	4.49	.47-43.02	.19
BMI	1.04	.96-1.13	.38			
Smoking	.78	.26-2.37	.66			
HT	3.31	1.28-8.58	.014	1.67	.55-5.06	.36
DL	1.30	.51-3.31	.59			
DM	1.06	.20-5.64	1.06			
DWM	1.94	.97-3.91	.063	1.86	.86-4.03	.12
PVH	2.27	.99-5.18	.050			
Plaque size	3.41	1.10-1.57	.033	2.57	.70-9.44	.16
Calcium score	1.00	.99-1.00	.67			

Abbreviations: BMI, body mass index; DL, dyslipidemia; DM, diabetes mellitus; DSWMH, deep white matter; ECAD, extracranial atherosclerotic disease; HTN, hypertension; PVH, periventricular hyperintensity.

performed in previous studies for detection of minor stenosis of intracranial artery. Second, the prevalence of ICAS was 47.7% in patients diagnosed with an ischemic stroke or transient ischemic attack, our findings would also include the selection bias criteria categorized as high risk. What is noteworthy in the present study is that known risk factors for lifestyle diseases and the set of disorders comprising MetS are not factors associated with mild cerebral arteriosclerosis. Thus, in the mild stage before stroke onset, progression of intracranial arterial sclerotic foci can be prevented by detecting the foci on carotid arteriosclerotic findings obtained in the screening for intracranial arteriosclerotic lesions, in addition to screening for traditional risk factors. Moreover, regarding secondary prevention of cerebral infarction, as in our investigation of the importance of ultrasonographic evaluation of the progression of intracranial arterial stenosis in patients subject to secondary prevention of cerebral infarction,[25] the results of this study indicate that in early ICAD also detected in workplace health checkups, carotid arteriosclerotic findings may be associated with the presence of ICAD. Recently, medical therapies are the best treatment for asymptomatic carotid arterial stenosis,[26] therefore, detection of early arteriosclerotic factors, including the detection of intracranial arterial sclerotic foci by MRA will also be significant in the future.

Several limitations to the present study must be considered. First, the study was a pilot study with a small, mostly male cohort. Second, this was a single-center study conducted in a relatively young population of examinees who underwent a workplace health checkup and had a history of mild arteriosclerosis, and who thus may not reflect a population with severe stenosis of intracranial arteriosclerosis. Third, the severity of plaque best suited to serving as a risk factor for intracranial arterial stenosis has yet to be established, and suitable criteria for MRA in health checkups remain unknown.

In conclusion, carotid atherosclerosis could predict intracranial atherosclerosis in middle-aged people. However, further study with large sample size is warranted.

Conflict of Interest

The authors have no conflicts of interest directly relevant to the content of this article.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.06.029.

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