Asymptomatic Coronary Artery Disease in Japanese Patients With the Acute Ischemic Stroke

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Objective: To investigate the prevalence and outcomes of asymptomatic coronary artery disease (CAD) in patients with the first episode of ischemic stroke. *Methods:* Patients admitted to our hospital between November 2001 and January 2009 for the episode of an acute ischemic stroke/transient ischemic attack were included. Stress-Tl-201 scintigraphy was performed and followed by coronary angiography (CAG). The prevalence and risks for asymptomatic CAD, and long-term outcomes were studied. *Results:* Of 1309 patients, only 15 (1.1%) patients presented with a history of CAD. Excluding 406 patients because of severity, systemic infection, early transfer to another hospital, or a refusal to participate, myocardial scintigraphy was performed in 903 patients (mean age, 72 ± 10 years, male 63.9%), and myocardial ischemia was diagnosed in 214 patients (23.7%). Of these patients, 76 patients underwent CAG, and showed significant stenosis (>75%) of a coronary artery in 61 (80.3%) patients. The risk factors for positive scintigraphy findings and CAG were high-grade premature complexes via Holter monitoring ($P < .0001$), enlarged left ventricle ($P = .0051$) and wall motion abnormalities ($P = .0014$) observed on echocardiography, and carotid artery stenosis observed in magnetic resonance angiography imaging ($P < .0001$). During the follow-up periods of 83 ± 47 months and of 91 ± 47 months, 17.2% of scintigraphy-positive and 2.8% of scintigraphy-negative patients developed episodes of myocardial ischemia, respectively ($P < .001$). *Conclusions:* Symptomatic CAD was rare in Japanese patients with the first episode of ischemic stroke, but asymptomatic CAD was identified by stress Tl-201 myocardial scintigraphy in one-quarter of the patients. Positive scintigraphy was associated with asymptomatic CAD and future cardiac events.
Key Words: Ischemic stroke—coronary artery disease—thalium-201 myocardial scintigraphy—magnetic resonance angiography—electrocardiography—echocardiography

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Introduction

Stroke and myocardial infarction share common risk factors and pathological mechanisms,[1-2] and coronary artery disease (CAD) has been observed in patients with ischemic stroke.[3-5] The mortality becomes higher when patients with ischemic stroke are complicated by acute myocardial infarction,[3-5] and it may be desirable to identify the presence of CAD among patients with ischemic stroke for proper management.

The prevalence and effects on long-term outcomes of asymptomatic CAD is poorly known in the Japanese patients who had the first episode of acute ischemic stroke/transient ischemic attack (TIA). We attempted a systematic screening of asymptomatic CAD by myocardial scintigraphy followed by coronary angiography (CAG) in the first stroke/TIA patients , and assessed the risks for the presence of asymptomatic CAD from the clinical and laboratory data including imaging from magnetic resonance imaging (MRI) or angiography (MRA).

Materials and Methods

Patients

Patients admitted to the Department of Neurosurgery or Neurology, Nagaoka Chuo General Hospital between November 2001 and January 2009 for the episode of an acute stroke/TIA were included in this study. Ischemic stroke was diagnosed using brain computed tomography (CT), MRI, and/or MRA.

Blood samples were collected to determine complete blood counts, blood chemistry, serology, and status of coagulation. An electrocardiogram (ECG), chest X-ray, and echocardiography (UCG) were routinely obtained after admission. When consideration needed, CT and MRI of the brain were repeated. Holter ECG and echocardiography were performed during the hospital stay.[6-8]

When the patients were considered clinically stabilized, further studies for the diagnosis of CAD were performed after obtaining informed consent.

Neurovascular Imaging

Ischemic stroke was diagnosed according to neurological signs, brain CT results (Aquilion VR TSX-021A and Aquilion V8 TSX-101A, Toshiba Co., Tokyo) and/or MRI and MRA results (Visart MRT-200 and Vantage MRT-2003/P3, Toshiba Co., Tokyo). Based on the results of CT imaging, ischemic stroke was classified into large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology according to the Trial of Org 10172 in Acute Stroke Treatment classification.[9]

Using MRI and MRA images, vascular lesions were surveyed in the carotid and vertebral arteries, and stenosis is greater than 50% was considered significant.[10]

Myocardial Scintigraphy

Drug-stress myocardial scintigraphy was used as a screening test for asymptomatic CAD.[10-12] In brief, dipyridamole was administered intravenously at .14 mg/kg in 4 minutes, followed by a Tl-201 injection, and myocardial scintigraphy images were obtained (Star cam 4000XC/T, General Electric Co, Boston MA and E. CAM. Toshiba Co., Tokyo) immediately and at 180 minutes, and a 3-dimensional stack of a single-photon emission tomographic image was reconstructed (11.12). Myocardial ischemia was diagnosed as a defect immediately after drug administration, but no defect was detected in late imaging (a reversible defect). A persistent defect (a fixed defect) was diagnosed as an infarct. With either defect, scintigraphy was considered positive for myocardial ischemia.

Scintigraphy was not performed in the patients who had severe brain damage, concomitant infection, or who were transferred early to another hospital for interventional treatment, or if they refused to participate in the study. The patients with a history of myocardial infarction or angina pectoris were also excluded.

Coronary Angiography

When myocardial scintigraphy was positive for myocardial ischemia, CAG was performed after an informed consent was obtained. Stenosis greater than 75% in proximal coronary arteries was defined as significant.

Data Analysis

In the original patient population, the prevalence of symptomatic CAD was determined. In terms of the cardiovascular clinical risks, hypertension was diagnosed when the patient had a systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg or when patients were taking medication for hypertension.[13] Diabetes mellitus and dyslipidemia were diagnosed according to guidelines or when patients were under medication for these conditions.[14,15]

On the 12-lead ECG, the presence and prevalence of either ST-T depression and/or elevation, T-wave inversion, abnormal Q wave, or bundle branch block were determined, and the severity of premature ventricular contractions was determined on Holter ECG using the Lown grading system (7.8). Cardiac dimensions and wall motion were evaluated by echocardiography.[6]

The patients were divided into the scintigraphy-positive and the scintigraphy-negative groups, and the demographic data, clinical data, ECG findings, echocardiographic findings, and vascular lesions in the carotid arteries were compared between the 2 patient groups.

The data were interpreted, and diagnoses were rendered by 2 neurosurgeons or cardiologists, respectively, and when there was a discrepancy in the diagnosis, a discussion occurred until a consensus was reached.

The event-free survival rate was compared between the scintigraphy-positive and the scintigraphy-negative patient groups who had been followed at our outpatient clinic.

Statistical Analysis

The numerical data are presented as the mean ± standard deviation, and comparisons were performed using the JMP statistical software (Statistical Discovery Software, version 8.01, SAS Institute, Inc., Cary, NC). EZR (Easy R) was used to perform statistical analyses. Categorical variables are presented as absolute numbers or percentiles (%). Welch's t test or the Mann-Whitney U test was used for comparison of the value of HbA1c and each value of cholesterol.

We performed a multivariate analysis to see the correlation of the results of Tl-201 myocardial scintigraphy with age, gender, and coronary risk factors such as hypertension, hyperlipidemia, diabetes, and smoking history. By a multivariate analysis, the results of the Tl-201 myocardial scintigraphy were compared with those of ECG, UCG, and Holter ECG according to age, gender, and coronary risk factors.

A correlation between the results of the Tl-201 myocardial scintigraphy and stenosis or occlusion in cervical carotid arteries and the type of cerebral infarction such as large-artery atherosclerosis, small-vessel occlusion, and cardioembolism, associated with age, gender, and coronary risk factors were also analyzed by multivariate analysis. P less than .05 was considered significant, and we then calculated the odds ratio and the 95% confidence interval. The study was approved by the Institutional Board of Review at the Nagaoka Chuo General Hospital, and a written informed consent was obtained from each patient.

Results

Prevalence of CAD

Consecutive1309 patients (597 men and 336 women, aged 72.0 ± 10.0 years) were admitted for an initial occurrence of an ischemic stroke. Of these, 15 patients (1.1%) had a history of CAD and/or had been treated by reperfusion therapy were excluded from the further study. Fifteen patients who complained of chest pain when confirming complaint after admission but had not checked cardiovascular examines before admission, were also excluded. Another 376 patients were excluded because of severe brain damage (n = 119), concomitant infection (n = 3), much older age (n = 24), early transfer to another hospital (n = 6), and refusal to participate in the study (n = 224).

Finally, 903 asymptomatic patients underwent scintigraphy, and 214 (23.7%) were positive for myocardial ischemia; a reversible defect was observed in 157 patients, a fixed defect was observed in 10 patients, and both types of defect were observed in 47 patients. The scintigraphy was negative in 689 patients (76.2%). Seventy-six (35.5%) of the 214 scintigraphy-positive patients underwent CAG, and significant stenosis (>75%) was observed in 61 patients (80.3%).

Clinical Features of Patients With and Without Asymptomatic CAD

The baseline characteristics of the scintigraphy-positive and scintigraphy-negative groups are summarized in Table 1. The large-artery atherosclerosis type of stroke

Table 1. *Comparisons of the characteristics between the nonischemic and ischemic groups according to myocardial scintigraphy*

	Nonischemic (n = 689)	Ischemic (n = 214)	OR (95% CI)	*P* value
Age	72 ± 10	71 ± 9	-	NS
Male, n (%)	423 (61.4)	154 (72.0)	-	NS
Subtypes, n (%)			-	.0459
Large-artery atherosclerosis	240 (34.8)	98 (45.8)	-	-
Cardioembolism	153 (22.1)	46 (21.5)	-	
Small-vessel occlusion	234 (34.0)	58 (27.1)	-	-
Other	8 (1.2)	0(0)	-	-
Undetermined	54 (7.8)	12 (5.6)	-	-
Smoking	250 (36.3)	100 (46.7)	-	NS
Hypertension	480 (69.7)	158 (73.8)	-	NS
Dyslipidemia	288 (41.8)	84 (39.3)	-	NS
DM	183 (26.6)	72 (33.6)	-	NS
HbA1c	6.24 ± 1.5	6.57 ± 1.7	-	.0423
Total Chol	200.7 ± 42.8	198.3 ± 40.3	-	NS
HDL-Chol	55.7 ± 15.6	54.0 ± 13.7	-	NS
LDL-Chol	119.1 ± 40.9	116.0 ± 43.0	-	NS

Abbreviations: CI, confidence interval; DM, diabetes mellitus; HDL-chol, high density lipoprotein; LDL, low density lipoprotein; NS, non-significant; OR, odds ratio.

Nonischemic/ischemic, group with negative and positive findings for myocardial ischemia on myocardial scintigraphy.

was observed more often in the scintigraphy-positive patients.

Age and the prevalence of cardiovascular risks were common, and only HbA1c was significantly higher in the scintigraphy-positive group than in the nonischemic group: 6.57 ± 1.7% versus 6.24 ± 1.5%, respectively, (P = .0423). Otherwise, there was no significant difference in laboratory data or smoking history (Table 1).

In addition, abnormal Q wave and ventricular premature beats of Lown Grade 2 or higher were frequent in the scintigraphy-positive patients (Table 2). In echocardiography, a larger end-diastolic dimension and wall motion abnormality were found more often in the scintigraphy-positive group. Carotid artery stenosis (>50%) by MRA was more prevalent in the scintigraphy-positive patients (Table 2).

Course After Hospitalization

Among 214 scintigraphy-positive patients, 24 patients underwent coronary intervention therapy as follows: percutaneous coronary intervention (PCI) in 17 patients, coronary artery bypass graft (CABG) in 6 patients, and PCI followed by CABG in 1 patient before discharge.

After discharge, 185 scintigraphy-positive patients and 547 scintigraphy-negative patients were followed for 83 ± 47 months and for 91 ± 47 months. Angina pectoris developed in 17.2% and 2.8% of patients, respectively (P < .0001). During the follow-up period, 4 patients who yielded positive results of scintigraphy died following angina attack. Moreover, 1 patient died because of another stroke; 7 patients died because of cerebral hemorrhage; and 61 patients died because of malignancies, pneumonia, congestive heart failure, or other reasons.

Discussion

In the present study, CAD was rare (1.1%) in Japanese patients with the first stroke, and Tl-201 stress myocardial

scintigraphy using dipyridamole identified myocardial ischemia in 214 (23.7%) of 903 patients (the mean age, 71 ± 9 years, male 72.0%). Significant stenosis (>75%) was proved in 61 (80.3%) of 76 scintigraphy-positive patients who underwent CAG, and 24 (31.6%) of 76 patients with CAD underwent coronary intervention therapy. HbA1c, Q wave on ECG, high-grade premature complexes, echocardiography, and MRA findings were predictors for asymptomatic CAD. During the follow-up, coronary events more frequently occurred in the scintigraphy-positive patients.

Myocardial Ischemic in Stroke Patients

Stroke and myocardial infarction share common risk factors and common vascular pathology, and CAD is a major cause of death during and after stroke.[1-5]

The stress ECG test or stress myocardial scintigraphy has been employed to detect asymptomatic CAD in ischemic stroke/TIA patients with no history of CAD. In Western countries, 20% to 40% of stroke patients are considered to have abnormal tests for silent cardiac ischemia.[5,16-21] In this country, stress scintigraphy revealed myocardial ischemia in 34 (52.3%) of 65 stroke patients.[22] In the present study, drug-induced stress scintigraphy was positive for myocardial ischemia in one-quarter of the patients who had no history of CAD.

Coronary Angiography Stenosis

Multislice computed tomography (MSCT) is another tool used to detect asymptomatic CAD in patients with ischemic stroke. In 104 Japanese[23] and 1304 Korean stroke/TIA patients[24] with no history of CAD, MSCT demonstrated stenosis of coronary arteries greater than or equal to 50% in 37.5% and 33.1%, respectively. The calcium score for the coronary arteries on MSCT was highly associated with CAD.[25] However, CAG is essential to

Table 2. *Comparisons of the laboratory findings between the nonischemic and ischemic groups by multivariate analysis*

	Nonischemic (n = 689)	Ischemic (n = 214)	OR (95% CI)	P value
ECG findings*				
ST elevation, n (%)	3 (0.4)	1 (0.4)	-	NS
ST depression, n (%)	58(8.4)	28 (13.1)	-	NS
T-wave inversion, n (%)	75 (10.9)	33 (15.4)	-	NS
Abnoranal Q, n (%)	3 (0.4)	6 (2.8)	-	.0079
LBBB, n (%)	11 (1.6)	4 (1.8)	-	NS
Lown grade (2-5), n (%)	54 (7.8)	41 (19.2)	1.78 (1.23-2.56)	<.0001
LVEDD (mm), mean ± SD	4.6 ± .5	5.0 ± 2.9	1.39(1.02-1.89)	.0051
LVEF (%), mean ± SD	73.2 ± 8.6	69.1 ± 11.2	-	NS
WMA, n (%)	18 (2.6)	31 (14.5)	2.79 (1.33-5.84)	.0014
MRA, n (%)	166 (24.1)	93 (43.5)	2.55 (1.83-3.55)	<.0001

Abbreviations: CI, confidence interval; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic dimension; LVEF, ejection fraction of the left ventricle; MRA, magnetic resonance angiography; NS: non-significant; OR: odds ratio; WMA, Wall motion abnormality.
*either abnormality of ST-T depression and/or elevation, T-wave inversion, abnormal Q wave, or bundle branch block.

assess the severity and location of stenosis of coronary artery.[5,16,19,20,26]

When CAG was performed within a median of 8 days after stroke onset in patients without a history of CAD, coronary stenoses ($\geq$50%) were found in 25.7% of 315 patients.[26] In the present study, positive stress thallium scintigraphy was highly associated with CAD: 80.3% of scintigraphy-positive patients revealed significant (>75%) stenosis of the coronary arteries, and 24 patients underwent coronary intervention therapy for severe CAD: PCI in 17 patients, CABG in 6 patients, and PCI followed by CABG in 1 patient before discharge. None developed acute myocardial infarction during stay in the hospital.

Long-Term Outcomes

During short-term follow-up for up to 90 days, 2% to 5% of patients with acute ischemic stroke were observed to develop fatal cardiac-related events after stroke, but deaths due to acute myocardial infarction was only 0.2%.[27]

Whereas the baseline CAG findings can predict the long-term risk of stroke patients, and at 2 years, the estimated risk for major cardiovascular events (myocardial infarction, resuscitation for cardiac arrest, hospitalization with unstable angina pectoris, stroke, or major peripheral arterial disease) was 3.4% in patients with no CAD (n = 120), 8.0% in patients with asymptomatic coronary artery stenosis less than 50% (n = 113), 16.2% in patients with asymptomatic coronary artery stenosis greater than or equal to 50% (n = 81), and 24.1% in patients with known CAD (P < .0001).[28] Thus, the long-term risk of CAD seems not benign.

The incidence of cardiac events at 2 years was estimated 2.5 % for the scintigraphy-positive Japanese patients and 0.4 % for the scintigraphy-negative Japanese patients: lower than those reported in the Western country.[28]

Predictors of Asymptomatic CAD

The following clinical factors have been reported as predictors of abnormal scintigraphy or abnormal MSCT: male gender,[29-31] dyslipidemia (hypercholesterolemia or elevated LDL-cholesterol,[21,24] high Lp(a),[21] elevated TG[24] or DM.[22,23,32,33] The presence of multiple cardiovascular risk factors or metabolic syndrome was a risk for CAD with an odds ratio of 5.008 (95% confidence interval 1, 538-16.309, P < .01).[23] An elevated homocysteine level was a risk factor for CAD in one study.[21]

Vascular lesions determined by MRA in intracranial large arteries,[23] vertebrobasilar arteries,[21,24] internal,[21,23,24] and the extracranial carotid arteries[24,26] or the femoral artery[26] were associated with asymptomatic CAD. MRA can be another useful tool to predict CAD in patients with a stroke/TIA.

In addition, a presence of Q wave and high-grade premature complexes via Holter monitoring was a risk for
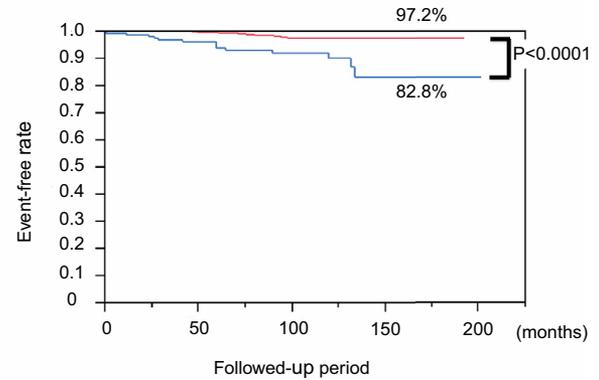

Figure 1. *The event-free survival curves of the scintigraphy-positive and scintigraphy-negative patient groups. The 185 scintigraphy-positive patients and 547 scintigraphy-negative patients were followed for 83 ± 47 months and for 91 ± 47 months and 17.2% and 2.8% developed angina pectoris, respectively (P <.0001).*

myocardial ischemia in scintigraphy in the present study, but the former was observed in a few patients. Echocardiography was another useful tool, and wall motion abnormality and enlarged left ventricle were associated with positive scintigraphy and CAD.

Limitations

The study has some limitations. First, the study was from a single center. However, the large number of patients with the first ischemic stroke were included for stress Tl-201 myocardial scintigraphy, and earlier observations were confirmed. Second, the study of myocardial ischemia was limited to those who provided informed consent, and patients with severe brain damage were excluded. However, it is likely that patients with severe stroke may have a more extensive vascular pathology, and the results of the present study might underestimate but not overestimate the prevalence of asymptomatic CAD.

Conclusions

Symptomatic CAD was very rare in Japanese patients with the first ischemic stroke, but approximately one-quarter had asymptomatic CAD proven by stress Tl-201 myocardial scintigraphy. The majority of the scintigraphy-positive patients had significant stenosis of the coronary arteries. The long-term outcome of coronary events was more eventful in the scintigraphy-positive patients (Fig. 1).

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