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Original article

Prevalence of subclinical coronary artery disease in ischemic stroke patients

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ABSTRACT

Background: Recently, ischemic stroke has emerged as a new coronary artery disease (CAD) risk equivalent. Our purpose is to study the prevalence of CAD in ischemic stroke patients compared with that in non-stroke patients.
Methods and results: We measured coronary calcium score (CCS) in 151 ischemic stroke patients without known CAD (stroke group) and compared it with 151 age- and sex-matched non-stroke patients (control group). CCS was significantly higher in the stroke group than in the control group (stroke group, median: 64, interquartile range: 3–382 vs. control group, median: 3, interquartile range: 0–65, $p < 0.0001$). High-risk CAD, defined as a CCS $\geq$ 400, was detected in 24.5% of the stroke group compared with 9.3% of the control group ($p < 0.0001$). Agreement between the Framingham risk score and CCS was found in only 62 patients (41.1%). In a multiple logistic regression analysis, age [hazard ratio (HR) 1.09, 95% confidence interval (CI) 1.03–1.14], diabetes (HR 2.97, 95%CI 1.52–5.78), stroke (HR 3.85, 95%CI 1.89–7.81), and male sex (HR 4.41, 95%CI 1.82–0.75) were significantly associated with high-risk CAD ($p < 0.001$).
Conclusions: Our results show that the prevalence of subclinical CAD in ischemic stroke patients was high, and that a quarter of them had high-risk CAD. Age, diabetes, stroke, and male sex were independent predictors of high-risk CAD.

Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality in both developing and developed countries [1]. Current guidelines for the primary and secondary prevention of cardiovascular disease, such as the American Heart Association guidelines and the National Cholesterol Education Program Adult Treatment Panel III guideline, define patients with coronary heart disease (CHD) risk equivalents as those who are at the same elevated risk as patients with ischemic heart disease [1–3]. CHD risk equivalents include diabetes mellitus, peripheral artery disease, carotid artery disease, and abdominal aortic aneurysm.

Recently, ischemic stroke without carotid artery disease has emerged as a new CHD risk equivalent. Dhamoon and Elkind [4], in a review of evidence from hospital- and population-based studies, proposed that stroke could be designated as a CHD risk equivalent, and that could be included in the outcome cluster for absolute estimation of risks in primary and secondary prevention [4]. More recently an American Heart Association/American Stroke Association Scientific Statement was released [5]. This statement concludes that patients with atherosclerotic stroke should be included among those deemed to be at high risk ($\geq$20% over 10 years) of further atherosclerotic coronary events.

Several studies have investigated the prevalence of significant CAD in ischemic stroke or transient ischemic attack patients [6–8]. However, few studies measured coronary calcium score (CCS), which is a powerful predictor of cardiac events in stroke patients [9–11]. One study measured CCS and carotid intima–media thickness in community-dwelling men and women with a mean age of 80 years and found that CCS and carotid intima–media thickness can similarly predict total cardiovascular events, myocardial infarction, and stroke [12]. Furthermore, no study has compared the prevalence of CAD in stroke patients with that in

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non-stroke patients. We therefore measured CCS in ischemic stroke patients without known CAD and compared the results with those of age- and sex-matched non-stroke patients.

Methods

Patients

From September 2011 through September 2012, 184 patients with acute ischemic stroke were admitted to our hospital. The diagnosis of ischemic stroke was made according to the National Institute of Neurological Disorders and Stroke criteria [13]. We measured CCS of ischemic stroke patients. The following patients were excluded: (1) patients who died; (2) patients with disabling stroke (modified Rankin scale score ≧3); (3) patients older than 80 years; (4) patients with cardioembolic stroke; (5) patients with symptomatic carotid artery disease, defined as stenosis ≥50% by Duplex ultrasonography; (6) patients with known CAD; (7) patients with atrial fibrillation; or (8) patients who refused CCS measurement. Thus, 151 patients underwent CCS measurement (stroke group). Sixty-four patients had lacunar infarcts, 81 patients had atherothrombotic infarcts, and 6 patients had infarcts of an unknown type.

Over the same period, 407 non-stroke patients with coronary risk factors but without known CAD underwent CCS measurement. For inclusion in the control group, we randomly selected 151 patients from this group who were matched for age and sex with the above 151 ischemic stroke patients.

Framingham risk score

We calculated Framingham risk score (FRS) in each patient in the stroke group [14]. The 10-year risk of myocardial infarction and cardiac death was calculated using this score. Risk was defined as follows: low, less than 10%; intermediate, between 10% and 20%; or high, greater than 20%.

64-Multidetector computed tomography

All patients were scanned with a 64-multidetector computed tomography (64-MDCT) system (SOMATOM Sensation 64 Cardiac; Siemens Medical Solutions, Erlangen, Germany). A native scan without contrast dye was performed to determine the total calcium burden of the coronary tree (sequential scan with 32-mm × 0.6-mm collimation, tube current 60 mA s at 120 kV). A total of 64 overlapping 3.0-mm slices per rotation were acquired using a focal spot, periodically moving longitudinally (z-flying focal spot). The tube current was modulated according to the electrocardiogram (ECG), with a maximum current of 200 mA s during a period of approximately 330 ms centered at 375 ms before the next R-wave, and reduced by 80% during the remaining cardiac cycle (care dose system).

64-MDCT image interpretation

CT data sets were transferred to an offline workstation (Aquarius NetStation, Terarecon Inc., San Maeteo, CA, USA) for image analysis. One physician measured CCS in the right coronary artery, left main trunk, left anterior descending coronary artery, and left circumflex coronary artery, then calculated the total CCS with dedicated software. The results were expressed as Agatston score [15]. In 40 patients, inter-observer and intra-observer variability were low (interquartile range of 0–5%). We used the usual CCS risk classification definitions. Low risk was defined as a CCS between 0 and 99, intermediate risk was defined as a CCS between 100 and 399, and high risk was defined as a CCS equal to or greater than 400.

We studied the difference in CCS between the two groups and the relationship between the FRS and the CCS in the stroke group. We also performed univariate and multivariate analyses to identify factors associated with high-risk CCS (CCS ≥ 400).

Informed consent for clinical procedures and the research protocol was received from all patients studied. The study was approved by an institutional review board.

Statistical analysis

Data are expressed as mean ± SD. Continuous laboratory variables were compared using two-group *t*-test. Because the CCS data did not show a normal distribution, the Mann–Whitney test was used to determine differences between the two groups. Discrete variables were expressed as counts or percentages and were compared using the chi-square test or Fisher's exact test. The relationship between a high-risk CCS and patient characteristics was assessed using univariate and multivariate analyses. We performed a multiple logistic regression analysis that included all variables with a value of $p < 0.05$ in the univariate analysis. A *p*-value <0.05 was considered statistically significant.

Results

Clinical characteristics of the studied patients are shown in Table 1. Because of the selection criteria, age and the prevalence of male patients were the same in each group. The prevalence of hypertension was significantly higher in the stroke group, while the prevalence of hyperlipidemia, diabetes, smoking, and obesity was not significantly different between the two groups. Laboratory data were also not significantly different between the two groups. Regarding patient medication use, angiotensin-converting enzyme inhibitor and angiotensin receptor blocker use were more prevalent in the stroke group. The use of other medications was not significantly different between the two groups.

Fig. 1 shows the CCS of the two groups. The CCS was significantly higher in the stroke group than in the control group (median: 64, interquartile range: 3–382 in the stroke group vs.

Table 1
Clinical characteristics of patients.

	Stroke group *n* = 151	Control group *n* = 151	*p*
Age (years)	67.3 ± 7.8	67.3 ± 7.8	0.9999
Sex (male)	101 (66.9%)	101 (66.9%)	0.9999
Hypertension	114 (75.5%)	81 (53.6%)	<0.0001
Hyperlipidemia	86 (57.0%)	78 (51.7%)	0.3554
Diabetes	49 (32.5%)	54 (35.8%)	0.5439
Smoking	38 (25.2%)	45 (29.8%)	0.3669
Obesity	30 (19.9%)	35 (23.2%)	0.4839
Laboratory data			
TC (mg/dl)	216.7 ± 46.4	209.8 ± 43.2	0.4515
TG (mg/dl)	147.9 ± 90.6	157.9 ± 96.5	0.5878
HDL-C (mg/dl)	60.7 ± 15.3	61.3 ± 35.8	0.8935
LDL-C (mg/dl)	126.0 ± 39.6	120.2 ± 29.8	0.6706
HbA1c (%)	5.70 ± 0.90	5.72 ± 0.94	0.8743
BS (mg/dl)	131.2 ± 42.1	137.4 ± 41.8	0.6852
Medication			
Aspirin	28 (18.5%)	25 (16.6%)	0.6500
Statin	29 (19.2%)	36 (23.8%)	0.3270
CCB	61 (40.4%)	57 (37.7%)	0.6371
ACE-I/ARB	70 (46.4%)	42 (27.8%)	0.0009
β-Blocker	8 (5.3%)	6 (4.0%)	0.5841
Oral DM agent	21 (13.9%)	30 (19.9%)	0.1669
Insulin	2 (1.3%)	3 (2.0%)	0.6520

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BS, blood sugar; CCB, calcium channel blocker; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.