Silent Cerebral Infarction is Associated with Incident Stroke and TIA Independent of Carotid Intima-Media Thickness

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Abstract

Background  Both silent cerebral infarction (SCI) and carotid intima-media thickness (IMT) are associated with future stroke. We evaluated whether SCI could be a predictor for incident stroke independent of carotid IMT in high-risk patients.

Methods  We performed a prospective cohort study among 282 outpatients who had one or more atherosclerotic risk factors but without a history of cardiovascular disease. We conducted cranial MRI and measured carotid IMT at baseline, and then evaluated the risks of incident stroke and transient ischemic attacks (TIA) using Cox proportional hazards models.

Results  SCI was present in 67 patients (23.7%) at baseline. During 4.1 years of follow-up, stroke and TIA occurred in 8 patients (2.8%). The incidence of stroke/TIA was 22.3 per 1,000 person-years in those with SCI compared with 2.2 per 1,000 person-years in those without SCI. Both SCI and carotid IMT at baseline were associated with incident stroke/TIA events after adjustment for age, sex, and traditional vascular risk factors. The predictive value of SCI remained significant even after adjustment for carotid IMT (HR 8.56; 1.72-42.55).

Conclusion  SCI, similar to carotid IMT, is an independent predictor of stroke and TIA in high-risk patients.

Key words: silent cerebral infarction, carotid intima-media thickness, incident stroke, cohort study, magnetic resonance imaging

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Introduction

Silent cerebral infarction (SCI) is frequently observed in healthy elderly populations (1). Age and hypertension are the most widely recognized risk factors for SCI (1). The presence of SCI, independent of cardiovascular risk factors, more than doubles the risk of subsequent stroke in both population- and hospital-based cohort studies (2-7). Although the predictive value of SCI for incident stroke has been established, routine magnetic resonance imaging (MRI) screening of neurologically asymptomatic people is not cost-effective. In contrast, carotid-ultrasonography is noninvasive and widely used in clinical practice for the screening of atherosclerosis. Many prospective longitudinal studies have demonstrated that carotid intima-media thickness (IMT) is an independent predictor for the risk of incident stroke and myocardial infarction (8-11).

It seems reasonable that SCI and carotid IMT are independently associated with incident stroke because SCI and carotid IMT represent subtle changes in the cerebral small vessel and large artery, respectively. However, the significance of SCI for incident stroke has not been examined with respect to carotid IMT. In this study, we evaluated whether  

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the predictive value of SCI for subsequent stroke is independent of carotid IMT.

**Patients and Methods**

**Patients**

In this prospective observational cohort study, we enrolled patients from a group of neurologically asymptomatic patients who consecutively visited the Department of Neurology at Osaka University Hospital. These patients had undergone cranial MRI, MR angiography (MRA) and carotid ultrasound examination between April 2000 and December 2006; most of them had been referred from other hospitals or departments for a risk assessment and primary prevention of stroke. At the time of referral, comprehensive neurological evaluations were performed by stroke neurologists, including physical and psychological examinations. When no neurological signs/symptoms were identified, patients were eligible for inclusion in this study. Patients who had ever experienced nonspecific neurological symptoms, such as dizziness, vertigo, headache, tinnitus, and syncope, were included when those symptoms were not present at the time of referral. The patients were excluded if they had a history of stroke, TIA, ischemic heart disease, chronic heart failure, peripheral vascular disease, chronic renal damage, atrial fibrillation, chronic inflammatory disease, or malignant disease. To mitigate direct threats to the cerebral circulation, and to focus on SCI, patients with the following criteria were also excluded: carotid stenoses ≥60% or occlusion by duplex ultrasound, post carotid endarterectomy, post carotid stenting, intracranial large-artery stenoses ≥50% or occlusion by MRA (12). Consequently, this study comprised 282 neurologically asymptomatic patients [mean ± standard deviation (SD) age, 66.9±8.4 years, 128 males] who had one or more atherosclerotic risk factors but without a history of cardiovascular disease. This study was approved by the Ethics Committee of Osaka University Graduate School of Medicine. All patients gave written informed consent.

**Diagnosis of SCI**

All MR imaging was performed with 1.5-Tesla Signa Horizon (GE Medical Systems, Harvey, IL) or 1.5-Tesla Magnetom Vision (Siemens, Erlangen, Germany). The whole brain was scanned, and 20 axial images were produced; slice thickness was 5 mm and interslice gap was 2 mm. The imaging protocol was consisted of a T2-weighted spin-echo (repetition time/echo time [TR/TE] 5,000/130 ms), T1-weighted spin-echo (TR/TE=500/9 ms), and fluid-attenuated inversion-recovery (FLAIR) (TR/TE=8,000/155 ms, inversion time=2,000 ms) imaging. A single trained physician who was blinded to patients’ clinical details evaluated the existence, and location of infarcts on MRI. Thereby, SCI was defined as an area of focal hyperintensity on T2-weighted images with corresponding low signal intensity on T1-weighted images, which was ≥3 mm in diameter. Additionally, FLAIR was used to distinguish infarction from dilated perivascular spaces.

The degree of white matter lesion (WML) was rated on FLAIR. Periventricular hyperintensity (PVH) and deep and subcortical white matter hyperintensity (DSWMH) were graded on a scale of 0 to 3 according to the grading of Fazekas et al (13). The total burden of WML, defined as the WML grade, was estimated by summing the PVH and DSWMH grade, forming a scale from 0 to 6. We considered a scale score ≥3 of WML as advanced WML.

**Evaluation of cardiovascular risk factors**

Information on patient medical history and medication was obtained from the clinical records, with investigators blinded to the MR findings. Hypertension was defined by casual blood pressure ≥140/90 mmHg or by current use of antihypertensive agents. Diabetes mellitus was defined by fasting blood glucose level ≥126 mg/dL, a glycosylate hemoglobin Alc (HbA1c) concentration ≥5.8% or by use of glucose-lowering agents or insulin. Dyslipidemia was defined by fasting serum low-density cholesterol (LDL) level ≥140 mg/dL, high-density cholesterol (HDL) level ≤40 mg/dL or triglycerides (TG) level ≥150 mg/dL, or by use of cholesterol-lowering agents. Smoking status was evaluated based on self-reports. Smokers were defined as current smokers. Body mass index was calculated as weight (in kilograms)/height (in meters squared). Atrial fibrillation findings were obtained from a standard 12-lead ECG completed before the baseline examination.

**Evaluation of carotid atherosclerosis**

All ultrasound examinations were performed with a Philips SONOS 5500 (Philips Medical Systems, Andover, MA) equipped with a 7.5-MHz linear-array transducer. The carotid IMT, defined as the distance between the intimal-luminal interface and the medial-adventitial interface, was measured as previously described (14). In brief, we calculated carotid IMT by averaging the thickness at 12 sites: the near and far walls of both right and left distal common carotid artery, carotid bifurcation, and internal carotid artery.

**Ascertainment of incident stroke and TIA**

Participants were followed up to determine the incidence of clinical stroke and TIA until late December 2007. Participants who died were censored at the time of death or the occurrence of the event of interest, whichever came first. Futhermore, if we were unable to follow-up with participants by late December 2007, then they were censored at their last follow-up visit. The medical records were reviewed for the occurrence of stroke and TIA. When patients failed to come to the clinic, we interviewed them by telephone. Each physician, who was caring for the patient at the time of the event, diagnosed any vascular events. All cases were further reviewed and confirmed for the diagnosis of stroke and TIA by independent physicians. The criteria for the diagnosis of stroke was sudden onset of a neurologic deficit.
that persisted for ≥24 hours. Stroke events were confirmed by computed tomography scanning or MRI and classified for ischemic stroke (e.g., atherothrombotic infarction, lacunar infarction, cardiogenic embolism and others), cerebral hemorrhage, and subarachnoid hemorrhage according to TOAST criteria (15). TIA was defined as focal symptoms lasting <24 hours.

**Statistical analyses**

To evaluate the univariate cross-sectional association between SCI and the baseline characteristics of the patients, we used \( \chi^2 \) test for categorical data and 2-sample \( t \) test for continuous data. Values were expressed as mean ± SD. Cox proportional hazard regressions were used to estimate the hazard ratio (HR) of SCI and 1SD increase of carotid IMT for evaluating the risk of stroke and TIA. Hazard ratios were sequentially adjusted for the following variables: age and sex (model 1), hypertension, smoking, diabetes mellitus and dyslipidemia (model 2), and either SCI or carotid IMT (model 3). The Kaplan-Meier method with a log-rank test was used to compare event-free survival in the two groups (i.e., with and without SCI). To evaluate the joint effect of SCI and carotid IMT, we repeated the analysis classifying all patients in 1 of 4 groups on the basis of whether they have SCI and whether they were above or below the median carotid IMT value. However, the numbers of incident stroke and TIA in the groups below the median IMT value with and without SCI were small, we combined these 2 groups into one category (low IMT group) which was assigned as the reference group. All statistical analyses were performed with SPSS11.5J (SPSS Japan Inc) and \( p<0.05 \) was considered to be statistically significant.

The baseline characteristics of the patients are shown in Table 1. Sixty-seven (24% of the total) patients were found to have one or more SCIs on MRI. Among them, 43 (64%) patients had a single infarct, whereas 24 (36%) had between two to five infarcts. Moreover, 36% of the infarcts were located in the subcortical white matter (corona radiata, centrum semiovale, subcortical frontal, temporal and parietal lobes), and 55% were in the basal ganglia and thalamus. No patients had cortical infarcts. Advanced WML was found in 67 patients (24%). Age, prevalence of male gender, hypertension, advanced WML, and carotid IMT were significantly higher in the patients with SCI than in those without SCI. Both LDL- and HDL-cholesterol levels were lower in the patients with SCI (Table 1).

### Results

During an average duration of 4.1±2.0 years (range: 1 to 105 months, 1,165 person-years), 8 patients (2.8%) had a new stroke or TIA. Of these 8 patients, 3 had cerebral infarctions (2 lacunar infarctions and 1 atherothrombotic infarction), 2 had cerebral hemorrhages, 1 had TIA in the SCI group, and 2 had cardioembolic infarctions in the no-SCI group.

The characteristics of patients who had clinical stroke and TIA are shown in Table 2. Patients with incident stroke or TIA were more likely to have higher values of carotid IMT and SCI at baseline. The prevalence of advanced WML was not significant between the two groups in this study (\( p=0.16 \)).

Cumulative event-free survival (Fig. 1) shows that SCI was associated with the incidence of stroke and TIA. The Cox proportional hazard analysis (Table 3) revealed that
both SCI and 1SD increase of carotid IMT were significantly associated with risk of incident stroke and TIA after adjustment for age and sex (model 1), and traditional cardiovascular risk factor such as smoking, hypertension, dyslipidemia and diabetes mellitus (model 2). Even after additional adjustment to model 2 for carotid IMT and SCI (model 3), both SCI (HR: 8.56, 95%CI: 1.72-42.55, p=0.003) and 1SD increase of carotid IMT (HR: 1.86, 95%CI: 1.13-3.06, p=0.029) were significantly associated with risk of incident stroke and TIA.

To assess the joint effect of SCI and carotid IMT, we constructed survival curves after dividing patients into 3 groups according to SCI and carotid IMT values (Fig. 2). The incidence of stroke and TIA in patients with SCI who had the higher median value of baseline carotid IMT was striking. After adjustment for age, sex, and traditional risk factors, the SCI(+)/high IMT group had a significantly increased risk of stroke and TIA compared to the low IMT group (HR: 12.74, 95%CI: 1.45-111.58, p=0.022).

**Discussion**

We have shown that SCI is associated with incident stroke and TIA independent of carotid IMT. In this study, both SCI and carotid IMT at baseline are associated with incident stroke and TIA after adjustment for age, sex, and traditional cardiovascular risk factors. These results corroborate previous cohort studies with SCI (2-7) and carotid IMT (8-11). Kobayashi et al reported the HR of SCI was 10.5 for stroke in participants who received health screening (2). Similarly, the HR of SCI in the present study was close to 9.0. In elderly hypertensive or diabetic Japanese patients, the HR of SCI was between 4.6 and 4.9 (4, 5). However, the HR of SCI was lower in general populations. In the Cardiovascular Health Study, the HR of SCI was around 1.5 (6). In the Rotterdam Scan Study, the HR of SCI was 3.9 (7). The present study suggests that the presence of both SCI and carotid IMT may be sufficient for determining patients at high-risk for stroke. Carotid IMT represents early atherosclerosis in large arteries; therefore, carotid IMT is a predictor not only for stroke but also for myocardial infarction (8). Another index of carotid atherosclerosis, i.e., plaque score, was more closely associated with atherothrombotic brain infarction than with other subtypes in the cross-sectional study (16). In turn, SCI represents cerebral small vessel disease. The previous studies showed that patients with SCI likely had both cerebral infarction and cerebral hemorrhage.
Table 3. HR (95% CI) for Stroke/TIA according to SCI and Carotid IMT at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
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<tbody>
<tr>
<td>SCI</td>
<td>9.01 (1.81-44.88)</td>
<td>9.01 (1.81-44.88)</td>
<td>8.56 (1.72-42.55)</td>
</tr>
<tr>
<td>IMT 1SD (0.30 mm)</td>
<td>1.81 (1.15-2.84)</td>
<td>1.81 (1.15-2.84)</td>
<td>1.86 (1.13-3.06)</td>
</tr>
</tbody>
</table>

SCI = silent cerebral infarction, IMT = intima-media thickness.
Model 1 adjusted for demographic variables (age and sex).
Model 2 adjusted for demographic variables in model 1 and clinical variables; smoking, hypertension, diabetes mellitus, and dyslipidemia.
Model 3 adjusted for model 2, SCI, and carotid IMT.

Figure 2. Cumulative event-free survival for stroke and TIA in patients with/without SCI, above median carotid IMT value and in patients below median carotid IMT value.

during the follow-up period, which indicates that SCI represents a common vascular pathology underlying lacunar infarction and cerebral hemorrhage (2-4). A combination of different markers representing large and small vessel disease could be useful for efficient stratification of high-risk patients for stroke. In our study, however, the well-established associations between traditional risk factors and incident stroke were not clear; this may have been due to the inclusion of elderly high-risk patients who receive several medications (2, 6, 7).

Further this study had some additional limitations. First, the small number of incident stroke and TIA could not allow us to examine the predictive value of SCI and carotid IMT for each stroke subtype. Furthermore, the scarcity of incidence stroke in the low IMT group did not allow us to examine the predictive value of SCI in this group. Secondly, we used routine screening MRI and a visual rating scale, that would not allow us to examine the predictive value of white matter lesions, another sign for cerebral small vessel disease, for incident stroke. Quantitative evaluation of white matter lesions would be required for this purpose (17, 18). Thirdly, we measured SCI and carotid IMT under baseline conditions, thus, it remains to be seen whether longitudinal observation of SCI and carotid IMT is useful for predicting future risk of stroke and TIA.

In conclusion, SCI could be a marker of incident stroke and TIA independent of carotid IMT. The detection of SCI with MRI in combination with carotid IMT measurement could be used in routine clinical practice to enhance the predictability of stroke and TIA in high-risk patients.

References


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