

Risk Factors of Small Cortical Infarctions on Diffusion-Weighted Magnetic Resonance Imaging in Patients with Acute Ischemic Stroke

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Short title: Small Cortical Infarcts on DWI

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Key Words:

small cortical infarction, acute ischemic stroke, diffusion weighted MRI, carotid disease, coagulopathy

Abstract:

Background and purpose: Diffusion weighted MRI is sensitive for detecting acute ischemic lesions. Our purpose was to evaluate the factors which are associated with small cortical infarcts on diffusion weighted MRI.

Methods: We analyzed 123 patients with acute ischemic stroke retrospectively. We defined small cortical infarcts as cortical lesions displayed using diffusion weighted MRI whose diameter was <1.5cm. The risk factors and co-morbidities included hypertension, hypercholesterolemia, diabetes mellitus, cigarette smoking, potential cardiac sources of embolism, carotid disease, and coagulopathy. Carotid disease was defined as more than 50% stenosis or occlusion in internal carotid artery using carotid ultrasonography. In addition,

we analyzed plasma levels of coagulation and fibrinolysis markers. We also compared carotid disease, potential cardiac sources, and coagulopathy among localization of small cortical infarcts.

Results: Small cortical infarcts were identified in 22.8% of acute ischemic stroke. Carotid disease (OR 4.4, 95%CI 1.7 to 11.42, $p=0.002$) and coagulopathy (OR 6.8, 95%CI 1.33 to 35.17, $p=0.02$) were independent risk factors for small cortical infarcts. Small cortical infarcts with carotid disease were not associated with bilateral and multiple territorial lesions, while those with coagulopathy were associated with bilateral lesions. Borderzone lesions were not found in patients with cardiac sources.

Conclusions: Carotid disease and coagulopathy are independent risk factors for small cortical infarcts. Localization of small cortical infarcts is different depending on the underlying diseases.

Introduction

It is anticipated that the detection of SCI increased after the DWI technique was made available. There are some literatures that DWI is more usefully to detect previous minor strokes and transient ischemic attack than conventional T2 or proton density MRI ^{1, 2}. Small cortical infarcts (SCIs) are easy to be confused with signals of cerebrospinal fluid on T2 or proton MRI. Furthermore, small disseminated “satellite” lesions which are silent and would have gone unrecognized when the lesions are smaller than 1 cm in diameter. The high signal-to noise ratio of DWI allowed detection of disseminated small lesions on the cortical edge, which might often be missed on conventional T2-weighted imaging ³. Recent literature shows that multiple small lesions visible on DWI are likely to be caused by emboli from cardiac source or carotid occlusive disease ³⁻⁵. Another current study on microembolic signals (MES) detected by transcranial Doppler (TCD) showed that MES is associated with carotid occlusive disease and small spotty lesion in the cortex⁶. These results may support the hypothesis that the predominant mechanism of SCI is mainly emboli from carotid disease.

Many previous literatures studied about carotid disease with small infarcts in cortical area and multiple infarcts including cortical small lesions, though

there is few study on a mechanism of SCI. In this study, we examined the differences of vascular risk factors and blood coagulation parameters among patients with and without SCI and compared these risk factors with localization of the lesions in order to investigate the etiologies of SCI.

Subjects and Methods

Subjects consisted of 123 patients (82 men and 41 women; mean age of 67.8 years) who were consecutively admitted with acute ischemic stroke to the Tokyo Women's Medical University Hospital and underwent DWI from September 2003 to January 2006. The following clinical data were investigated for all patients: systematic investigations including blood chemistry studies, coagulation testing, urinalysis, chest radiography, electrocardiography, echocardiography, MRI, MR angiography, 24-hour electrocardiographic monitoring, and carotid ultrasonography. MR imaging was performed using a 1.5T system (Toshiba Excelart, Philips Intera, GE Signa, or Siemens Vision) equipped with single shot eco-planar imaging. Multimodal MRI included axial T1-weighted, T2-weighted, fluid attenuated inversion recovery (FLAIR), MRA and DWI sequence. The exact sequence parameters were as follows: TR/TE 6000/130, 3014/78, 1000/100.7, or 4000/100; matrix size 128×128 , 256×256 , 128×128 , or 96×128 ; field of view 270×300 , 250×250 , 220×220 , or 220×220 ; slice thickness 7mm; b-values 1000 s/mm^2 . Diffusion gradients were applied in successive scans in each of the x, y, and z directions, and DWI was formed from the average of these values. SCI was defined as a cortical hyperintense lesion with diameter of $<1.5\text{cm}$ on DWI. We analyzed differences in gender, age, risk factors for stroke and plasma levels of coagulation markers among patients with and without SCI.

The risk factors included hypertension (blood pressure $>140/90\text{mmHg}$ or a history of hypertension requiring medical treatment), hypercholesterolemia (serum total cholesterol level $>220\text{mg/dl}$ or a history of hypercholesterolemia requiring medical treatment), diabetes mellitus (glycosylated hemoglobin level $>6.5\%$ or a history of treatment with oral glucose depressants or insulin), regular cigarette smoking, potential cardiac sources of embolism including atrial fibrillation (AF), patent foramen ovale (PFO) and thrombus in left atrium (LA).

We used duplex ultrasound and power Doppler ultrasound (Toshiba SSA - 350A and SSA - 550A) in the assessment of 50% < stenosis or occlusion in carotid artery⁷. We used the criteria by the European Carotid Surgery Trial (ECST) for measuring carotid stenosis. For excluding carotid occlusions caused from cardiac embolisms in cardiac disease, the cases with both carotid occlusion and potential cardiac sources were classified only into potential cardiac sources but not into carotid disease. We also investigated a history of Trousseau's syndrome (coagulopathy induced by cancer) and antiphospholipid syndrome (fulfilled the Sapporo criteria⁸). Both of Trousseau's syndrome and antiphospholipid syndrome were classified as coagulopathy. Coagulation markers included β -thromboglobulin (β -TG), platelet factor 4 (PF4), thrombin-antithrombin III complex (TAT) and D-dimer. β TG and PF4 were measured using an Asserachrom β TG kit and PF4 kit (Diagnostica Stago, Asnières, France). TAT and D-dimer were measured using a TAT SRL kit (SRL, Tokyo, Japan) and an Lpia-ace D-dimer kit (Mitsubishi Kagaku Iatron, Tokyo, Japan), respectively. Plasma levels of these hemostatic markers were quantified using enzyme-linked immunosorbent assay.

We classified the localizations of SCI into bilateral lesions, territorial single circulation (anterior or posterior circulation) lesions, territorial multiple circulation (bilateral or anterior and posterior circulations) lesions, and borderzone lesions (Figure). Borderzone lesions were defined as SCI in superficial borderzone areas.

Six of 7 SCI patients with bilateral lesions were categorized into territorial multiple circulations. One SCI patient with bilateral lesions who had a coagulopathy as a risk factor had lesions into bilateral borderzone and categorized into borderzone.

We compared risk factors which were carotid disease, coagulopathy and potential cardiac sources among localization of SCI.

Statistical Analysis:

All data were entered into SPSS version 7.5 for Windows (Chicago, USA) for analysis. Differences in the prevalence of risk factors among patients with and without SCI were analyzed using chi-square test for the variables with 5 or more possible values. Fisher's exact test was used to analyze the prevalence of the

lesion patterns of SCI for the nominal variables with fewer than 5 possible values. A Mann-Whitney U test was used to test the distribution of the continuous variables such as age and plasma level of coagulation markers between patients with and without SCI. We also analyzed these risk factors as independent determinants for SCI by multiple logistic regression analysis. The results were expressed as odds ratios (ORs) of relative risk, with 95% confidence intervals (CI). Statistical significance was established at the $p < 0.05$.

Results

SCI was detected in 28 of 123 patients (22.8%). Carotid disease was significantly associated with SCI (Table 1) and all of the patients with SCI had the lesions in the same side with carotid disease. While, there were no significant differences in age, gender, or the prevalence of diabetes mellitus, hypertension, hypercholesterolemia, cigarette smoking and potential cardiac sources between patients with and without SCI. Multiple logistic regression analysis showed that carotid disease (OR 4.4, 95%CI 1.7-11.4, $p = 0.002$) and coagulopathy (OR 6.8, 95%CI 1.33-35.17, $p = 0.02$) were independent risk factors for SCI (Table 2). We analyzed plasma levels of coagulation parameters among patients with and without SCI (Table 3). However, there was no coagulation parameter significantly higher in SCI patients. We also analyzed plasma levels of coagulation parameters among SCI patients with carotid disease and with coagulopathy, though we could not show any significant difference among them (data was not shown).

Localization of SCI and underlying diseases was shown in Table 4. 13 SCI patients were associated with carotid disease, 8 with potential cardiac sources, 4 with coagulopathy, and 6 with unidentified sources of infarcts. Risk factors overlapped in 3 patients displaying the following pathology: carotid disease and potential cardiac sources, carotid disease and coagulopathy, and potential cardiac sources and coagulopathy. Bilateral lesions were less associated with carotid disease ($p = 0.009$). On the other hand, SCI with coagulopathy was associated with bilateral lesions ($p = 0.038$). Territorial multiple circulation lesions were less associated with carotid disease ($p = 0.037$) and tend to be associated with coagulopathy ($p = 0.058$). Borderzone lesions were not found in

SCI patients with potential cardiac sources.

Discussion

Recent literature has shown that multiple lesions detected by DWI which are often small and located in the cortex, are presumed to come from multiple embolus or the break-up of embolus³. Our study showed that SCI was associated with carotid disease and coagulopathy, but not with potential cardiac sources. We can presume that the size of the embolism, depending on its property, is an important factor for SCI. The size of the particle should be smaller in arterial sources of embolisms compared with cardiac sources of embolisms, so arterial sources of embolisms produce more distal infarction compared with cardiac embolisms⁹. The reason for this is that arterial embolisms are primarily due to smaller white thrombus (platelet aggregates) and cardiac embolisms are mostly from larger red thrombus (platelet and fibrin network). In addition, the fibrin network's size is 30 to 1500 μ m, while the platelet aggregates size is 10 to 35 μ m in the macroscopic study¹⁰.

Carotid disease was an independent risk factor for SCI. There are some current studies demonstrated with MES detected by TCD, suggested that embolisms from carotid disease are associated with SCI¹¹⁻¹⁶. Kimura et al⁶ showed that small spotty lesions (<10 mm) on DWI were more frequent in patients with MES detected by TCD and associated with large vessel disease. Molloy et al¹¹ reported that MES was detected in 41% among cases of >60% carotid stenosis particularly with ulcerated plaque. Others showed that the number of MES increased with increasing degree of stenosis¹². In this study, SCI with carotid disease was less associated with bilateral and territorial multiple circulation lesions. This result was supported by a recent study that multiple lesions in the unilateral anterior circulation and small scattered

lesions in one vascular territory were related to large-artery atherosclerosis ¹⁷.

There are some controversies about the etiology of infarcts with carotid disease. We did not see any significant difference between localization of SCI and the mean degree of carotid disease (data were not shown). Szabo et al ¹⁸ distributed that patients with high-grade (>70%) and subtotal stenosis had small lesions in hemodynamic risk zones. Another study also showed that borderzone infarcts appeared mostly in patients with 90% to 99% ICA stenosis ¹⁹. Many of recent studies on borderzone infarcts demonstrated that lesions which is so-called rosary-like infarcts, were the result of hemodynamic mechanisms of a high degree of ICA stenosis ²⁰⁻²⁷. On the other hand, there is a study reported that there was no etiologically difference among borderzone and territorial infarcts with carotid disease ²⁸. Furthermore, Caplan et al ^{29, 30} postulated that embolism and hypoperfusion play a synergistic role. Small embolic material prone to lodge in distal field arterioles because of a limitation to wash out would be more likely to result in cortical micro-infarcts when chronic hypoperfusion prevails.

Coagulopathy was also an independent risk factor for SCI in this study. Our results showed that embolic sources due to coagulopathy were likely smaller and caused SCI. Trousseau's syndrome is one of the paraneoplastic neurologic syndromes that patients with cancer have a high frequency of embolic infarcts due to cancer-induced hypercoagulability ³¹. Furthermore, one of the most important pathogenesis of embolic strokes in patients with Trousseau's syndrome is nonbacterial thrombotic endocarditis (NBTE). In a recent study about the stroke patterns of patients with NBTE detected by DWI showed that patients with NBTE had several smaller (<10mm) lesions which were distributed more than 1 arterial territory ³². In addition, other study showed that acute multiple infarcts in both anterior and posterior circulations were associated with malignancy and cardiac embolism³³. These studies support our results that SCI with coagulopathy was associated with bilateral lesions and tended to be associated with territorial multiple circulations.

TAT and D-dimer are coagulation and fibrinolysis markers, and they substantially increase in the hyper-coagulable states of Trousseau's syndrome accompanied by disseminated intravascular coagulation (DIC), and in cardiac

embolism³⁴⁻³⁶. Plasma levels of these coagulation markers were not elevated in patients with antiphospholipid syndrome³⁷. On the other hand, β TG and PF4 reflect the activation of platelets, and these markers are increased in atherothrombotic infarcts^{34,35}. Coagulation markers were not significantly different between patients with and without SCI. Coagulation markers were frequently increased also in patients without SCI but with large cortical or subcortical infarcts (mainly cardioembolic or atherothrombotic infarcts), that would be why there were no significant differences in coagulation markers between patients with and without SCI.

As the limitation of this study, we selected ultrasound as the primary diagnostic tool in assessment of stenosis and occlusion of ICA. MRA has a better discriminatory power compared with duplex ultrasound in diagnosing stenosis³⁸. However, the recent literature reported that the combination of power Doppler and color duplex sonography may be able to compensate for the lacking specificity of MRA, especially in high-grade stenoses and pseudoclosures⁷. In addition, we did not estimate the vertebrobasilar atherosclerosis from the reason that the evaluation of this by carotid sonography was difficult. Kock et al.³⁹ reported that vertebrobasilar occlusive disease was associated with multiple brain infarcts in the posterior circulation and made a suggestion of arterial embolism as the mechanism of infarcts. There are some disputes about an embolic source of infarcts of posterior cerebral artery territories⁴⁰⁻⁴². In addition, we did not assess the quality of match between volumes of DWI between MRI sequences. However, we used same b-values and the difference of the image qualities between sequences was seemed to be small because we assessed cortical lesions which were less affected by artifact. Furthermore, the number of population of SCI was small, hence we had a statistical limitation to demonstrate the association among localization, risk factors, degree of ICA stenosis and coagulation markers in SCI patients.

In conclusion, carotid disease and coagulopathy are associated with SCI. It might be possible to suggest that the localizations of SCI are different depending on the underlying disease and mechanisms of infarcts. Consequently, the early identification of SCI detected by DWI may help to clarify the pathogenesis of stroke and guide therapeutic options in acute stroke patients.

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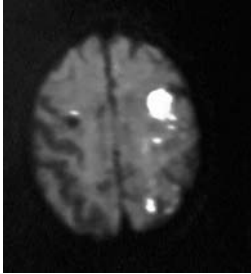
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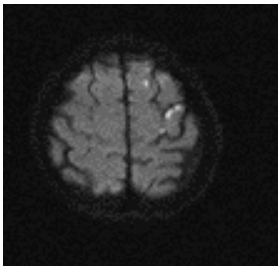
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Figure

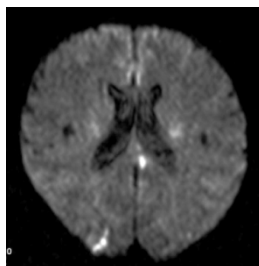
Bilateral lesions



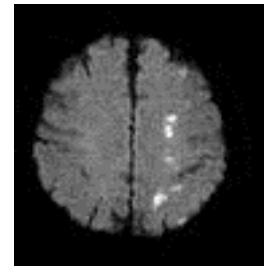
Territorial single circulation



Territorial multiple circulations



Borderzone



We classified the localizations of SCI into bilateral lesions, territorial single circulation (anterior or posterior circulation), territorial multiple circulation (bilateral or anterior and posterior circulations), and borderzone lesions (Figure). Borderzone lesions were defined as SCI in superficial borderzone areas.

Table 1. Background characteristics of patients with and without small cortical infarcts

<i>Characteristics</i>	<i>SCI (+)</i> <i>(n = 28)</i>	<i>SCI (-)</i> <i>(n = 95)</i>	<i>p value *</i>
Age, years \pm SD	69.8 \pm 14.1	67.0 \pm 13.4	0.21**
Male gender (%)	21 (75.0%)	61 (64.2%)	0.36
Diabetes mellitus	15 (53.6%)	42 (44.2%)	0.40
Hypertension	18 (64.2%)	65 (68.4%)	0.65
Hypercholesterolemia	12 (42.9%)	39 (41.1%)	1.00
Cigarette smoking	12 (42.9%)	44 (46.3%)	0.55
Potential cardiac sources	8 (28.6%)	20 (21.1%)	0.46
Atrium fibrillation	6	19	
PFO	1	1	
Thrombosis in LA	1	0	
Carotid disease	13 (46.4%)	12 (12.6%)	0.001
Occlusion	3	3	
Mean degree of stenosis	75.2 \pm 21.4	70.0 \pm 21.7	0.56**
Coagulopathy	4 (14.3%)	5 (5.3%)	0.21
Trousseau's syndrome	3	2	
APS	1	3	

SCI: small cortical infarcts, PFO: patent foramen ovale, LA: left atrium

APS: antiphospholipid syndrome

* Chi-square test ** Mann-Whitney U test

Table 2. Multiple logistic regression analysis of the association between risk factors and small cortical infarcts on DWI

<i>Risk factors</i>	<i>OR</i>	<i>95%CI</i>	<i>P value</i>
Age (years)	1.0	0.96 – 1.06	0.59
Male gender	2.1	0.7 – 6.2	0.18
Diabetes mellitus	1.4	0.54 – 3.76	0.45
Hypertension	0.8	0.25 – 2.15	0.58
Hypercholesterolemia	1.5	0.55 – 4.13	0.43
Cigarette smoking	0.6	0.27 – 1.41	0.25
Potential cardiac sources	1.3	0.46 – 3.91	0.59
Carotid disease	4.4	1.7 – 11.42	0.002*
Coagulopathy	6.8	1.33 – 35.17	0.022*

The table shows the odds ratios and 95% CI of SCI being present vs SCI not being present related to each risk factor.

OR: odds ratio 95%CI: 95% confidence interval

*Significant differences

Table 3. Blood coagulation markers in patients with and without small cortical infarcts

<i>Mean ± 2SD</i>	<i>p value*</i>
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	<i>SCI (+)</i>	<i>SCI (-)</i>	
TAT (ng / ml)	12.5 ± 25.9	7.2 ± 11.3	NS
DD (μg / ml)	19.3 ± 65.0	6.69 ± 25.6	NS
β TG (μg / ml)	148.0 ± 255	130.9 ± 292.7	NS
PF4 (ng / ml)	75.2 ± 180.5	45.9 ± 118.2	NS

TAT; thrombin-antithrombin III complex, DD; D-dimer, β TG; β-thromboglobulin,

PF4; platelet factor, SCI; small cortical infarcts

*Mann-Whitney U test

Table4. Localization of SCI and risk factors

<i>Localization of SCI</i>	<i>N</i>	<i>Risk factors</i>	<i>N (%)</i>
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Bilateral	7	Carotid disease	1 (7.7)**
		Coagulopathy	3 (75.0)*
		PCS	3 (37.5)
		Others	1 (16.6%)
Territorial single circulation	15	Carotid disease	8 (61.5)
		Coagulopathy	1 (25.0)
		PCS	5 (62.5)
		Others	3 (50%)
Territorial multiple circulations	8	Carotid disease	2 (15.4)***
		Coagulopathy	2 (50.0)
		PCS	3 (37.5)
		Others	1 (16.6%)
Borderzone	6	Carotid disease	3 (23.1)
		Coagulopathy	1 (25.0)
		PCS	0 (0)
		Others	2 (33.3%)

PCS; potential cardiac sources

“Others” include one patients with Thoracic aortic aneurysm and 5 patients whose mechanism of infarcts was undetermined.

Risk factors overlapped in 3 patients displaying the following pathology: carotid disease and potential cardiac sources, carotid disease and coagulopathy, and potential cardiac sources and coagulopathy. Bilateral lesions were associated with SCI with coagulopathy* ($p=0.038$) and less associated with those with carotid disease** ($P=0.009$). SCI with carotid disease was less associated with territorial multiple circulation*** ($p=0.037$). (Fisher’ s exact test)