Lesion Patterns and Mechanism of Ischemia in Internal Carotid Artery Disease

A Diffusion-Weighted Imaging Study

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Context: Although embolism and low-flow phenomenon are the 2 main mechanisms of stroke in internal carotid artery (ICA) occlusive disease, the mechanism of border-zone infarction remains controversial. Diffusion-weighted imaging (DWI) can more easily detect small or multiple ischemic lesions than conventional imaging.

Objectives: To investigate the ischemic lesion patterns on DWI and to discuss the mechanisms of stroke in ICA disease.

Design: Case series.

Setting: A tertiary referral center.

Patients: We enrolled 35 consecutive patients who had an acute ischemic stroke and (≥70%) stenosis or occlusion of the extracranial ICA confirmed by cerebral angiography and an acute relevant stroke lesion on DWI within 1 week of onset, but without cardiac sources of embolism and tandem intracranial arterial disease.

Main Outcome Measures: The lesion pattern on DWI was categorized as territorial or border zone. Multiple ischemic lesions were defined as noncontiguous lesions on DWI in more than 1 vascular territory.

Results: There were 3 distinctive stroke lesion patterns. (1) A territorial lesion without a border-zone lesion was found in 21 patients: superficial and superficial territorial in 9, superficial and deep territorial in 7, and single in 5. (2) A border-zone lesion with or without a territorial lesion was found in 10 patients: border zone and territorial in 9 and border zone alone in 1. (3) Bilateral hemispheric lesions were found in 4 patients. Multiple ischemic lesions were found in 29 (82.9%) of the 35 patients. No patient had episodes of hemodynamic compromise.

Conclusions: An acute ischemic lesion in ICA occlusive disease is mainly multiple. Border-zone infarction was mostly associated with territorial infarction. These results support the fact that embolism is the predominant stroke mechanism in ICA occlusive disease.

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The clinical syndromes from extracranial internal carotid artery (ICA) occlusive disease result from 2 basic mechanisms—from embolism and from low flow due to inadequate collateral circulation distal to a hemodynamically significant stenosis or occlusion. Concurrently, regarding the topography of the ischemic stroke lesion in extracranial ICA disease, territorial and border-zone infarctions are the 2 major patterns. Although hemodynamic compromise due to low flow in the border-zone areas has usually been postulated to explain the infarcts in these regions, the actual cause of border-zone infarction is still controversial.

Diffusion-weighted imaging (DWI) is sensitive to acute cellular injury in cerebral ischemia and can detect ischemic lesions within the first few hours. Diffusion-weighted imaging is superior to conventional magnetic resonance imaging (MRI) especially for detecting small or multiple new ischemic lesions. With this new MRI technique, we observed acute multiple ischemic lesions in both the territorial and border-zone areas in patients with extracranial ICA occlusive disease. Based on these observations, we aimed to investigate the ischemic lesion patterns resulting from ICA occlusive disease using DWI and to discuss their mechanism.

PATIENTS AND METHODS

We considered 51 consecutive patients with acute ischemic stroke who were admitted to our stroke unit from July 1997 to June 2001, who had stenosis (≥70%) or occlusion of extracranial ICA confirmed by cerebral angiography using a catheter and had an acute ischemic...
To determine the stroke pattern caused by ICA disease itself, we excluded 16 patients with potential cardiac sources of embolism (n=4), tandem intracranial occlusive disease (n=5), or irrelevant ischemic lesion to ICA disease (n=7, infratentorial stroke in 4 and contralateral hemispheric stroke caused by middle cerebral artery [MCA] disease in 3). Thus, the ischemic lesion patterns in the remaining 35 patients (32 men and 3 women; mean age [SD] 63.5 [8.6] years) who had acute ischemic lesion relevant to ICA disease were analyzed.

**CLINICAL EVALUATION**

All patients underwent systematic investigations including complete blood cell count, blood chemistry studies, lipid profiles, coagulation testing, urinalysis, chest radiography, electrocardiography, transthoracic echocardiography, computed tomographic scan, MRI, MR angiography, and cerebral angiography. In selected patients, transesophageal echocardiography including a microbubble test, 24-hour electrocardiographic monitoring, and transcranial Doppler were also performed.

The risk factors included hypertension (blood pressure >160/90 mm Hg on 2 separate occasions), hypercholesterolemia (cholesterol concentration >0.16 mg/dL [>6.22 mmol/L] or a low-density lipoprotein cholesterol level >0.11 mg/dL [4.14 mmol/L]), diabetes mellitus, regular cigarette smoking, myocardial ischemia, arrhythmia, valvular heart disease, a family history of stroke or ischemic heart disease, and a history of vascular disease or migraine. Patients with potential cardiac sources of embolism11 were excluded from this study.

**ANGIOGRAPHIC EVALUATION**

Intra-arterial cerebral angiography by femoral catheterization was performed within 30 days from the date of the MRI evaluation (mostly within 10 days), with informed consent from all patients. The degree of stenosis of the extracranial ICA indicated by angiography was evaluated using the North American Symptomatic Carotid Endarterectomy Trial method for stenosis measurements.11 Patients with tandem intracranial arterial stenosis (>50%) or occlusion or dissection of the ICA were excluded from this study.

In an attempt to evaluate the perfusion status, the collateralization through the circle of Willis, leptomeningeal vessels, and ophthalmic artery was graded on the basis of capillary blush in cases of ICA occlusion. In cases of ICA stenosis, it was determined based on the capillary blush by the flow distal to the stenosis or by collateral flows. The cerebral perfusion was classified as “poor” if no or minimal capillary blush in the MCA territory was visible; it was classified as “good” if there were moderate capillary blush with some filling defect or intact capillary blush in the entire MCA territory. Perfusion status was blindly determined to the clinical and MRI data.

**MAGNETIC RESONANCE IMAGING**

All patients underwent conventional MRI and DWI on a 1.5-T system with an echoplanar imaging capability (Signa Horizon, Echospeed; General Electric Medical Systems, Milwaukee, Wis) within 1 week of stroke onset. The conventional MRI consisted of transverse T2-weighted sequences (repetition time/echo time, 4000/98 milliseconds, 3 excitations) and sagittal T1-weighted sequences (repetition time/echo time, 450/10 milliseconds, 2 excitations) with 5-mm-thick slices. Diffusion-weighted imaging was obtained in the transverse plane using a single-shot echoplanar, spin-echo pulse sequence with a repetition time/echo time of 6500/107 milliseconds, 1 excitation, and 2 b values (0 and 1000 s/mm²). The diffusion-gradient pulse duration was 31 milliseconds with a gradient strength of 33 millisecond and a gradient strength of 2.16 g/cm. The diffusion-gradients were applied simultaneously along the 3 axes (x, y, and z).

**TOPOGRAPHY OF THE ISCHEMIC LESION**

The topography of the ischemic lesion was determined using the commonly accepted arterial supply templates for the territorial13,14 and border-zone areas. The arterial territories were divided for the anterior circulation as follows: ICA, anterior cerebral artery (ACA), superior division of the MCA, inferior division of the MCA, perforating branches of the MCA, and anterior choroidal artery. The arterial territories for the posterior circulation were posterior cerebral artery, basilar artery, and cerebellar arteries. The diagnosis of multiple ischemic lesions on DWI was made if there were noncontiguous high-signal intensities on DWI that were present in more than 1 vascular territory. An uninterrupted lesion visible in contiguous territories was considered a single lesion.9,10

We divided the ischemic lesion pattern into the territorial and border zone. The categorization of territorial infarcts was given if the lesion was located within the corticosubcortical vascular territories of the large cerebral arteries and their major pial branches.11 Territorial infarcts were also divided into superficial and deep infarcts. Superficial infarcts are located in the superficial cortical areas or the vascular territories supplied by the pial branches of the large cerebral arteries. Deep infarcts include striatocapsular infarcts and perforating vessel infarcts. A categorization of striatocapsular infarct was given if the lesion was 15 mm or larger in diameter and restricted to the territory of the lenticulostriate arteries.18 A perforating vessel infarct was defined as any infarct with a diameter smaller than 15 mm involving the area supplied by perforators of the MCA, ACA, ICA, or anterior choroidal artery. Border-zone ischemic lesions were considered when the lesions involved either the border zone between the superficial territories of the MCA and ACA (anterior border zone), the border zone between the superficial territories of the MCA and posterior cerebral artery (posterior border zone), or the border zone between the superficial and deep territories of the MCA (subcortical border zone).15,16 Ischemic lesion patterns were also determined without knowing the clinical and angiographic data.

**DATA ANALYSES**

The Fisher exact test or χ² test was performed to determine the presence of a relationship between lesion patterns and various clinical or radiological findings. Statistical significance was set at P<.05, 2-sided.

**RESULTS**

The neurologic manifestations and radiological features of all patients are summarized in the Figure. Twenty-six patients had first-ever stroke, and 9 patients had recurrent ischemic stroke. No patient had an episode of hemodynamic compromise that included systemic hypotension, dehydration, or diarrhea. No patients suffered more than 1 clinical event from the beginning of the stroke to the neuroradiological evaluation. The situation at the time of the stroke was normal activity in 19 patients, on awakening in 15, and traumatic in 1. The mode of symptom progression before hospitalization was sudden maximal deficit at onset in 16 patients, progres-
sive in 15, and fluctuating in 4. A history of transient ischemic attack was present in 12 patients. The risk factors for stroke were regular smoking in 22 patients, hypertension in 21, diabetes mellitus in 14, a family history of stroke in 6, hypercholesterolemia in 4, ischemic heart disease in 2, malignancies in 2, and peripheral vascular disease in 1. There were no identifiable risk factors for stroke in 1 patient. No patient had polycythemia (hematocrit of >50%), but 20 patients had hyperfibrinogenemia (fibrinogen level of >302.63 g/dL [>10.3 µmol/L]).

Twenty-eight patients had unilateral (15 on the right side and 13 on the left side) ICA occlusive disease; an occlusion in 14 patients, 90% to 99% stenosis in 7, and 70% to 89% stenosis in 7. In those patients who had stenosis, 7 had a mild stenosis of the contralateral ICA (50%-69% in 3, <30% in 4). Bilateral ICA occlusive diseases were found in 7 patients; bilateral occlusions in 1 patient, bilateral stenoses (90%-99%) in 1, unilateral occlusion and contralateral stenosis (70%-89%) in 2, and unilateral stenosis (90%-99%) and contralateral stenosis (70%-89%) in 3. Based on the angiographic capillary
blush, 27 patients had good cerebral perfusion and 8 had poor cerebral perfusion.

**DISTRIBUTION OF ISCHEMIC LESIONS**

Diffusion-weighted imaging was superior to conventional MRI in 23 patients (65.7%). Diffusion-weighted imaging demonstrated additional ischemic lesions not observed on conventional MRI in 12 patients. Diffusion-weighted imaging discriminated recent infarcts from old ones or nonspecific, periventricular high-signal intensities in 13 patients.

We found 3 distinctive patterns of acute ischemic lesion distribution (Table 1). First, territorial distribution without a border-zone lesion in the unilateral hemisphere was found in 21 patients (Figure A). In these patients, 9 had a superficial and superficial pattern (Nos. 1-9), 7 had a superficial and deep pattern (Nos. 10-16), and another 5 had single lesion (Nos. 17-21).

Second, border-zone distribution with or without a territorial lesion in the unilateral hemisphere was found in 10 patients (Figure B); 9 of them were associated with superficial or deep territorial lesion (Nos. 22-30) and only 1 had an acute lesion in the border-zone area alone (No. 31). The border-zone lesion distribution in those 10 patients was anterior or posterior cortical border zone in 5, subcortical border zone in 3, and corticosubcortical border zone in 2.

Third, bilateral hemispheric stroke lesions were demonstrated in 4 patients (Figure C). Three patients (Nos. 32, 33, and 35) had bilateral ICA occlusive diseases. All 3 patients had elevated fibrinogen levels. The other patient (No. 34) with unilateral left-sided ICA stenosis had a common ACA trunk supplied from the left carotid for the bilateral ACA territories, which resulted in an ACA infarct contralateral to ICA disease.

Overall, multiple ischemic lesions were found in 29 patients (82.9%). Among those, 3 patients (Nos. 9, 16, and 33) had multiple lesions in the anterior and posterior circulations and all 3 had fetal-type posterior cerebral artery circulation or prominent posterior communicating artery.

**CLINICORADIOLOGICAL DIFFERENCE BETWEEN THE PATIENTS WITH TERRITORIAL LESION ALONE AND THOSE WITH BORDER-ZONE LESION**

The various clinical and radiological findings between the patients with territorial ischemia without (n=21) and with (n=10) a border-zone lesion were compared. No statistically significant difference between these 2 groups in terms of the mode of stroke onset and symptom progression, a history of transient ischemic attack, hyperfibrinogenemia, bilaterality of ICA disease, degree of stenosis, and cerebral perfusion status was found (Table 2).

**COMMENT**

In this study, an attempt was made to analyze the topographical patterns of acute ischemic lesions in ICA occlusive disease. Despite the small number of patients, the following methodological advantages were noted. The degree of ICA stenosis or occlusion was evaluated by cerebral angiography using a catheter according to the North American Symptomatic Carotid Endarterectomy Trial method in all patients, providing a high rate of accuracy for assessing ICA stenosis. Diffusion-weighted imaging was used to determine the ischemic lesion patterns, giving a high sensitivity for detecting small or multiple lesions. The patients with potential sources of cardioem-
bolism or tandem intracranial arterial diseases were excluded; thus the infarct pattern caused by the extracranial ICA disease itself could be determined.

It was surprising that multiple ischemic lesions were found in 29 patients with ICA occlusive disease (82.9%) in this study. There have been few studies that have addressed multiple stroke lesions in ICA disease. A recent study reported that only 9% of patients with ICA stenosis greater than 50% had multiple pial or deep infarcts. The frequency of multiple infarcts in that study may have been underestimated because they did not use DWI in evaluating infarct topography. In about two thirds of the patients in this study, diffused-weighted imaging could identify additional ischemic lesions that were not observed on conventional MRI or discriminate recent infarcts from old ones or nonspecific periventricular high-intensity signals.

The overall frequency of acute multiple ischemic lesions on DWI was reportedly 17% and 28.9%. Another recent study using DWI reported that 57.8% of the patients with ICA disease had various types of multiple ischemic lesions including subcortical ischemia with embolus fragmentation, disseminated lesions in distal cortical regions, or multiple lesions in hemodynamic risk zones. The different frequency between these previous studies and the present study may partly be owing to the differences in the interval between stroke onset and imaging, the definition of multiple lesions, inclusion criteria, and sample size. In addition, large territorial infarction was rare in the present study, while it was reported to constitute 29.4% of the patients with ICA disease. We believe that the patients with large territorial infarction could not undergo conventional angiography owing to severe disability and were possibly excluded from this study.

The main mechanism of acute multiple ischemic lesions was presumed to be embolism. They could be caused by multiple emboli or the breakup of an embolus. Additionally hypercoagulability and vascular anatomical variations might also play a role in the pathogenesis of bihemispheric ischemic lesions. Although no patients had more than 1 clinical event between the stroke onset and the neuroimaging evaluation in this study, a relatively long interval (1 week) between onset and imaging might have contributed to the high frequency of multiple ischemic lesions. Therefore, in the current study multiple lesions may have occurred simultaneously or within a few days of the clinically relevant lesion. Nevertheless, these results support the idea that the predominant mechanism of ischemic stroke in ICA occlusive disease is embolic.

The most common topographical pattern was superficial and superficial territorial distribution in our study population. It was reported that the most frequent type of infarct in patients with double infarction in 1 cerebral hemisphere was also superficial and superficial (47%), and the most common cause of stroke in that study was ipsilateral ICA disease (72%). According to another study, all 7 patients with superficial acute multiple infarcts in the unilateral cerebral hemisphere were associated with ipsilateral or bilateral ICA disease, although 2 of them also had a tandem intracranial carotid stenosis or atrial fibrillation. The authors also reported that 4 of 5 patients with multiple ischemic lesions in the superficial and superficial territories in 1 cerebral hemisphere were associated with ipsilateral ICA disease. It is believed that multiple emboli or the breakup of an embolus that originated from proximal ICA disease have a high chance of passing through the superior and inferior divisions of the MCA.

Ten patients (28.6%) with ischemic lesions in border-zone areas were identified, and 9 of them were associated with a superficial or deep territorial lesion. This was the other most frequent topographical pattern. Several authors previously assumed that the mechanism of border-zone infarcts was hemodynamic based on the computed tomography or MRI topography of these infarcts. However, Belden et al reported in 1999 that embolism was the predominant stroke mechanism in unilateral posterior border-zone infarcts, whereas bilateral lesions were due to systemic hypotension. They suggested that variability of the territories of the major cerebral arteries, the passage of emboli to the border-zone areas, and the decreased clearance (washout) of the emboli in these areas could be explanations for the unilateral border-zone lesions. The coexistence of a border-zone lesion with multiple embolic infarcts on DWI has recently been documented in patients with neurologic complications after cardiac surgery. As postulated by Caplan and Hennerici, altered physics of blood flow probably caused by decreased perfusion in hemodynamically significant ICA disease may encourage emboli to reach border-zone regions, and decreased blood flow also likely impedes clearance of emboli because perfusion is most impaired in border-zone regions. The fact that no patient in our study had a documented systemic hypotension and border-zone infarction was mostly associated with a territorial infarct supports the idea that the mechanism of border-zone infarct is predominantly embolic.

Bilateral hemispheric infarcts associated with bilateral ICA disease were identified in 3 patients (8.6%). All 3 patients had elevated fibrinogen levels. We believe that bilateral cerebral infarcts were probably caused by bilateral ICA disease because we could not find either potential cardiac sources of embolism or any systemic causes for stroke in these patients. It was previously reported that bilateral cerebral infarcts were caused mainly by large artery atherosclerosis and were significantly associated with malignancy, an elevated fibrinogen level, and polycythemia. Although the factors that determine the contemporary bilateral infarcts remain still unclear, hypercoagulable state, infection, or inflammatory process might increase acute-phase reactants and render bilateral ICA occlusive lesions symptomatic at the same time.

Bogousslavsky and Regli reported that syncope at onset, focal limb shaking, hemodynamically significant cardiopathy, increased hematocrit, or severe contralateral ICA disease were significantly associated with unilateral border-zone infarction. However, no patient with syncope at onset or focal limb shaking was identified in this study. Furthermore, no difference was found between the patients with territorial lesion alone and those with border-zone lesion in terms of the mode of stroke onset and symptom progression, a previous history of tran-
sient ischemic attack, an elevated fibrinogen level, bilaterality of ICA disease, the degree of stenosis, and cerebral perfusion status. This again suggested an embolic mechanism for these infarcts.

CONCLUSIONS

This study shows that the ischemic lesion patterns caused by ICA occlusive disease are mainly multiple, and most border-zone ischemic lesions are accompanied by territorial ischemia. We suggest that these results provide supporting evidence that embolism is the predominant stroke mechanism in patients who have ICA disease.

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