Mechanisms of Recurrence in Subtypes of Ischemic Stroke

A Hospital-Based Follow-up Study

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Background: Information on the mechanism of recurrent stroke may help physicians treating patients with ischemic stroke. However, the mechanisms of recurrence in each stroke subtype are not well known, especially in Asians.

Objective: To compare the mechanisms of the index and recurrent stroke.

Design: Analysis of data from a prospective acute stroke registry.

Setting: University hospital.

Patients: Using the clinical syndrome, diffusion-weighted imaging, and vascular studies, we divided 901 patients into 5 groups: large-artery atherosclerosis, cardioembolism, small-artery disease, parent-artery disease occluding the deep perforators, and no determined cause. The patients with large-artery atherosclerosis were subdivided into 2 groups: intracranial and extracranial.

Main Outcome Measures: The mechanisms of recurrent vascular events (strokes or coronary heart disease) in subtypes of ischemic stroke were compared.

Results: Ninety-three recurrent vascular events (86 strokes and 7 instances of coronary heart disease) were evaluated. The pattern of recurrent stroke differed for the intracranial and extracranial groups; unlike the patients with intracranial large-artery atherosclerosis, recurrent strokes in the extracranial group were often unpredictable with respect to the site of recurrence and degree of preexisting stenosis. None of the patients in the extracranial group had recurrences that were caused by intracranial large-artery atherosclerosis or vice versa. In patients with small-artery disease and stroke with no determined cause, intracranial stenosis was often found at the time of recurrence.

Conclusions: From prognostic and therapeutic perspectives, patients with atherosclerosis should be divided into those with intracranial large-artery atherosclerosis and extracranial large-artery atherosclerosis. In addition, intracranial large-artery atherosclerosis may be important in the development of small-artery disease and stroke with no determined cause, especially in the population with a higher frequency of intracranial large-artery atherosclerosis.

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Because the ultimate aim of subdividing stroke mechanisms is to prevent the recurrent stroke, knowledge of the mechanisms of recurrent stroke in each subgroup of stroke will help physicians treating patients with ischemic stroke. Moreover, this knowledge might tell whether the index stroke classification is correct and whether each subgroup has unique characteristics.

A study comparing the pattern of recurrent stroke during follow-up of patients with ischemic stroke could answer this question. However, most studies focused on the mechanisms of the index stroke, and mechanisms of recurrence in each subtype of ischemic stroke remain unsettled.

This study investigated the mechanisms of recurrent stroke in each stroke subtype of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria in patients with ischemic stroke. We compared the mechanisms of the index and recurrent strokes.

METHODS

PATIENTS

Between July 2000 and October 2003, we prospectively studied consecutive patients who were admitted with ischemic stroke to Ajou University hospital, Suwon, South Korea. Patients who were admitted and who underwent a complete workup concerning the mechanisms of both index and recurrent strokes were included in this study.
PATIENT GROUPING

Patients were evaluated using a protocol that included demographic data, medical history, and vascular risk factors. We used the same criteria for vascular risk factors as in our previous study; hypertension, diabetes mellitus, hypercholesterolemia, and smoking. Laboratory tests were performed in all of the patients, including brain magnetic resonance imaging (1.5 T), a vascular study (digital subtraction or magnetic resonance angiography), electrocardiography, echocardiography (transthoracic or transesophageal), and routine blood tests. Hemostatic markers of prothrombotic tendency, including protein C, protein S, antithrombin III, and antiphospholipid antibodies (lupus anticoagulant and anticardiolipin IgG and IgM), were checked in all of the patients younger than 50 years.

Based on their clinical syndrome, infarct size on diffusion-weighted imaging (DWI), and the results of vascular, cardiologic, and laboratory studies, we divided the patients into 3 groups using the TOAST criteria. Both the index and recurrent strokes were classified into 1 of the following: (1) large-artery atherosclerosis (LAA) (ie, nonlacunar syndrome, larger lesion on DWI, and occlusive lesion on the relevant artery); (2) cardioembolism (CE) (ie, clinical and neuroradiological findings similar to the LAA group but potential source of CE present); (3) small-artery disease (SAD) (ie, traditional lacunar syndrome and symptomatic small deep infarcts on DWI and no occlusive lesion on the relevant artery); (4) parent-artery atherosclerosis (ie, traditional lacunar syndrome and symptomatic small deep infarcts on DWI and large intracranial arterial disease occluding the deep perforators); and (5) no determined cause despite an extensive evaluation, nonlacunar syndrome or larger lesion on DWI, and no source of CE or occlusive lesion on the relevant artery. The LAA group was subdivided into 2 groups: (1) patients with occlusive lesions of the extracranial arterial system, such as the carotid sinus or extracranial vertebral artery (the extracranial group) and (2) patients with occlusive lesions of the large intracranial arterial system, such as the proximal portion of the middle cerebral artery or basilar artery, and no significant stenosis of the extracranial arteries (the intracranial group). Potential sources of CE were defined as atrial fibrillation, mitral stenosis, a prosthetic valve, hypertension, diabetes mellitus, hypercholesterolemia, and smoking. Laboratory tests were performed in all of the patients younger than 50 years.

The mechanisms of the index and recurrent strokes for each patient were presented in the Table. The mechanism of recurrent stroke in patients with an LAA index stroke differed according to the location of atherosclerosis. During the follow-up period, 23 patients in the extracranial group experienced clinical end points. Of these, only 8 (35%) had the same site and mechanism of recurrent stroke as compared with the index stroke. In the other 15 patients, the clinical end points had different phenotypes as compared with the index stroke. Ischemic stroke occurred in a different vascular territory (the opposite carotid sinus in 4 patients, the vertebral artery in 1 patient) or with other mechanisms (negative evaluation, multiple potential sources of cerebral infarcts, and newly developed atrial fibrillation in 1 patient and SAD in 2 patients); CAOD occurred in 5 patients.

CLINICAL END POINTS (RECURRENT STROKE AND ANY VASCULAR EVENTS)

One of us (O.Y.B.) evaluated the patients at the outpatient clinic at 3-month intervals for up to 40 months after stroke onset. Outcome events included stroke (all, fatal, nonfatal) and coronary arterial occlusive disease (CAOD). To determine the occurrence of an outcome event, patients or family members were asked to report the event immediately to the Department of Neurology. All patients with an outcome event were readmitted. Recurrent stroke was defined as (1) a local neurological deficit occurring suddenly in a vascular territory, lasting more than 24 hours, and occurring at any time after 1 week from the index stroke and (2) acute infarcts on DWI. Coronary arterial occlusive disease was defined as either myocardial infarction or angiographically documented angina pectoris. In every patient, the type of recurrent stroke was evaluated using clinical, vascular, and cardiologic data.

STATISTICAL ANALYSIS

Differences in the site and mechanism of recurrent stroke between the groups were examined using the χ² test. Statistical significance was established at the P<.05 level.

RESULTS

Of 1197 patients who were admitted during the study period, 296 patients were excluded; 66 had other determined etiologies, 94 underwent incomplete workup, 28 had 2 or more causes, and 108 patients (9%) were lost to follow-up after the index stroke (LAA, 35 patients; CE, 23 patients; SAD, 26 patients; parent-artery atherosclerosis, 6 patients; and no apparent cause, 19 patients). Among the 901 patients included in the study, 532 (59%) were men and 369 (41%) were women, with a mean±SD age of 62±11 years (range, 35-87 years). According to the clinical, DWI, and angiographic findings, 352 patients (32%) were classified as being in the LAA group (extracranial, 152 patients; intracranial, 200 patients), whereas 163 (15%) were in the CE group, 281 (25%) in the SAD group, 78 (7%) in the parent-artery atherosclerosis group, and 231 (21%) in the no apparent cause group.

A total of 86 recurrent strokes and 7 instances of CAOD in 91 patients was evaluated during the follow-up period (mean, 2 years; range, 7 months to 3.5 years). The mechanisms of the index stroke were as follows: 23 extracranial LAA, 18 intracranial LAA, 9 SAD, 12 CE, 23 no apparent cause, and 8 parent-artery atherosclerosis. The mechanisms of the index and recurrent strokes for each patient are presented in the Table.

PATIENTS WITH EXTRACRANIAL LAA INDEX STROKE

The mechanism of recurrent stroke in patients with an LAA index stroke differed according to the location of atherosclerosis. During the follow-up period, 23 patients in the extracranial group experienced clinical end points. Of these, only 8 (35%) had the same site and mechanism of recurrent stroke as compared with the index stroke. In the other 15 patients, the clinical end points had different phenotypes as compared with the index stroke. Ischemic stroke occurred in a different vascular territory (the opposite carotid sinus in 4 patients, the vertebral artery in 1 patient) or with other mechanisms (negative evaluation, multiple potential sources of cerebral infarcts, and newly developed atrial fibrillation in 1 patient and SAD in 2 patients); CAOD occurred in 5 patients.
As shown in Figure 1, unexpected patterns of recurrence were observed frequently in the extracranial group. Cerebral infarcts involved previously normal vessels (the posterior circulation or contralateral carotid sinus) while the carotid Doppler ultrasound revealed marked improvement in the degree of carotid stenosis.

**PATIENTS WITH INTRACRANIAL LAA OR PARENT-ARTERY ATHEROSCLEROSIS INDEX STROKE**

Unlike the extracranial group, recurrent strokes occurred in the same vascular territory and by the same mechanism in most patients of the intracranial group (89% [16/18]) (Table). Most patients with intracranial LAA had similar symptoms and the same location and pattern on DWI (Figure 2).

Of the 8 patients in the parent-artery atherosclerosis group who had large intracranial stenosis occluding deep perforators, 5 had recurrences with similar symptoms, and their stroke recurred at the same site as the index stroke. In the other 3 patients, the stroke recurred in a different territory, and the stroke mechanisms differed from those of the index stroke (SAD, CE, and hemorrhage in 1 patient each).

In both the intracranial and parent-artery atherosclerosis groups, vascular studies showed that the recurrent stroke was related to the progression of preexisting intracranial stenosis in most of the patients. None of them showed significant, newly developed stenosis involving the extracranial vessels on the symptomatic side; CAOD occurred in none of the patients.
PATIENTS WITH SAD OR NO APPARENT CAUSE SUBTYPE INDEX STROKE

Recurrent strokes were also observed in patients who had normal results on vascular, cardiologic, and laboratory studies at the time of the index stroke (ie, the SAD and no-apparent-cause groups). Some of them had recurrences using different mechanisms.

In the SAD group, the most common mechanism of recurrent stroke was SAD (4 of 9 patients). In another 4 patients, the recurrent strokes were related to large intracranial arterial atherosclerosis and were classified as either intracranial (2 patients) or parent-artery atherosclerosis (2 patients); although the vessels on the symptomatic side were normal at the time of the index stroke, follow-up angiography showed progression to stenosis to a significant degree (>50%) (Figure 3).

Of the 23 patients in the no apparent cause group, the mechanism of recurrent stroke was documented in 14 patients, and LAA (7 patients [30%]) was twice as prevalent as CE (3 patients [13%]). In the other 9 patients, the mechanism of recurrent stroke could not be documented. Six of them recurred at the same site or a site adjacent to the index stroke on DWI (Figure 4), suggesting that a nonsignificant degree of stenosis plays an important role in the development of stroke in the no-apparent-cause group.

PATIENTS WITH CE INDEX STROKE

Of the 12 patients in the CE group, stroke recurred by a cardioembolic mechanism in 8 patients (67%). In the remaining patients, ischemic stroke due to carotid artery stenosis or multiple potential sources, intracranial hemorrhage, and myocardial infarct occurred in 1 patient each.

COMMENT

Although several studies have examined the risk factors and rate of recurrence in each subtype of ischemic stroke, the mechanisms of recurrent stroke in Asians are unclear and may differ from those in Westerners because there are racial differences in the risk factor profiles and distribution of occlusive disease. Information on the mechanisms of recurrent stroke, as opposed to the index stroke, may provide more accurate guidelines for treating and preventing recurrent strokes or vascular deaths. Moreover, it may help us to improve stroke classification. If distinct patterns of recurrence exist in 1 subtype of ischemic stroke, it is more reasonable that this subtype should be subdivided into separate groups rather than lumped together. Likewise, if a similar pattern and mechanism of recurrence is observed in distinct stroke subtypes, they should be lumped together in 1 stroke subtype.

Figure 2. A 56-year-old woman who was initially seen with left hemiparesis and sensory change. She had an index stroke involving large-artery atherosclerosis of an intracranial vessel. A, Right cortical borderzone infarcts with right middle cerebral artery proximal stenosis at the index stroke. B, Magnetic resonance angiography showed mild stenosis of the right middle cerebral artery. C, One year after the index stroke, she experienced progression of the previous deficits with new lesions at the same site. D, Magnetic resonance angiography showed the progression of preexisting stenosis of the right middle cerebral artery at the time of recurrence.

Figure 3. A 63-year-old man with an index stroke with small-artery disease as the mechanism and recurrent stroke with parent-artery disease as the mechanism. A and B, Small pontine infarcts on diffusion-weighted imaging with intact basilar artery on magnetic resonance angiography at the index stroke. C, Diffusion-weighted imaging showed a new acute lesion causing the recurrent stroke. D, Magnetic resonance angiography showed a stenotic lesion of the basilar artery (arrow).

Figure 4. A 74-year-old woman with an index stroke involving small-artery disease; a second stroke had normal evaluation findings, and a third stroke involved intracranial large-artery atherosclerosis. A-C, Recurrent small pontine infarcts at the same site on diffusion-weighted imaging were observed during the 3 strokes. At the index stroke, the patient had pure motor hemiparesis (A), and magnetic resonance angiography showed that the basilar artery was intact at that time (D). At the second attack, she complained of diplopia, and 3 months later, she was readmitted with a deteriorating mental state. Magnetic resonance angiography showed diffuse stenotic lesion of the basilar artery (E).
CLINICAL IMPLICATIONS

This study had 2 interesting results. First, the pattern of recurrence differed for the extracranial and intracranial groups, although in the TOAST criteria both are lumped together as the LAA subtype. In this study, none of the patients in the extracranial group had intracranial recurrences, and only 1 patient in the intracranial group had an extracranial recurrence. While the site of recurrent stroke and the mechanisms of recurrence were the same as the index stroke in most of the intracranial group, the pattern of recurrence was unpredictable in the extracranial group. That is, recurrence was frequent in different vascular territories because of the sudden occlusion of previously normal vessels in the extracranial group, whereas recurrent stroke occurred at the site of the index stroke because of the progression of stenosis in the intracranial group. Our data are consistent with previous studies; progression of middle cerebral artery occlusive disease was associated with an increased risk of vascular events. For carotid sinus occlusive lesions, it was reported that approximately 20% and 45% of strokes in the territory of symptomatic and asymptomatic carotid arteries with 70% to 99% stenosis, respectively, are unrelated to carotid stenosis. Moreover, high rates of progression of stenosis were reported in asymptomatic carotid stenosis (26% of patients who underwent contralateral endarterectomy [41-month follow-up]).

Our results suggest that extracranial LAA is a form of systemic atherosclerosis and that plaque stability rather than the degree of stenosis is more important in this ischemic mechanism, whereas intracranial LAA is a form of local (intracranial) disease or arteriosclerosis. Our findings, in agreement with published data, suggest that CAOD occurred more frequently in the extracranial group than in the intracranial group (Table). In patients with ischemic heart disease, Uehara et al reported that the incidence of progression of atherosclerosis was higher at the extracranial carotid artery than intracranial arteries and that the severity of coronary atherosclerosis was correlated with the incidence of extracranial carotid stenosis but not with that of intracranial stenosis. In patients with stroke and middle cerebral artery lesions, progression of stenosis was associated with an increased risk of transient ischemic attack or ischemic stroke but not acute coronary syndromes.

Second, in the patients where no cardioembolic source or vascular stenosis was found at the index stroke, the mechanism of stroke recurrence was either the same as that of the index stroke (no apparent cause or SAD) or the progression of intracranial stenosis (parent–artery atherosclerosis or intracranial). Our results suggest that in ethnic groups with a high prevalence of intracranial stenosis, such as Asians, the progression of intracranial LAA from nonsignificant (<50%) to significant (≥50%) may account for the recurrent stroke in patients in the SAD and no apparent cause groups. In other words, it is possible that SAD or no apparent cause subtype ischemic stroke is caused by a nonsignificant (<50%), but symptomatic, stenosis.

We found that intracranial stenosis accounted for the recurrent stroke in some patients in the SAD group; this finding is supported by reports that a significant fraction of patients with small deep infarcts had large intracranial arterial lesions occluding the orifices of perforators and that small deep infarcts were found in about half of patients with middle cerebral artery stenosis. These possibilities lead us to deduce that in ethnic groups with a high prevalence of intracranial stenosis, some patients with SAD are eventually included in the intracranial subtype with the progression of intracranial stenosis. Further studies with long-term angiographic follow-up are needed.

In addition, we found that LAA (either intracranial or extracranial) was the major mechanism of recurrence in the no-apparent-cause group. This contrasts with Western studies in which the main pathogenesis of the no-apparent-cause subtype was cardioembolic sources that could not be documented easily, such as a patent foramen ovale, mitral valve prolapse, and aortic arch atheroma. However, the role of uncommon causes of embolism in the no-apparent-cause subtype is still unsettled and might be low in our series.

Recently, we reported that the clinical features and risk factors did not differ for the no-apparent-cause and LAA groups and that the recurrence rate was high in those who had a coexisting cause of stroke (a stenotic lesion other than the significant stenosis of the relevant artery). Therefore, occlusive lesions other than significant stenosis of the relevant artery should not be ignored clinically.

A NEW CLASSIFICATION IS NEEDED FOR ASIAN PATIENTS WITH ISCHEMIC STROKE

The TOAST criteria constitute a widely used classification scheme for ischemic stroke subtype; stroke progression, risk recurrence, and choice of management are influenced by the ischemic stroke subtype. However, it remains unsettled whether the TOAST criteria are appropriate as a mechanism-oriented classification, especially in Asians. Intracranial LAA causes approximately 10% of all ischemic strokes in the United States. Athro- sclerotic involvement of the intracranial vessels occurs more frequently in Asians than in white individuals. Consequently, the mechanisms that cause strokes and the treatment both of patients with stroke and patients with intracranial stenosis are particularly important for Asian individuals.

Our results lead us to suggest several modifications when applying the stroke classification to a population with a high prevalence of intracranial LAA. First, because of the difference in the pattern and mechanism of recurrence between extracranial and intracranial LAA seen in this study, from a therapeutic and prognostic perspective, it is reasonable to separate these subgroups. In Western studies, because of the paucity of patients with intracranial LAA, the major concern in patients with occlusive lesions of the large intracranial vessels is to document the potential source of cardioembolism, and both intracranial and extracranial LAA are classified as the LAA subtype, regardless of the location of the lesion.

Second, the TOAST criteria only consider stenosis of 50% or higher for symptomatic vessels. However, we re-
recently demonstrated that the recurrence rate in patients in the no-apparent-cause group was high when there were occlusive lesions other than significant stenosis of the relevant artery. Stroke with no determined etiology should not be considered a homogeneous disease condition, and in these patients should be divided according to the presence of mild (<50%) stenosis at the relevant site and a significant degree of stenosis at a nonrelevant site. This information is mandatory for focused planning and implementation of primary and secondary prevention programs.

Finally, the TOAST criteria classify patients in the parent-artery atherosclerosis group as having 2 or more etiologies identified, and these patients are lumped together with patients with an incomplete or negative evaluation into a group with so-called ischemic stroke of unknown cause. However, we recently reported that the recurrence rate in the parent-artery atherosclerosis group was significantly higher than that of the SAD group, but similar to that of the LAA group, and suggested that the parent-artery atherosclerosis group represents an intracranial type of LAA. Therefore, it is more reasonable to classify this group as intracranial rather than as an undetermined etiology.

LIMITATIONS

This study has several limitations. The chief limitation is that our study was hospital based and a relatively small number of patients with recurrent strokes were included. Although we performed a complete workup concerning the mechanisms of recurrent strokes in most patients, further studies with many patients are needed to exclude the possible sampling error. Second, although transthoracic echocardiography was performed in every patient, transesophageal echocardiography was performed in a limited number of patients, and contrast was not determined in all patients. In addition, laboratory tests for coagulopathy were performed in patients younger than 50 years.

CONCLUSIONS

In summary, because of the high frequency of intracranial LAA in Asians as opposed to Westerners, who have extracranial stenosis more frequently, the mechanism of recurrence in Asian patients with ischemic stroke may differ from that of Westerners. Our results indicate that, from a prognostic and therapeutic perspective, patients with atherosclerosis should be divided into intracranial and extracranial groups. In addition, intracranial LAA may be more important in the development of SAD and stroke with no apparent cause, especially in the population with higher frequency of intracranial LAA.

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REFERENCES