ORIGINAL CONTRIBUTION

Stroke With Internal Carotid Artery Stenosis

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Background: Stroke patterns in patients with different degrees of carotid stenosis have not been systematically studied.

Objective: To determine first-ever stroke subtypes in nonselected patients with extracranial internal carotid artery (ICA) stenosis, based on a primary care hospital stroke registry.

Methods: One hundred seventy-three patients who experienced their first-ever stroke and who had 50% or greater (North American Symptomatic Carotid Endarterectomy Trial method) ipsilateral extracranial ICA stenosis, corresponding to 6.5% of 2649 patients with anterior circulation stroke included in the Lausanne Stroke Registry, were studied. All these patients underwent Doppler ultrasonography, carotid angiography (conventional or magnetic resonance angiography), neuroimaging (computed tomography or magnetic resonance imaging), and other investigations from the standard protocol of the Lausanne Stroke Registry.

Results: We found the following types of infarct in the middle cerebral artery territory: anterior pial in 54 (31%) of the patients; subcortical, 34 (20%); posterior pial, 32 (19%); large hemispheral, 20 (12%); and border zone, 17 (10%). There were multiple pial in 14 (8%) and multiple deep infarcts in 2 (1%) of the patients. Moderate (50%-69%) ICA stenosis was significantly associated with large hemispheral infarcts and a normal contralateral ICA ($P=.04$ and $P=.02$, respectively). Seventy percent to 89% of ICA stenosis was associated with prior transient ischemic attacks ($P=.02$). After adjusting for cardioembolism, border zone infarcts showed a strong trend to appear mostly in patients with 90% to 99% ICA stenosis ($P=.06$).

Conclusions: The association of a large hemispheral infarct with moderate ICA stenosis suggests a large embolism and/or an inadequate collateral supply. While an embolism may also contribute, the association of border zone infarcts with 90% to 99% ICA stenosis emphasizes the significance of hemodynamic disturbance in the pathogenesis of these types of infarct.

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VARIOUS ASPECTS of the relation between extracranial internal carotid artery (ICA) occlusive disease and stroke have been widely explored in the medical literature.[1-6] Nevertheless, little is known concerning different types of stroke and especially the topographic patterns of infarcts associated with ICA stenosis. From this point of view, large randomized trials, such as the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[7] and the European Carotid Surgery Trial,[8] are not representative, as only patients with transient ischemic attacks (TIAs) and nondisabling strokes are thought to be candidates for endarterectomy, and these reports often give no details of the type of brain infarct associated with the degree of underlying stenoses. Other relevant sources of information[9-12] mainly analyzed stroke subtypes with ICA occlusion rather than stenosis. The few studies[13-16] assessing patients with ICA stenosis and subsequent stroke have indicated that the risk of stroke increases with the degree of stenosis and that stroke is typically associated with tight stenosis, but did not give details of the stroke subtype and topography. The present study analyzes infarct patterns associated with ICA stenosis by comparing data from patients with different degrees of ICA stenosis, based on a large prospective stroke registry.

RESULTS

From January 1, 1979, to December 31, 1999, 2649 patients with anterior circulation stroke were recorded in the LSR, of

PATIENTS AND METHODS

Patients with a cerebral infarct distal to a stenotic extracranial ICA were selected from patients with first-ever ischemic stroke consecutively admitted to our primary care center. These patients are systematically included in the prospective Lausanne Stroke Registry (LSR), the characteristics of which have been presented in detail elsewhere.[17] All patients with initial stroke are examined by a senior neurologist (J.B.), and the systematic investigations performed on every patient include at least 1 brain computed tomographic (CT) or magnetic resonance (MR) imaging scan, continuous-wave Doppler ultrasonography with spectral analysis, B-mode echotomography and transcranial Doppler ultrasonography, 3-lead electrocardiographic monitoring for at least 24 hours, 12-lead electrocardiography, and blood tests. Catheter cerebral angiography and MR angiography are performed on selected patients. Two-dimensional echocardiography and delayed 24- to 48-hour electrocardiographic monitoring are done in all patients with evidence of heart disease on medical history or electrocardiogram and in all patients younger than 50 years.

Extracranial ICA stenosis was first assessed by continuous-wave Doppler ultrasonography based on the Doppler frequency shift and by the aspect of spectral disturbances (spectral analysis), as described elsewhere.[18] In addition, the degree and aspect (ulceration) of ICA stenosis were determined by pulsed-wave duplex and color flow imaging. Using these techniques, we classify ICA stenosis by taking into consideration the hemodynamic criteria (peak systolic velocity and end diastolic velocity)[19] and the morphological appearance (reduction of lumen diameter on longitudinal sections and of lumen surface on cross sections). The possible value intervals for the degree of ICA stenosis were obtained using spectral Doppler analysis.[18,20] In the present study, angiography (conventional or MR angiography) was performed systematically on all patients with ICA stenosis on Doppler ultrasonography. The degree and aspect of stenosis on angiography were evaluated using the NASCET method for stenosis measurement.[7] In the cases of disagreement between ultrasonographic and MR angiographic data regarding degree of ICA stenosis, catheter cerebral angiography was performed. Based on the NASCET criteria[7] and the standard protocol of the LSR,[17] we classified ICA stenosis into 3 categories (50%-69%, 70%-89%, and 90%-99% stenosis). Stenoses that were smaller than 50% were described as plaques and were not included in the study, since, in the LSR, large-artery disease is considered a potential cause of cerebral infarcts only when there is 50% or greater narrowing of the artery appropriate to the infarct.[21] Other main potential causes of cerebral infarcts included the following: (1) small-artery disease (patients with hypertension or diabetes, a maximal diameter of infarct $<$15 mm on CT or MR imaging, and no other determined cause of stroke); and (2) emboligenic heart disease (intracardiac thrombus or tumor, mitral stenosis, prosthetic aortic or mitral valves, endocarditis, left ventricular aneurysm or akinesia following myocardial infarction, acute myocardial infarct, global cardiac hypokinesia or dyskinesia, paradoxical embolism, mitral valve prolapse, interatrial septum aneurysm, atrial fibrillation, or sick sinus syndrome). In the study patients, a coexisting cardiac source of emboli was presumed when at least 1 of the previously mentioned findings was present.

We recorded vascular risk factors such as hypertension (blood pressure $>$160/90 mm Hg at least twice before stroke), diabetes ($\geq$2 fasting blood glucose samples with levels $>$6.0 mmol/L [$>$108 mg/dL] known to exist before stroke), regular cigarette smoking, hypercholesterolemia (fasting blood cholesterol level $>$6.5 mmol/L [$>$251 mg/dL]), and any history of cardiac or peripheral vascular disease.

Infarct topography was assessed and classified using the templates developed in our center.[22,23] We also assessed the presence of infarcts unrelated to the acute stroke ("silent" infarcts). Stroke characteristics in patients with varying degrees of ICA stenosis were studied. Statistical comparison was performed using the χ^2 test. $P<.05$, 2-sided, was considered statistically significant.

which 354 showed ipsilateral extracranial ICA stenosis of 50% or greater. For further analysis, 145 patients without available carotid angiography (either conventional or MR angiography) results were excluded. We also excluded 36 patients with negative CT or MR imaging scan results in whom infarcted territory was assigned based on clinical data only. The remaining 173 patients constituted the subjects of our study.

In considering the degree of ipsilateral ICA stenosis, our 173 patients were divided into 3 subgroups: 42 with 50% to 69% ICA stenosis, 55 with 70% to 89% stenosis, and 76 with 90% or greater stenosis. The demographics and risk factors for these subgroups and the frequency of some concurrent diseases were similar in almost all respects (**Table 1**). However, there was a nonstatistically significant (P=.15) trend toward increased blood cholesterol levels with increasing degree of ICA stenosis. There was also another nonsignificant (P=.19) trend for a potential cardiac source of emboli (PCSE), as a coexisted presumed cause for stroke, to be recognized mainly in the subgroups of patients with 50% to 69% and 70% to 89% ICA stenosis than in the patients with 90% to 99% ICA stenosis. Ipsilateral TIAs before stroke were more frequent in the subgroup of patients with 70% to 89% stenosis than in the other subgroups.

As shown in **Table 2**, a normal contralateral ICA was seen more frequently in the subgroup of patients with 50% to 69% ipsilateral stenosis than in the other subgroups.

For infarct topography in the entire group of patients (**Table 3**), the most frequent type was an anterior pial infarct, followed by subcortical and posterior pial infarcts. Table 3 also summarizes infarct topography in patients with different degrees of ICA stenosis. There was a significant tendency for large hemispheral (LH) infarcts to appear more frequently in the subgroup of patients with 50% to 69% ipsilateral ICA stenosis than in the other subgroups.

After excluding the patients with PCSE, LH infarcts were still more frequent in the subgroup of patients with 50% to 69% ICA stenosis, but this association lost statistical power. Conversely, border zone (BZ)

Table 1. Demographics, Vascular Risk Factors, and Some Concurrent Diseases in Patients With Internal Carotid Artery Stenosis*

Variable	Internal Carotid Artery Stenosis, % 50-69 (n = 42)	70-89 (n = 55)	≥90 (n = 76)	Total (N = 173)
Age, mean ± SD, y	60 ± 13	66 ± 10	62 ± 10	63 ± 14
Hypertension	18 (43)	27 (49)	36 (47)	**81** (47)
Diabetes mellitus	3 (7)	9 (16)	19 (25)	**31** (18)
Cigarette smoking	19 (45)	27 (49)	31 (41)	**77** (45)
Hypercholesterolemia	9 (21)	16 (29)	29 (38)	**54** (31)
Male sex	24 (57)	37 (67)	58 (76)	**119** (69)
Venous hematocrit >0.45	7 (17)	11 (20)	18 (24)	**36** (21)
Angina pectoris	8 (19)	8 (15)	9 (12)	**25** (14)
Myocardial infarct (>3 mo)	1 (2)	7 (13)	7 (9)	**15** (9)
Potential cardiac source of emboli	6 (14)	7 (13)	4 (5)	**17** (10)
Vascular claudication of lower limbs	4 (10)	10 (18)	7 (9)	**21** (12)
Prior transient ischemic attacks	12 (29)	28 (51)	25 (33)	**65** (38)
Ipsilateral†	8 (19)	25 (45)	22 (29)	**55** (32)
Other	5 (12)	3 (5)	3 (4)	**11** (6)

*Data are given as the number (percentage) of patients unless otherwise indicated.
†P = .02 (χ^2 test).

Table 2. Vascular Patterns in Patients With Internal Carotid Artery Stenosis*

Vascular Pattern	Internal Carotid Artery Stenosis, % 50-69 (n = 42)	70-89 (n = 55)	≥90 (n = 76)	Total (N = 173)
Ipsilateral bruit	9 (21)	21 (38)	29 (38)	**59** (34)
Contralateral internal carotid artery				
Normal†	22 (52)	13 (24)	20 (26)	**55** (32)
Stenosis, %				
<50 (plaque)	12 (29)	27 (49)	38 (50)	**77** (45)
50-69	4 (10)	9 (16)	7 (9)	**20** (12)
70-89	2 (5)	4 (7)	2 (3)	**8** (5)
≥90	0	0	6 (8)	**6** (3)
Occlusion	2 (5)	1 (2)	3 (4)	**6** (3)
Contralateral bruit	3 (7)	0	2 (3)	**5** (3)

*Data are given as the number (percentage) of patients.
†P = .02 (χ^2 test).

infarcts have shown a strong trend to appear mostly in the subgroup of patients with 90% to 99% ICA stenosis (**Table 4**).

We analyzed the demographic and risk factors profile not only for different degrees of ICA stenosis but also for different infarct topographies. Distribution of almost all of these factors, except hypertension and PCSE, was similar among patients with different infarct subtypes. Thus, the patients with LH infarcts have shown less frequency of hypertension than those without (25% [5/20] vs 50% [76/153]; *P*=.03), while hypertension was more frequent in patients with BZ infarcts than in those

Table 3. Infarct Topography in Patients With Internal Carotid Artery Stenosis*

Infarct Topography	Internal Carotid Artery Stenosis, % 50-69 (n = 42)	70-89 (n = 55)	≥90 (n = 76)	Total (N = 173)
Large hemispheral†	9 (21)	3 (5)	8 (11)	**20** (12)
Anterior pial	13 (31)	19 (35)	22 (29)	**54** (31)
Posterior pial	7 (17)	12 (22)	13 (17)	**32** (19)
Subcortical	9 (21)	12 (22)	13 (17)	**34** (20)
Multiple pial	2 (5)	5 (9)	7 (9)	**14** (8)
Multiple deep	0	0	2 (3)	**2** (1)
Border zone	2 (5)	4 (7)	11 (15)	**17** (10)

*Data are given as the number (percentage) of patients. Percentages may not total 100 because of rounding.
†P = .04 (χ^2 test).

Table 4. Distribution of LH and BZ Infarcts Among Patients With ICA Stenosis After Excluding the Patients With PCSE*

Type of Infarct	ICA Stenosis, % 50-69 (n = 36)	70-89 (n = 48)	≥90 (n = 72)	Total (N = 156)	*P*
LH	6 (17)	3 (6)	8 (11)	**17** (11)	.31
BZ	1 (3)	2 (4)	10 (14)	**13** (8)	.06

*Data are given as the number (percentage) of patients unless otherwise indicated. LH indicates large hemispheral; BZ, border zone; ICA, internal carotid artery; and PCSE, potential cardiac source of emboli.

without (71% [12/17] vs 44% [69/156]; *P*=.04). There was a nonsignificant trend for PCSE to be linked with LH infarcts (3 [15%] of 20 cases of PCSE in patients with LH infarcts vs 14 [9%] of 153 cases in patients with other types of infarcts; *P*=.18) and multiple pial infarcts (3 [21%] of 14 vs 14 [9%] of 159; *P*=.05). We also found a significant association of PCSE with BZ infarcts (4 [24%] of 17 vs 13 [8%]of 156; *P*=.03).

COMMENT

In the present study, we tried to analyze the association between first-ever stroke subtypes and various degrees of ICA stenosis in patients enrolled in a primary care hospital registry. This study also has the following methodological advantages: the degree of ICA stenosis was estimated either by conventional angiography according to the NASCET method or by a combination of Doppler ultrasonography and MR angiography, which, although not always consistent with angiographic measures, gives a high accuracy for the assessment of ICA stenosis.[24] In the case of disagreement between ultrasonographic and MR angiographic data, we used catheter cerebral angiography as a gold standard for ICA stenosis measurement; CT and MR imaging data obtained for each patient were classified using recently published lesion mapping templates.[22,23]

It was striking that the proportion of prior TIAs was the highest in the subgroup of patients with 70% to 89%

ICA stenosis. It means that in patients with carotid stroke, the incidence of prior TIAs increases in parallel with the degree of obstructive lesion up to a critical degree of 90% stenosis; thereafter, the frequency of TIAs decreases. It can be speculated that TIAs in our patients are not merely markers of stenotic plaque instability and that some other factors might be involved. A lower incidence of TIAs in patients with 50% to 69% and 90% to 99% ICA stenoses may be explained by the hypothesis that the plaque is more stable in the former case, while in the latter, the low poststenotic flow fails to dislodge emboli from the plaque surface and carry them out distally, even if the plaque is "active" (emboligenic). Such a "low-flow cerebral protection hypothesis" was recently proposed for explanation of low stroke risk in patients with carotid near occlusion.[25] Our findings indicate that approximately half of patients with 70% to 89% ICA stenosis–associated stroke had prior TIAs. This allows us to conclude that the occurrence of warning TIAs for such patients is typical.

In the entire group of patients with ICA stenosis, pial (anterior and posterior) infarcts in the middle cerebral artery territory were typical, which supports the results of a previous report[26] and suggests the relatively good condition of primary collateral pathways.[27] The proportion of LH infarcts in our series was similar to that reported previously in patients with ICA occlusive disease.[26] We suggest that a cardioembolic mechanism was responsible for the development of some LH infarcts, since a coexisting PCSE was present in 3 (15%) of 20 patients with LH infarcts compared with 14 (9%) of 153 patients with other types of infarct, and cardioembolism is considered to be the second common cause of LH infarcts after large-artery atherosclerotic disease in the LSR.[17] It has also been suggested that brain infarcts from a cardiac source are larger than those of artery-to-artery origin.[28]

The low frequency of BZ infarcts in our series, despite ICA stenotic disease, may be explained by excluding patients with ICA occlusion. This also points to the relatively undamaged primary collateral pathways that do not allow cerebral blood flow in watershed areas to fall below a critical level sufficient enough to lead to a BZ infarct. Such a protective role of collateral circulation against BZ infarcts has been previously mentioned.[26,29,30] We also found an association of PCSE with BZ infarcts, which allows us to speculate that some BZ infarcts in our series were cardioembolic in their origin.

Concerning the topography and size of infarcts in the subgroups of patients with different degrees of stenosis, the most important feature was the significant association of LH infarcts with ICA stenosis of less than 70%. This result contrasts with those from previous studies,[26,31-33] which indicated that infarct size is correlated with the degree of ICA disease. It is likely that cardioembolism was responsible for the development of some LH infarcts in the case of moderate (50%-69%) ICA stenosis. The recent analysis[34] of NASCET data has shown that, even in patients with symptomatic carotid stenosis carefully selected based on not having a PCSE, 10.8% of subsequent strokes were attributed to cardioembolism. Furthermore, according to the same report,[34] the cardiogenic stroke was more often diagnosed in patients with moderate (60%-69%) ICA stenosis than in patients with severe (70%-99%) stenosis (12.0% vs 6.9%). A similar tendency (14.3% [6/42] vs 8.4% [11/131]), although statistically nonsignificant, in our opinion because of the small number of patients, was observed in our series. However, we do not think that cardioembolism, in itself, is the sole possible contributor of LH infarcts in patients with low-grade carotid stenosis. This latter speculation is based on the fact that a coexisting PCSE was almost equally distributed among patients with 50% to 69% and 70% to 89% ICA stenosis (14% [6/42] vs 13% [7/55]), while LH infarcts were significantly associated merely with 50% to 69% stenosis. Even though we a priori accept a hypothesis that most LH infarcts in patients with carotid stenosis are of cardiogenic origin, the prevalence of this type of infarct in the subgroup of patients with 50% to 69% ICA stenosis in our series should not be analyzed without considering the collateral circulation concept. Several studies[27,35,36] have emphasized the importance of the collateral circulation in determining the size of infarcts. Radü and Moseley[9] have shown that, in patients with ICA occlusive disease, the severity of the neurological deficit is less and the extent of the infarct smaller on a CT scan if there is an adequate collateral supply. It is well-known that high-grade occlusive disease and chronic hypoperfusion lead to the mobilization of secondary collateral leptomeningeal pathways, which are normally nonmobilized. In contrast to the primary collateral system, which responds immediately to a focal failure of circulation, this is a time-consuming process.[37-39] The inverse association between infarct size and the degree of ICA stenosis in our patients may be explained by the hypothesis that in the case of moderate stenosis of the ICA with either minimally compromised or noncompromised distal hemodynamics, the secondary collateral pathways are poorly functioning, the brain not being "ready" for ischemia. Consequently, stroke in such patients may be more severe and the territory of infarction larger. We suppose that, in patients with 70% or greater ICA stenosis, large emboli either of arterial or cardiac origin may also be a cause of infarcts in certain cases, but prior mobilization of the secondary collateral pathways may have better protected the brain against LH infarcts.

The fact that after adjusting for cardioembolism, BZ infarcts have appeared mostly in patients with 90% to 99% ICA stenosis is in agreement with the accepted notion that such infarcts are related to severe ICA occlusive disease (tight stenosis and occlusion),[40] even though embolic phenomena may be involved besides hemodynamic disturbances.[41] Several studies[29,42,43] have suggested that high-grade occlusive disease of the ICA leads to hypoperfusion of the watershed areas, with subsequent BZ infarcts. Wodarz[30] found changes in borderline zones in more than 40% of the patients with ICA stenosis or occlusion. While in our patients BZ infarcts were not as common, even in patients with tight stenosis, our findings are in agreement with those of a previous study[44] in which BZ infarction was rarely an initial manifestation of ICA occlusive disease.

In summary, our findings highlight the various patterns of brain infarction in patients with extracranial

ICA stenosis. This heterogeneity depends on the degree of underlying stenotic disease and on several other factors, among which different stroke mechanisms and peculiarities of the collateral circulation may play a critical role.

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