Progression and Clinical Recurrence of Symptomatic Middle Cerebral Artery Stenosis
A Long-Term Follow-Up Transcranial Doppler Ultrasound Study

Juan F. Arenillas, MD; Carlos A. Molina, MD; Joan Montaner, MD; Sònia Abilleira, MD; Miguel A. González-Sánchez; José Álvarez-Sabin, PhD

Background and Purpose—Patients with symptomatic intracranial atherosclerotic stenosis have a high rate of recurrence. We conducted a prospective study to determine which factors are associated with the progression of symptomatic middle cerebral artery (MCA) stenosis and to evaluate the relationship between progression and clinical recurrence.

Methods—Between January 1996 and February 2000, of a total of 2564 consecutive first-ever transient ischemic attack (TIA) or stroke patients admitted to our cerebrovascular unit, 145 showed an MCA stenosis signal on transcranial Doppler (TCD) on admission, and 40 fulfilled all criteria to enter this study, including angiographic confirmation. Patients were prescribed antiplatelet or anticoagulant agents following the criteria of the neurologist in charge. TCD recordings and clinical interviews were performed regularly during follow-up. Progression of MCA stenosis was defined as an increase $>30$ cm/s in TCD-recorded maximum mean flow velocity. Logistic regression analyses were used to identify predictors of progression and clinical recurrence.

Results—With a median follow-up of 26.55 months, 13 (32.5%) MCA stenoses progressed, 3 (7.5%) regressed, and 24 (60%) remained stable. Absence of significant extracranial internal carotid artery (ICA) stenosis ($P=0.049$) and the use of oral anticoagulants ($P=0.045$) were significantly associated with a lower progression rate in univariate analysis, and anticoagulation remained an independent predictor when a logistic regression model was applied (OR $7.25$, CI 1.1 to 48.1, $P=0.019$). A new ischemic event during follow-up in the territory supplied by the stenosed MCA occurred in 8 cases (20%), and 13 patients had a major vascular event. Progression of the MCA stenosis detected by TCD was independently associated with a new ipsilateral ischemic event (OR $2.89$, CI 1.09 to 7.71, $P=0.031$) and with the occurrence of any major vascular event (OR $7.03$, CI 1.6 to 30.9, $P=0.0071$).

Conclusions—Progression of symptomatic MCA stenosis detected by means of TCD predicts clinical recurrence. Anticoagulation is independently associated with a lower progression rate of symptomatic MCA stenosis. (Stroke. 2001; 32:2898-2904.)

Key Words: atherosclerosis ■ cerebral ischemia ■ middle cerebral artery ■ stenosis ■ ultrasonography, Doppler, transcranial

Intracranial atherosclerosis is considered to be the leading cause of approximately 8% of all strokes in white patients1–3 and is the most commonly found vascular lesion in Asian acute stroke patients,4–6 being responsible for one third of strokes in a Chinese population.4 The traditional dependence on invasive vascular imaging techniques to diagnose intracranial stenosis has probably underestimated its real prevalence.

Patients with symptomatic intracranial atherosclerosis have unacceptable high rates of recurrent cerebrovascular ischemic events, coronary heart disease, and death.5 Currently, secondary prevention is done empirically,6 and because our knowledge about the natural history of this disease derives from a few retrospective studies,8–17 we have little scientific evidence to predict which patients are at a higher risk of suffering new ischemic events and, therefore, to make appropriate therapeutic indications.18 In 1995, the results of the Warfarin-Aspirin Symptomatic Intracranial Disease retrospective study were published.8 Compared with aspirin, warfarin seemed to have a more favorable risk/benefit ratio for the prevention of major vascular events in patients with symptomatic intracranial large-artery stenosis. However, this study did not take into account if the lower stroke recurrence rate observed in patients treated with oral anticoagulants is related with a lower progression rate of their stenosis. We designed a prospective, long-term transcranial Doppler (TCD) follow-up study to determine which factors are associated with the progression of symptomatic middle cerebral
artery (MCA) atherosclerotic stenosis and to evaluate the relationship between stenosis progression and the occurrence of new ischemic events.

Subjects and Methods
We selected and prospectively followed patients with symptomatic MCA stenosis to assess their progression and clinical recurrence rates. Inclusion criteria for this study included positively diagnosed TIAs or strokes attributed to significant intracranial atherosclerotic stenosis of the MCA, detected by TCD, and confirmed by MR or conventional angiography. Uncertain diagnosis of TIA or stroke, presence of a poor temporal acoustic window, imperfection of the TCD stenosis signal during admission, absence of angiographic confirmation, inability to prove that the MCA stenosis was responsible for the ischemic event, presence of another potential cause of stroke or TIA (such as significant ipsilateral extracranial carotid artery stenosis or potentially embolic geographic pathologies), and nonatherosclerotic causes of intracranial stenosis (stenosis in the context of moyamoya disease, vasculitis, vasospasm, basilar meningitis, or arterial dissection) were considered exclusion criteria.

Patient Selection
Between January 1996 and February 2000, 2564 consecutive patients with a first-ever TIA or stroke were admitted and studied in our cerebrovascular unit. The baseline examinations included a medical history, physical examination, routine blood biochemistry and blood count, ECG, chest x-ray, and cranial CT scan. Doppler ultrasound examination of the extracranial arteries and TCD were performed in all patients within 72 hours of symptom onset. In 145 patients, an MCA stenosis signal as defined by previously published criteria was detected on the initial TCD recording. The stenosed MCA was considered to be potentially responsible for the patients symptoms. MRI was performed on all these patients within the first 5 days after admission. Twenty-four patients with a history of a potential source of cardioembolism were initially excluded. To rule out nonatherosclerotic stenosis, transthoracic echocardiography, ECG-Holter, and extracranial echo-Doppler were systematically performed on the remaining patients. Thirty-four patients underwent transesophageal echocardiography. A potentially embolic geographic pathopathy was demonstrated in 18 cases. Seventeen patients had an extracranial ICA (internal carotid artery) stenosis >70% ipsilateral to the MCA stenosis and were excluded from the study. In 21 patients, a resolution of the stenotic signal was observed with TCD monitoring during admission, suggesting a partially recanalized embolus. On the remaining 65 patients, an angiographic technique (3-dimensional time-of-flight MR angiography in 58 cases, conventional angiography in 7) was performed. In 5 cases, all of them examined with MR angiography, the absence of angiographic confirmation. One patient had several intracranial stenoses in the context of a moyamoya disease. In 13 patients, MRI showed a unique ischemic lesion in a vascular territory not corresponding to the stenosed MCA (4 thalamic, 3 pontine, 4 occipital, and 2 parietal frontal infarctions), so that the initially presumed symptomatic confirmed MCA stenosis had to be considered not responsible for the ischemic event, and these patients were therefore also excluded. Finally, 46 patients with a first-ever TIA or stroke were considered to have an atherosclerotic symptomatic MCA stenosis, gave informed consent, and were initially enrolled in the study. Six of these patients were lost during follow-up; 3 of them voluntarily refused to continue, and the rest moved to other distant Spanish cities and could not be further studied. Forty patients completed the study protocol and their data were statistically analyzed.

This study was approved by the local ethics committee.

Treatment Allocation
When the diagnosis of cerebrovascular event potentially caused by an MCA stenosis was made, treatment with antiplatelet or anticoagulant agents was begun, following the criteria of the neurologist in charge. The doses of the approved antiplatelet agents that were used were 500 mg aspirin per day and 75 mg clopidogrel per day. Anticoagulation therapy with acenocoumarol was typically adjusted to maintain the prothrombin time (PT) internal normalized ratio (INR) between 2 and 3. Two treatment groups were established for statistical analysis: oral anticoagulants and inhibitors of platelet aggregation.

Transcranial Doppler Protocol
TCD recordings were performed using a Multi-Dop X/TCD (DWL Elektronische Systeme GmbH) device, with a hand-held transducer in a range-gated, pulsed-wave mode at a frequency of 2 MHz. All patients underwent extracranial carotid ultrasound examinations. We used a standard method of insonation without compression testing, as previously described.20–22 All recordings were performed by 2 experienced stroke-neurologists (C.M., J.F.A.).

The MCA was insonated through the temporal window at a depth between 45 and 65 mm. According to previously defined criteria,19 MCA stenosis was diagnosed if the mean blood flow velocity (MFV) at a circumscribed insonation depth was >80 cm/s, with side-to-side differences of MFV >30 cm/s. All further references to velocities in this report refer to the time-averaged mean maximum velocity that was recorded for each MCA symptomatic stenosis. According to the current accepted criteria, MCA stenosis was classified as follows: mild stenosis (80 to 120 cm/s), moderate stenosis (120 to 140 cm/s), and severe stenosis (>140 cm/s). This classification is based on previously validated criteria that reflect the relationship between the reduction of the cross-sectional area and the increase in blood flow velocity in the stenotic MCA.23–24

The velocity recorded on day 7 after symptom onset was considered the baseline velocity. Serial TCD examinations were performed on each patient with the following frequency: at 1, 3, 6, 9, and 12 months after admission during the first year, and then every 6 months until the end of the study. Maximum mean flow velocities observed were recorded for each stenosis at every time point. At each follow-up visit, extracranial carotid ultrasound was performed to rule out significant ipsilateral extracranial stenosis that could affect MCA velocities.25 Presence of significant contralateral cervical ICA stenosis was registered for statistical analysis.

Progression of an MCA stenosis was defined as an increase >30 cm/s between the recorded velocity values from 2 consecutive TCD examinations that persisted in the next possible examination. If the changes in the velocity values remained below this threshold, the stenosis was considered to be stable. When a decrement >30 cm/s was observed, we considered that MCA stenosis had regressed. The threshold value of 30 cm/s for sonographic progression and regression was arbitrarily taken out of the definition of MCA stenosis. Side-to-side differences of flow velocity >30 cm/s are considered to be hemodynamically significant as to define an MCA stenosis. Therefore, an increase >30 cm/s observed during follow-up in the stenosed MCA could represent hemodynamically relevant changes in the stenotic channel.19

Clinical and Radiological Variables
Age; sex; cigarette smoking (defined as present if the patient had smoked at least an average of 10 cigarettes per day during the past 5 years); and medical history of hypertension, diabetes, hypercholesterolemia, diagnosed coronary heart disease, and intermittent claudication were recorded. The clinical presentation of the qualifying cerebrovascular event (TIA lasting <24 hours, or stroke) was also registered for further analysis.

Presence and location of infarctions on MRI were classified as follows: normal (absence of abnormalities), lacunar infarctions, subcortical watershed areas infarctions, or cortical territorial infarctions. The number of coexistent asymptomatic intracranial stenosis detected by TCD and confirmed angiographically was also registered.

To assess clinical recurrence, all ischemic vascular events during follow-up were registered through a personal interview performed after each TCD examination. Major vascular events included certainly diagnosed stroke or TIA in the vascular territory of the studied stenosed MCA, stroke or TIA in any vascular territory, coronary ischemic event (angina or myocardial infarction), appearance of
TABLE 1. Characteristics of the Study Population

<table>
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<th>Yes (n=13)</th>
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<td>Sex (F), n (%)</td>
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<td>Smoker, n (%)</td>
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<td>Medical history, n (%)</td>
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<td>Hypertension</td>
<td>25 (62.5)</td>
<td>23 (85.2)</td>
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<td>Hypercholesterolemia</td>
<td>15 (37.5)</td>
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<td>6 (22.2)</td>
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<tr>
<td>Intermittent claudication</td>
<td>4 (10)</td>
<td>2 (7.4)</td>
<td>0.584</td>
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</table>

Percentages or SDs are shown in brackets as appropriate.

Statistical analyses were made by use of the SPSS statistical package, version 9.0. χ² tests were used to compare rates and proportions of discrete variables, and t tests or Mann-Whitney U tests were used to assess statistical differences between continuous variables. Potential predictors of MCA stenosis progression were initially compared, and variables that showed a P<0.1 were included in a logistic regression model. Results were expressed as adjusted odds ratio and corresponding 95% confidence intervals. The same analysis was made with potential predictors of major vascular events during follow-up, and separately with potential predictors of TIA or stroke in the territory distal to the MCA stenosis. Finally, cumulative event-free rates for the time to a major vascular event were estimated by the Kaplan-Meier product limit method, and the 2 groups attending to MCA stenosis progression (progression and no progression), were compared by the log-rank test. A P value <0.05 was considered statistically significant.

Results

Demographic characteristics of the study population and vascular risk factors are shown in Table 1. Concerning clinical data, 20 patients (50%) presented with a TIA, 10 of whom had crescendo TIAs during the first 24 hours from admission. The remaining 20 (50%) suffered a stroke. Of these, 5 patients had had previous TIAs within 24 hours before stroke, and 7 patients had fluctuations of the intensity of the neurological deficit.

Brain MRI showed lacunar infarctions in 7 cases (17.5%), subcortical infarctions in 10 cases (25%), and cortical infarctions in 16 patients (40%). In the remaining 7 cases (17.5%), who presented with a TIA, MRI showed no abnormalities. All definitive lesions had been produced in the vascular territory distal to the MCA stenosis.

Carotid ultrasound examination detected an ipsilateral ICA <70% stenosis in 1 patient (2.5%), contralateral ICA >70% stenosis in 4 patients (10%), and contralateral ICA <70% stenosis in 4 patients (10%), with absence of cervical carotid pathology in the remaining 31 patients (77.5%). According to the classification of MCA stenosis in severity, 26 stenoses (65%) were considered severe, 10 (25%) moderate, and only 4 (10%) mild. Coexistent silent intracranial stenosis was detected in 21 patients (52.5%), making a total of 33 asymptomatic stenoses. Eleven patients had 1 asymptomatic stenosis, 8 had 2 coexistent stenoses, and in 3 patients, 3 asymptomatic stenoses were found.

Presence of stenosis was confirmed by MRI angiography in 33 patients, by conventional arteriography in 4, and by both means in the remaining 3 patients. Therefore, 7 patients (17.5%) underwent intra-arterial angiography.

Twenty-five patients received antiplatelet agents, and 15 were treated with oral anticoagulation.

Median follow-up was 26.55 months. During follow-up, 13 (32.5%) symptomatic MCA stenosis progressed, 3 (7.5%) regressed, and 24 (60%) remained stable. During the same period of time, 8 patients (20%) had a new ischemic vascular event (6 TIAs and 2 strokes) in the territory dependent of the stenosed MCA, for a recurrence rate of 9.05% per year, which can be divided into an ipsilateral stroke rate of 2.25% per year and an ipsilateral TIA rate of 6.79% per year. New ischemic lesions in the stenosed MCA territory were demonstrated by means of diffusion-weighted MRI in 4 of the 6 TIA patients.

Nine patients (22.5%) suffered a TIA or stroke in any vascular territory, 5 (12.5%) experienced a coronary ischemic

The table shows the results of the univariate analysis of variables associated with MCA stenosis progression.

*Extracranial ICA status, extension of intracranial atherosclerosis, and treatment were included into the logistic regression model (see Results).
event, and 4 (10%) began to suffer intermittent claudication. None of the patients died during follow-up.

### Potential Predictors of MCA Stenosis Progression

Table 2 shows data of variables associated with MCA stenosis progression. Absence of significant cervical ICA stenosis ($P=0.049$) and treatment with anticoagulants ($P=0.045$) were significantly associated with lower progression rates in univariate analysis. The presence of coexistent asymptomatic intracranial stenosis showed a trend toward higher progression rates ($P=0.094$). These variables were included in the multiple logistic regression model. Anticoagulation remained an independent predictor of the absence of MCA symptomatic stenosis progression in the logistic regression model (OR 7.25, 95% CI 1.09 to 48.15; $P=0.019$).

### Potential Predictors of Ipsilateral Cerebral Ischemic Event During Follow-Up

Only progression of MCA stenosis was significantly associated with clinical recurrence in the univariate analysis ($P=0.004$), as shown in Table 3. Sex (female patients, $P=0.068$) and extension of intracranial atherosclerosis ($P=0.066$) showed a trend toward higher recurrence rates. Only 1 of the 8 patients who experienced a new ipsilateral ischemic event was receiving oral anticoagulants, but treatment was not significantly associated with recurrence.

#### TABLE 3. Potential Predictors of Recurrent Ipsilateral Stroke and Any Major Vascular Event

<table>
<thead>
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<td>26 (81.3)</td>
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<td>14 (43.8)</td>
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<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>2 (25)</td>
<td>13 (40.6)</td>
</tr>
<tr>
<td>Coronary disease, n (%)</td>
<td>1 (12.5)</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>Intermittent claudication, n (%)</td>
<td>1 (12.5)</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>Stroke,† n (%)</td>
<td>4 (50)</td>
<td>16 (50)</td>
</tr>
<tr>
<td>MRI,‡ n (%)</td>
<td>0.381</td>
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</tr>
</tbody>
</table>

On the left half of the table, results of the univariate analysis of potential predictors of a new ipsilateral stroke or TIA. Sex, coexistence of asymptomatic stenosis, treatment, and progression were included into the logistic regression model. Results of the multivariate analysis are shown in text. On the right half, univariate analysis of potential predictors of any ischemic event during follow-up.

*Variables included in the logistic regression model.
†Clinical presentation as a stroke.
‡Neuroradiological findings.
§Number of coexistent asymptomatic stenoses.
Potential Predictors of Any Major Vascular Event During Follow-Up

Only progression of MCA stenosis was significantly associated with higher recurrence rates in the univariate analysis (P=0.007). A trend toward higher recurrence rates was observed for the presence of coexistent stenosis (P=0.078). Both variables were included in the logistic regression model, and progression of MCA stenosis remained an independent predictor for the occurrence of any major vascular event (OR 7.03; 95% CI 1.6 to 30.9; P=0.0071). The Kaplan-Meier curves in Figure 2 show that a significantly higher proportion (P=0.0151) of patients whose MCA stenosis did not progress remained free of a major vascular event compared with patients who showed progression of their MCA stenosis.

Discussion

This study, performed in a highly selected population, provides evidence about the dynamic nature of symptomatic MCA atherosclerotic stenosis and demonstrates that patients whose stenosis progress are at a higher risk of clinical recurrence.

We observed a recurrence rate for ipsilateral ischemic events of 9.05% per year, which is in accordance with previous series in white patients. A recent study in a Chinese population has shown even higher recurrence rates.26 The frequency of other major vascular events during follow-up is also consistent with other series, with a lower risk of coronary ischemic events and sudden death than that observed in patients with atherosclerotic stenosis of intracranial ICA.13,27 Our results support previously reported studies, showing a lack of correlation between the initial severity of the stenosis and the clinical recurrence rate. Moreover, no statistically significant differences were observed between both treatment groups. Interestingly, the extension of the atherosclerotic intracranial disease, defined by the number of coexistent asymptomatic stenosis, showed a trend toward a higher recurrence rate. It has been recently described in a Chinese population that the number of occlusive arteries predicts further vascular events or death.26 In addition, the only factor that remained as a predictor of clinical recurrence was the progression of the MCA stenosis detected by TCD. It is well known for other vascular territories that progression of arterial disease predicts new clinical events.28 However, to our knowledge, this statement had not been previously demonstrated in patients with intracranial atherosclerotic stenosis.

The pathophysiological mechanisms of ischemia should be taken into account in the assessment of the risk of recurrence of intracranial stenosis. The atherosclerotic process may differ between intracranial and extracranial arteries.12,15 In coronary or cervical arteries, ulceration or rupture of previously unstable atherosclerotic plaques causing thromboembolic phenomena would be much more relevant than in intracranial arteries, where fibrous or fibrocalcific stable plaques are usually found.12 Furthermore, microembolic signals (MES) are detected by TCD distally to unstable embolic sources.29 No MES were identified in a recent study during long-term chronic MCA stenosis TCD-monitoring, suggesting that clinical recurrence is mainly caused through hemodynamic mechanisms.30 In cerebral circulation, progression of an intracranial stenosis and parallel affection of other large arteries within the circle of Willis may lead to a more severe hemodynamic compromise and higher risk of clinical recurrence. The results of this study support this hypothesis. Our progression rate of 32.5% is in line with that observed in previous retrospective studies.10 However, it should be noted that the present study is restricted to MCA stenosis. In the univariate analysis, anticoagulation and absence of significant cervical ICA atherosclerotic lesions were signifi-
cantly associated with a lower rate of progression of MCA stenosis. Only anticoagulation remained as independent predictor of a lower progression rate in the multivariate analysis. Besides their potential effect in reducing distal embolization, we hypothesize that oral anticoagulants decrease the risk of recurrence by reducing the progression of intracranial stenosis. In addition to the above-mentioned differential characteristics of the intracranial atherosclerotic process, it has been suggested that associated local thrombus may contribute to the angiographic or sonographic progression of intracranial large artery stenosis. In this setting, oral anticoagulants may play an important role in preventing the deposition of new thrombotic material on the artery wall. Moreover, as in other vascular territories such as carotid cervical arteries and coronary bypass grafts, the apparent long-term benefit of oral anticoagulants cannot be explained by a clear reduction of atherosclerotic plaque progression or through anti-inflammatory mechanisms. Because neither TCD nor angiography provides information regarding the pathological nature of the stenosis progression process, more prospective and histopathological studies are needed to elucidate how oral anticoagulants modify the progression of intracranial stenosis.

This study has some limitations. First, the significance of our findings is diminished by the small size of the series and the numerous risk factors assessed. Second, transesophageal echocardiography, which is more sensitive than the transthoracic in the detection of aortic arch atheromatous disease and atrial-septal defects, was performed in only 19 of the 40 selected patients, and this might have resulted in an underestimation of potential embolic sources. Finally, although conventional angiography is still considered the gold standard examination to detect and quantify intracranial stenosis, we relied on 3-dimensional time-of-flight MR angiography alone to confirm the MCA stenosis in 33 patients, given that it is a noninvasive examination with high sensitivity and specificity values.

In conclusion, the use of oral anticoagulants is significantly associated with a lower progression rate of symptomatic MCA stenosis. Progression of an MCA stenosis detected by TCD predicts clinical recurrence. We suggest that sonographic follow-up of MCA stenosis is useful to detect patients at a higher risk of recurrence and could guide therapeutic decisions.

References


10. Akins PT, Pilgram TK, Cross DT III, Moran CJ. Natural history of TCD nor angiography provides information regarding the intracranial stenosis. In conclusion, the use of oral anticoagulants is significantly associated with a lower progression rate of symptomatic MCA stenosis. Progression of an MCA stenosis detected by TCD predicts clinical recurrence. We suggest that sonographic follow-up of MCA stenosis is useful to detect patients at a higher risk of recurrence and could guide therapeutic decisions.

References


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