Atherosclerotic Disease of the Middle Cerebral Artery

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FOR THE EC/IC BYPASS STUDY GROUP

SUMMARY Three hundred and fifty-two patients with atherosclerotic middle cerebral artery stenosis (MCAS, 53%) or occlusion (MCAO, 47%) have been systematically studied. The study involved all patients entered into the EC/IC Bypass Study with isolated MCA disease or a tandem lesion predominating in the MCA ipsilateral to the ischemic events (18 patients with a tandem lesion of greater magnitude in the internal carotid artery were not included). The Asian patients represented 58% of all Asians entered into the EC/IC Bypass Study, whereas the white patients represented 18% of all whites and the black patients 34% of all blacks. Isolated TIAs were less frequent in MCAO (12%) than in MCAS (34%). Warning TIAs before a stroke occurred in one third of the cases. Presentation with stroke or isolated TIA was not influenced by sex, age, level of MCA obstruction, collateral circulation nor associated carotid disease. In MCAS, no major difference in presentation was found between severe and moderate stenosis. Pure motor hemiparesis occurred in 15% and pure sensory stroke in 2% of the patients with stroke and 30% of the MCA territory infarcts were small and limited to the lenticulocapsular area, confirming that so-called lacunar infarcts may be due to large vessel disease.

During follow-up (42 months) of 164 medically-treated patients, further cerebrovascular events (TIA and stroke) occurred in 11.7% of the patients per year. In MCAO the stroke rate was 10.1% per patient-year and the ipsilateral infarct rate was 7.1% per patient-year. In MCAS, the stroke rate was 9.5% per patient-year and the ipsilateral stroke rate was 7.8% per patient-year. The location and severity of lesion did not influence the occurrence of ipsilateral ischemic events during follow-up. Reopening of an artery-to-artery embolic occlusion of the MCA, with subsequent embolic reocclusion, may explain some of the ipsilateral ischemic events during follow-up. The annual death rate was 3.3% in MCAS and 2.6% in MCAO. Less than 15% of the survivors were severely disabled at the end of follow-up and nearly two-thirds were able to resume previous activities both in MCAO and MCAS. The type of delayed ischemic events tended to be the same as that of the presenting event, but no factor could significantly predict the occurrence of stroke or death. This study suggests that long-term prognosis of patients with MCA occlusion, who present with TIA or non-devastating stroke, is reasonable.

Extracranial/Intracranial Arterial Anastomosis provided the opportunity to study a large series of patients with symptomatic occlusion or stenosis of the MCA. All of these lesions were judged to be of atherosclerotic origin, and this study analyzes the presenting clinical and radiologic features of these patients and presents long-term follow-up data in 164 medically-treated patients.

Patients and Methods

During the Cooperative Study of Extracranial/Intracranial Arterial Anastomosis, 370 patients were randomized to medical treatment or medical treatment plus bypass surgery for an MCA (from origin to bifurcation or trifurcation included) occlusion or stenosis demonstrated on angiography. Only those patients with TIA (episode of less than 24 hours duration) or mild to moderate stroke were admissible and all were required to have experienced at least one ischemic event in the territory supplied by the diseased MCA in the three months prior to entry. Evidence of atherosclerotic vascular disease was required; patients with evidence of or suspected of fibromuscular dysplasia, arteritis, blood dyscrasia, and heart disease as source of cerebral emboli or decreased cerebral perfusion (vascular disease, atrial fibrillation and other major arrhythmia, cardiomyopathy) were excluded. A narrative summary of cerebrovascular history, concomitants of vascular disease, ECG findings, neurological and vascular examination, and functional status were...
MCA disease was present in 22% of the patients, but years in the patients with MCAS and 54 years in the bilateral MCAS, 4 with bilateral MCAO on one side was symptomatic on both sides only in 11 (6 with involved (67%) than the right MCA (55%). Bilateral MCA disease was present in 22% of the patients, but was symptomatic on both sides only in 11 (6 with bilateral MCAS, 4 with bilateral MCAO on one side and MCAS on the other side). Mean age was 58.2 years in the patients with MCAS and 54 years in the patients with MCAO. The proportion of females with MCAS (122 males [65%]: 65 females [35%]) was about twice as high as in MCAO (138 males [84%]: 27 females [16%]). The relative proportion of whites (18% of all whites entered into the Bypass Study), Asians (58% of all Asians) and blacks (34% of all blacks) was similar for MCAS and MCAO.

**Type of Presenting Event**

Patients with MCAO more frequently presented with a stroke than the patients with MCAS (p < 0.0001) (table 2). No difference in the type of presenting event (TIA or stroke) was found between the patients with moderate and severe MCAS. Warning TIAs were observed in approximately one third of the patients with stroke, without difference between MCAO and MCAS. Stroke(s) or isolated TIA(s) occurred in the same proportions in whites, Asians and blacks. No significant difference between age groups (<40, 41-50, 51-60, 61-70, >70 years) was found for the type of presenting event, either in males or females.

### Transient Ischemic Attacks

The TIAs were appropriate to the MCA lesion in 100% of the patients with MCAS and 94% of the patients with MCAO (table 3). Among the patients who suffered TIAs appropriate to the MCA lesion, 6% of those with MCAO and 8% of those with MCAS also had TIAs in remote territories (contralateral carotid and/or vertebrobasilar territory). In TIAs appropriate to the MCA lesion, the most common type of TIA was motor weakness on one side of the body associated with speech disturbances (dysarthria or dysphasia), either in MCAS (27%) or in MCAO (22%). There were 14% of the 158 patients with more than one TIA appropriate to the MCAS who showed variable attacks and 86% who showed identical repetition of TIAs.

Overall, 52% of the patients with moderate MCAS, 67% of the patients with severe MCAS and 51% of the patients with MCAO suffered TIAs. In 55% of the patients with MCAS, TIAs were not followed by a stroke, compared to only 24% of the patients with MCAO (p < 0.001). This difference may partially be explained by the fact that time elapsed from the first TIA to entry into the study was much longer in MCAO (16.6 months, 5 days–10 years) than in moderate MCAS (3.3 months, 1 day–2 years) and severe MCAS (5.5 months, 1 day–3.5 years). However, even if this imbalance between groups is adjusted, the difference remains significant (p < 0.02, Mantel-Haenszel Chi square test).

The mean number of TIAs was higher in the patients

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**Table 1** 352 Patients with MCA Stenosis or Occlusion

<table>
<thead>
<tr>
<th>Type of Presenting Event</th>
<th>Moderate stenosis</th>
<th>Severe stenosis</th>
<th>Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated TIA(s)</td>
<td>28%</td>
<td>37%</td>
<td>12%</td>
</tr>
<tr>
<td>Stroke(s) preceded by TIA(s)</td>
<td>20%</td>
<td>25%</td>
<td>30%</td>
</tr>
<tr>
<td>Stroke(s) only</td>
<td>52%</td>
<td>38%</td>
<td>58%</td>
</tr>
</tbody>
</table>
TABLE 3  Transient Ischemic Attacks

<table>
<thead>
<tr>
<th>MCA lesion</th>
<th>Moderate stenosis (71)</th>
<th>Severe stenosis (116)</th>
<th>Occlusion (165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with TIA(s)</td>
<td>37</td>
<td>78</td>
<td>84</td>
</tr>
<tr>
<td>isolated TIA(s)</td>
<td>54%</td>
<td>54%</td>
<td>24%</td>
</tr>
<tr>
<td>TIA(s)→stroke(s)</td>
<td>38%</td>
<td>38%</td>
<td>58%</td>
</tr>
<tr>
<td>TIA(s) after a stroke(s)</td>
<td>8%</td>
<td>8%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Patients with TIA(s) appropriate to the MCA lesion

- 100%

Patients with other TIA(s)

- 8%

Mean duration of TIA

- 77' (range: 1 sec to 12h)
- 138' (range: 1 sec to 24h)
- 57' (range: 1 sec to 15h)

Mean number of TIAs per patient

- 4.4 (range: 1 to 50)
- 8.1 (range: 1 to 132)
- 11.9 (range: 1 to 371)

Patients with only one TIA

- 19%

TIA

- 13%

with MCAO (11.9) and severe MCAS (8.1) than in the patients with moderate MCAS (4.4), but this was related to the fact that a few patients with MCAO or severe MCAS suffered a very large number of TIAs. The mean duration of TIAs was about twice as long in the patients with severe MCAS (138 minutes) than in the other patients (77 minutes in moderate MCAS, 57 minutes in MCAO), but this finding is not statistically significant (p = 0.189).

**Strokes**

Seventy-two percent of the patients with moderate MCAS, 63% of the patients with severe MCAS and 88% of the patients with MCAO suffered at least one stroke (table 4). The stroke was preceded by TIA(s) in respectively 28%, 40%, and 34% of the cases. Multiple strokes occurred in 24% of the stroke patients, with a mean of 1.3 per patient. The most common type of onset was an immediately completed deficit (65%), either in MCAS or in MCAO. The frequency of associated headache did not differ, being present in 15% of the cases. Focal convulsions with the stroke were common (2%). Syncope at the onset of stroke was observed only in MCAO, but was rare (3%). A decreased level of consciousness on admission was also much more common in MCAO (28%) than in MCAS (14%) (p = 0.01) patients with stroke.

Stroke appropriate to the MCA lesion occurred in 96% of the patients with moderate MCAS, 93% of the patients with severe MCAS and 99% of the patients with MCAO. Stroke(s) in other territory(ies) occurred in 9% of the patients. Overall, the strokes were appropriate to the MCA lesion in 67 of the 72 (86%) patients with moderate MCAS, 85 of the 92 (92%) patients with severe MCAS and 172 of the 182 (95%) patients with MCAO.

In the patients with stroke(s) appropriate to the MCA lesion, as it was for TIAs, the most common clinical picture was unilateral motor weakness associated with dysarthria or dysphasia (35%). Pure motor hemiplegia was present in 20 of the patients with MCAS and appropriate stroke (17%) and in 19 of the patients with MCAO and appropriate stroke (13%). Pure sensory stroke occurred in respectively 4 (3%) and 1 (1%), and isolated dysphasia in respectively 6 (5%) and 5 (4%).

**Motor and Sensory Involvement in TIAs and Strokes**

Motor symptoms appropriate to the MCA lesion were found in 143 of the 194 patients with TIA(s) who had motor symptoms (74%) and 95 who had sensory symptoms (49%). Of the 261 patients with a stroke(s) appropriate to the MCA lesion, motor symptoms/signs occurred in 237 (91%) and sensory symptoms/signs occurred in 117 (45%). No difference in the distribution (face-arm-leg) of motor or sensory involvement was found between MCAS and MCAO. In each instance, the arm was more frequently involved than the leg, which was more frequently involved than the face. This finding was not statistically significant (TIAs: p = 0.568, strokes: p = 0.863), but this trend observed in either strokes or TIAs is clinically meaningful. In the patients with stroke, the most common type of motor involvement was simultaneous involvement with dysarthria or dysphasia (35%). Pure motor hemiplegia was present in 20 of the patients with MCAS and appropriate stroke (17%) and in 19 of the patients with MCAO and appropriate stroke (13%). Pure sensory stroke occurred in respectively 4 (3%) and 1 (1%), and isolated dysphasia in respectively 6 (5%) and 5 (4%).

**TABLE 4  Strokes**

<table>
<thead>
<tr>
<th>MCA lesion</th>
<th>Moderate stenosis (71)</th>
<th>Severe stenosis (116)</th>
<th>Occlusion (165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with stroke(s) preceded by TIA(s)</td>
<td>51</td>
<td>73</td>
<td>145</td>
</tr>
<tr>
<td>without preceding TIA(s)</td>
<td>28%</td>
<td>40%</td>
<td>34%</td>
</tr>
<tr>
<td>Patients with stroke(s) appropriate to the MCA lesion</td>
<td>96%</td>
<td>93%</td>
<td>99%</td>
</tr>
<tr>
<td>Patients with other strokes</td>
<td>10%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Patients with multiple strokes</td>
<td>29%</td>
<td>19%</td>
<td>24%</td>
</tr>
<tr>
<td>Mean number of strokes per patient</td>
<td>1.4 (range: 1 to 5)</td>
<td>2.2 (range: 1 to 3)</td>
<td>1.3 (range: 1 to 3)</td>
</tr>
<tr>
<td>Onset of last stroke</td>
<td>66%</td>
<td>70%</td>
<td>62%</td>
</tr>
<tr>
<td>maximal at onset</td>
<td>18%</td>
<td>18%</td>
<td>22%</td>
</tr>
<tr>
<td>smoothly progressive</td>
<td>12%</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>stepwise</td>
<td>4%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>fluctuating</td>
<td>1%</td>
<td>unknown</td>
<td></td>
</tr>
<tr>
<td>Associated features of last stroke</td>
<td>0%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>syncope</td>
<td>12%</td>
<td>14%</td>
<td>16%</td>
</tr>
<tr>
<td>headache</td>
<td>16%</td>
<td>12%</td>
<td>28%</td>
</tr>
<tr>
<td>decreased consciousness</td>
<td>2%</td>
<td>focal seizure</td>
<td>2%</td>
</tr>
</tbody>
</table>
of the face, arm, and leg (58%). This distribution was also the most common for sensory defects (47%). In the patients with TIA, the motor/sensory distribution was more heterogenous, but the most common type of motor distribution appeared to be simultaneous involvement of the arm and leg, with facial sparing (37%). For sensory symptoms, involvement of the arm only (31%), of the arm and leg (24%), or of the face, arm, and leg (24%) were the most frequent types of distribution. In TIAs or strokes, isolated motor or sensory involvement of one limb or of the face alone only occurred uncommonly: arm only in 17%, face only in 5%, and leg only in 2%.

Angiographic Features

In moderate MCAS the entire length of artery affected with the stenosing lesion was 5 mm (0.8–12.2) and the length of stenosis which was at its maximum was 2 mm (0.3–8.5). An ulcer was suggested in only 2 of the 82 (2%) moderately stenosed MCA where this finding could be evaluated. In severe MCAS the total length of stenosis was 6.8 mm (1–20) and the length of maximal stenosis was 2.9 mm (0.3–20). An ulcer was suggested only in 5 of the 142 (4%) severely stenosed middle cerebral artery where this finding could be evaluated (76%). In MCAO, distal MCA branch occlusion was visualized in 66% of the cases. The level of MCA lesion was pre-ganglionic in 208 (48%) patients, ganglionic in 93 (22%) and post-ganglionic in 129 (30%) patients, without difference between MCAS and MCAO.

The presence of an associated lesion of the ipsilateral ICA (tandem lesion) was evaluated in 350 of the 352 patients and was found proximal to 67% of the stenosed or occluded MCAs, without any difference between MCAS and MCAO. Eighteen patients with tandem lesion of more severe lesion in the ICA were excluded from this review.

Associated disease of the ICA, either ipsilateral or contralateral to the MCA lesion, more often involved the intracranial segment of the ICA (45%) than the extracranial segment (34%), without difference between MCAS and MCAO. Lesions of the contralateral ICA were more frequently found in MCAS (83%) than in MCAO (48%). Associated lesions of the ICAs were more frequent in the intracranial than in the extracranial segment for all 3 races, but this was more marked for Asians (112 of 168 obstructions were intracranial (67%) and blacks (35 of 57 obstructions were intracranial — 61%) than for whites (174 of 338 obstructions were intracranial — 52%).

Tandem lesions had no influence on the type of presenting event: isolated TIA(s) occurred in 29 of the 118 patients with an isolated MCA lesion (25%) and in 55 of 232 patients with tandem lesion (24%), while stroke(s) occurred respectively in 89 (75%) and 177 (76%) patients.

The level of MCA obstruction had no influence on the type of presenting event: 72% of the patients with pre-ganglionic MCA lesion had a stroke and 28% had isolated TIA(s); 80% of the patients with MCA lesion at the ganglionic branch level had a stroke and 19.7% had isolated TIA(s); and 80% of the patients with post-ganglionic MCA lesion had a stroke and 21% suffered only from isolated TIA(s).

CT Scan

Ten of the 57 patients (18%) with isolated TIA(s) who underwent a CT scan 1 day to 3 months after the last TIA had an infarct appropriate to their symptoms (deep infarct in 40%, superficial infarct in 60%).

A visible infarct was present in 177 of the 239 (74%) stroke patients who underwent a CT scan. The infarct occurred in the appropriate MCA territory in 166 patients. This infarct was confined to deep structures (lenticulocapsular, corona radiata) in 39% of the patients with MCAS and in 25% of the patients with MCAO. Infarcts limited to the superficial MCA territory were the most frequent (61%), infarcts involving both the superficial and deep MCA territory were uncommon (6%).

Concomitants of Vascular Disease

No major difference between the patients with MCAS or MCAO was found for the prevalence of associated diabetes mellitus (16%), hypertension (48.7%), high blood cholesterol (11%), angina pectoris (5%), old myocardial infarct (11%), left ventricular hypertrophy on ECG (12%), and vascular claudication (3%). The prevalence of cigarette smoking was 80% in MCAO and 62% in MCAS. The mean number of "risk factors" (diabetes mellitus, hypertension, cigarette smoking, elevated blood cholesterol) did not differ (1.4 in moderate MCAS, 1.5 in severe MCAS or MCAO).

Follow-up Study of Medically-Treated Patients

For this analysis, which was done 6 months before the completion of the EC/IC Bypass Study, the follow-up period was 40.4 months (46 months in survivors) in MCA occlusion and 43.3 months (48 months in survivors) in MCA stenosis. In order to check the accuracy of this analysis, Kaplan-Meier estimates of 3 year failure rates (95% confidence intervals) were done after completion of final follow-up of the EC/IC Bypass Study. These estimates were not different from the results presented here (see Addendum). There were 137 patients who were put on antiplatelet aggregating therapy (acetylsalicylic acid), which was stopped or irregularly followed in 19, and 17 patients who were put on warfarin. Appropriate medical treatment was prescribed in all patients with risk factors such as hypertension, diabetes mellitus or heart disease.

Prognosis in MCA Occlusion

Cerebrovascular events during follow-up were recorded in 31 (39%) patients, with isolated TIA(s) in 10 (13%), and stroke(s) in 21 (27%). Seven (9%) patients died, one (1%) patient had a nonfatal myocardial infarct, and one (1%) patient had an acute heart failure without myocardial infarction. Thus, 7.9% of the patients per year suffered a stroke and 5.6% of the pa-
tients per year suffered an infarct ipsilateral to the MCA occlusion. As 6% of the patients had more than one stroke, the stroke rate was 10.1% per patient-year and the ipsilateral infarct rate was 7.1% per patient year. The mortality rate was 2.6% per year.

Eight (10%) patients had TIAs ipsilateral to the MCA occlusion and 10 (12%) had TIAs only in remote or uncertain territories. The TIAs occurred 1 to 61 months (mean 16 months) after entry into the study. Six of the 21 patients with a stroke during follow-up experienced warning TIAs before the stroke (28.6%). No period of increased risk for stroke was noted and the median time from entry into the study to a stroke was 1.5 years (range 3 weeks to 4.2 years). Seventy point four percent of the strokes were infarcts ipsilateral to the MCA occlusion. Five infarcts occurred in the contralateral MCA territory, 1 was a brainstem infarct; 1 was due to a cerebellar pontine hemorrhage and 1 due to an intraparenchymatous hematoma on the side of the MCA occlusion.

The occurrence of ischemic events (TIA and stroke) during follow-up was analyzed with regard to race, age, sex, presenting manifestations and angiographic findings. Race, age, sex had no significant influence. The location of the occlusion had no significant influence on the occurrence of ipsilateral ischemic events, which occurred in 29% of the patients with a pre-ganglionic occlusion, 17% of the patients with occlusion at the level of the ganglionic branches, and in 26% of the patients with a post-ganglionic occlusion. This finding suggests that most of the ipsilateral ischemic events were distal to the occlusion, although some may have occurred in the territory of the ganglionic branches in the patients with post-ganglionic occlusion. The presence of an associated lesion of the ipsilateral ICA (tandem lesion) correlated with the occurrence of ischemic events ipsilateral to the occlusion; actually, ischemic events during follow-up occurred in 34% of the patients with tandem lesions, compared with only 10% of the patients with isolated MCA occlusion (p = 0.03). No other angiographic finding correlated with occurrence of ischemic events during follow-up. Ischemic events during follow-up occurred equally in the patients who had initially presented with isolated TIA or with a stroke. There was no statistically significant association between the type of presenting event (isolated TIA or stroke) and the type of event during follow-up (isolated TIA or stroke), either for TIAs (p = 0.14) or strokes (p = 0.27); however, there was a tendency for the patients to suffer the same type of event during follow-up as they had suffered before entry into the study.

Seven (9%) patients died during follow-up, 3 to 44 months after entry into the study (mean 14.8 months). None of them died of an ischemic stroke, but 2 died of a cerebral hemorrhage (29% of the deaths) and 3 died of another cause (43% of the deaths): pneumonia in 1, ruptured aneurysm of the aorta in 1, diabetic coma in 1. Overall, 9.5% of the patients with a stroke during the follow-up died as a consequence of it. Age and sex did not have a significant influence on death. No black, but 10% of the whites and 9% of the Asians died; however, there were too few blacks to consider this finding significant.

Neurological examination performed at the end of the follow-up was abnormal in 47 of the 72 survivors (65%). Speech disturbances (dysphasia, dysarthria) were present in 16 (22%) patients, impaired mentation without dysphasia in 2 (2%) and abnormal limb examination in 41 (57%). The functional ability at the end of follow-up in the 72 survivors is summarized as follows: only 11% were severely disabled (unable to work or go shopping), whereas 64% could return to their previous activities without difficulty. Overall, improvement was noted in 28 (39%) patients and stabilization was obtained in 34 (47%) patients. Ten (14%) patients worsened, in 8 (11%) from stroke(s) and in 2 (3%) from unrelated events.

**Prognosis in MCA Stenosis**

Cerebrovascular ischemic events during follow-up were recorded in 36 (42%) patients, with isolated TIA(s) in 18 (21%) and stroke(s) in 18 (21%). Ten (12%) patients died, 1 (1%) had nonfatal myocardial infarction and 1 (1%) had an acute heart failure without myocardial infarction. No significant difference between moderate and severe MCA stenosis was noted for the incidence of TIA, stroke, and death.

Twenty patients (23.5%) had TIAs distal to the MCA stenosis and 6 (7.1%) had TIAs in remote or uncertain areas (contralateral carotid TIAs in 2, verteobasilar TIAs in 2, uncertain type of TIAs in 2). Isolated TIAs occurred in 18 patients, TIAs preceded a stroke in 7 patients and they followed a stroke in 1 patient. The occurrence of TIAs without stroke did not differ between the patients with moderate or severe MCA stenosis (p = 0.27). The mean duration of the TIAs was 48.7 min in moderate MCA stenosis and 94.3 min in severe MCA stenosis, but this difference, also noted for presenting TIAs, was not statistically significant (p = 0.37).

The characteristics of strokes during follow-up are summarized as follows: seven (38.9%) of the 18 patients with a stroke during follow-up experienced warning TIAs. Warning TIAs were more common in the patients with moderate MCA stenosis (71%) than in the patients with severe MCA stenosis (18%) (p = 0.049). The patients with moderate MCA stenosis also suffered more strokes (14% had multiple strokes) than the patients with severe MCA stenosis (5% had multiple strokes), but this finding was not statistically significant (p = 0.33). No period of increased risk for stroke was noted and the median time from entry into the study to a stroke was 1.3 year (range 2 weeks to 4.2 years). Eighty-three percent of the strokes occurred ipsilaterally to the MCA stenosis. Two strokes occurred in the contralateral MCA territory, 1 stroke occurred in the ipsilateral anterior cerebral artery territory, and there were 2 brainstem strokes. All of these strokes were infarcts. Overall, 5.9% of the patients per year suffered a stroke and 4.6% of the patients per year suffered a stroke distal to the MCA stenosis. As 8% of
the patients had more than one stroke, the overall stroke rate was 9.5% per patient-year and the ipsilateral stroke rate was 7.8% per patient-year. Nineteen (66%) strokes were immediately completed, 8 (28%) had a progressive or stepwise onset, and in 2 (7%) the type of onset could not be established.

Race, sex, presence of hypertension or diabetes had no significant influence on the occurrence of delayed ischemic events. The location of stenosis with regard to the origin of the lenticulostriate arteries did not influence the occurrence of ipsilateral ischemic events during follow-up (table 5), nor did the presence of an associated lesion of the ipsilateral ICA (tandem lesion). Ischemic events occurred equally in the patients who had initially presented either with isolated TIA or with stroke. However, the type of the ischemic event during follow-up tended to correlate with the type of the presenting event: 35% of the patients who initially presented with isolated TIs never TIs during follow-up and 12% suffered a stroke (p = 0.025); and 14% of the patients who initially presented with a stroke suffered isolated TIs during follow-up and 25% suffered a stroke (not statistically significant: p = 0.167).

Ten (12%) patients died during follow-up (3.3% per year), 7 to 54 months after entry into the study (mean: 30.1 months). Three patients died from cerebral infarct (30% of the deaths), 2 died from a myocardial infarct (20% of the deaths), and 5 died of another cause. Overall, 11% of the patients who suffered a stroke during follow-up died as a consequence of it. Age, sex, and race had no significant influence on death. Because of the small number of deaths, no difference was found between the patients with moderate and severe MCA stenosis who died.

Fifty-one percent of the survivors had an abnormal neurological examination, without difference between the patients with moderate and severe MCA stenosis. Only 15% of the 73 survivors were severely disabled (unable to work or go shopping), whereas 65.3% could return to their previous activities without difficulty (table 6). The patients with the less severe MCA stenosis were not less disabled than the patients with the more severe MCA stenosis. Overall, improvement was noted in 21 (28%) patients and stabilization was obtained in 36 (48%) patients. Eighteen (24%) patients worsened, 12 (16%) from a stroke and 6 (8%) from unrelated events.

### Table 5 Location of Stenosis and Ipsilateral Ischemic Events during Follow-up

<table>
<thead>
<tr>
<th>Location of stenosis</th>
<th>Pre-ganglionic</th>
<th>Level of the ganglionic branches</th>
<th>Post-ganglionic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>43</td>
<td>17</td>
<td>25</td>
</tr>
<tr>
<td>Patients with ischemic events in the ipsilateral MCA territory</td>
<td>15 (35%)</td>
<td>7 (41%)</td>
<td>6 (24%)</td>
</tr>
</tbody>
</table>

### Table 6 Capacity to Resume Previous Activity at the End of Follow-up in Living Patients

<table>
<thead>
<tr>
<th></th>
<th>MCA stenosis</th>
<th>MCA occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients previously employed</td>
<td>17</td>
<td>54</td>
</tr>
<tr>
<td>can work without difficulty</td>
<td>70%</td>
<td>65%</td>
</tr>
<tr>
<td>cannot work</td>
<td>21%</td>
<td>22%</td>
</tr>
<tr>
<td>Patients previously unemployed</td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td>can go shopping without difficulty</td>
<td>57%</td>
<td>61%</td>
</tr>
<tr>
<td>cannot go shopping</td>
<td>18%*</td>
<td>33%</td>
</tr>
<tr>
<td>cannot go shopping</td>
<td>25%*</td>
<td>6%</td>
</tr>
</tbody>
</table>

*From an unrelated cause in one case.

### Discussion

In this study, the proportion of MCAO (47%) was slightly lower than that of MCAS (53%). This is in contradistinction to prior studies, which found that MCAO represented two thirds to three quarters of MCA lesions on angiography. This discrepancy is probably explained by the fact that all cases with evidence for a cardiac source of emboli were excluded from the present study. In unselected series, 21% to 38% of MCAOs are attributed to an embolus from the heart. The published studies devoted to MCAO did not exclude embolic occlusions from the heart, and the present study provides a more accurate overview of atherosclerotic MCA disease. Embolic MCAO related to migration of a detached fragment from an atherosclerotic lesion of the ipsilateral ICA has been reported frequently in MCAO; this phenomenon may have occurred in some of the 60% of the MCAO with associated disease of the ipsilateral ICA.

In a pathologic study, Lhermitte et al. found that only 12.5% of 40 MCAOs were due to local thrombosis, opposed to 40% embolic occlusions from the heart or the ICA and 47.5% occlusions of undetermined origin. Angiography does not provide an accurate assessment of which occlusions are due to local thrombosis or to emboli from the ipsilateral ICA, and these proportions remain unknown in this study. Compared to the previous studies, our study is also unique in that 36% of the patients were Asians and corresponded to 58% of all Asians entered into the EC/IC Bypass Study; on the other hand, whites with MCA lesion corresponded to only 18% of all whites. This emphasized clearly the predilection for MCA lesions to affect Asians.

The findings of this study indicate that 66% of the patients with symptomatic MCAS and 88% of the patients with symptomatic MCAO present with a stroke. This is close to the figures found in the literature. The presence of collateral filling of the MCA territory could not be appropriately evaluated in this study; in previous studies, the correlation between the development of the collateral circulation and the extent of the neurological dysfunction is controversial. Angiographic evidence for distal branch occlusion was present in two thirds of the MCAOs and 11% of the MCASs but is difficult to differentiate from
a flow phenomenon. This finding did not correlate with the severity of the presenting event.

TIAs were experienced by 51% of the patients with MCAO and 61.5% of the patients with MCAS. When the patients experienced repeated TIAs, the repetition was usually identical. An appropriate infarct in the MCA territory was present on CT in 18% of the patients with TIAs alone. Visible infarction may be present in as many as 28% of consecutive patients with TIAs. This finding may be particularly suggestive of TIAs related to large vessel disease. One sixth to one fourth of TIAs may in fact be infarcts with rapid and complete recovery.

An immediately completed deficit was the most common type of stroke onset, but as many as one third of the strokes had a progressive or fluctuating onset. Headache at onset (14.5%) was less frequent than in Fisher's study (36%). A decreased level of consciousness was much more common in MCAO than in MCAS. Seizures at onset of stroke have been described in as many as 12% of the patients, but were present in only 2% of this series and were always focal. A pure motor hemiplegia, usually facio-brachio-crural, was the result of 15% of the strokes in the MCA territory. This finding confirms that this syndrome can be due to occlusion of the MCA and is not synonymous with a lacune due to small-vessel disease. Approximately 30% of the strokes in the MCA territory corresponded to a purely deep infarct (lenticulostriate) on CT scan, indicating that infarcts due to occlusion or stenosis of the MCA trunk do not necessarily involve the superficial territory and may mimic lacunar infarcts. A pure sensory stroke (2%) or isolated dysphasia (4%) were much less common than pure motor hemiplegia.

The male-female ratio was 4:1 and did not confirm that MCA obstruction more often affects women than ICA obstruction. The mean age of 56.2 years is slightly lower than the 58-64 years usually reported in extra- or intracranial ICA disease, although a series of 100 patients with ICA occlusion reported a mean age of 51.2 years. In the 1377 patients entered into the EC/IC Bypass Study, mean age was 56 years. Race seemed to influence the site of associated ICA obstruction. Associated disease of the ICAs more frequently involved the intracranial than the extracranial segment in the three races, but this was much more marked in Asians than in whites, while blacks were intermediate. This finding re-emphasizes the predilection for intracranial lesions to affect predominantly Asians. The most common concomitant of vascular disease was a history of cigarette smoking (% of the patients), followed by hypertension (% of the patients). The prevalence of risk factors was similar to that found in the 1377 patients entered into the EC/IC Bypass Study. No parallel was found between the severity of MCA obstruction and the number of presumed risk factors (hypertension, diabetes mellitus and hypercholesterolaemia), except for cigarette smoking, although this parallel has been observed in ICA disease.

This study did not include the 5-21% of patients who may die during the acute phase of MCAO. However, it is highly representative of the patients who survive the initial event and who may then be considered for prognostic studies and for prophylactic therapy. A comparison of our findings to the recent series of extracranial ICA occlusion suggests that MCAO presents as frequently with isolated TIAs as does ICA occlusion. In MCAS, the prevalence of presenting TIAs is also similar to what has been reported in extra- or intracranial ICA stenosis. Thus, our findings do not support the claim that the clinical presentation of atherosclerotic disease of the MCA differs substantially from the presentation of ICA occlusion or stenosis.

The prospective follow-up study shows that in MCA occlusion or stenosis, stroke during follow-up may be more frequent than previously assumed in retrospective smaller studies (table 7). On the other hand, it also suggests that death may occur less often than reported in these studies.

### Table 7 Follow-up Studies

<table>
<thead>
<tr>
<th></th>
<th>Follow-up</th>
<th>TIA</th>
<th>Stroke</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA occlusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaste et al†</td>
<td>74</td>
<td>2.5 years</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Sacquegna et al†</td>
<td>56</td>
<td>6 years</td>
<td>1.6%*</td>
<td>1.2%*</td>
</tr>
<tr>
<td>Moulin et al†</td>
<td>19</td>
<td>4.5 years</td>
<td>6.4%*</td>
<td>1.6%*</td>
</tr>
<tr>
<td>Present study‡</td>
<td>78</td>
<td>3.4 years</td>
<td>6.9%</td>
<td>7.9%</td>
</tr>
<tr>
<td>MCA stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hinton et al**†  1979</td>
<td>16</td>
<td>1 month-6 years</td>
<td>0</td>
<td>?</td>
</tr>
<tr>
<td>Feldmeyer et al**† 1983</td>
<td>13</td>
<td>5.3 years</td>
<td>2.8%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Corston et al**† 1984</td>
<td>21</td>
<td>6.8 years</td>
<td>1.4%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Present study‡</td>
<td>85</td>
<td>3.6 years</td>
<td>5.8%</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

*In survivors only.
†Retrospective.
‡Prospective.
We found that the incidence of cerebrovascular events was similar in patients with MCA occlusion (11.6%/year) or MCA stenosis (11.8%/year). More than two-thirds of the strokes were infarcts ipsilateral to the MCA lesion. Overall, 5.7% of the patients per year suffered ipsilateral infarction(s).

The occurrence of further ipsilateral ischemic events was not related to age, sex, race, hypertension, diabetes, smoking, or hypercholesterolemia. The location of lesion of the MCA had no significant influence on delayed events; one might have expected that patients with post-ganglionic occlusion would have more ipsilateral ischemic events during follow-up, because they would still be vulnerable to embolic occlusion of the more proximal ganglionic branches, but this was not the case here.

It is intriguing to speculate on the pathogenesis of further ipsilateral ischemic events occurring in patients with MCA occlusion. In ICA occlusion, migration of fibrin-platelet micro-emboli through collateral channels (as branches of the external carotid artery and the anterior or posterior communicating arteries) has been suggested to be responsible for most of the ischemic events distal to the occlusion. This type of anterograde arterial collateral circulation is not available in MCA occlusion, where the collateral supply is retrograde through arteriolar leptomeningeal anastomosis from the meningeal-cortical branches of the anterior and posterior cerebral arteries. It is very unlikely that any micro-embolus would be able to reach the MCA territory via this retrograde route, because of the small diameter of the leptomeningeal arterioles. A hemodynamic mechanism may be responsible for certain ischemic events, but in ICA occlusion, it is usually associated with a generalized hypotensive event, which was absent in our patients. A third mechanism may be worth considering, i.e. "recanalization" of the occlusion with subsequent embolization through the re-opened MCA. Recanalization of an in situ arterial thrombosis is certainly a very uncommon event, if it ever occurs. On the other hand, recanalization of an embolic occlusion, by fragmentation of the embolus, is a much more common event. It can occur in cases of embolization from the heart, but also in artery-to-artery emboli, when the ipsilateral ICA is stenosed or occluded ("occlusion supra occlusionem"). Patients with obvious embolicogenic heart disease were excluded from the EC/IC Bypass Study, but it is possible that a substantial number of the MCA occlusions correspond to artery-to-artery emboli, arising from a more proximal lesion on the ICA. Actually, nearly two-thirds of our 79 patients with MCA occlusion had an associated lesion of some degree of the ipsilateral ICA, although we did exclude those with severe extracranial ICA stenosis. Moreover, the presence of an ipsilateral ICA lesion was significantly associated with the occurrence of ipsilateral ischemic events during follow-up. As no follow-up angiography was done, it is impossible to know the frequency of reopening of the MCA occlusion. In a comparable group of patients with MCA occlusion, recanalization on follow-up angiography 2 weeks after ipsilateral bypass surgery was found in 9.2%. Day reported recanalization in 5 of 9 patients with MCA occlusion on angiography performed after bypass surgery. These findings suggest that recanalization of the occluded MCA may not have been an uncommon event in our patients. In the cases with a recanalized occlusion, either further artery-to-artery emboli arising from the ipsilateral ICA or recurrent thrombus formation at the site of previous embolic lodgement might have been the common phenomena as the origin for further ipsilateral TIA or infarct.

Our study, as distinct from previous reports, showed that patients with MCA stenosis suffered isolated TIA as commonly as stroke. The severity of MCA stenosis had little value in predicting the clinical evolution of the patients. It did not influence the type of ischemic events, the number of strokes per patient, death, nor the functional disability in survivors. The only significant difference between patients with severe or moderate stenosis was that strokes during follow-up were more often preceded by warning TIAs in severe stenosis than in moderate stenosis.

The death rate (3%/year) was relatively low in our patients, compared with previous studies. Stroke and myocardial infarction and no other factor was significantly associated with death. A relationship between death from stroke and poor collateral circulation has been suggested, but the data were not convincing; it was not assessed here. Previous studies have also suggested that 50-100% of the patients who suffer strokes during follow-up will die of a stroke, but this occurred in less than 20% of the patients here.

Nearly two-thirds of the survivors were able to go back to their previous activities without difficulty, and less than 15% of the survivors were severely disabled. Overall, improvement or stabilization of the functional state was obtained in 80% of the survivors. Age, sex, race, presence of hypertension or diabetes did not seem to influence the functional outcome. As in previous studies, no significant predictor of disability was found. Except for the occurrence of stroke during follow-up, incidental events including congestive heart failure and the development of parkinsonism were the causes of functional disability.

Our results show that in MCA disease, the death rate is similar to the death rate (2.5%-4.4%/year) reported in the recent literature on extracranial ICA occlusion. Also, the ipsilateral stroke rate is certainly as high as reported in extracranial ICA disease (1.6%-5%/year). However, in the patients presenting with TIA or nondevastating stroke, long-term disability tends to remain low with medical treatment alone. The prognosis of MCA occlusion is similar to that of MCA stenosis in patients who present with TIA or minor stroke.

EDITORS NOTE: In accordance with STROKE policy this paper was Guest Edited by Dr. Fletcher McDowell.

References
44. EC/IC Bypass Study Group: unpublished data.

Addendum: Kaplan-Meier estimates of 3 year failure rates with 95% confidence intervals (estimation after completion of final follow-up of the EC/IC Bypass Study)
Atherosclerotic disease of the middle cerebral artery.

J Bogousslavsky, H J Barnett, A J Fox, V C Hachinski and W Taylor

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