Nonembolic Occlusion of the Middle Cerebral and Carotid Arteries—A Comparison of Predisposing Factors

BY SIEGFRIED HEYDEN, M.D.,* ALBERT HEYMAN, M.D.,† AND JOHN A. GOREE, M.D.‡

Abstract: Nonembolic Occlusion of the Middle Cerebral and Carotid Arteries—A Comparison of Predisposing Factors

Selected clinical characteristics of patients with nonembolic occlusion of the middle cerebral artery were compared with those of patients with atherosclerotic occlusive lesions at the bifurcation of the common carotid artery. Unexpected differences were observed in the race-age distribution, in the presence of systemic vascular disease, and in the frequency of factors predisposing to atherosclerosis. The group with intracranial arterial lesions included more Negro patients than the group with lesions in the extracranial carotid artery. Ischemic heart disease, intermittent claudication and hypercholesterolemia were more frequent among the patients with extracranial cerebrovascular lesions, but the incidence of hypertension and diabetes was the same in both groups. These findings suggest differences in the etiological and pathogenetical mechanisms of the vascular disease in patients with extracranial and intracranial cerebral arterial occlusive lesions.

ADDITIONAL KEY WORDS: predisposing factors to atherosclerosis, carotid and coronary artery disease, race differences

Introduction

Atherosclerosis is generally considered to be the major underlying factor in occlusive disease of the intracranial and extracranial cerebral arteries. However, recent reports suggest that it may not have as significant a role in occlusion of the middle cerebral artery. L’Hermitte’s study of a large series of patients with ischemic disease of the territory of the middle cerebral artery showed that most such cases were caused by emboli. Silverstein reported that patients with occlusion of the middle cerebral artery had less evidence of systemic vascular disease, hypertension and ischemic heart disease than patients with carotid artery occlusion, suggesting that atherosclerosis may not be an important factor in the pathogenesis of middle cerebral artery occlusion.

The present study of patients with nonembolic occlusive lesions of the carotid or middle cerebral arteries compares the age, race, and sex, the incidence of certain predisposing factors and the presence of ischemic cardiovascular disease in the two groups of patients. If atherosclerosis is indeed the cause of occlusion in the middle cerebral artery, the frequency of these findings should be similar to that of patients with proved atherosclerotic disease of the extracranial carotid artery. Recent papers on middle cerebral artery occlusive disease have emphasized the neurological manifestations, arteriographical findings, and pathological anatomy. The presence of systemic vascular disease and factors predisposing to atherosclerosis in these cases has not been completely evaluated.

Methods

The case material for this study consists of three groups of patients with angiographically proven...
occlusive lesions in the cerebral arteries who were admitted to Duke Medical Center between January, 1963 and June, 1969: (1) Twenty-three patients with occlusion of the middle cerebral artery or one or more of its major branches, with no evidence of occlusive disease in the extracranial cerebral arteries. (2) Eighty-five patients with stenosis or occlusion of the bifurcation of one or both common carotid arteries, with or without occlusive lesions in the other extracranial cerebral vessels. (3) Seven patients with occlusion of the middle cerebral artery in addition to stenosis (five cases) or occlusion (two cases) of the bifurcation of the common carotid artery.

Although there was no problem in finding adequate numbers of patients with occlusive disease of the carotid artery, the number of patients with angiographically proven occlusion of the middle cerebral artery was surprisingly small, perhaps as a result of the rigid selection of cases. The criteria for inclusion of patients in this group consisted of complete obstruction on arteriographical examination of the main stem or major branches of the middle cerebral artery in the absence of an embolic etiology. Patients with arterial embolism in the retina, limbs, or other tissues were excluded from this study along with those with cerebrovascular disease associated with endocarditis, rheumatic heart disease or cardiac surgery. In addition, patients were excluded if their cerebrovascular lesions could possibly be attributed to head injury, arteritis, neurosyphilis, sickle cell anemia or other hematological diseases. The trunk of the middle cerebral artery was completely obstructed in 12 of the 23 cases; the remaining 11 cases had occlusion of one or more of the major branches of the middle cerebral arteries on serial arteriographical films.

Of the 85 patients with extracranial carotid disease, 56 had endarterectomy and their carotid lesions were found to be due to atherosclerosis. The remaining 29 cases were not treated surgically, but the same etiology seems likely. Bilateral arteriography of the carotid arteries was carried out in 63 of these 85 cases. Complete obstruction of one carotid artery was present in 45 patients and of both carotids in eight additional cases. The remaining 32 cases had stenosis of one or both carotids with 40% or more of the transverse diameter of the artery obstructed on arteriographical examination.

Only seven patients in this study had obstruction of the middle cerebral artery in addition to an occlusive lesion at the bifurcation of the common carotid artery. As indicated in the foregoing paragraph, bilateral arteriography was not carried out in 22 of the 85 patients with extracranial carotid disease. In these cases there is no information as to the presence of occlusive lesions in either the middle cerebral arteries contralateral to the carotid stenosis or the degree of the cross filling of the middle cerebral artery ipsilateral to the occluded carotid. For these reasons our case material may not represent the actual frequency of combined extracranial and intracranial vascular disease. The lack of such information in our study population does not seriously interfere with the interpretation of our data which are concerned primarily with possible differences in the etiological mechanisms for occlusion of the larger intracranial vessels alone, as compared with those of the extracranial carotid artery. The occlusive lesions in the carotid artery are undoubtedly due to atherosclerosis, and the presence of a concurrent intracranial lesion in some cases is probably caused by the same underlying process. In other instances, however, the extracranial occlusion is due to emboli arising from an ulcerative carotid plaque or to propagation of a thrombus extending from the extracranial to the intracranial portion of the carotid artery.

All the patients in the study had been admitted to the hospital with acute manifestations of cerebral ischemia or infarction. In general, the patients with middle cerebral artery occlusion had more severe neurological deficits than patients with extracranial carotid disease. The medical records of each patient were abstracted for pertinent information regarding the presence of ischemic heart disease, intermittent claudication, hypertension, xanthelasma, hypercholesterolemia, diabetes and electrocardiographical abnormalities. In addition, an analysis was made of the significant predisposing factors in white men with occlusion of the middle cerebral artery, and these were compared with those of an age-matched sample of patients with carotid disease. The small number of cases in this study did not permit matching for the other sex and race groups.

Results

RACE, SEX, AGE

The race, sex and age distribution of the 115 patients in this study are shown in table 1. It is apparent that occlusive disease of the carotid artery occurs mostly in white men who comprised 57 or 67% of the 85 cases with carotid disease. There were 27 white women. Only one of the patients with carotid artery occlusion was a Negro. He was a 47-year-old man who had stenosis of both internal carotid
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TABLE 1
Distribution of Patients by Diagnosis, Age, Sex, Race

<table>
<thead>
<tr>
<th>Age (yrs.)</th>
<th>White males</th>
<th>White females</th>
<th>Negro males</th>
<th>Negro females</th>
<th>All cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MCA</td>
<td>CAR</td>
<td>MCA</td>
<td>CAR</td>
<td>MCA</td>
</tr>
<tr>
<td>&lt;49</td>
<td>2</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>50–59</td>
<td>4(2)</td>
<td>24</td>
<td>1</td>
<td>8</td>
<td>2(2)</td>
</tr>
<tr>
<td>60–69</td>
<td>23</td>
<td>11</td>
<td>3(1)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td>2</td>
<td>3</td>
<td>0(1)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8(2)</td>
<td>57</td>
<td>5(1)</td>
<td>27</td>
<td>9(3)</td>
</tr>
</tbody>
</table>

MCA—Patients with occlusion of middle cerebral artery alone.
CAR—Patients with occlusive lesions in the internal carotid artery alone.
Figures in parentheses indicate number of cases with occlusive lesions in the middle cerebral as well as in the carotid artery.

TABLE 2
Frequency of Ischemic Heart Disease and Diabetes Mellitus Among Patients with Intracranial and Extracranial Arterial Disease

<table>
<thead>
<tr>
<th></th>
<th>Middle cerebral artery occlusion</th>
<th>Carotid artery occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total patients</td>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>White males</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>White females</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Negro males</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Negro females</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>17%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Arteries and a history of myocardial infarction and diabetes. In contrast, the 23 cases with lesions solely in the middle cerebral artery included ten (43%) Negro patients. The racial pattern of the seven patients with combined intracranial and extracranial occlusive lesions was similar to those with middle cerebral artery occlusion alone (four patients were Negroes and three were white). The high incidence of Negro patients with intracranial arterial lesions was surprising but cannot be explained by any known bias in selection of such patients for hospitalization or for arteriographical examination. Indeed, one might have expected a higher frequency of arteriographical examinations among patients with clinical signs of extracranial carotid disease (i.e., bruits, ophthalmic artery pressure differences, etc.) because of the interest among the physicians on our staff in the surgical treatment of this condition. The ratio of white to Negro patients admitted to the neurology and neurosurgical wards (from which these patients were largely drawn) was 4:1 during the period of this study. On the basis of this ratio, one would have expected 17 Negro patients in the group with carotid artery lesions and 4.6 Negro patients among those with occlusion of the middle cerebral artery. The observed number of Negro patients in each of these groups was one and ten respectively.

Approximately 70% of the patients with intracranial lesions (alone or in combination with carotid disease) were men, as compared with 68% men among the cases with carotid artery disease.

There appeared to be a significant difference between the age of the patients with middle cerebral artery occlusion and those with carotid lesions. A high proportion, 43%, of the patients with middle cerebral artery disease (10 of the 23 cases) were under 49 years of age, as compared with only 12% of those with carotid disease (11 of the 85 cases). Of the ten patients under 49 years of age with occlusion of the middle cerebral artery, four were Negro men and two were white men. In contrast, of the eleven patients under 49 years of age in the
carotid artery group, seven were white men and only one was a Negro man. It would appear, therefore, that the patients with middle cerebral artery occlusion differ from those with carotid artery disease in that the former comprise a higher percentage of young Negro men whereas the latter consist mostly of middle-aged or older white men.

**ISCHEMIC HEART DISEASE**

Table 2 shows the number of patients with clinical or electrocardiographical manifestations of ischemic heart disease. The patients with lesions in the middle cerebral artery had significantly less evidence of myocardial infarction or angina pectoris than those with carotid disease. Only four of the 23 patients (17%) of the former had a history or electrocardiographical manifestations of ischemic heart disease, as compared with 40 (47%) of the 85 patients with carotid artery lesions. The seven patients with combined intracranial and extracranial disease included but one patient with myocardial infarction. Among the patients with carotid artery lesions alone, the percentage of white men and women with ischemic heart disease was almost the same (47% and 44% respectively). As would be expected, the incidence of ischemic heart disease increased significantly with age over 55 years.

Twenty-two of the 40 patients with ischemic heart disease and carotid lesions gave a history of previous myocardial infarction, all of whom had confirmatory electrocardiographical findings. Of the remaining 18 cases, seven gave a history of myocardial infarction, but their electrocardiograms showed nonspecific abnormalities. Eleven had angina pectoris only and required nitroglycerin therapy.

Normal electrocardiograms were found in 31 of the 85 carotid artery cases (36%) and in none of the 23 patients (39%) with occlusion of the middle cerebral artery. The electrocardiographical findings in the remaining cases (i.e., those without a history of myocardial infarction) consisted of a variety of abnormalities including left ventricular hypertrophy, left ventricular ischemia, arrhythmia or left axis deviation. These electrocardiographical abnormalities, however, may have been caused by the acute brain damage and may not represent myocardial ischemia.

**PERIPHERAL VASCULAR DISEASE**

A history of intermittent claudication was given by 13 (15%) of the 85 patients with carotid artery disease. Nine of these 13 patients also had angina pectoris or evidence of myocardial infarction by history or electrocardiogram. In contrast, only one of the 23 patients with middle cerebral artery occlusion (a 67-year-old Negro man with diabetes) complained of intermittent claudication. It is of interest that none of the seven patients with combined carotid and middle cerebral artery disease gave a history of intermittent claudication.

<table>
<thead>
<tr>
<th>TABLE 3</th>
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</thead>
<tbody>
<tr>
<td><strong>Frequency of Hypertension Among Patients with Intracranial and Extracranial Arterial Disease</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Middle cerebral artery occlusion</th>
<th>Carotid artery occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total patients</td>
<td>Elevated BP*</td>
</tr>
<tr>
<td>White males</td>
<td>8</td>
<td>5(2)</td>
</tr>
<tr>
<td>White females</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Negro males</td>
<td>9</td>
<td>8(3)</td>
</tr>
<tr>
<td>Negro females</td>
<td>1</td>
<td>0(1)</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>14(6)</td>
</tr>
<tr>
<td></td>
<td>65%</td>
<td>35%</td>
</tr>
</tbody>
</table>

*Includes all patients with history of elevated arterial blood pressure, or antihypertensive therapy, or with at least one measurement in hospital of ≥160 mm Hg or greater.

†Includes only patients with blood pressure determinations consistently greater than ≥170 mm Hg. Figures in parentheses indicate number of cases with occlusive lesions in the middle cerebral as well as in the carotid artery.
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DIABETES MELLITUS
As shown in table 2, overt clinical diabetes appeared to be as frequent among the patients with carotid artery disease as among those with middle cerebral artery disease (18% versus 13% respectively). Hyperglycemia (fasting blood sugar levels greater than 110 mg%) was found slightly more often in the group with thrombosis of the carotid artery than in those with middle cerebral artery disease (33% and 23% respectively). The significance of the elevation of fasting blood sugar in these cases is not known since follow-up studies for diabetes were not available in most cases and the presence of hyperglycemia might represent only a transient nonspecific reaction to stress.

HYPERTENSION
The incidence of hypertension in patients with middle cerebral artery disease was approximately the same as that among patients with carotid artery disease (65% and 75% respectively) (table 3). Our criteria for hypertension consisted of a history of elevated blood pressure, previous antihypertensive therapy or any one blood pressure measurement during hospitalization of 160 mm Hg (or more) systolic or 95 mm Hg (or more) diastolic. Several of the patients with a previous diagnosis of hypertension had normal blood pressure determinations while in the hospital. Conversely, some normotensive patients may have had transient elevation of their blood pressure related to the increased intracranial pressure caused by massive cerebral infarction and edema.

For these reasons, it was considered worthwhile to employ more rigid criteria for the diagnosis of hypertension. Table 3 shows also the number of patients whose blood pressure measurements in the hospital were consistently greater than 170 mm Hg systolic or 95 mm Hg diastolic. The incidence of this degree of hypertension was found to be the same in the patients with intracranial as in those with extracranial occlusive lesions (35% and 33% respectively). It should be noted, however, that none of the women with middle cerebral artery occlusion had severe hypertension, whereas eight of the 17 men with such lesions had blood pressures in this range.

CONGESTIVE HEART FAILURE
Congestive heart failure was noted in four (17%) of the patients with middle cerebral artery disease and in six (7%) of those with carotid lesions. Of the four patients with heart failure and intracranial vascular lesions, two were white men with chronic renal failure and severe hypertension. The remaining two were Negro men, both of whom had hypertensive heart disease. The six patients with cardiac failure and carotid disease included three men with negative cardiac angiographical studies, one woman with pulmonary edema following her stroke, one man with a history and treatment of hypertension and another man with electrocardiographical changes suggesting myocardial infarction. None of these cases had clinical evidence of embolic phenomena or atrial fibrillation.

HYPERCHOLESTEROLEMIA
Extreme hypercholesterolemia, with serum levels ranging from 350 to 600 mg %, was noted in five patients with carotid artery disease. None of the patients with middle cerebral artery occlusion had a similar elevation in serum cholesterol. Two of the five carotid cases had xanthelasma and a family history of cardiac death. All five had other manifestations of systemic vascular disease such as myocardial infarction, hypertension, congestive heart failure or sudden death. The age of two patients was 42 years; the others were between 55 and 65 years old. No attempt was made to determine the frequency of less severe instances of hypercholesterolemia because of changes in the laboratory methods during the six and one-half year period covered by this study.

CLINICAL FINDINGS IN MATCHED CASES
The clinical findings of eight patients with intracranial arterial disease only were compared with those of 16 patients with extracranial disease who were matched by age, race, sex, and year of hospitalization and admission to public or private wards. Because of the small number of patients, only white men could be selected for this analysis. Our findings confirmed the observations described above. The frequency of hypertension was comparable in both groups. Only one of the eight patients with middle cerebral artery disease had a history of myocardial infarction, whereas seven cases of myocardial infarction were noted among the 16 men with carotid lesions (only
two cases were expected). Similarly, none of the patients with middle cerebral artery occlusion had angina pectoris or intermittent claudication, but one or the other of these symptoms was present in four of the patients with carotid disease who also had a history of myocardial infarction. Although diabetes mellitus was not present in any of the eight patients with intracranial arterial disease, this condition appeared in four of the 16 patients with carotid lesions.

**Discussion**

These results indicate that patients with nonembolic occlusion of the middle cerebral artery had less evidence of ischemic heart disease and fewer factors predisposing to atherosclerosis than patients with occlusive lesions of the extracranial portion of the carotid artery. The group with intracranial vascular lesions was also younger in age and included a much larger percentage of Negro patients. The incidence and degree of hypertension were, however, similar in both groups. Extreme hypercholesterolemia was found among patients with carotid lesions, but did not appear in any of those with intracranial vascular lesions. The overall frequency of diabetes was comparable in both groups, but there were more cases of diabetes in white men with carotid lesions than among men with intracranial occlusive disease who were matched for age, race and other characteristics.

The frequency of myocardial infarction, angina pectoris and symptoms of peripheral vascular disease was much greater in patients with extracranial carotid lesions than in those with occlusion of the middle cerebral artery. Whether these findings are sufficient to support a nonatherosclerotic etiology in the patients with intracranial lesions is conjectural. The fact that approximately one-half (43%) of the patients with intracranial arterial occlusion were Negroes and that an equal percentage were under 49 years of age is particularly noteworthy in this regard, since such age and race characteristics are unusual in patients with atherosclerotic disease of the coronary or carotid arteries. The frequency of hypertension in the group with occlusion of the middle cerebral artery was as great as that among patients with carotid artery occlusion. Indeed, congestive heart failure due to hypertension was perhaps more frequent among patients with intracranial vascular lesions, suggesting that the severity and duration of the hypertensive disease was greater. Fisher and others have found that occlusive lesions in the intracranial cerebral arteries were more severe in patients with hypertension. Thus, the vascular lesions in our patients with occlusion of the middle cerebral artery alone may be related primarily to severe, progressive hypertensive disease, a condition known to occur particularly in young Negro men. In such patients, the mechanisms for development of cerebral occlusive disease may not necessarily include such conditions as hypercholesterolemia, diabetes and xanthelasma.

The incidence of ischemic heart disease in the patients with occlusion of the middle cerebral artery alone was quite low when compared with patients with carotid disease. This finding, however, was not unexpected in view of the pathoanatomical studies of Solberg and his associates. These workers found little correlation between the presence of atherosclerotic disease of the intracranial arteries and that of the coronary arteries, but noted a direct relationship between the degree of atherosclerosis in the coronary and the carotid vessels. The present clinical study tends to confirm their results. Similar findings were described by Silverstein, who noted atherosclerotic heart disease in 48% of his patients with carotid artery occlusion. Several of his patients with intracranial lesions, however, were known to have cerebral embolism rather than thrombosis. Our investigation also differs from his in that we have included white and Negro patients in our study population.

The question arises as to the certainty of the diagnosis of a nonembolic etiology in our patients with occlusion of the middle cerebral artery. Although, as stated in the section on Methods, we excluded from this study all patients with clinical manifestations usually associated with cerebral embolism (i.e., rheumatic valvular disease, cardiac surgery, endocarditis, etc.), the possibility of cerebral embolism in the four patients with congestive heart failure cannot be completely ruled out.

It is also possible that occlusion of the middle cerebral artery in our patients was caused by emboli arising from ulcerative...
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atheromatous lesions in the proximal common carotid artery, the innominate artery or aorta which may not have been visualized in the arteriographical examinations. The findings in this study, however, indicate this source of embolism is unlikely since these patients showed very few of the age, race and sex characteristics and other factors predisposing to atherosclerosis which were present among the patients known to have atheromatous lesions in the extracranial carotid arteries.

Although hypertensive vascular disease was probably an important underlying factor in the production of the middle cerebral artery occlusion in most men with this condition, it was not a major factor in the women with intracranial vascular disease. None of the six women in this group had severe hypertension or clinical evidence of ischemic heart disease and all of them had normal electrocardiograms. Two of them, however, had diabetes mellitus. Whether the use of oral contraceptives in three of these women was a significant factor in the pathogenesis of the intracranial occlusive lesion remains to be determined.

This study sheds some light on the relationship of generalized atherosclerosis to cerebral arterial occlusive disease. Some workers believe that atherosclerosis in one arterial territory is an indication of a similar degree of involvement in other arteries as well. Other investigators, including Solberg, emphasize the absence of a definite correlation between the degree of atherosclerosis in one vascular bed compared to another. On the basis of our findings, there seems little doubt that patients with atherosclerotic lesions in the carotid arteries have a high frequency of overt ischemic heart disease and, to a lesser extent, peripheral vascular disease caused by atherosclerosis. Hypertension, diabetes and extreme hypercholesterolemia were also present. In contrast, these manifestations of atherosclerotic disease were less frequent in patients with middle cerebral arterial lesions, suggesting a difference in the etiological mechanism for occlusion of the larger intracranial arteries as compared to that in the extracranial cerebral vessels.

References


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