ography, TIAs may be the most common initial manifestation. Pessin et al. divided strokes associated with stenosis or occlusion of the extracranial internal carotid artery into 2 groups based on angiographic criteria; an embolic or suspected embolic group, and a non-embolic group. In the non-embolic group, 73% had TIAs and 41% had angiographic evidence of a hemodynamically significant stenosis in the internal carotid artery. In the embolic or suspected embolic groups, strokes were more severe but few were heralded by TIAs and none had hemodynamically significant stenoses. Thus, 2 subgroups of patients may be identified with vascular lesions at the same site but different mechanisms producing ischemic symptoms. These subgroups may differ in prognosis or response to therapy.

In our study there was no definite correlation between clinical or angiographic data and subsequent ischemic events ipsilateral to the siphon stenosis, but the number of events during follow-up was small. We suggest that future studies of prognosis in patients with vascular disease include angiographic analysis of hemodynamic significance and patterns of collateral flow to assess whether hemodynamic abnormalities and crossflow are important factors predisposing to recurrent ischemic events.

References


Spontaneous History of Asymptomatic Internal Carotid Occlusion

M. HENNERICI, M.D., H.-B. HÜLSBÖMER, M.D., RAUTENBERG, M.D., AND H. HEFTER, PH.D.

SUMMARY Forty-nine patients with ICA occlusion, who presented without any neurological signs or symptoms, were prospectively followed for an average of 31.2 months. Eight patients (16%) suffered a stroke during follow-up, of which five were within the vascular territory of the occluded artery — 5 patients (10%) developed TIAs of which were ipsilateral to the occluded artery. Non-invasive vascular follow-up did not reveal a progression of extracranial arterial disease in the majority of later symptomatic patients. Twenty-three patients (46.9%) died during follow-up, coexisting coronary artery disease being the major cause of death.

IN A RECENT PAPER Cote et al. reported a study of 47 patients with occlusion of the internal carotid artery (ICA), who presented with transient ischemic attacks (TIA) or mild strokes and were identified by angiography during the Canadian Cooperative Study. Since none of them were submitted to extra-intracranial (EC/IC) bypass surgery, their spontaneous risk of repetitive cerebral infarction could be studied prospectively. Among the literature reviewed by these authors, this was the first published series of a large group of patients without major neurological deficits studied prospectively. Their results indicated that the risk of subsequent cerebral infarction ipsilateral to an occluded carotid artery was comparable to the general risk of patients suffering from TIAs indicating that ICA occlusion was not a stable situation, as might have been suggested.

The present paper attempts to define whether patients with symptomless ICA occlusions have a better prognosis. Such patients have been selected in a large prospective series since 1977. The risk of stroke in this group of asymptomatic patients with obstructive extracranial arterial disease (EAD) has been shown to be rather small, although the probability of EAD progression was high as was the mortality rate. This was mainly due to frequent coexisting silent coronary artery disease (CAD). The present comparison of both prospective series, including rather similar preliminaries, should provide further insight into the natural history of obstructive EAD and hence optimize therapy.
Patients and Methods

In a prospectively selected group of neurologically asymptomatic patients with EAD, 339 patients were studied since 1977. Forty-nine patients revealed occlusions of one or both carotid arteries at initial non-invasive continuous wave (CW) Doppler and/or duplex-system examinations. None of them had any signs or symptoms of a focal cerebral deficit at entry into the study. In addition, computerized tomography (CT) being performed in 23 patients did not show any focal lesions. Absolute endpoints were death or the occurrence of TIAs or stroke. Follow-up examinations consisted in neurological and non-invasive vascular studies every 6 months. When a patient died, follow-up was accomplished with respect to cause of death and vascular territory of neurological symptoms. Due to the prospective manner of this study, information about the latter were missed in only 2 cases while causes of death were always noticed. The incidence and symptomatology of TIAs were determined at re-examination.

A directional CW-Doppler device (Debimetre ultrasonique directionnel Delalande) and a specially designed duplex-system incorporating a high resolution real-time B-mode imaging component (10 MHz) and a 16-range-gated 5 MHz pulsed Doppler system recently described were used for all recordings, the principle and feature of both methods have been described in detail elsewhere. The sensitivity and specificity of both methods for the diagnosis of extracranial internal carotid occlusion were 96.3% and 98.4% respectively and the overall accuracy was 98.1% (positive and negative predictive values were 89.6% and 99.5% respectively), when compared with selective carotid arteriography in 431 cases studied. If only high resolution imaging techniques had been used, the reliability of the method would have been considerably reduced due to overestimation of severe stenosis. This disadvantage could be balanced by combining these imaging techniques with a pulsed Doppler device for simultaneous display of the morphology and hemodynamics of the obstructive lesions considered.

Four different degrees of carotid obstructions were classified according to different ultrasound findings for a numerical interpretation of the natural history of the vascular process: mild stenosis (50-60% narrowing of the lumen), moderate stenosis (60-80%), severe stenosis (>80%) and total occlusion. Progression of EAD was stated if either stenosis occurred in the initially unaffected contralateral carotid artery or a deterioration within these classes was observed.

Results

Forty-nine patients were followed during 1977-1984, the average follow-up being 31.2 months (table 1). Ages of the patients ranged from 39-84 years with a mean of 62.4 years. There were 38 males and 11 females, none of them had signs or symptoms of permanent or transitory focal neurological deficits originally. Patients were mainly admitted because of coexisting usually mild peripheral artery disease (PAD), only four times requiring surgical treatment (n = 20; 40.1%), coronary artery disease (CAD) (n = 5; 10.2%), cervical bruits (n = 7; 14.3%) and/or because of risk factors of atherosclerosis (hypertension n = 29; 59.2%, diabetes n = 14; 28.6%, hyperlipidemia n = 9; 18.4% and smoking n = 24; 49%). Five patients presented with signs or symptoms of CAD already at their entry into the study (3 myocardial infarction, 2 angina only), and eight developed cardiovascular problems during follow-up (16.3%). Patients with cardiogenic sources for cerebral emboli were excluded as revealed by cardiovascular examination, ECG recordings and/or standard M-mode echocardiograms.

The ICA was occluded in 43 patients unilaterally, 6 patients had bilateral ICA occlusions. Fifteen patients presented with ICA occlusions in the presence of a contralateral hemodynamically significant stenosis (7 mild, e.g. <60% lumen reduction, 3 moderate, e.g. 70-80%, 5 severe, e.g. >80%) and 5 patients had a subclavian steal phenomenon with retrograde perfusion of at least one vertebral artery in addition to the ICA occlusion. Thus, twenty-six (53%) patients had evidence of additional atherosclerotic obstructions either involving the contralateral carotid or the vertebral arteries. Comprehensive angiography has not been performed regularly in these asymptomatic patients, however, it confirmed the non-invasive ultrasound diagnosis in 10 cases.

Twenty-three patients died during follow-up, resulting in a mortality rate of 46.9% and 18% when adjusted on an annual basis (fig. 1). As shown in table 2, cardiac disease was a far more common cause of death (n = 13) than stroke (n = 5) and mainly accounted for a mortality rate higher than in the series reported by Cote et al. However, this is probably neither due to a different incidence of patients with CAD included in both series (30% vs 27%), nor to a more severe degree of these diseases: cardiac mortality was indeed not significantly higher in those patients with CAD (23%) than in those without clinical cardiovascular signs or symptoms (27%). However, the prognosis of the former was probably better as a result of adequate cardiac treatment including coronary artery bypass surgery performed in three patients successfully.

There are, however, two different parameters likely to explain the worse overall prognosis of our patients. In the first place, different from the series of Cote et al., we did not exclude patients likely to die within the first year of observation from the study. Secondly, the percentage of patients with evidence of peripheral vascular disease was considerably higher (41% vs 15%). Since symptomatic PAD is frequently associated with clinically silent, but advanced stages of atherosclerosis
FIGURE 1. Stroke (A) and mortality (B) probability after initial demonstration of extracranial ICA occlusion in 49 asymptomatic patients.

in various regions of the body, the higher incidence of PAD may indicate a worse individual prognosis.

Sixteen percent of the patients experienced a stroke, at least two-thirds of these occurred on the side of the initial ICA occlusion. This results in an annual stroke rate ipsilateral to an occluded artery of 4% without respect to death or survival. Patients with multi-vessel disease were more likely to suffer a stroke (n = 6; 23%) than patients with unilateral ICA occlusions (n = 2; 9%), at first sight indicating on a progressive insufficiency of collateral blood flow likely to be responsible for the symptomatic event. However, of 5 dead patients suffered a stroke ipsilateral to the occluded artery — in 2 the vascular territory was unknown — and 2 among 3 patients still alive presented with a stroke ipsilateral to the occluded artery. In all, the EAD remained unchanged during follow-up involving the contralateral ICA (moderate stenosis) in one and the vertebro-basilar system (subclavian-steal-phenomenon) in 2 patients. Furthermore 4 among 5 patients with late TIA's reported symptoms ipsilateral, one contralateral to the initially occluded artery, and none originating from the brain-stem. Only one of them revealed a deterioration of his extracranial EAD.

Thus the majority of patients became symptomatic ipsilateral to the occluded ICA in the absence of any progression of their extracranial EAD as revealed by non-invasive ultrasound methods, whereas half of those patients deteriorated still asymptomatically (table 3). Altogether, non-invasive re-examination of the EAD showed progression in sixteen (32.6%), and stability in seventeen patients (34.8%), while sixteen could not repetitively be followed due to death or severe disability after stroke. Progression of EAD was more frequently observed in patients already affected by multi-vessel disease (42%) than in patients with one-vessel disease initially (22%).

The pathogenic mechanisms responsible for late cerebrovascular transitory and permanent events are unknown. Since progression of the extracranial atherosclerotic process was not associated with late cerebrovascular events, intracranial arterial stenosis or insufficient collateralization, embolism from ulcerative lesions either intracranially or within the ipsilateral common and/or external carotid arteries, as well as propagation or embolism from the occlusive thrombus of the ICA may explain these symptoms.

Fourteen patients were treated with antiplatelet therapy, one of them suffered a stroke and two died either of myocardial infarction or cancer. Two patients were treated with anti-coagulant therapy, one of them suffered a hemorrhagic stroke, the second suffered a nonvascular death. Two patients were submitted to carotid surgery for repair of a contralateral ICA stenosis, although they remained asymptomatic during follow-up.

Discussion

Different studies recently reviewed by Cote et al have examined the cerebrovascular risk associated with occlusion of the internal carotid arteries. Some of them were retrospective in character and included patients already suffering from moderate or severe disability after completed strokes. Most of these patients were treated either with anticoagulants or surgery had been performed reducing the percentage of patients suitable for spontaneous follow-up. The evidence of these studies is further restricted by their considerable lack of information about the vascular territories involved by subsequent cerebral infarction and the ignorance of the late vascular status of the brain arteries. The latter unfortunately is similarly true of other studies having considered patients with TIAs or mild strokes only. The reasons for this is the lack of a reliable non-invasive method for their study and the risks associated with repetitive arteriography. Consequently, even if the vascular territories of subsequent cerebrovascular symptoms were noted, their pathogenesis remained unknown due to the lack of information about the actual distribution of obstructive lesions and their collateralization at the time the cerebrovascular event occurred. Again some of these studies were retrospective and included heterogeneous forms of therapy.

Apart from two prospectively selected studies which, however, are too small for any definite statement, the report by Cote et al was the first thoroughly discussing this problem. In contrast to our report dealing with asymptomatic patients exclusively, their study concentrated on patients with transitory or mild permanent neurological deficits, both groups being at risk to suffer a major stroke and hence suggested to suitable candidates for EC/IC bypass surgery. Thus, selection of patients was identical for both studies with
TABLE 2 Prognosis of Carotid Artery Occlusion

<table>
<thead>
<tr>
<th>Number of patients (males/females)</th>
<th>47 (39/8)</th>
<th>49 (38/11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range (mean age)</td>
<td>40-83 (58.9) yrs.</td>
<td>39-84 (62.4) yrs.</td>
</tr>
<tr>
<td>Mean time of follow-up</td>
<td>34 months</td>
<td>31 months</td>
</tr>
<tr>
<td>Type of study</td>
<td>prospective</td>
<td>prospective</td>
</tr>
<tr>
<td>Patient's clinical stages</td>
<td>27 TIA</td>
<td>49 asymptomatic</td>
</tr>
<tr>
<td>hypertension</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>cardiac disease</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>peripheral vascular disease</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>Vascular findings</td>
<td>initial unilateral 47</td>
<td>bi lateral 0</td>
</tr>
<tr>
<td></td>
<td>late multi vessel disease 19 (43%)</td>
<td>multi vessel disease 26 (53%)</td>
</tr>
<tr>
<td>Deaths during follow-up</td>
<td>4 (9%)</td>
<td>23 (47%)</td>
</tr>
<tr>
<td>cardiac</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>stroke</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>others</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Strokes during follow-up*</td>
<td>ipsilateral 11 (24%)</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>contralateral/brain-stem</td>
<td>7 (15%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>unknown</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

*Lethal strokes included.

The main difference between the two studies is the significantly higher death rate in our population (47% vs 9%), being due to myocardial infarction primarily but also to a higher stroke-related death rate, although the overall stroke rate tended to be even smaller in our series (16% vs 24%). The degree and extent of atherosclerosis manifested in various vascular systems of the body as well as the occurrence and probably also the management of certain risk factors which were quite different in both populations, are suspected to represent the main reasons for this difference in the natural history. Patients included in our study presented with a more severe extracranial arterial process (6 patients had bilateral occlusions and 26 a contralateral stenosis of more than 50% lumen narrowing and/or a vertebral steal-phenomenon) and a more generalized atherosclerosis. Forty-one percent vs 15% had symptomatic peripheral vascular disease and, different from the Canadian study, patients with severe cardiac disease and those, who died within the first year of observation, were not excluded. As in the majority of cases the origin of late cerebrovascular events did not result from progression of EAD (as revealed by non-invasive ultrasound examinations performed for the first time in such a study). ICA occlusion is considered not to represent a stable condition but to be associated with a

TABLE 3 Follow-up of 49 Patients with ICA Occlusion with Respect to Degree and Extent of Initial EAD

<table>
<thead>
<tr>
<th>One-Vessel Disease</th>
<th>Multi-Vessel Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients total</td>
<td>23</td>
</tr>
<tr>
<td>Patients dead total</td>
<td>13 (2)</td>
</tr>
<tr>
<td>stroke</td>
<td>2</td>
</tr>
<tr>
<td>cardiac</td>
<td>8 (1)</td>
</tr>
<tr>
<td>cancer</td>
<td>1</td>
</tr>
<tr>
<td>others</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Patients alive total</td>
<td>10 (3)</td>
</tr>
<tr>
<td>asymptomatic</td>
<td>5 (2)</td>
</tr>
<tr>
<td>TIA</td>
<td>5 (1)</td>
</tr>
<tr>
<td>stroke</td>
<td>0</td>
</tr>
</tbody>
</table>

No. of patients with EAD progression at follow-up in parentheses.

*Contralateral carotid endarterectomy was performed in two patients still asymptomatic.
considerable risk of stroke even if extracranial collateralization is preserved. This risk is similar to the estimated stroke rate of 5% to 6% a year for groups of patients suffering from TIs in general. In accordance with these studies, the risk of stroke seems to decrease with time after occurrence of TIs and of detection of asymptomatic ICA occlusion respectively (fig. 1), which may be explained by various pathogenic mechanisms associated with alterations of cerebral circulation caused by occlusion of the ICAs. Other factors already mentioned may, however, be of similar importance, since the probability of late events within the territory of the occluded ICA was 0.087 by chance — to gain significance at a 5% level (sign-test) 10 instead of 9 patients among 13 in the present series should have fulfilled these criteria (0.035). In general, our results extend the observation reported by Cote et al. indicating that, not only patients with TIs and/or minor strokes due to ICA occlusions are at considerable risk to suffer from stroke, but the same is true for asymptomatic patients.

Although non-invasive techniques performed by experienced examiners are prepared to detect extracranial ICA occlusion as accurate as less harmful neuroradiological procedures, and hence enabled repetitive examinations of large series of unselected subjects, the incidence of true symptomless patients with ICA occlusions remains small, but is most frequently observed in patients with PAD. Patients included in this report were selected from a prospective study on the natural history of EAD collected on the basis of an annual ultrasound examination rate of about 4,000 patients since 1978. Apparently similar reasons accounted for the equally small number of patients studied in the series reported by Cote et al. Therefore interpretation of the data reported from both series may be of limited value but are based on at least the best available today. The unanimous observation of a similarly high risk of stroke from ICA occlusion in patients who originally presented with either mild symptoms or without any signs of cerebrovascular insufficiency may counter-balance this disadvantage with view to a better treatment based on an extended knowledge of the spontaneous history of their disease.

Although cardiac mortality was higher in initially neurologically asymptomatic patients probably due to the advanced stages of generalized atherosclerosis, this is not the cause for the high incidence of cerebrovascular symptoms during follow-up. A comparison of an age- and sex-matched population (of similar manifestation parameters for atherosclerosis followed in our large prospective study), who presented with moderate or severe carotid stenosis instead of ICA occlusion at entry, had a similar high mortality rate (37%) but a considerably smaller overall stroke rate (6%) during identical observation periods (in preparation).

The high mortality rate recorded in this report is quite comparable to other long-term follow-up studies and strengthens the need to carefully search for coexisting CAD even in the absence of obvious clinical signs or symptoms. This is particularly important, since recent results from the International Cooperative Study of EC/IC Arterial Anastomosis failed to show any improvement in the prognosis of patients suffering from ICA occlusion by this procedure.

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