Carotid Transient Ischemic Attacks and Normal Investigations: A Follow-up Study

Ashfaq Shuaib, MD, FRCP(C), and Vladimir C. Hachinski, MD, FRCP(C), DSc(Med)

Reports on the long-term prognosis of patients with transient ischemic attacks and normal angiograms have revealed variable results, some suggesting a good prognosis while others report an outcome no different from that of patients with transient ischemic attacks and atherosclerotic vascular narrowing. Normal cerebral angiograms do not exclude disease in the heart or hematologic disorders. The prognosis for patients with transient ischemic attacks, normal angiograms, and normal results of cardiac and hematologic investigations is not known. We report our experience with 43 patients (26 men and 17 women, mean age 55.6 years) with transient ischemic attacks and normal findings on all investigations (including angiography, cranial computed tomography, echocardiography, and Holter monitoring). The patients were followed for a mean of 4.43 years. Six patients had recurrent transient ischemic attacks and six developed angina pectoris. No patient developed a stroke. In the presence of normal cerebral, cardiac, and hematologic findings, the long-term prognosis of patients with transient ischemic attacks is good. However, the development of cardiac disease during follow-up could not be predicted using the available diagnostic methods. (Stroke 1990;21:525–527)

The long-term prognosis of patients with transient ischemic attacks (TIAs) and normal angiograms is not well defined. Some studies report a good outcome, whereas others suggest a prognosis similar to that of TIA patients with atherosclerotic vascular disease.1-5 We recently reported a study of 68 TIA patients with normal cerebral angiograms,6 which suggested that a history of cardiac disease was a significant risk factor for the development of subsequent cardiac and neurologic complications. However, other studies have suggested a low incidence of cardiac disease in TIA patients with normal cerebral angiograms.7 With wider availability of newer technology, it is not unusual to find cerebral infarcts on cranial computed tomograms (CT scans) or abnormalities during cardiac or hematologic evaluations that may explain the transient cerebral symptoms even if the angiograms are normal. While there are several reports of TIA patients with normal angiograms, there have to date been no publications specifically reviewing the long-term follow-up of TIA patients with normal cerebral, cardiac, and hematologic findings. Therefore, we reviewed a subgroup of patients from our previously reported study6 in whom the results of all investigations were normal and follow-up was available. Our goals were to assess the risks of recurrent TIAs and the development of new cardiac or cerebral symptoms (including stroke) during follow-up.

Subjects and Methods

Sixty-eight patients admitted to University Hospital, London, Ontario, Canada between 1980 and 1984 had a TIA and a normal angiogram. TIAs were defined as ischemic hemispheric and/or retinal symptoms resolving ≤24 hours after onset,8 and carotid-territory TIAs were defined following the guidelines of the Ad Hoc Committee of the National Institute of Neurological and Communicative Disorders and Stroke.9 Angiograms were considered normal only if, after careful review of a four-vessel study, there was no evidence of atheroma or ulcer. The Seldinger technique was used and biplane evaluations were completed in all angiographic studies. We did not include TIA patients with normal angiograms and a history of migraine defined according to Friedman et al.10 All patients had cranial CT, and we excluded 10 with abnormal scans because first, we wanted the results of all investigations to be normal and second, in several patients the CT abnormalities did not

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Presented in part at the American Academy of Neurology, Cincinnati, Ohio, April 1988.
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Received April 18, 1989; accepted November 22, 1989.
correspond to the TIA symptoms. We also excluded patients with cardiac abnormalities; nine had abnormal two-dimensional echocardiograms (Hewlett-Packard 77020-A ultrasound imaging system, Palo Alto, California) and six had abnormal findings on Holter monitoring (two-channel Zymed recorder, Camarillo, California). Four of the 15 patients with cardiac abnormalities had already been excluded on the basis of their cranial CT investigations. Contrast or intrasophageal echocardiography was not performed in any patient. Because carotid Doppler studies were performed in only a few patients and the findings were all normal, ultrasonographic results were not analyzed. Four patients were excluded for other reasons (in three the diagnosis of TIA was changed, and one patient died of unrelated disease). Hematologic investigations included a complete blood count in all patients, and prothrombin and partial thromboplastin times were measured in 34. Further details are described elsewhere.6 The patients were 24-72 (mean 55.6) years old; 26 were men and 17 women. Symptoms of carotid-territory ischemia were ocular in 13 patients and cerebral in the other 30 (Table 1), left-sided in 60%. The symptoms lasted <0.5 hour in 26 patients (60%), 0.5–1 hour in eight (19%), 1–5 hours in five (12%), and >5 hours in four (9%). The patients' risk factors for cerebrovascular disease are shown in Table 2. No patient had hypercholesterolemia.

Thirty-four patients were treated with oral medications; 28 received acetylsalicylic acid, two antiocoagulants, and one dipyridamole. Three patients were part of the Canadian-American Aspirin Ticlopidine Study,11 and the exact medications used were not available due to the double-blind nature of that study. The remaining nine patients were not offered any treatment. Normal findings on all investigations were an important factor in not offering any medical treatment.

Follow-up lasted 3.1–6.7 (mean 4.43) years. Six patients had recurrent TIAs (three were in the cerebral distribution and the other three were recurrent amaurosis fugax). The recurrent TIAs were in distributions similar to that of the initial TIA. Duration of the initial TIA was not predictive of recurrence. No patient developed a stroke. Angina pectoris developed in six patients; two of the six also had recurrent TIAs, and two others developed myocardial infarction during follow-up.

Subsequent events during follow-up were more common in the group presenting with multiple TIAs. Of the 16 patients presenting with a single TIA, recurrence was seen in one patient and angina pectoris in another (12.5%). In contrast, eight of the 27 patients presenting with multiple TIAs (29.6%) had recurrent TIAs or developed new cardiac symptoms during follow-up. However, the difference between the groups was not significant (χ²=1.61, df=1, p<0.20).

Discussion

TIA is diagnosed on the basis of clinical information. According to current diagnostic criteria, focal symptoms lasting <24 hours are the only requirement to make such a diagnosis.8,5 It is thus not surprising that a number of conditions such as seizures, subdural hematomas, intracerebral hematomas, and neoplasms cause transient focal symptoms that can be confused with those of a TIA.12-15 Furthermore, as more information becomes available it is being appreciated that TIAs are not homogeneous.15 Patients with carotid artery disease form the largest proportion of such cases. Cardiac emboli, cardiac arrhythmias, transcardiac shunts, and lacunar infarctions are becoming increasingly recognized as conditions that can cause symptoms identical to those of large-vessel atherosclerotic disease.16,17 Concomitant cardiac and carotid disease, each potentially a source of small emboli, may occur in up to 25% of TIA patients.16 Duration of the symptoms may be an important predictor of prognosis. The longer they last, the greater the chance of cardiac morbidity or cerebral infarction.18

Up to a third of TIA patients have a normal angiogram.6 In these patients, the prognosis is not well defined. Some authors3 report a good outcome while others5 suggest a prognosis similar to that of TIA patients with atherosclerotic disease. Although

### Table 1. Symptoms of Transient Carotid-Territory Ischemia in 43 Patients With Normal Investigations

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>n</th>
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</thead>
<tbody>
<tr>
<td>Visual</td>
<td>13</td>
</tr>
<tr>
<td>Sensory</td>
<td>10</td>
</tr>
<tr>
<td>Motor</td>
<td>5</td>
</tr>
<tr>
<td>Sensory and motor</td>
<td>7</td>
</tr>
<tr>
<td>Speech problems</td>
<td>7</td>
</tr>
<tr>
<td>Sensory, motor, and visual</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 2. Risk Factors for Cerebrovascular Disease in 43 Patients With Transient Ischemic Attacks and Normal Investigations

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>16</td>
<td>37.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3*</td>
<td>7.0</td>
</tr>
<tr>
<td>Smoking</td>
<td>7</td>
<td>16.3</td>
</tr>
<tr>
<td>Family history</td>
<td>8</td>
<td>18.6</td>
</tr>
</tbody>
</table>

*Developed during follow-up.
several studies have looked at TIA patients with normal angiograms\textsuperscript{1-6} and TIA patients with normal cardiac findings, no previous study has assessed outcome in TIA patients with normal angiograms, normal cranial CT scans, normal cardiac findings, and normal results of hematologic investigations. Our study suggests that TIA patients in whom the results of all investigations are normal have a good long-term outcome. No such patient developed a stroke during a mean follow-up of 4.43 years. Patients with recurrent TIAS were not disabled by their symptoms. Six patients developed coronary artery disease, two of whom also suffered myocardial infarctions. We could not prospectively distinguish TIA patients who developed recurrent symptoms from those who did not, although there seemed to be a trend for patients presenting with multiple TIAS to have more complications. However, this difference was not significant.

We were unable to identify any risk factor that distinguished patients at risk for future cardiac disease. The prevalences of a family history of stroke, smoking, and hypertension were similar in the two groups (data not shown). Age at onset, sex, and the frequency and type of TIAs were also similar in the two groups (data not shown). In a recent report, 83 consecutive TIA patients were subjected to extensive cardiac investigations including treadmill testing and thallium-201 myocardial scintigraphy; 28% with asymptomatic cardiac disease were identified.\textsuperscript{19} If the same methods are applied to our TIA patients with normal results on all investigations, it may be possible to identify those at risk for developing cardiac disease.

The mechanism(s) producing TIAs in patients with normal results on all investigations are not clear. Several possibilities can be entertained. Transient arrhythmias or cardiac abnormalities below the resolution of echocardiography could result in hypotension or embolization.\textsuperscript{16,20} Alternatively, a small carotid ulcer may be missed by angiography\textsuperscript{2} or a fibrin clot may originate from the aortic arch, an area not well visualized. It is unfortunate that Doppler studies were not done in most of our patients as an occasional ulcer or early atheroma may be visualized by that method when the angiogram is normal.\textsuperscript{21} Finally, we cannot rule out the possibility that the symptoms were related to conditions such as migraine or focal seizures.

The best treatment in TIA patients with normal findings is difficult to decide. Doppler ultrasonography should also be done in such patients as it may pick up pathology missed by angiography.

Acknowledgment

We gratefully acknowledge the help of Danielle Sikander in the preparation of this manuscript.

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Key Words: angiography • cerebral ischemia, transient • prognosis
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*Stroke*. 1990;21:525-527
doi: 10.1161/01.STR.21.4.525

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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http://stroke.ahajournals.org/content/21/4/525

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