Transient Ischemic Attacks and Normal Cerebral Angiograms: A Follow-up Study

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To determine the outcome of patients with carotid transient ischemic attacks (TIAs) and normal cerebral angiograms, we assessed 68 patients (40 men, 28 women) aged 24–72 (mean 53.5) years for recurrent TIAs and strokes and for the development of cardiac disease over 2–6 (mean 4.4) years. All but one patient had a follow-up interview in early 1987; that patient had died of an unrelated cause (lung cancer) 18 months after the presenting TIA. The diagnosis was changed at the follow-up interview in three patients (multiple sclerosis, meningioma, migraine). Among the 64 remaining patients, at admission cranial computed tomography had shown cerebral infarction in 11 of 64, two-dimensional echocardiography had been abnormal in nine of 61, Holter monitoring had been abnormal in eight of 45, and twelve-lead electrocardiography had been abnormal in three of 64. Two patients had abnormalities on both echocardiography and Holter monitoring. At the follow-up interview of the 64 remaining patients, TIAs had recurred in nine and three had developed a completed stroke; cardiac disease (angina in seven, myocardial infarction in four) was noted in 11 patients. Findings from cardiac investigations on admission in the nine patients with recurrent TIAs had been abnormal in six and normal in three; all three patients who developed a stroke had had abnormal cardiac findings. Overall, further neurologic or cardiac events occurred in 12 of 46 patients (26%) with normal and in 10 of 18 patients (55.5%) with abnormal findings on admission (*p*<0.01). In the presence of normal angiograms, extensive cardiac investigations may help predict the outcome of patients with TIAs. 

(Cerebral angiography shows atherosclerosis in the majority of patients who have transient ischemic attacks (TIAs) in the carotid artery territory,1–3 with the subsequent risk of stroke over 5 years ranging from 10% to 43%.4–9 Angiograms may, however, be normal in approximately 25% of these patients.10 The reported frequency of normal angiograms in patients with TIAs has varied from as low as 7%11 to as high as 40%.12 The etiology, natural history, and prognosis in these patients is not well defined. Some articles suggest an excellent prognosis13 while others report an outcome similar to that of patients in whom angiography shows atherosclerotic narrowing.11,14 However, few patients were studied,11 angiography was incomplete,14,15 and follow-up was limited13; therefore, no definite conclusions can be drawn from these studies.

Our study was undertaken to evaluate the outcome of patients admitted over a 4-year period to University Hospital, London, Ontario, Canada, with TIAs and normal angiograms in whom cardiac investigations were extensive. Our results suggest that patients with cardiac disease (previously known or newly diagnosed during evaluation) have a higher incidence of subsequent cardiac and noncardiac complications. Cardiac investigations separate patients with TIAs and normal angiograms into two subsets with different prognoses.

**Subjects and Methods**

The angiographic results of all patients with TIAs admitted to our hospital between 1980 and 1984 were reviewed. We included the records of 68 patients (40 men, 28 women) aged 24–72 (mean 53.5; men 54.3, women 51.1) years with entirely normal angiograms and TIAs in the carotid artery distribution. In 66 of the 68 patients, complete angiography with visualization of the aortic arch and cerebral vessels was carried out, whereas two patients had only selective carotid angiography.
The Seldinger technique was used in all patients, and biplane evaluations were carried out in all angiograms. Angiograms were considered normal if careful review showed no evidence of atheroma or ulcer formation. A TIA was defined as ischemic hemispheric and/or retinal symptoms resolving within 24 hours after onset.16 Carotid TIAs were defined following the guidelines of the Ad Hoc Committee of the National Institute of Neurological and Communicative Disorders and Stroke.17 The type, duration, and clinical features of the TIAs on admission were recorded. Risk factors including hypertension, known cardiac disease, smoking, family history of stroke or heart disease, hypercholesterolemia, and diabetes mellitus were analyzed.

Cranial computed tomography (CT) was performed on admission in all patients. All 68 patients had at least one twelve-lead electrocardiogram (ECG) on admission, and 65 patients underwent two-dimensional echocardiography (2-DE) (Hewlett-Packard 77020-A ultrasound imaging system, Palo Alto, California); three patients failed to undergo 2-DE for no obvious reason. Mitral valve prolapse (MVP), segmental wall hypokinesia or akinesia, rheumatic mitral stenosis, global myocardial hypokinesia, left ventricular aneurysm, bacterial endocarditis, mitral anulus calcification, and intracardiac thrombus were considered to be potential sources of emboli.18-19 In addition, 45 of the 68 patients underwent 24-48-hour Holter monitoring (HM) (two-channel Zymed recorder, Camarillo, California) on admission. Intermittent atrial fibrillation and sick sinus syndrome were considered to indicate heart disease and/or to be potential sources of cardiac emboli.20,21

Follow-up was available in all 68 patients; one patient died of lung carcinoma 18 months after a single TIA. The surviving patients were interviewed by telephone in early 1987 regarding the development of any further cardiac or ischemic neurologic symptoms. The diagnosis was changed at the follow-up interview in three patients. One 30-year-old woman was diagnosed as having multiple sclerosis. Symptoms on admission had been numbness of her right arm and leg, and multiple sclerosis had been considered in the differential diagnosis; however, with cerebrospinal fluid negative for oligoclonal bands and visual and somatosensory evoked responses normal, the diagnosis was not pursued further. The second patient, a 62-year-old woman, presented with two episodes of right-sided weakness and numbness, but cranial CT was normal; 2 years later another episode of similar symptoms was accompanied by diplopia (sixth nerve palsy), and cranial CT showed a left tentorial meningioma. In the third patient, a 27-year-old man, initial symptoms consisted of right-sided weakness and aphasia; subsequently, similar episodes of weakness and aphasia were followed by typical migraine headaches. Further discussion will include only the 64 remaining patients. In all patients in whom new symptoms developed after hospital discharge, symptoms and physical examination were verified from the records of the family practitioner's office.

The χ² test for contingency tables was used for statistical analysis.

Results

On Admission

Symptoms on admission and risk factors for cerebrovascular disease for the 64 remaining patients are shown in Table 1.

The TIAs lasted <½ hour in 39 patients (60.9%), ½-1 hour in 10 patients (15.6%), 1-5 hours in 12 patients (18.8%), and 5-24 hours in three patients (4.7%). Episodes were single in 23 and multiple in 41 patients (Table 2). Multiple episodes were identical in the majority of the patients (29 of 41), and of the 12 patients with nonidentical TIAs, seven had multiple episodes in the same vascular territory whereas in five the other carotid territory was involved as well.

Cranial CT was performed on admission in all 64 remaining patients and showed 14 infarcts in 11 patients. The sites of infarction were frontal in five (left in two and right in three), parietal in three (left in two and right in one), occipital in two (left in one and right in one), thalamic in one (right), the internal capsule in two (right), and the caudate nucleus in one (right); three patients had more than one infarct (bifrontal in one, biparietal in one, right occipital and frontal in one). TIAs were appropriate to the side of the infarction and could have been related to the symptoms in only two patients. In the nine other patients, no definite association could be established between the clinical symptoms on admission and the CT findings. 2-DE was performed on admission in all 11 patients with cerebral infarction and was abnormal in four (MVP in two, abnormal
TABLE 2. Complications During Follow-up in Relation to Number of TIAs on Admission in 64 Patients With TIAs and Normal Angiograms

<table>
<thead>
<tr>
<th>TIAs on admission</th>
<th>Complications during follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Only 1 episode</td>
<td>23</td>
</tr>
<tr>
<td>Multiple episodes</td>
<td>41</td>
</tr>
<tr>
<td>Identical</td>
<td>29</td>
</tr>
<tr>
<td>Nonidentical</td>
<td>12</td>
</tr>
<tr>
<td>Same vascular territory</td>
<td>7</td>
</tr>
<tr>
<td>Both carotid territories</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>64</td>
</tr>
</tbody>
</table>

Data are number of patients. TIAs, transient ischemic attacks; MI, myocardial infarction.

wall motion in one, mitral anulus calcification in one). HM was performed on admission in 10 of the 11 patients with infarction and was abnormal (frequent premature ventricular contractions (PVCs)) in three.

Table 3 shows the findings of the cardiac investigations on admission. Sixty-one of the 64 remaining patients underwent 2-DE on admission, with abnormalities noted in nine (14.8%); five had MVP, three had segmental wall abnormalities (two were known to have old myocardial infarction), and one had mitral anulus calcification. Cardiac rhythm abnormalities were noted in eight of the 45 patients (17.7%) who completed 24–48 hours of HM on admission; the abnormalities included frequent PVCs in six patients, intermittent atrial fibrillation in one, and wandering atrial pacemaker in one. Retrospectively, frequent PVCs were considered a risk factor for cerebrovascular disease as three of six patients (50%) with frequent PVCs had subsequent complications (recurrent TIAs in two and stroke in one). Two patients had abnormalities on both 2-DE and HM on admission (MVP and frequent PVCs in one and mitral anulus calcification and frequent PVCs in the second). ECG abnormalities on admission were noted in three patients, two demonstrating changes consistent with old myocardial infarction and one showing acute ischemic changes. On admission, a total of 18 of the 64 remaining patients had abnormalities on cardiac investigations.

At Follow-up Interview

The 64 remaining patients had been admitted between 1980 and 1984 and were interviewed in early 1987; thus, most patients had at least 2 years' follow-up, 6 years in 14, 5 years in 15, 4 years in 15, 3 years in 12, and 2 years in eight patients (mean 4.43 years).

During follow-up, nine patients had recurrent TIAs; three patients developed completed stroke in addition to TIAs; angina occurred in seven patients, one of whom had a history of ischemic heart disease (IHD); and myocardial infarction occurred in four patients, two of whom had a history of IHD (Table 2). One patient developed symptoms suggestive of peripheral vascular disease but was not investigated further, and one patient had an embolus to the axillary artery requiring embolectomy 2 years after the initial TIA. Angiography was repeated in two patients, to investigate cerebral infarction in one and persistent TIAs in the other, and both studies were normal.

Ten of 39 patients with symptoms lasting <½ hour developed complications during follow-up (IHD in four, TIA in six), six of 10 patients with symptoms lasting ½–1 hour developed complications (IHD in five, stroke in one), seven of 12 patients

TABLE 3. Relation of Development of Complications During Follow-up to Abnormalities on Cardiac Investigations in Patients With TIAs and Normal Angiograms

<table>
<thead>
<tr>
<th>Abnormalities on admission</th>
<th>Complications during follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Two-dimensional echocardiography (n=61)</td>
<td></td>
</tr>
<tr>
<td>Mitral valve prolapse*</td>
<td>5</td>
</tr>
<tr>
<td>Abnormal wall motion</td>
<td>3</td>
</tr>
<tr>
<td>Mitral anulus calcification*</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>9 (14.8%)</td>
</tr>
<tr>
<td>Holter monitoring (n=45)</td>
<td></td>
</tr>
<tr>
<td>Frequent premature ventricular contractions</td>
<td>6</td>
</tr>
<tr>
<td>Intermittent atrial fibrillation</td>
<td>1</td>
</tr>
<tr>
<td>Wandering atrial pacemaker</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>8 (17.7%)</td>
</tr>
<tr>
<td>Twelve-lead electrocardiography</td>
<td>3</td>
</tr>
</tbody>
</table>

Data are number of patients. TIAs, transient ischemic attacks.

*One patient also had premature ventricular contractions on Holter monitoring.
with symptoms lasting 1–5 hours developed complications (IHD in two, stroke in two, TIA in three), and none of three patients with symptoms lasting >5 hours developed complications. There were significantly fewer complications during follow-up in patients with symptoms lasting <½ hour than in patients with symptoms lasting >½ hour (p<0.05).

The influence of the number and type of previous TIAs on the development of complications during follow-up is also shown in Table 2. Overall, patients with one TIA on admission had fewer complications during follow-up than patients with more than one TIA on admission (p<0.01).

No difference in the incidence of complications was observed between patients with hypertension and those with normal blood pressure (p>0.01). Similarly, the incidence of complications in patients with CT-documented cerebral infarction on admission was no different from those with normal CT scans (p>0.01).

The relations of the 2-DE and HM results on admission to the incidence of complications during follow-up is shown in Table 3. Twelve of the 46 patients with normal cardiac findings on admission (26%) developed cardiac (six) or neurologic complications (TIAs in six) during follow-up; 10 of the 18 patients with abnormal cardiac findings (55.5%) developed cardiac (one) or neurologic complications (TIAs in six, stroke in three) (p<0.01).

Discussion

It has long been known that patients with TIAs may have normal angiograms; however, publications of prolonged follow-ups of such patients are rare. Published studies have shown conflicting results, possibly because the number of patients was small and because investigations were limited to blood workup, ECG, electroencephalography, skull x-rays, and nuclear brain scans.

In the report of Marshall and Wilkinson, cardiac evaluation of 64 patients with TIAs and normal angiograms was limited to physical examination and ECG. Only four patients had complete angiography, and in the others angiography was limited to the appropriate side. The occurrence of cerebral infarction in the territory contralateral to the TIA in 50% of the patients, a high incidence of cardiac complications, and the poor prognosis may simply reflect an incomplete evaluation of potentially more diffuse atherosclerosis.

In the report of Toole and Yuson, although no embolic source was found in any of 16 patients with TIAs and normal angiograms followed for 3–8 years, 10 patients were hypertensive, nine had known heart disease, and the cause of death was myocardial infarction in two. Bradshaw and Gumpert reported 45 patients with TIAs and normal angiograms; angiography was restricted to the appropriate side, and cardiac investigations were restricted to chest x-rays and ECG. Prognosis in this study was believed to be related to the presence or absence of hypertension; outcome was good in 80% of the normotensive and in 60% of the hypertensive patients. Five patients had verified strokes during follow-up, and autopsy of one patient with a stroke revealed complete occlusion of the carotid artery contralateral to the TIA. Descriptions of the other four patients with strokes were limited, thus precluding a definite etiology. In more recent studies, prognosis is believed to be somewhat better. Al-Mefty et al. reported 22 patients with TIAs and normal angiograms had no strokes in a 1–5-year follow-up; however, three patients were lost to follow-up. Cardiac investigation included 2-DE and HM when indicated, and workup for collagen diseases produced negative results. Mendelowitz et al. reported 32 patients with normal angiograms among 358 patients with TIAs over 10 years. No patient suffered cerebral infarction during follow-up. In only three of six patients with recurrent "transient cerebral symptoms" was the cause believed to be ischemic. Patients with known cardiac diseases of potential embolic etiology were excluded from the study. Finally, in the review of Poole et al., of 16 patients with amaurosis fugax under the age of 40 years, carotid angiograms were normal in the 10 patients in whom it was performed; all patients were free of cardiac or cerebral disease on follow-up.

Our study of 68 patients, with a mean follow-up of 4.43 years, reveals several important points:

1. Complete cardiac evaluation of patients with TIAs is very important, especially when angiography fails to show any atherosclerosis. Cardiac abnormality frequency may be as high as 54% in studies dealing with TIAs.

2. Patients in whom cardiac findings are abnormal appear to be at increased risk for recurrent TIAs, completed strokes, and IHD. Our study shows an increased relative risk of 2.35 for further events in patients with abnormal cardiac findings (61% vs. 26%). Moreover, all three patients with TIAs who subsequently developed a stroke during follow-up had cardiac abnormalities on admission.

3. Although a small proportion of cases with normal angiograms and normal cardiac findings may continue to have TIAs or may develop cardiac disease or even completed strokes (none in our series), the number of such events is small and these events are usually mild. Only two of our 46 patients with normal cardiac findings developed myocardial infarction during follow-up.

The etiology of TIAs in patients with normal angiograms is not well understood. The quality of the angiogram is important as a poor-quality study would easily miss mild to moderate atheroma. In addition, angiography should be complete, with visualization of all four extracranial vessels. Atherosclerosis may be asymmetric, and its absence from one site does not rule out its presence elsewhere. Moreover, carotid plaque ulcers may occur in mild atheromatous disease and may be potentially embolic. Such small, shallow ulcers can easily be
Missed at angiography. The study of Edwards et al.\textsuperscript{27} of carotid endarterectomy for symptomatic TIA showed two patients with carotid artery ulcers whose angiograms, even in retrospect, were normal. The possibility of dislodgement of the clot or healing of an atheromatous lesion before angiography has also been mentioned in the literature,\textsuperscript{11} and such explanations are understandably difficult to prove. Finally, the aortic arch may be the source of platelet fibrin or cholesterol embolus. This area has been difficult to study accurately radiologically.

Cardiac conditions that may lead to focal neurologic symptoms include valvular defects, wall movement abnormalities, septal defects, and cardiac arrhythmias.\textsuperscript{18,19} In the majority of such cases the underlying mechanism is cardioembolic. Additionally, some reports have implicated cardiac arrhythmias in the production of focal neurologic symptoms by means of regional hypoperfusion. Angiography has usually shown severe carotid atherosclerosis in patients in whom arrhythmia was responsible for the TIA.\textsuperscript{20,21} Hemodynamic focal hypoperfusion as an underlying mechanism in patients with normal angiograms appears very unlikely.

It is important to appreciate the limitations of available cardiac investigations. The sensitivity of 2-DE for diagnosis of thrombus appears to be between 77\%\textsuperscript{22} and 92\%\textsuperscript{23} in patients with ventricular lesions and may be even lower for atrial disease.\textsuperscript{29,30} In addition, 2-DE may be of limited value secondary to technical difficulties in 10–20\% of investigations.\textsuperscript{31} This percentage could possibly be increased if transesophageal echocardiography,\textsuperscript{32} indium-111 scintigraphy,\textsuperscript{33} motorized treadmill testing, and thallium-201 scans\textsuperscript{34} are used in addition to the standard ECG, 2-DE, and HM in patients with TIA and normal angiograms. Other authors have speculated that a patent foramen ovale may predispose a patient to paradoxical embolism, and here again routine cardiac findings are usually normal.\textsuperscript{35,36} Diagnosis is confirmed by contrast echocardiography or cardiac angiography.

Altered coagulation with increased potential for thrombus formation and embolism may cause TIA in the presence of normal angiograms.\textsuperscript{22,23,37} Platelet abnormalities were found in all patients with normal angiograms and TIA in the study of Al-Mefty et al.\textsuperscript{22} Symptoms were improved and platelet coagulation dysfunction was corrected by treatment with aspirin.\textsuperscript{22} In the report of Poole et al.,\textsuperscript{23} among 14 patients with amaurosis fugax platelet hypercoagulability to low concentrations of arachidonic acid and adenosine diphosphate with spontaneous aggregation was seen in four of 10 patients in whom the test was done. We did not assess platelet dysfunction in any of our patients. As similar platelet abnormalities have been reported with atherosclerotic narrowing or occlusion of the carotid arteries\textsuperscript{31,38} and conditions unrelated to atherosclerotic disease,\textsuperscript{39} the significance of such findings remains in doubt.

Patients with normal angiograms and normal cardiac findings who have TIA could resemble patients with completed strokes who had similar findings. The preliminary results of the Stroke Data Bank\textsuperscript{40} show that 20\% of the patients with completed stroke had "infarction, etiology unproven," defined as "no source of embolism, no bruises or prior TIA, normal CT scans beyond 1 week of stroke or normal angiogram within 2 days of stroke, yet a clinical deficit persisted beyond 24 hours even if eventual clinical resolution occurred." The number of patients with infarction, etiology unproven varied among the various participating centers; centers with more aggressive investigative procedures appeared to have the most patients in this group. Mohr and Barnett,\textsuperscript{27} in a study of 713 patients over 2 years, observed 153 (24\%) patients that fit a similar category. The subject of normal findings and stroke was recently reviewed by Mohr and Barnett\textsuperscript{37} in relation to the classification of stroke. These authors believe that such events most likely represent patients with embolic strokes in whom a specific lesion cannot be defined by existing investigations. Moreover, they estimate the recurrence rate of stroke to be as high as 10\%/yr among these patients. TIA with normal findings in all likelihood also fit in a similar subcategory in which a source of the embolic etiology cannot be defined using existing diagnostic techniques.

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