

# Transient ischaemic attacks in young patients: a thromboembolic or migrainous manifestation? A 10 year follow up study of 46 patients

Birgitte Holt Larsen, Per Soelberg Sørensen, Jørgen Marquardsen

## Abstract

**Forty six patients aged 18-39 years with transient ischaemic attacks (TIA) were studied; two thirds were women. Twenty five patients had attacks accompanied by headache, and seven gave a history of common migraine. Only four of 27 angiograms were abnormal; no operable carotid lesion was demonstrated. Over a mean follow up period of 10 years stroke or myocardial infarction (AMI) occurred in all four patients who presented major cerebrovascular risk factors, but in only two of the remaining 42 patients. Thus irrespective of age thromboembolic TIA is a harbinger of stroke or AMI. However, most TIAs under the age of 40 years are caused by a non-embolic benign vascular disorder. The clinical characteristics, long-term prognosis, and possible pathogenesis, for such attacks are often indistinguishable from those of classical migraine. In the absence of cardiovascular risk factors, arteriography does not provide much diagnostic and prognostic information.**

It is generally accepted that the pathogenesis of most cases of TIA is thromboembolism due to atheromatous lesions in the neck vessels or the heart. Other pathogenetic possibilities include non-arteriosclerotic vascular disease, mitral leaflet prolapse, haematological diseases, and abnormal blood pressure fluctuations. Even in series of fully investigated TIA cases, however, there still remains a considerable proportion with no cardiac disease, normal arteriograms, and normal blood pressure.<sup>1</sup> In particular, many young patients belong to this category<sup>2,3</sup> and the prognosis in such cases seems to be favourable.<sup>4-6</sup> It thus appears that some TIAs are caused by a comparatively benign vascular disorder, probably some type of vasomotor disturbance. This raises the question whether such cases are really TIAs in the usual sense of the term, or rather atypical cases of migraine. The differences of opinion concerning this issue are illustrated by the variety of selection criteria used in previous studies of TIA. Some workers excluded all patients with a history of migraine,<sup>7</sup> some only those with recent attacks of classical or complicated migraine,<sup>6,8</sup> others excluded those with attacks associated with certain migrainous features,<sup>4,9</sup> whereas others

still did not state whether suspected subjects with migraine were included or not.<sup>10-12</sup> It is therefore difficult to compare the results obtained in different prognostic studies.

We present the results of a follow up study of a series of young patients who were admitted to hospital because of focal cerebral (or retinal) ischaemic episodes. The aims of the study were: to classify the patients according to pathogenesis; to assess the long-term prognosis in different pathogenetic categories of patients; and to consider the implications of the findings for the management of young TIA patients.

## Patients and methods

The study comprised patients who in the 10 year period 1971-80 were admitted to either of the three participating neurological departments because of a recent TIA. Since some attacks accompanied by headache might have been classified as migraine, we searched the diagnostic indices of the three participating hospitals of all patients who in the above period were discharged with a diagnosis of either TIA or migraine, and who on admission were under 40, but over 18 years of age. We reviewed the records of these patients and selected those whose episodes conformed to the following definition of TIA: an episode of focal neurological dysfunction of presumed vascular origin, with sudden onset and complete recovery within 24 hours.<sup>13</sup> Excluded from the study were: a) patients who had suffered a stroke before the onset of TIA; b) patients with a past history of migraine with aura (classical migraine); c) patients whose recent episode according to the "Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain" would conform with the diagnostic criteria for migraine with aura: "Idiopathic, recurring disorder manifesting with attacks of neurological symptoms unequivocally localisable to cerebral cortex or brain stem, usually developing gradually over five to 20 minutes and usually lasting less than 60 minutes. Headache, nausea and/or photophobia usually follow neurological aura symptoms directly or after a free interval of less than an hour. The headache usually lasts four to 72 hours, but may be completely absent";<sup>14</sup> d) those in whom subsequent examination disclosed an intracranial lesion (such as, tumour, abscess, vascular malformation, encephalitis) as the obvious cause of the symptoms.

Department of  
Neurology,  
Rigshospitalet,  
Copenhagen  
B Holt Larsen

Department of  
Neurology, Bispebjerg  
Hospital, Copenhagen  
P Soelberg Sørensen

Department of  
Neurology, Ålborg  
Hospital, Ålborg,  
Denmark  
J Marquardsen  
(died September 1989)

Correspondence to:  
Dr Holt Larsen,  
Department of Neurology,  
Rigshospitalet, DK-2100  
Copenhagen Ø, Denmark.

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For all eligible patients we recorded data concerning the TIA, any history of migraine, headache disorders, previous diseases and conditions associated with thromboembolic cerebrovascular disease, for example, heart disease, hypertension, peripheral arteriosclerosis, diabetes mellitus, and the use of oral contraceptives. Examination included a full clinical neurological examination, measurement of blood pressure, cardiac evaluation: auscultation of the heart and neck, ECG, chest radiograph, haematological examination, plasma cholesterol and lipids, EEG (in 37 patients) and angiography (mainly direct carotid arteriography) in 27 patients.

Risk factors were defined according to the Stroke Council of the American Heart Association.<sup>15</sup> Special attention was paid to the following: hypertension (160/95 or greater), acute myocardial infarction (AMI) (documented in hospital medical records by accepted clinical symptoms together with typical transaminase pattern or a pathological Q wave or localised ST changes on the ECG), angina pectoris, hyperlipidaemia (plasma triglyceride > 2.20 mmol/l), hypercholesterolaemia (> 8.2 mmol/l) and diabetes mellitus (documented by a physician and treated with insulin, oral antidiabetics, or diet).

The follow up was carried out in 1986. We contacted all survivors, by telephone or mail, thus obtaining information about recurrence of TIA, occurrence of stroke and myocardial infarction, development or progression of other medical conditions, treatment received, and changes in functional status and working capacity. For the deceased patients we consulted hospital records, death certificates, and necropsy reports.

The occurrence of stroke and AMI was estimated by Kaplan-Meier life-table methods.

## Results

Forty six patients met the criteria for admission to the study. They were 14 men and 32 women with a mean age of 29 years (range 18-39 years). All patients had been admitted to hospital within a month after the attack in question. Of the 46 patients 31 had been discharged with a diagnosis of TIA, among them were all six patients with later vascular events; 15 were discharged with a diagnosis of migraine.

### Characteristics of the attacks

According to the information given in the case-notes, the recent TIA had involved the carotid arterial system in 37 patients, and the vertebrobasilar system in nine. The total number of TIAs, the duration and symptoms of the recent TIA and the presence of concomitant headache are listed in table 1. The most common focal symptoms were amaurosis fugax, hemianopia, hemi- or monoparesis, hemisensory symptoms and dysphasia; 35 had a combination of focal symptoms. Only one patient had pure sensory symptoms, and none of the patients reported scintillating scotoma. The

Table 1 Characteristics of the attacks

Symptoms	No of patients
Amaurosis fugax	4
Hemianopia	9
Hemi- or monoparesis	26
Hemisensory symptoms	27
Dysphasia	20
No of attacks	
One attack only	23
2-5 attacks	17
> 5 attacks	4
Insufficient information	2
Duration of symptoms	
< 15 min	9
15-60 min	18
1-24 h	19
Concomitant headache	
No headache	12
Unilateral headache	13
Bilateral headache	12
Insufficient information	9

development of the focal neurological symptoms was instantaneous in 34 patients. In 12 patients the symptoms progressed, but only over one or two minutes, and none of the patients had a gradual development of symptoms over five to 20 minutes, typical of the migraine aura. Headache accompanied the recent attack in 25 patients, of whom four gave a history of migraine without aura (common migraine). The pain quality was usually described as mild to moderate.

### Possible risk factors for cerebrovascular disease

On presentation, one patient suffered from angina pectoris and another from diabetes mellitus as well as from intermittent claudication. Furthermore, among 29 patients examined, hyperlipidaemia was shown in three (one of whom was the patient suffering from diabetes and claudication). We found no cases of hypertension, non-arteriosclerotic heart disease, collagen disease, or blood dyscrasia. Ten of the 34 women used contraceptive pills; six were pregnant.

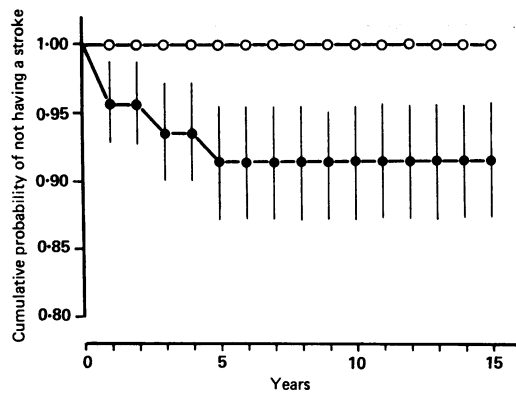
### Migraine

Migraine was reported in the family history of seven patients, and migraine without aura (common migraine) in the personal history of seven (one male, six female). In four of those with migraine the TIA was accompanied by headache, which in some of the cases was reported to differ from the usual migraine headache in being less severe, pressing rather than pulsating, and without nausea. Cerebrovascular risk factors were absent in the migraine patients.

### Clinical and angiographic findings

The neurological examination was normal in all cases. One patient only had a cervical arterial bruit. Hypertension was found in none of the patients. Twenty seven patients had angiograms, mainly obtained by direct carotid arteriography. Only four showed abnormalities, all on the side relevant to the neurological symptoms. One patient had a stenosis at the origin of the internal carotid artery and an occlusion of the carotid siphon. Another had mild arteriosclerotic changes in

Figure 1 Estimated probability of not having a stroke after TIA (●—●) compared with the expected survival without a stroke calculated from the mean annual incidence rates of cerebral infarction in the age group 25–44 years in the period 1977–1982 in Denmark (○—○). Vertical lines indicate SE.



the siphon. One patient had a partial occlusion of the stem of the middle cerebral artery. Finally, one patient, who had amaurosis fugax and a cervical bruit, had a low-grade stenosis of the innominate artery (without any carotid lesion).

**Therapy**

The following types of medical therapy were administered in hospital: none (34 patients); platelet antiaggregants (three patients); anticoagulants (two patients); prophylactic treatment against migraine (seven patients). None of the patients had carotid surgery.

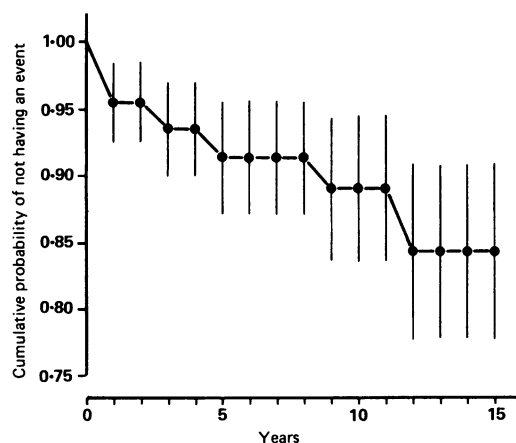
**Follow up and survival**

The follow up period from the time of admission averaged 10 years (range 5 to 15 years). None of the patients was lost to follow up. During the follow up period, covering 492 patient-years, five deaths occurred: two from myocardial infarction (four and 11 years after admission, respectively) and three from non-vascular causes (suicide, accident).

**Vascular events during follow up**

Twenty six patients had no further TIAs, two patients had one, and 15 had two or more episodes. For three of the deceased patients no information about TIA could be obtained. Four patients (three men, one woman) had a stroke, which in every case was a hemispherical infarction affecting the same vascular territory as the original TIA. None was fatal. The mean interval between the primary admission and

Figure 2 Estimated probability of not having a stroke or myocardial infarction (AMI) after TIA. Vertical lines indicate SE.



the stroke was two years. The risk of having a stroke among the TIA patients was compared with the expected stroke rate (fig 1) calculated from the mean annual incidence rates of cerebral infarction in the age group 25–44 among men (16/100 000) and women (15/100 000) in the period 1977–82 in Denmark.<sup>18</sup> Acute myocardial infarction occurred in three patients, all of whom were males. Two of these cases were fatal; one of them was preceded by a stroke. This makes a total of six patients (five males, one female) who had either a stroke or a myocardial infarction, or both. The vascular events occurred one to 11 years after admission (mean five years). None of the patients with presumed vertebrobasilar TIA had stroke or AMI. The cumulative risk of having a stroke or AMI is shown in fig 2.

In addition to the seven patients who on admission had a history of migraine without aura (common migraine), eight developed migraine attacks in the observation period (five migraine without and three with aura). None of the major vascular events occurred in these 15 patients, only 2 of whom were men.

As for the correlation between risk factors, as recorded on admission, and subsequent vascular morbidity and mortality, table 2 shows that four of the six cases of stroke or myocardial infarction occurred in patients with antecedent angina pectoris, peripheral arteriosclerosis or hyperlipidaemia. Of the two patients who had a stroke apparently without preceding vascular disease, one had a normal angiogram. The other patient did not have arteriography, but he had no cervical bruits; the lipid status was not examined.

**Functional status**

At the time of follow up, four patients had been granted disablement pension, in three cases because of rest-symptoms from stroke. In the remaining 42 cases the original functional and social status remained unchanged until follow up or death, except that two patients were unemployed, and two were reported sick.

**Discussion**

Compared with series of middle-aged and elderly TIA patients,<sup>9,16</sup> this series is characterised by a predominance of women, and by a low prevalence of associated cardiovascular disease and arteriographic abnormalities. (Echocardiography was not commonly used at the time that these TIA patients were admitted to hospital). Only four patients, all males, presented any of the traditional risk factors for cerebrovascular disease, and of the 27 angiograms only four showed abnormalities, including one case of carotid stenosis. These findings, which agree with those previously published,<sup>24</sup> suggest that TIA caused by thromboembolism is rare in young people, particularly in women.

Since none of the 46 patients were suspected of having mitral valve prolapse (based on cardiac auscultation), this study cannot shed any light on the problem of whether there is an association between ischaemic attacks and

Table 2 Stroke and myocardial infarction (AMI) during follow up

Pt	Sex/age	Risk factors at entry	Angiogram	Follow up (months)	Vascular events during follow up
1	M/39	Angina	Normal	110	Stroke
2	F/27	None	Not done	144	Stroke
3	M/38	Diabetes Claudication Hyperlipidaemia	Arteriosclerosis of carotid siphon	117	Stroke, AMI
4	M/37	None	Normal	154	Stroke
5	M/35	Hyperlipidaemia	Normal	162	AMI
6	M/37	Hyperlipidaemia	Normal	126	AMI

mitral valve prolapse.<sup>17</sup> The proportion of female patients using oral contraception: 32%, (95% confidence interval: 16–58%) was not significantly higher than the 25% reported in the age-matched female Danish population.<sup>18</sup> The number of pregnant women seemed higher than expected, but again the difference was not significant.

Seven of our patients gave a history of common migraine, and eight more developed migraine. No fewer than 25 patients (63%) had experienced headache in relation to the recent TIA. The latter figure, which is higher than those found in other TIA-series<sup>11,19–21</sup> clearly reflects the differences in pathogenesis of TIA. Unlike most other investigators, we did not exclude patients whose attack was accompanied by headache, unless the episode had certain characteristics of classical migraine, that is, a visual aura or a “march” of focal symptoms developing over five to 20 minutes.<sup>14</sup>

As expected, the long-term prognosis was found to be strongly influenced by the presence or absence of cerebrovascular risk factors. The 15 patients with migraine (12 without, three with aura), whether started before or after admission to the study, had a strikingly good prognosis; no major vascular event occurred over an observation period averaging 10 years. In the non-migraine group the 19 women also fared well, the only vascular event being one stroke, occurring in a 27 year old woman who was neither pregnant nor using contraceptive pills. Hence, in young female TIA patients with or without a history of migraine, the risk of having a stroke does not seem to be different from that of other women of the same age. By contrast, five of the 12 males without migraine suffered either a stroke or a myocardial infarction; four of these five patients presented cardiovascular risk factors at the time of admission. This high morbidity is comparable to that observed in series of elderly TIA patients.<sup>4,22,23</sup>

The prognostic value of the arteriographic findings was small. Only one of the four strokes occurred in a patient who had an abnormal angiogram; this was a 38 year old man (patient 3) who had mild arteriosclerotic changes in the carotid siphon. On the other hand, the only patient with major lesions of the internal carotid artery (extracranial stenosis as well as intracranial occlusion) did not suffer any cerebrovascular accident over an observation period of nearly 11 years.

The results of this study indicate that in most of our patients the cause of the focal episode was not thromboembolism, but vasomotor dis-

turbances. It might of course be argued that the findings merely reflect a “contamination” of the series with cases of migraine masquerading as TIA. The logical consequence of this view would be to restrict the definition of TIA to include only cases “assumed to be due to vascular disease of an arterial embolic or thrombotic kind,” as attempted by the United Kingdom TIA study Group.<sup>24</sup> In this series, however, the clinical characteristics of the focal episodes were similar in patients with and without a history of migraine. Moreover, in some patients migraine with aura (classical migraine) developed several years after the onset of an apparently typical TIA. This seems to indicate that, at least in young people, cases of TIA and those of migraine with aura (classical migraine) are often indistinguishable, probably because of a similar pathogenesis. This is in accordance with the suggestion, recently put forward by Peatfield,<sup>25</sup> that both the migraine aura and TIAs might be associated with micro-emboli following platelet aggregation. According to the theory, a small embolus entering the cerebral micro-circulation may precipitate either a classical migraine attack or a TIA of the ordinary type, the decisive factor being whether or not the patient is inherently susceptible to “spreading cortical depression”. Support for the theory of vasospasm has been produced by recent cerebral blood-flow studies.<sup>26</sup>

It is concluded that most cases of TIA in young people, particularly in women, are not thromboembolic but caused by flow disturbances related to, but not necessarily identical with those seen in migraine with aura.<sup>27</sup> In such patients, many of whom have migraine, the angiograms are nearly always normal, and the long-term prognosis is excellent. In a minority of the young patients, however, TIA is caused by thromboembolism; such cases, being characterised by the presence of cardiovascular risk factors, carry the same high risk of stroke and AMI as that observed in elderly TIA patients. We recommend that, in the management of TIA in young patients, arteriography is performed principally in those patients, mainly males, who present cardiovascular risk factors.

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