A case-control study of transient global amnesia

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SUMMARY To evaluate risk factors and prognosis of transient global amnesia (TGA), three groups of 30 subjects each affected respectively by: (1) first-ever TGA; (2) first-ever transient ischaemic attack (TIA); (3) depressive neurosis, were compared. Prevalence of cerebrovascular risk factors was similar in patients with TGA and TIA, but significantly lower in the third group. CT showed more hypodense lesions in TIA patients than in those with TGA. In a mean follow-up of 36 months, five TGA patients experienced a TIA and three others had recurrence of TGA, but none suffered stroke or myocardial infarction. In the TIA group, four had recurrence of TIA, two suffered a stroke and two others a myocardial infarction, whereas none had TGA attacks. None of the patients of the third group had any ischaemic event during follow-up. The similar prevalence of risk factors, but the different prognosis between TGA and TIA patients, suggest that TGA is an ischaemic event, probably not triggered by thromboembolism but by a different, possibly vasospastic, mechanism.

Although transient global amnesia may occur in association with several morbid conditions,¹⁻⁶ most authors have attributed this syndrome to reversible ischaemia affecting the inferomedial part of the temporal lobes.⁷⁻¹⁰ This view is supported by the high prevalence of cerebrovascular risk factors often observed in these patients.^{11,12} However, most studies lacked data from suitable control groups.

A recent case study of TGA concluded that this condition is closely linked to cerebrovascular disease, but its results were probably influenced by the unusually frequent prevalence of previous cerebrovascular attacks in the series.¹³

The prognosis of TGA is generally considered benign as most authors report a favourable long-term outcome in these patients.¹⁴⁻¹⁶ This fact is at variance with the assumption that TGA is a manifestation of cerebrovascular ischaemia, which carries a serious prognosis.

To determine the prevalence of cerebrovascular risk factors and the prognosis of TGA, we studied a series of patients with this condition, and compared them with a group of patients with their first TIA and with another group with only minor psychiatric symptoms.

Patients and methods

From June 1979 to May 1986 we observed a consecutive series of 30 patients presenting with their first-ever attack of TGA. All these patients were seen during the TGA attack at the emergency room by a member of our neurological staff. Strict criteria were adopted for diagnosis, namely: spontaneous acute onset of recent memory loss; preservation of consciousness and identity; demonstrated inability to retain new memories; regression of symptoms within 24 hours, with only persistent amnesia for the period of the attack. No patient had focal neurological deficits during TGA event. Patients with a history of recent head trauma, alcohol or drug intoxication, or psychosis were excluded from the study, whereas patients with previous TIA and stroke were not excluded. All patients underwent neurological and cardiological examinations as well as routine blood tests, ECG, EEG, continuous-wave (CW) Doppler study and CT.

The events and the patients' activities just antedating the TGA attack were recorded. In all patients a prospective follow-up was conducted by the same neurologists who observed the patients during the TGA attack, until June 1987.

Control groups

The (Group 1) patients were compared with two other groups of age- (± 3 years) and sex-matched patients affected by transient ischaemic attacks (Group 2) or by depressive neurosis (Group 3), the latter diagnosed according to criteria consistent with DSM III.¹⁷

Group 2 patients had experienced their first-ever TIA within the previous month. Transient ischaemic attacks were

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defined as a period of focal cerebral dysfunction produced by ischaemic vascular mechanisms, lasting less than 24 hours. Diagnosis of arterial territory distribution followed established criteria.¹⁸

Those of the third group were outpatients, and the chronic depressive disorder was defined "minor". They were not selected on the basis of previous TIA or TGA episodes. This fact makes these subjects representative of the general population as far as it concerns the risk of cerebrovascular disease. The presence or absence of cerebrovascular risk factors was assessed as follows: (1) hypertension: the repeated finding of systolic blood pressure higher than 160 mm Hg, diastolic blood pressure more than 90 mm Hg, or regular use of antihypertensive drugs; (2) hyperlipidaemia: fasting serum cholesterol over 215 mg/dl or triglycerides higher than 170 mg/dl (the 90th percentiles of a control population in our laboratory); (3) diabetes mellitus: fasting blood sugar higher than 140 mg/dl or therapy with hypoglycaemic drugs; (4) smoking: more than 10 cigarettes daily; and (5) cardiac disease: past or present evidence of ischaemic heart disease, heart failure, significant dysrhythmias, valvular disease.

In the two control groups, case histories were collected and the same clinical tests done, except for CW-Doppler, EEG and CT, which were not performed in Group 3.

All control patients were also followed-up, and particular attention was paid to occurrence of cerebral ischaemia, myocardial infarction or TGA.

Treatments assigned to the three groups were also recorded.

Statistical analysis

To analyse the prevalence of risk factors, odds ratio were calculated, and their confidence limits following the Miettinen procedure.¹⁹ The significance test of odds ratio were calculated by the chi-square for two by two table.

The frequency of detectable abnormalities demonstrated by CT in the three groups was compared using the chi-square, whereas to evaluate the time of onset of events during follow-up, product-limit survival curves were produced; and their significance tested by the log-rank test.²⁰

Table 2 CT results

	Normal	Hypodensity
Group 1 (TGA)	29 (96.7%)	1 (3.3%)
Group 2 (TIA)	23 (76.7%)	7 (23.3%)
Group 3 (depressive neurosis)	not done	

$$\chi^2 = 5.192 \quad p < 0.05$$

Results

Group 1 (TGA)

Patients' age ranged from 42 to 81 years (mean: 60.4). 13 were males (43%), with a mean age of 56.5 years, and 17 females (mean age: 63.7).

History. Most patients were in good health at the time of their TGA. Three subjects had experienced previous TIA in the carotid territory, Four suffered from migraine, none had epilepsy. 27 patients (90%) had one or more risk factors for cerebrovascular disease (table 1).

Factors potentially triggering TGA attack were identified in 26 patients; 21 had their episode during exertion, whereas five during emotional stress.

Clinical and instrumental findings. Neurological examination was normal in all patients after their attack. EEG was normal in 28 (93%), and in two cases it showed left temporal slow waves, without epileptic discharges.

CT (table 2) was normal in 28 cases (93%); in one patient it demonstrated a right deep hemispheric hypodensity, and in another diffuse cerebral atrophy. These two patients had no history of previous TIA, or of migraine.

CW-Doppler examination revealed absence of haemodynamically significant stenoses in all patients.

Outcome. Within a mean follow-up of 39.6 months

Table 1 Cerebrovascular risk factors. Odds ratio and 95% confidence limits

	Group 1 (n = 30)	Group 2 (n = 30)	Group 3 (n = 30)	Odds ratio Group 1 vs 2	Odds ratio Group 1 vs 3
Hypertension	14	14	5	1 (-----) p = 1	4.37 (1.37 - 13.93) p = 0.013
Smoking	8	8	3	1 (-----) p = 1	3.27 (0.81 - 13.17) p = 0.1
Hyperlipidemia	10	9	5	1.16 (0.39 - 3.46) p = 0.78	2.5 (0.75 - 8.34) p = 0.14
Diabetes mellitus	3	8	1	0.30 (0.07 - 1.23) p = 0.1	3.22 (0.35 - 29.53) p = 0.30
Cardiopathy	7	11	1	0.52 (0.17 - 1.60) p = 0.26	8.8 (1.35 - 57.44) p = 0.02

Table 3 Results of survival curve analysis

	Group 1 (TGA)	vs Group 2 (TIA)
TIA	$\chi^2 = 0.10$	(p = n.s.)
"Major" ischaemic events (stroke and myocardial infarction)	$\chi^2 = 4.400$	(p < 0.04)
TGA	$\chi^2 = 2.809$	(p = n.s.)

(range: 13–96), 22 patients (73%) remained asymptomatic. Five patients (16%) presented TIAs, four in the carotid artery territory (three had single attack, whereas one had multiple episodes), and one in the vertebrobasilar territory.

None of the patients with previous TIA developed TGA or any ischaemic attack during the follow-up.

Two patients with TIA had suffered previous TIAs in the same territory. Three patients (10%) had recurrence of TGA, but none experienced stroke or myocardial infarction, and none died during follow-up.

Group 2 (TIA)

None of these subjects had a history of previous TGA. Twenty-nine patients had at least one cerebrovascular risk factor (table 1).

Eleven patients had their attacks in a carotid artery distribution, 13 in the vertebrobasilar territory, whereas the distribution of the attack remained undetermined in six cases.

CT was normal in 23 cases (77%), whereas it demonstrated hypodense hemispheric lesions in seven patients.

Among patients with carotid territory attacks, six had ipsilateral stenosis on CW-Doppler examination. No lesions were found in the other patients. Angiography was performed in 16 patients, and in all cases it confirmed the Doppler findings, without false positives or negatives.

Outcome. Within a mean follow-up of 36 months (range: 12–80), 22 patients (73%) remained asymptomatic. Four patients had recurrence of TIA, two (7%) had a stroke in the previously symptomatic carotid territory, and two others (7%) had a myocardial infarction. No patients had TGA during follow-up. No patients died during follow-up.

Group 3 (Depressive neurosis)

None of these patients had a previous history of ischaemic cerebral attacks. 14 (47%) presented at least one atherosclerotic risk factor (table 1).

Outcome. In a mean follow-up of 35 months (range: 12–68), no patients experienced cerebrovascular attacks, myocardial infarction or TGA. All patients were alive at the end of the follow-up.

Discussion

In this study we have compared a consecutive series of patients with first TGA episode with a group of patients with definite transient cerebral ischaemia and with a third group of subjects representative of the general population as far as concerns their risk of cerebrovascular disease. Accordingly, in TGA patients we have found a low incidence of prior cerebrovascular episodes, as reported in most studies,^{4 20 21} although it was at variance with data from other reports, which could have selected their patients in some way.

Nonetheless our results show that patients with TGA have a prevalence of risk factors similar to those with TIA, and different from the third group (depressive neurosis). On the contrary, the prognosis in TGA patients were similar to those with depressive neurosis regarding major vascular events, but different from the TIA group. These data are in agreement with those reported in the series of patients with "pure" TGA,^{14 21} without associated neurological sign.

On the other hand, 17% of TGA patients experienced TIA during follow-up, and 10% had recurrence of TGA. These findings may offer some clue as to the pathogenesis of TGA, since the high incidence of TIAs during follow-up (slightly higher than in the TIA group) suggests a further link between this condition and an ischaemic pathogenesis.

One possible explanation of the apparent paradox of the absence of "serious" episodes, as opposed to a "normal" incidence of transitory events, is that TGA represents an ischaemic episode not caused by vascular occlusion due to microemboli arising from atheromatous lesions. To support this, negative angiographic and Duplex examinations^{22 23} are often seen in TGA; and also in our patients all the Doppler examinations excluded stenotic lesions. In agreement with this, we have observed a similar prognosis, characterised by the recurrence of TIA but not of stroke or myocardial infarction, in a group of patients with reversible ischaemic attacks and completely negative angiograms.²⁴

An alternative cause of ischaemia might be a vasomotor disturbance, and this hypothesis, suggested in the past, has been recently taken up again by Hinge *et al*¹⁴ on the basis of the favourable prognosis observed in a large study of TGA cases.

Moreover, this pathogenetic hypothesis is supported by the often-reported association between TGA and migraine.^{25–27} Unlike migraine, which is prevalent in young adults, the occurrence of TGA in elderly patients with cerebrovascular risk factors would suggest that vasomotor phenomena may give rise to TGA in the presence of some impairment of cerebral circulation, probably involving microvessels. In fact,

the elevated presence of risk factors for atherosclerosis leads one to hypothesise a vascular involvement, even if the large arteries are not affected as shown by our CW-Doppler results.

Even taking into account that the population examined here was not as large as that in other studies on TGA, we hold that the homogeneity of the groups studied and the statistical significance obtained give our results reliability and legitimise several points made.

In conclusion, the occurrence of a TGA episode without other neurological deficit in patients without histories of vascular pathology should be considered benign and does not seem to warrant antithrombotic therapy, even if an eventual reassessment of atherosclerotic risk factors may appear appropriate.

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