

Long-term risk of stroke after transient global amnesia in two prospective cohorts

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ABSTRACT

Objective: Transient global amnesia (TGA) is known as a benign syndrome, but recent data from neuroradiological studies support an ischaemic aetiology in some cases, which might suggest an increased susceptibility to cerebrovascular events. We determined the long-term risk of stroke after a first TGA in two independent prospective cohorts.

Methods: In two independent prospective cohorts of patients with TGA (Oxford Vascular Study - OXVASC, population-based; Northern Umbria cohort (NU), TGA registry), cardiovascular risk factors and long-term outcomes including stroke and major cardiovascular events were identified on follow-up. Cardiovascular risk factors were treated according to primary prevention guidelines. In OXVASC, the age/sex-adjusted risk of stroke during follow-up was compared with that expected from the rate in the underlying study population.

Results: Among 525 patients with TGA (425 NU, 100 OXVASC), mean (SD) age was 65.1 (9.5) years and 42.5% male. Hypertension (58.1%), dyslipidemia (40.4%) and smoking (36.4%) were the most frequent cardiovascular risk factors. The risk of stroke was similar in the two cohorts, with a pooled annual risk of 0.6% (95%CI 0.4-0.9) and a 5-year cumulative risk of 2.7% (1.1-4.3). Moreover, the stroke risk in OXVASC cases was no greater than that expected in the underlying study population (adjusted-RR=0.73, 0.12-4.54, p=0.74).

Conclusion: TGA does not carry an increased risk of stroke, at least when cardiovascular risk factors are treated according to primary prevention guidelines.

Background

Transient global amnesia (TGA) is characterised by sudden onset of anterograde amnesia lasting up to 24 hours and is commonly considered as a benign syndrome.^{1,2} Although TGA was first described in 1964, its cause is still uncertain. One of the main hypotheses on the pathogenesis of TGA is arterial ischaemia,^{3–5} which is supported by recent neuroimaging studies using diffusion- and perfusion-weighted imaging techniques,^{3,5,6} suggesting that patients with TGA may have an increased susceptibility to cerebrovascular events. However, clinical studies looking at risk of stroke after TGA have reported conflicting results.^{7–11} Whilst some studies suggested that up to 46% of TGA patients had stroke during a follow-up of 2-7 years,^{8,12} other studies found no increased long-term risks of stroke after TGA compared to healthy controls, or patients with migraine or seizures.^{10,11} No study compared the absolute risks of stroke after TGA to the expected risks of the underlying general population.

Using data from two independent prospective cohorts of TGA patients, we therefore aimed to determine the risks of stroke and major cardiovascular events during long-term follow-up and to compare the risks to those expected based on the underlying general population event rates.

Methods

Consecutive patients with first-in-study-period TGA from two independent prospective cohorts (2002-2018) were analysed, which included a population-based study of TGA, transient ischaemic attack (TIA) and stroke in Oxfordshire, UK (Oxford Vascular Study – OXVASC)¹³ and a hospital-based TGA registry in Northern Umbria, Italy (Northern Umbria Study –NU). Both protocols were approved by the local research ethics committees (OXVASC-OREC A:05/Q1604/70, NU-CEAS:12976).

In both OXVASC and NU, patients with suspected TGA were assessed as soon as possible by study physicians and standard clinical diagnostic criteria for TGA were used.² Demographic data, previous medical history and clinical features of the presenting episode were collected from face-to-face interview and validated from medical records. Patients were treated according to primary prevention guidelines for vascular risk factors identified.

All patients were followed-up by a combination of face-to-face interview, telephone interview, electronic records and administrative follow-up to identify any stroke, major cardiovascular events (MaCE), recurrent TGA, seizure/epilepsy or death. Stroke is defined as rapidly developing clinical symptoms and/or signs of focal, and at time global (applied to patients in deep coma and to those with subarachnoid haemorrhage), loss of brain function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.¹⁸ Major cardiovascular events (MaCE) included a composite outcome of nonfatal stroke, or nonfatal acute coronary syndrome (myocardial infarction -MI- with or without ST-segment elevation or unstable angina followed by urgent catheterisation), or death from cardiovascular causes.

Statistical analysis

Continuous variables are presented as means and standard deviation (SD) and categorical variables as number and percentage. Kaplan-Meier survival analyses were used to present the time-course and risks of vascular events during follow-up, censored at death or October 31st Oct 2018. We also calculated the annual rates of MaCE, stroke, MI, cardiovascular death, recurrent TGA and seizure/epilepsy using Poisson distribution. In OXVASC, the risk of stroke after TGA was also compared with the expected risk of the OXVASC underlying study population adjusting for age and sex using data on stroke incidence rates from the ongoing contemporaneous population-based incidence study. All statistical analyses were carried out using SPSS 25.0.

Results

Overall, 525 patients were included (425 NU, 100 OXVASC). The mean age at event was 65.1 ± 9.5 years, and 42.5% were male (table 1). Hypertension was the most frequent cardiovascular risk factor (58.1%; table 1), followed by dyslipidemia (40.4%; table 1) and smoking (36.4%; table 1). Of all 525 patients, 67 (12.8%) were on antithrombotic treatment before the TGA, 240 (45.7%) were on antihypertensive treatment and 75 (14.3%) were on a statin prior to the event. At discharge, antihypertensive treatment was initiated in 115 patients and statin was started in 74 patients (table 1).

During a follow-up of 3905 patient-years, there were 46 MaCE, 24 strokes, 39 recurrent TGA and 6 seizure/epilepsy (table 2). The annual rate for any major cardiovascular event (MaCE) was 1.3% (95%CI 0.9-1.6; table 2), with a 5-year cumulative risk of 4.9% (95%CI 2.7-7.1). The risk of stroke was similar in the two cohorts ($p=0.21$), with a pooled annual risk of 0.6% (95%CI 0.4-0.9; table 2) and a 5-year cumulative risk of 2.7% (95%CI 1.1-4.3; figure 1). The results were also consistent in analyses stratified by use of antithrombotic treatment, antihypertensive treatment or statin (supplementary table). Moreover, the stroke risk in OXVASC cases was no greater than that expected in the underlying general population in OXVASC (adjusted-RR=0.73, 0.12-4.54, $p=0.74$). Similarly, risks of recurrent TGA or seizure/epilepsy were also low following a TGA event (table 2).

Discussion

We showed in two independent contemporary studies that TGA does not carry an increased risk of stroke or major cardiovascular events, at least when any coincidental cardiovascular risk factors are treated according to primary prevention guidelines. They also have very low risk of seizure/epilepsy.

Our finding that TGA was not associated with an increased risk of stroke is consistent with a previous nested case-control study which also found no difference in stroke risk between 221 patients with TGA vs. 221 age/sex-matched healthy controls,¹¹ although absolute risks of stroke were not reported in this study. The absolute annual stroke risk of 0.6% in our study was consistent with the 1-year estimate of 0.54% reported in a recent retrospective study.¹⁰ Our estimates are however much lower than reported from old case-control studies in the 1990s,^{8,12} which perhaps reflects the overall improvement in primary prevention for cardiovascular disease in the last 3 decades.

Our results have implications, particularly in relation to regulations/policies for driving or piloting after TGA. In the UK, the Driver and Vehicle Licensing Agency (DVLA) requires appropriate investigations to exclude seizure after a brief episodes of amnesia (<https://www.gov.uk/transient-global-amnesia-and-driving>) and the absolute risks for seizure and stroke have implications on if a bus, coach or lorry driver can resume driving after TGA. Similarly, the Civil Aviation Authorities requires the individual to have an event-free time of up to 12-month after TGA before applying for recertification (<https://www.caa.co.uk>; www.faa.gov). We found that risk of stroke after a TGA was no greater than the expected risk in the general population matched for age and sex. Moreover, the annual rate of seizure/epilepsy was only 0.2%. Therefore our data suggest that TGA should not be regarded as a risk factor for stroke or seizure/epilepsy and future regulations/policies should take into account these risk estimates.

Limitations of the study

This study has some limitations. First, we cannot be completely certain that we identified all cases of TGA in the underlying population of the two cohorts. However, the inclusive nature of the NU-registry and the population-based nature of OXVASC would minimise any potential selection bias. Secondly, clinicians tended to treat all cardiovascular risk factors both in the OXVASC and NU TGA cohorts, which might have contributed to the very low stroke risk during follow-up. However, no difference in risk of stroke was found in analyses stratified by use of preventative medication.

Conclusion

In conclusion, we found that TGA does not carry an increased risk of stroke or major cardiovascular events, at least when cardiovascular risk factors are treated. Our findings reiterate the benign vascular prognosis of TGA and do not support the hypothesis of an increased cerebral susceptibility to ischaemia.

Declaration of interests

No competing interest to be reported.

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Table 1. Demographic data and prevalence of cardiovascular risk factors of the combined TGA cohorts

	TGA (n=525)
Age at event (mean±SD)	65.1 ± 9.5
Male sex	223 (42.5%)
Clinical presentation	
Memory deficit duration (h) (mean ± SD)	4.4 ± 4.7
Wake-up onset	60 (11.4%)
Patchy recollection of memory disturbances	63 (12.0%)
Retrograde amnesia	248 (47.2%)
Cardiovascular risk factors	
Hypertension	305 (58.1%)
Dyslipidemia	212 (40.4%)
Smoking	191 (36.4%)
Premorbid medication	
Antihypertensive drug	240 (45.7%)
Statins	75 (14.3%)
Medication at discharge	
Antihypertensive drug	355 (67.6%)
Statins	149 (28.4%)

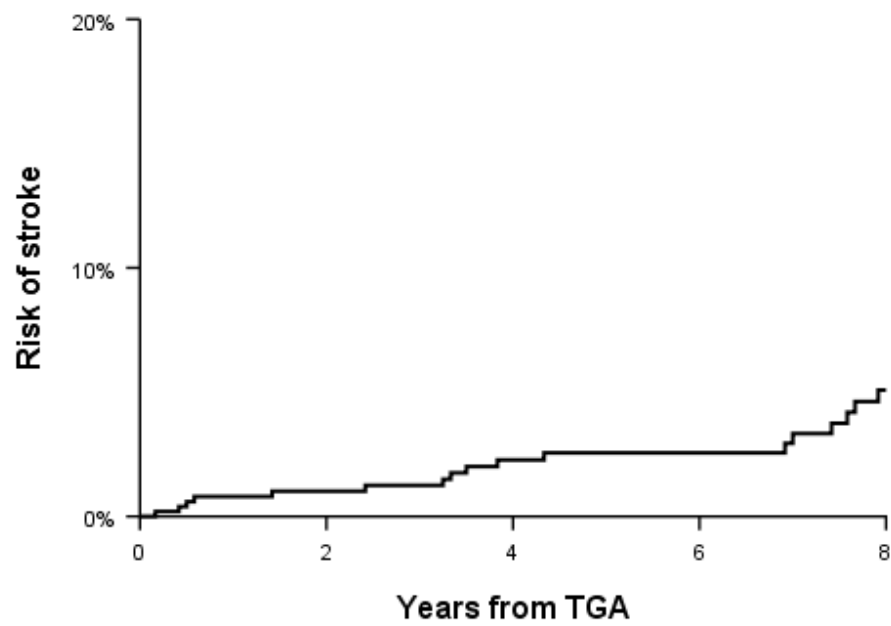
Numbers are presented as number (%) unless otherwise stated.

Table 2. Annual rates for vascular event in the combined TGA cohorts

Outcome	Number of events	Patient-years	Annual rate (95% CI)
Major cardiovascular event	46	3645	1.3 (0.9-1.6)
Myocardial infarction	19	3819	0.5 (0.3-0.7)
Stroke	24	3768	0.6 (0.4-0.9)
Cardiovascular death	14	3902	0.4 (0.2-0.5)
Seizure/Epilepsy	6	3898	0.2 (0.0-0.3)
TGA recurrence	39	3723	1.0 (0.7-1.4)

TGA=transient global amnesia.

Figure 1. Long-term risk of stroke after TGA in the Oxford Vascular Study and the Northern Umbria Study combined



Supplementary table 1 Demographic data and prevalence of cardiovascular risk factors in the Oxford Vascular Study (OXVASC) and the Northern Umbria Study (NU)

	NU (n=425)	OXVASC (n=100)
Age at event (mean±SD)	64.4 ± 9.5	68.2 ± 8.9
Male sex	174 (40.9)	49 (49.0)
Clinical presentation		
Wake-up onset	46 (10.8)	14 (14.0)
Patchy recollection of memory disturbances	45 (10.6)	18 (18.0)
Retrograde amnesia	201 (47.3)	47 (47.0)
Cardiovascular risk factors		
Hypertension	257 (60.5)	48 (48.0)
Dyslipidemia	178 (41.9)	34 (34.0)
Smoking	150 (35.3)	41 (41.0)
Premorbid medication		
Antihypertensive drug	196 (46.1)	44 (44.0)
Statins	49 (11.5)	26 (26.0)
Medication at discharge		
Antihypertensive drug	290 (68.2)	65 (65.0)
Statins	101 (23.8)	48 (48.0)

Numbers are presented as number (%) unless otherwise stated.

Supplementary table 2 Risks of major cardiovascular event or stroke stratified by the two cohorts and by the use of preventative drugs at discharge

	NU cohort (n=425)						OXVASC (n=100)					
	Antithrombotics		Antihypertensives		Lipid-lowering		Antithrombotics		Antihypertensives		Lipid-lowering	
	no (n=254)	yes (n=171)	no (n=135)	yes (n=290)	no (n=324)	yes (n=101)	no (n=54)	yes (n=46)	no (n=35)	yes (n=65)	no (n=52)	yes (n=48)
Major cardiovascular event	17 (6.7%)	21 (12.3%)*	11 (8.1%)	27 (9.3%)	32 (9.9%)	6 (5.9%)	3 (5.6%)	5 (10.9%)	2 (5.7%)	6 (9.2%)	3 (5.8%)	5 (10.4%)
Stroke	11 (4.3%)	11 (6.4%)	6 (4.4%)	16 (5.5%)	16 (4.9%)	6 (5.9%)	1 (1.9%)	1 (2.2%)	0 (0%)	2 (3.1%)	0 (0%)	2 (4.2%)

*p<.05