Royal College of Surgeons
ADVANCING SURGICAL CARE

VASCULAR SURGERY

Ann R Coll Surg Engl 2019; **101:** 579–583
doi 10.1308/rcsann.2019.0071

Carotid artery stenosis, an underestimated cause of stroke recurrence in patients with ischaemic monocular visual loss

SF Cheng[1,2], A Zarkali[3], T Richards[1,2], R Simister[3], A Chandratheva[3]

[1]Department of Vascular Surgery, University College Hospital NHS Trust, London, UK
[2]Division of Surgery and Interventional Science, University College London, UK
[3]Department of Stroke, University College Hospital NHS Trust, London, UK

ABSTRACT

INTRODUCTION Isolated monocular ischaemic events are thought to be low risk for stroke recurrence. In the presence of carotid stenosis however, the risks should not be treated similarly and surgical intervention should be considered at an early stage. The aim of this study was to determine the vascular risk profile and stroke recurrence in patients with ischaemic monocular visual loss.

METHODS AND METHODS Consecutive records for all patients with monocular ischaemia were reviewed from January 2014 to October 2016. Stroke, transient ischaemic attack or monocular ischaemia recurrence within 90 days were recorded. Carotid stenosis was assessed with duplex ultrasound, computed tomography or magnetic resonance angiography.

RESULTS In total, 400 patients presented with monocular ischaemia; 391 had carotid imaging (97.8%). Causality was symptomatic carotid stenosis ≥ 50% in 53 (13.6%), including carotid stenosis ≥ 70% in 31 (7.9%). Patients with permanent visual loss (n = 131) were more likely to have significant stenosis compared with patients with transient visual loss (n = 260), 19.8% compared with 10.4% (P = 0.012). Recurrent stroke, transient ischaemic attack or monocular ischaemia within 90 days after presentation occurred in three patients (5.7%) in the carotid stenosis group, compared to three (0.9%) who did not have stenosis (P = 0.035). Age, male sex and hypertension were associated with carotid stenosis but hypercholesterolaemia, diabetes and smoking were not.

CONCLUSIONS Carotid stenosis ≥ 50% is present in patients with ocular ischaemia in approximately 20% of those with persistent visual loss and in 10% with transient visual loss. Those with carotid stenosis have a higher risk of stroke recurrence and should be considered urgent surgical intervention as other forms of stroke.

KEYWORDS

Carotid stenosis: Carotid endarterectomy – Stroke – Amaurosis fugax – Monocular blindness

Accepted 21 April 2019

CORRESPONDENCE TO

Suk F Cheng, E: amanda.cheng@nhs.net

Introduction

Ischaemic monocular visual loss is defined as a sudden visual loss in one eye, lasting for seconds to hours.[1,2] It is often known as amaurosis fugax or transient monocular blindness, or retinal artery occlusion if it lasts for more than one day.[2–4] The causes are similar to those with ischaemic stroke, and are often classified according to the TOAST classification.[5] Carotid artery stenosis is a common and a surgically treatable cause. Carotid endarterectomy, or carotid stenting, is an effective method to reduce the risk of ischaemic stroke.[6]

The risk of recurrent stroke after a cerebral transient ischaemic attack (TIA) is reported 12% at 90 days after onset of symptoms.[7] With initial treatment after assessment, the risk falls to 2% at 90 days.[8] Risk stratification for stroke recurrence in TIA is often done by using the ABCD2 scoring system, which includes the age of the patient, blood pressure, clinical features of focal weakness, speech or visual impairment, duration of the symptoms and presence of diabetes.[9,10] Patients with an isolated monocular ischaemia have been described as having a lower risk of future stroke compared with cerebral TIA in several studies.[11–13] In the presence of carotid stenosis in monocular ischaemia, however, these risks should not be managed similarly. In the current National Institute for Health and Care Excellence guidelines for TIA management, it is suggested that patients with a low risk of recurrent stroke based on an ABCD2 score less than four should be seen within one week of onset by a specialist stroke team.[14] In the case of a patient with low risk for stroke recurrence

and an undiscovered symptomatic carotid stenosis, this could delay urgent carotid revascularisation.

In University College London Hospitals, stroke care is supported by a TIA walk-in clinic. This is a daily service where adult patients with a recent suspected TIA are referred to by their general practitioner or other referring doctor and seen on the same day by a stroke physician. This TIA clinic is the regional referral centre for North-Central London and Moorfields Eye Hospital in London. The clinic, therefore, represents a comprehensive adult population above the age of 17 years, aiming to assess the vascular risk profile and the prevalence of carotid stenosis in patients with monocular visual loss.

In this study, we aimed to determine the prevalence of carotid stenosis as the cause of ischaemic monocular visual loss. We also determined the vascular risk factors in patients with carotid stenosis and carotid stenosis as a predictor for stroke recurrence.

Materials and methods

Setting and patient selection

All consecutive patients with the diagnosis of transient monocular visual loss (TMVL) or persistent monocular visual loss (PMVL) presented at the TIA clinic in University College London Hospital from January 2014 to October 2016 were retrospectively reviewed using electronical medical records. The diagnosis of TMVL and PMVL was confirmed by a stroke consultant and defined as monocular visual loss of vascular of origin for less than 24 hours (TMVL) or more than 24 hours (PMVL). To capture patients with an isolated monocular ischaemia, we excluded patients with a cortical infarct on brain imaging (computed tomography or magnetic resonance imaging). Moorfields Eye Hospital in London is the main referral pathway for patients presenting with visual loss, where patients received a comprehensive ophthalmological assessment prior to presenting to us. Thus, other ocular causes than a vascular origin were excluded prior to referral to the TIA clinic. All patients diagnosed with monocular ischaemia were started on antiplatelet therapy and were initiated treatment for vascular risk factors if necessary, including starting statins or antihypertensive therapy, or referral for diabetic glucose control. Patients who were seen more than once were only included once. Patients were excluded from the final analysis if no carotid artery imaging examination was performed.

This observational study was registered with the local hospital stroke audit database for observational studies. Owing to its observational design, it was not necessary to obtain informed consent from the patients. All data were anonymised by two investigators (SC and AZ), who also ensured confidentiality under their professional standards and employment requirements. This study was completed in accordance with the Helsinki Declaration as revised in 2013.

Data sources

Patient demographics and the presence of vascular risk factors, including hypertension, diabetes, hypercholesterolaemia, history of smoking, previous ischaemic heart disease, previous ischaemic stroke or TIA, previous TMVL or PMVL and atrial fibrillation, were collected from patients' medical records. Hypertension was defined as a blood pressure of ≥ 140/90 mmHg in clinic, a past medical history or taking antihypertensives prior to clinic visit. Diabetes was defined as a HbA1C level ≥ 48 mmol/l in clinic, a past medical history or treatment for diabetes prior to clinic. Hypercholesterolaemia was defined as a total cholesterol of ≥ 5 mmol/l or low-density lipoprotein (LDL) ≥ 3 mmol/l, a past medical history or lipid-lowering treatment prior to clinic. The presence of significant carotid stenosis on carotid imaging studies with duplex ultrasound, computed tomography angiography (CTA) or magnetic resonance angiography (MRA), was collected.

If the patient had more than one carotid imaging modality with a discrepancy in the degree of stenosis between modalities, the average degree of stenosis between the modalities was used in the analysis. All carotid duplex ultrasound scans were performed by qualified clinical vascular scientists. The degree of stenosis of the internal carotid artery and the common carotid artery was defined according to standard velocity criteria based on the following criteria: moderate carotid stenosis was defined as a peak systolic velocity (PSV) greater than 1.25 m/s and PSV ratio of greater than 2, severe carotid stenosis as a PSV of greater than 2.30 m/s and PSV ratio of greater than 4, and very severe carotid stenosis as a PSV of greater than 4.00 m/s and PSV ratio of greater than 5. Total occlusion of the internal carotid or common carotid arteries was diagnosed when there was no identifiable patent lumen on greyscale B-mode imaging, and no detectable flow using spectral, power and colour Doppler ultrasound. The degree of stenosis on CTA or MRA was reported by a qualified neuroradiologist and measured according to the North American Symptomatic Carotid Endarterectomy Trial criteria.[15,16] Outcome variables included stroke, TIA or ischaemic monocular visual loss recurrences within 90 days and were evaluated by the stroke consultant who attended the TIA clinic on the day. Recurrences within 90 days was recorded to ensure that data for the specified period were available for all included patients. To avoid underestimates in the recurrence rate, we also included recurrent events occurred prior to the patient's assessment in clinic.

Statistical methods

The prevalence of ipsilateral carotid stenosis was estimated using the normal approximation to calculate the standard error. Univariate analyses (Mann–Whitney U test for continuous data and chi square test or Fisher's exact test for dichotomous data) were used to evaluate factors associated with carotid stenosis ≥ 50%. The effect of the vascular risk factors on the presence of recurrences were analysed using univariate and multivariate logistic

regression. The results are presented as *P*-values, 95% confidence intervals and odd ratios. *P*-values less than 0.05 were considered statistically significant for all analyses. Statistical analysis was performed using IBM SPSS version 25.

Results

In total, 400 patients presented with an isolated, ischaemic monocular visual loss. The mean age was 64.5 years (standard deviation, SD, 15.1, range 18–94 years) and 224 were male (56.0%). The carotid arteries were assessed on significant stenosis in 391 (97.8%) of the patients. Only these patients were included for further analysis. TMVL was diagnosed in 260 (66.5%) patients, and 131 (33.5%) patients presented with PMVL with symptoms lasting more than 24 hours (Table 1). Patients with PMVL were more likely to be male, to have diabetes, hypertension and a history of ischaemic heart disease compared to patients with TMVL.

Carotid artery stenosis and presence of vascular risk factors

The overall prevalence of ipsilateral carotid stenosis ≥ 50% in patients with monocular ischaemia was 13.6% (53 patients; 95% CI 10.5–17.3) and more common in patients with PMVL compared with TMVL (19.8% vs 10.4%, P = 0.012). Ipsilateral carotid stenosis ≥ 70% was present in 7.9% (31 patients; 95% CI 5.6–11.0). Twenty-one patients had carotid stenosis ≥ 50% on the contralateral asymptomatic side (5.4%), and twelve patients (3.1%) had bilateral ≥ 50% carotid stenosis. Patients with significant carotid stenosis were found to be more commonly male (71.7%) and have a history of hypertension (71.7%; Table 2). The median ABCD2 score of the whole patient population was 2 (range 0–5) and the median ABCD2 score of patients with carotid stenosis was 3 (range 0–5). Nineteen patients underwent carotid endarterectomy. Of those with ≥ 70% carotid stenosis who did not undergo carotid endarterectomy, four had an occlusion, two were enrolled in the Second European Carotid Surgery Trial (ECST-2) and six declined surgery. The ECST-2 trial is an international, randomised controlled trial, enrolling patients with significant carotid stenosis with a low risk of future ipsilateral stroke (a carotid artery risk score of < 20%).[17] This study randomises patients to optimised medical treatment alone compared with carotid revascularisation in combination with optimised medical treatment. None of the patients had carotid artery stenting.

Recurrent ischaemic events

In total, there were six patients who had a recurrent ischaemic event within 90 days after presenting to the TIA clinic. Two patients had a recurrent PMVL, three patients had a TIA or TMVL, and one patient had an ischaemic stroke. Comparing patients with significant ipsilateral carotid stenosis ≥ 50% with patients without significant carotid stenosis, it was shown that patients with stenosis more often had recurrent stroke events. Three patients with stenosis (5.7%) had recurrent events compared with three patients without stenosis (0.9%; P = 0.035). 35 patients had multiple events within 90 days prior to being seen. If combining both recurrences and stroke events prior to clinic visit, ten patients (18.9%) had multiple events in the carotid group and 31 patients (9.2%) in the no stenosis group (P = 0.0497).

Looking at the vascular risk factors for stroke, carotid stenosis was found to be the only independent predictor for multiple stroke events (within 90 days before and after presentation at the TIA clinic) in univariate analysis and when

Table 1 Patient demographics, divided into transient and persistent monocular visual loss at presentation.

Demographic	Overall (n = 391)	Transient monocular ischaemia (n = 260, 66.5%)	Persistent monocular ischaemia (n = 131, 33.5%)	*P*-value
Age, years (mean ± SD)	64.60 ± 15.03	64.78 ± 14.53	64.24 ± 16.04	0.746
Male sex, *n* (%)	218 (55.8)	132 (50.8)	86 (65.6)	**0.007**
Hypertension, *n* (%)	198 (50.6)	115 (44.2)	83 (63.4)	**< 0.001**
Diabetes, *n* (%)	56 (14.3)	29 (11.2)	27 (20.6)	**0.014**
Hypercholesterolaemia, *n* (%)	139 (35.5)	86 (33.1)	53 (40.5)	0.179
History of smoking, *n* (%)	136 (34.8)	82 (31.5)	54 (41.2)	0.072
Previous IHD/MI, *n* (%)	38 (9.7)	17 (6.5)	21 (16.0)	**0.004**
Previous monocular ischaemia, *n* (%)	47 (12.0)	41 (15.8)	6 (4.6)	**0.001**
Previous TIA, *n* (%)	25 (6.4)	24 (9.2)	1 (0.8)	0.001
Previous stroke, *n* (%)	20 (5.1)	12 (4.6)	8 (6.1)	0.627
Atrial fibrillation, *n* (%)	31 (7.9)	21 (8.2)	10 (7.1)	1
Ipsilateral carotid artery stenosis ≥ 50%, *n* (%)	53 (13.6)	27 (10.4)	26 (19.8)	**0.012**

IHD, ischaemic heart disease; MI, myocardial infarct; TIA, transient ischaemic attack.

Table 2 Risk factors and presence of recurrences in patients with and without ipsilateral significant carotid stenosis ≥ 50%.

Risk factor	No carotid stenosis (*n* = 338, 86.4%)	Significant carotid stenosis (*n* = 53, 13.6%)	*P*-value
Age, years (mean ± SD)	63.74 ± 15.48	70.08 ± 10.33	**< 0.001**
Male sex, *n* (%)	180 (53.3)	38 (71.7)	**0.017**
Hypertension, *n* (%)	160 (47.3)	38 (71.7)	**0.001**
Diabetes, *n* (%)	47 (13.9)	9 (17.0)	0.531
Hypercholesterolaemia, *n* (%)	117 (34.6)	22 (41.5)	0.356
History of smoking, *n* (%)	114 (33.7)	22 (41.5)	0.280
Previous IHD/MI, *n* (%)	29 (8.6)	9 (17.0)	0.076
Atrial fibrillation, *n* (%)	26 (7.9)	5 (9.4)	0.598
ABCD2, median (range)[a]	2 (0–5)	3 (0–5)	0.114
Recurrences within 90 days after clinic visit, *n* (%)	3 (0.9)	3 (5.7)	**0.035**
Any stroke event prior to and after clinic visit, *n* (%)	31 (9.2)	10 (18.9)	**0.0497**

IHD, ischaemic heart disease; MI, myocardial infarct; TIA, transient ischaemic attack.
[a] Unable to calculate in 103 patients (26.3%) due to 1 or more factors missing.

adjusted for the other factors (Table 3). History of smoking was also an independent factor for multiple events, but this was not seen when adjusted for the other vascular risk factors.

Discussion

In our study, we have found that ipsilateral carotid stenosis ≥ 50% was common in patients presenting with monocular ischaemia with a prevalence of 13.6%. The prevalence of carotid stenosis ≥ 70% was 7.9%. This is a lower prevalence compared with a recent study by Kvickström *et al*, conducted on 310 patients diagnosed with TMVL.[18] The prevalence of carotid stenosis ≥ 70% in their study was reported to be 18.9%. The difference in prevalence is most likely related to the variation in carotid studies used to diagnose carotid stenosis, considering they used ultrasound only to diagnose carotid stenosis. Another recent study looking at the prevalence of co-occurring cerebral ischaemia in patients with acute retinal ischaemia, found a similar prevalence of 17.0% of the 112 patients.[19] Another study by Donders *et al* reported a prevalence of carotid stenosis ≥ 70% including carotid occlusion, of as high as 45.0% in patients with retinal ischaemia.[20] This suggests that the prevalence of carotid stenosis in patients with monocular ischaemia in the literature has a great variety in its range.

We have found that carotid disease was more common in patients who were diagnosed with PMVL compared with the group diagnosed with TMVL. The prevalence of carotid stenosis seems to differ between the type of ocular ischaemic syndrome.[21] Interestingly, it was found that patients with TMVL more commonly were diagnosed with carotid stenosis on the relevant side compared with patients with

Table 3 The association between stroke recurrence within 90 days after clinic and cardiovascular risk factors.

	Univariate analysis			Multivariate analysis		
Variables	Odds ratio[a]	95% CI	*P*-value	Odds ratio[a]	95% CI	*P*-value
Sex (male/female)	1.21	0.62–2.36	0.569	0.93	0.45–1.95	0.854
Age	1.00	0.98–1.02	0.892	0.99	0.96–1.02	0.404
Hypertension	1.72	0.87–3.36	0.117	1.36	0.61–3.05	0.457
Diabetes mellitus	1.88	0.84–4.19	0.124	1.51	0.63–3.65	0.357
Hypercholesterolaemia	1.39	0.71–2.70	0.334	1.12	0.52–2.39	0.778
History of smoking	2.03	1.05–3.91	**0.036**	1.73	0.85–3.49	0.128
Atrial fibrillation	2.33	0.89–6.08	0.085	2.20	0.78–6.18	0.134
Ipsilateral carotid stenosis ≥ 50%	2.39	1.09–5.23	**0.029**	2.31	1.01–5.29	**0.047**

[a] Each odds ratio is adjusted for all other variables in the table.

PMVL, which is in contradiction with our study. This might be explained by the fact that many of our patients only sought medical attention after they have had multiple events, with 35 patients coming into clinic after they had multiple eye symptoms.

Despite the small numbers of patients who have found to have recurrent ischaemic events after presentation, it was shown that patients with ipsilateral significant carotid stenosis more often had a recurrent event. The recurrent rate of retinal ischaemia, TIA or ischaemic stroke in patients with monocular ischaemia was 1.5%. Monocular ischaemia is known to be an event with a relatively lower risk of recurrent ischaemic stroke compared with patients presenting with TIA or ischaemic stroke.[22] Our study suggests that patients with carotid stenosis and monocular ischaemia more commonly have recurrent stroke events. This is of importance in the decision to surgically intervene in patients with significant carotid stenosis and monocular ischaemia to reduce the risk of future stroke. In our cohort, it was also found that patients with carotid stenosis do not have a higher vascular risk profile based on their ABCD2 score. Patients with a new monocular ischaemia should be considered for early referral to assess for an underlying carotid stenosis, regardless their initial vascular risk profile.

There are several limitations to this study. First, this was a retrospective review of patient medical records and discharge summaries presenting to the TIA clinic. This limits the available recorded data and could lead to underestimation of recurrent events due to non-recording of out of area events. Second, not all patients presenting with monocular visual loss had regular follow-up in our hospital after their first presentation. Patients were often found to be followed-up by their own general practitioner, resulting in loss of patients who had a recurrent stroke event after first presentation. We would have included a potential recurrent stroke event only for patients presenting for the second time at our TIA clinic or stroke unit. Third, we have also found that not all patients were found to have carotid artery imaging done. Nine patients did not have any carotid imaging. For future studies, patients with monocular ischaemia should be followed-up prospectively to identify any recurrent ischaemic events.

Conclusion

Carotid stenosis ≥ 50% in patients with monocular ischaemia is higher than previously described, approximately 20% of those with persistent visual loss and 10% of those with transient visual loss. Those with carotid stenosis have a higher risk of recurrence and should be investigated and treated as aggressively as other forms of TIA. All patients with monocular ischaemia should have at least one modality done to image the carotid arteries. Carotid endarterectomy should be considered in patients with monocular ischaemia, especially with high-grade stenosis. Patients presenting with monocular ischaemia should be referred to a local stroke unit for assessment urgently despite its risk for recurrent stroke based on their current vascular risk factors. Urgent carotid imaging needs to be done and urgent referral to a vascular service in those with significant carotid stenosis. Owing to its high risk of stroke recurrence, carotid endarterectomy should be considered in patients with monocular ischaemia, especially those with high-grade stenosis.

Acknowledgements

Agnes Dados for her great assistance in the TIA clinic.

References

1. Bernstein EF. *Amaurosis Fugax*. New York: Springer-Verlag; 1987, pp. 286–303.
2. Kappelle LJ, Donders RCJM, Algra A. Transient monocular blindness. *Clin Exp Hypertens* 2006; **28(3–4)**: 259–263.
3. Fisher CM. Transient monocular blindness 'versus' amaurosis fugax. *Neurology* 1989; **39**: 1,622–1,624.
4. The Amaurosis Fugax Study Group: current management of amaurosis fugax. *Stroke* 1990; **21(2)**: 201–208.
5. Adams HP, Bendixen BH, Kappelle LJ *et al*. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993; **24**: 35–41.
6. Naylor AR, Ricco JB, de Borst GJ *et al*. Management of atherosclerotic carotid and vertebral artery disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* 2018; **55(1)**: 3–81.
7. Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol* 2007; **6**: 1,063–1,072.
8. Rothwell PM, Giles MF, Marquardt L *et al*. Effect of urgent treatment of transient ischemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet* 2007; **6**: 953–960.
9. Rothwell PM, Giles MF, Flossmann E *et al*. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet* 2005; **366**: 29–36.
10. Johnson SC, Gress DR, Browner WS *et al*. Short-term prognosis after emergency department diagnosis of TIA. *JAMA* 2000; **284(22)**: 2901–2906.
11. Johansson E, Cuadrado-Godia E, Hayden D *et al*. Recurrent stroke in symptomatic carotid stenosis awaiting revascularization: A pooled analysis. *Neurology* 2016; **86**: 498e504.
12. De Schryver EL, Algra A, Donders RC *et al*. Type of stroke after transient monocular blindness or retinal infarction of presumed arterial origin. *J Neurol Neurosurg Psychiatry* 2006; **77**: 734e738.
13. Lavallée PC, Cabrejo L, Labreuche J *et al*. Spectrum of transient visual symptoms in a transient ischemic attack cohort. *Stroke* 2013; **44**: 3312e3317.
14. National Institute for Health and Care Excellence. Stroke overview. NICE Pathways. http://pathways.nice.org.uk/pathways/stroke (cited May 2019).
15. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *New Engl J Med* 1991; **325**: 445–453.
16. North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. *Stroke* 1991; **22**: 711–720.
17. ISRCTN Registry. European Carotid Surgery Trial 2. http://www.isrctn.com/ISRCTN97744893. (cited May 2019).
18. Kvickström P, Lindblom B, Bergström G *et al*. Amaurosis fugax: risk factors and prevalence of significant carotid stenosis. *Clin Ophthalmol* 2016; **10**: 2165–2170.
19. Golsari A, Bittersohl D, Cheng B *et al*. Silent brain infarctions and leukoaraiosis in patients with retinal ischemia, a prospective single-center observational study. *Stroke* 2017; **48**: 1392–1396.
20. Donders RCJM, for the Dutch TMB Study Group. Clinical features of transient monocular blindness and the likelihood of atherosclerotic lesions of the internal carotid artery. *J Neurol Neurosurg Psychiatry* 2001; **71**: 247–249.
21. Hayreh SS, Zimmerman MB. Ocular arterial occlusive disorders and carotid artery disease. *Ophthalmol Retina* 2017; **1(1)**: 12–18.
22. Benavente O, Eliasziw M, Streifler JY *et al* for the North American Symptomatic Carotid Endarterectomy Trial Collaborators. Prognosis after transient monocular blindness associated with carotid-artery stenosis. *N Engl J Med* 2001; **345**: 1,084–1,090.