Carotid artery web and ischemic stroke

A case-control study

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ABSTRACT

Objective: To determine whether there is an association between carotid artery web and ischemic stroke.

Methods: This was a single-center, age- and sex-matched, case-control study. Cases were consecutive patients with anterior circulation ischemic stroke of undetermined etiology (Trial of Org 10172 in Acute Stroke Treatment [TOAST] classification). Controls were consecutive patients with cerebral aneurysms, arteriovenous malformations, or primary intracerebral hemorrhages. Additional inclusion criteria were age <60 years and CT angiography of the neck. Two neuroradiologists diagnosed webs according to previously published criteria. One neuroradiologist also assessed for nonstenotic atherosclerotic plaque (carotid wall thickness ≥ 3 mm or intramural calcification). We used conditional logistic regression to estimate the odds ratio between carotid web and ischemic stroke and its 95% confidence interval.

Results: Fifty-three of 62 cases (85%) were matched by age (within 1 year) and by sex to 102 controls. There was a carotid web in 4 of 53 cases (9.4%) vs 1 of 102 controls (1.0%, odds ratio = 8.0, 95% confidence interval = 1.2–67, $p = 0.032$). There was no significant difference in the prevalence of nonstenotic carotid atherosclerotic plaque between the case and control groups. There was agreement on diagnosis of web for 163 of 164 patients (99%) and 7 of 8 webs (88%), and the Cohen κ for interobserver agreement was 0.93.

Conclusions: There is an association between carotid artery web and ischemic stroke in patients who lack an alternative cause of stroke. Carotid web may be an underappreciated risk factor for stroke. **Neurology® 2017;88:65–69**

GLOSSARY

AVM = arteriovenous malformation; **CI** = confidence interval; **CTA** = computed tomography angiography; **NASCET** = North American Symptomatic Carotid Endarterectomy Trial; **TOAST** = Trial of Org 10172 in Acute Stroke Treatment.

Therapeutic decision making for secondary stroke prevention relies on determining the cause of the initial transient ischemic attack or ischemic stroke. However, in one-third of cases, there is no apparent cause.¹

A potentially underrecognized source of cerebral embolus is a carotid artery web. A carotid web is a thin, membrane-like shelf of tissue that extends from the wall of the carotid artery into the lumen, usually at the origin of the internal carotid artery. Carotid webs were first described 4 decades ago in a study of catheter angiograms at the Massachusetts General Hospital,² and subsequent case reports have added ≈ 50 cases to the literature. It is hypothesized that blood stasis along the downstream surface of a web may lead to thrombus formation and thromboembolic stroke.³ However, evidence of an association between carotid web and ischemic stroke has been only anecdotal.

We conducted a case-control study to determine whether there is an association between carotid artery web and ischemic stroke.

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METHODS Study design. This was an age- and sex-matched case-control study.

Cases and controls. Patients with ischemic stroke of undetermined etiology (Trial of Org 10172 in Acute Stroke Treatment [TOAST]⁴ definition) in a unilateral internal carotid artery territory were identified from a prospective single-center registry of consecutive patients with ischemic stroke admitted to the University Health Network, Toronto, between January 2012 and March 2015. Controls were selected from consecutive patients with primary intracerebral hemorrhage from the same registry and patients with a brain arteriovenous malformation (AVM) or cerebral aneurysm identified from a prospective single-center registry of consecutive patients seen in the Aneurysm and AVM Clinic of the University Health Network. Additional inclusion criteria for both cases and controls were age <60 years and CT angiography (CTA) of the neck arteries. We chose the age threshold of 60 years because most patients in the carotid web case reports were under this age. For the control group, we excluded patients with previous transient ischemic attack or ischemic stroke.

Data abstraction from registries. For each patient, we abstracted age, sex, and atherosclerotic risk factors (hypertension, dyslipidemia, diabetes mellitus, and coronary artery disease). For cases, we also abstracted NIH Stroke Scale score at admission, whether patients received medical thrombolysis or endovascular therapy, and which investigations were performed to determine stroke etiology.

CTA of the carotid arteries. Imaging was performed with 64- and 320-detector row scanners (Toshiba Medical Systems, Tokyo, Japan) in 64-row mode. Intravenous iodinated contrast was iodixanol (Visipaque 320, GE Healthcare, Cleveland, OH) 60 to 80 cm³ injected at 5 cm³/s. Acquisitions were helical, covering aortic arch to vertex, with 0.5-mm section thickness (100–120 kV, auto-mA), gantry speed of 0.5 seconds per rotation, table speed of 25.5 mm per rotation, and reconstruction in the axial plane with 0.5-mm slice thickness.

Image analysis. Images were viewed with the Coral Workstation software (University Health Network, Toronto). Each CTA was reviewed by a neuroradiologist (S.D.) who had access to axial images and oblique sagittal reformats. Images above the skull base were concealed, and the reader was blinded to all other imaging and clinical information, including whether the patient was a case or control. The reader first assessed image quality and then determined whether there was an artifact (such as patient motion) that would impede evaluation of one or both carotid arteries, and these patients were recorded and censored from further analysis.

Carotid web was diagnosed when there was a thin, smooth, membrane-like intraluminal filling defect along the posterior wall of the carotid bulb on oblique sagittal images and a corresponding thin septum on axial images. A recent study showed that this appearance on CTA correlates with histopathologically confirmed carotid web.³ A second neuroradiologist (D.M.M.), similarly blinded, assessed all CTAs. A final diagnosis of web was established only if both neuroradiologists independently scored the CTA as positive for web. The second reader also viewed the common and internal carotid arteries from 2 cm proximal to the bifurcation and recorded whether there was carotid wall calcification or carotid wall thickness ≥ 3 mm. We used the latter criterion for wall thickness because previous CTA studies have suggested that there is an association between carotid plaque and

ipsilateral ischemic stroke when wall thickness is (approximately) above this threshold.^{5,6}

Statistical analysis. We paired each case with up to 2 controls, matched by sex and by age within 1 year. We performed a supplementary analysis using an age caliper of 3 years because this match included all of the carotid webs identified in both the case and control groups. We used conditional logistic regression to estimate the odds ratio between carotid web and ischemic stroke, along with its 95% confidence interval (CI). We calculated the Cohen κ for interobserver agreement on the diagnosis of carotid web on a per-patient basis. We performed Fisher exact tests to determine whether there was a difference in the prevalence of atherosclerotic risk factors or CTA evidence of nonstenotic atherosclerotic plaque (wall thickening or calcification) between the case and control groups. Analyses were performed with R software (version 3.2.5).

Standard protocol approvals, registrations, and patient consents. The Institutional Review Board of the University Health Network, Toronto, approved the study protocol and waived the requirement for written consent.

RESULTS Cases. Of 1,189 consecutive patients with ischemic stroke, there were 120 patients with stroke of undetermined etiology and age <60 years. We excluded 27 of these patients because the stroke was not in an internal carotid artery territory. We excluded 31 of the remaining patients because there was no CTA or the technical quality of the CTA was too poor to determine whether there was a web. Therefore, 62 cases were included in the analysis. For these cases, median NIH Stroke Scale score at admission was 7 (interquartile range 2–15), 26 of 62 patients (42%) received intravenous thrombolysis, and 6 of 62 (10%) had mechanical thrombectomy. Investigations to determine stroke etiology included brain CT in 61 of 62 (98%), brain MRI in 48 of 62 (77%), ECG in 60 of 62 (97%), 24-hour Holter ECG in 41 of 62 (66%), and an echocardiogram in 60 of 62 (97%).

Controls. There were 959 potential control patients (569 AVMs, 361 aneurysms, and 29 primary intracerebral hemorrhages) with age <60 years in the registries, and 228 of these patients had CTA of the carotid arteries. We excluded 9 of these patients because of poor quality of the CTA. Therefore, 219 controls were included in the analysis.

Carotid artery web and ischemic stroke. Fifty-three of 62 cases (85%) were matched by age (within 1 year) and sex to 102 control patients. The table compares the demographics of the case and control groups. There was a carotid web in 4 of 53 cases (9.4%) vs 1 of 102 controls (1.0%, odds ratio = 8.0, 95% CI = 1.2–67, $p = 0.032$).

Fifty-six of 62 cases (90%) were matched by age within 3 years and by sex to 108 control patients. This match included all webs identified in the both the case and control groups. There was a carotid

Table	Characteristics of the age- and sex-matched cases and controls		
Variable	Cases (n = 53)	Controls (n = 102)	p Value
Age, median (IQR), y	51 (44–56)	51 (44–55)	
Male sex, %	56.6	55.9	
Atherosclerotic risk factors, n (%)			
Hypertension	27/53 (51.9)	47/102 (46.1)	0.613
Diabetes mellitus	10/53 (19.2)	7/102 (6.9)	0.031
Dyslipidemia	7/53 (13.5)	7/102 (6.9)	0.239
Coronary artery disease	4/53 (7.7)	4/102 (3.9)	0.446
CTA evidence of carotid atherosclerotic disease, n (%)			
Carotid artery wall calcification	13/53 (25.0)	24/102 (23.5)	1.000
Carotid artery wall thickness ≥ 3 mm	5/53 (9.6)	9/102 (8.8)	1.000

Abbreviations: CTA = computed tomography angiography; IQR = interquartile range.

web in 5 of 56 cases (8.9%) vs 2 of 108 controls (1.9%, odds ratio = 5.0, 95% CI = 1.1–35, $p = 0.040$).

There was agreement on diagnosis of web for 163 of 164 patients (99%) and 7 of 8 webs (88%), and the Cohen κ for interobserver agreement was 0.93.

Among the cases with webs, 4 of 5 patients were women, and the age range was 34 to 57 years. Baseline NIH Stroke Scale scores ranged from 2 to 21. Each of these cases had a web ipsilateral to the ischemic stroke, and 2 patients also had a contralateral web. The degree of carotid artery stenosis (North American Symptomatic Carotid Endarterectomy Trial [NASCET] measurement)⁷ from the webs was 0% in 4 patients. In the fifth patient, the web ipsilateral to the stroke resulted in carotid occlusion, and a contralateral web resulted in 0% stenosis. No patient had surgical removal of a web. The figure shows a representative carotid artery web from a case (figure, A and B) and thrombus adherent to the downstream surface of a web from a different case (figure, C).

Atherosclerotic disease. Diabetes mellitus was more common in the cases than controls, and the other 3 atherosclerotic risk factors had similar prevalences in both groups (table). In a model adjusted for diabetes mellitus, the odds ratio (for presence of a carotid web in 4 of 53 cases vs 1 of 102 controls) was 9.4 (95% Wald CI = 1.0–86, $p = 0.022$).

There was no difference in the prevalence of nonstenotic atherosclerotic disease on CTA between the cases and controls (table). Five patients with webs had no evidence of atherosclerotic disease on CTA. Another patient had a web at the internal carotid artery origin and a separate region of nonstenotic atherosclerotic plaque at the distal aspect of the carotid bulb (figure, D). Another patient had thickening of the wall of the carotid bulb in addition to the web and no mural calcification.

Figure Representative images of carotid artery webs in the study

Carotid artery web in a patient with cryptogenic stroke (A and B). Axial CT angiography (CTA) image (A) and magnified view (inset in A) show a thin, membrane-like structure in the carotid artery lumen. Sagittal oblique CTA image (B) of the same artery shows that the membrane is shelf-like, consistent with a carotid artery web. Catheter angiogram, lateral projection (inset in B), shows the same web. Coronal CTA image from a different patient with cryptogenic stroke (C) shows a carotid web (black arrow) and thrombus (white arrows) along the downstream surface of the web. Sagittal oblique CTA image from a third patient (D) shows both a carotid web (black arrow) and nonstenotic, partially calcified, atherosclerotic plaque (white arrows) involving the distal aspect of the carotid bulb.

DISCUSSION We conducted a case-control study to determine whether carotid web is a risk factor for ischemic stroke. We found that 1 in 13 patients with ischemic stroke of undetermined etiology had a carotid web. Carotid web was ≈ 8 times more common in patients with stroke than in controls. These findings suggest that carotid web may be an important risk factor for ischemic stroke when no other cause is found.

The prevalence of carotid artery webs in our case group is relatively high in comparison with the total

number of cases previously reported in the literature. This may reflect a combination of a lack of widespread familiarity with carotid webs and the highly selected group of patients (age <60 years, anterior circulation, cryptogenic ischemic stroke) we have studied. In addition, there is a lack of data on the accuracy of various imaging techniques for the diagnosis of carotid artery web, but our experience has been that contrast-enhanced angiography (CTA, magnetic resonance angiography, digital subtraction angiography) may be better than Doppler ultrasound or time-of-flight magnetic resonance angiography, which are also used to assess the carotid arteries in patients with stroke.

The 1.0% prevalence of carotid webs in our control group is similar to the 1.2% prevalence of webs in a sample of consecutive patients who underwent CTA for suspected stroke at a single hospital.³ This is not surprising because the latter sample was from a much less selected group of patients and likely included patients with stroke mimics, posterior circulation strokes, and a majority of noncryptogenic strokes.

The concept that carotid web is a risk factor for stroke was previously based on anecdotal evidence: case reports of webs in patients with stroke of no other apparent cause and a small number of cases with luminal thrombus residing on a web.⁸ This lack of strong evidence may partly explain why few physicians are familiar with this entity. However, lack of familiarity may also reflect the mild (<50%) stenosis caused by most carotid webs and a pervasive preconception that mild carotid artery stenosis is an unlikely cause of stroke. For atherosclerotic plaque, recent evidence suggests that the clinical significance of nonstenotic plaque has been underappreciated.⁹ Furthermore, the mechanisms by which carotid webs and atherosclerotic plaque lead to thromboembolic stroke likely differ. In addition, a relatively large web can result in 0% stenosis when the NASCET calculation of percentage stenosis is used because the calculation compares luminal diameter at the level of the web, located within the normally rounded carotid bulb, with luminal diameter beyond the bulb. In our study, one case had bilateral carotid webs and a web resulting in carotid occlusion ipsilateral to the ischemic stroke. This patient had no evidence of atherosclerotic plaque or other arterial disease on CTA or high-resolution vessel wall MRI of the carotid arteries. In this particular case, it is conceivable that the contralateral carotid web is the culprit, with embolus traversing the anterior communicating artery to reach the territory of the stroke, but we cannot be sure.

Optimal therapy for a patient with a carotid web and otherwise unexplained ischemic stroke is not yet known. If thrombus formation in the relatively stagnant blood along the downstream surface of

a web is analogous to thrombus formation in the left atrial appendage of the heart, perhaps anticoagulation is warranted.³ Antiplatelet therapy, carotid angioplasty and stenting, and endarterectomy are other potential options. In the largest case series of carotid webs, after a mean follow-up of 2 years, the recurrent stroke rate was 0% (0 of 7 patients) in the surgical group compared with 30% (6 of 20 patients) in the antiplatelet therapy-only group.⁶

A limitation of our study is that the control group included patients with cerebral aneurysms and AVMs. There is a known association between aneurysms and fibromuscular dysplasia, and carotid webs may be a type of intimal fibromuscular dysplasia.¹⁰ However, such an association would lead to overestimation of the prevalence of webs in the control group and thus an underestimation rather than overestimation of the strength of association between carotid webs and stroke. If aneurysms or AVMs are somehow protective against the development of carotid artery webs, this could bias our results toward overestimation of the association between webs and stroke. However, to the best of our knowledge, there is no literature suggesting that such a protective phenomenon exists. In addition, the limited evidence available suggests the contrary: the prevalence of webs in our control group (1.0%) is similar to the prevalence of webs (1.2%; 95% CI = 0.4–2.5) in a previously published series of 576 patients who had CTA for suspected stroke.³ If our control group had a reduced prevalence of webs due to an inverse association between aneurysms or AVMs and webs, then one would expect that the prevalence of webs in our control group would be lower than in a group of unselected stroke patients.

The workup of patients in our registry reflects routine clinical care at our institute, and it is possible that more prolonged cardiac rhythm monitoring would have diagnosed paroxysmal atrial fibrillation in some of the patients in our cryptogenic stroke group. If there is an association between paroxysmal atrial fibrillation and carotid artery web, then false-negative diagnosis of atrial fibrillation in the cryptogenic stroke group would result in overestimation of the association between carotid artery web and stroke. However, we are not aware of any evidence of an association between atrial fibrillation and carotid web; and in the absence of such an association, false-negative diagnosis of paroxysmal atrial fibrillation would lead to underestimation rather than overestimation of the association between web and stroke.

Another limitation is subjectivity in the diagnosis of very small carotid webs. We dealt with this issue by including only webs for which 2 independent neuro-radiologists considered the findings definitive, recognizing that we may have underdiagnosed the smallest

webs. Because the readers did not know whether a given patient was a case or control, this issue should not bias the observed association.

Finally, our study has used a morphological definition of carotid web derived from a previous imaging-histopathological comparison, but we were not able to obtain tissue samples for the webs in our study. Previous investigation has suggested that these lesions are nonatherosclerotic and noninflammatory and are likely developmental in origin.³

We found a statistically significant and strong association between carotid artery web and ischemic stroke in young patients who lack an alternative cause of stroke. Carotid web may be an underappreciated risk factor for stroke.

AUTHOR CONTRIBUTIONS

J.M.C. contributed to the study design, data acquisition, and data analysis and wrote the initial draft of the report with D.M.M. L.K.C. and F.L.S. were the domain experts on vascular neurology and contributed to the study design and revision of the final report. S.D. contributed to the study design, data acquisition, data analysis, and revision of the final report and was 1 of 2 readers of CTA images. A.R.J.P. contributed to the data acquisition and revision of the final report. G.T. contributed to the data analysis (including statistical analysis) and revision of the final report. G.T.'s professional affiliation is academic (University of Toronto). D.M.M. was the principal investigator of the study and was responsible for the study conception and design, interpretation of data, and writing of the initial draft of the report with J.M.C. and was 1 of 2 readers of CTA images obtained during the study.

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DISCLOSURE

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