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Carotid Artery Stenosis as a Cause of Stroke

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Key Words
Carotid stenosis · Carotid atherosclerosis · Intracranial atherosclerosis · Stroke · Stroke etiology · Epidemiology · Carotid occlusion

Abstract
Background: Population-based studies have estimated that about 15% of ischemic strokes are caused by large-vessel cerebrovascular disease. We determined the types of large-vessel atherosclerosis responsible for ischemic strokes in a population-based stroke study. ***Methods:*** Patients with first-ever or recurrent ischemic stroke in the Greater Cincinnati area were identified during 2005 at all local hospitals. Study physicians assigned ischemic stroke subtypes. Overall event rates and incidence rates for first-ever events were calculated, and age-, race- and sex-adjusted to the 2000 US population. ***Results:*** There were 2,204 ischemic strokes, including 365 strokes of large-vessel subtype (16.6% of all ischemic strokes). Extracranial internal carotid artery (ICA) stenosis was associated with 8.0% of all ischemic strokes, while extracranial ICA occlusion and intracranial atherosclerosis were each associated with 3.5% of strokes. The annual rate of first-ever and recurrent stroke attributed to extracranial ICA was 13.4 (11.4–15.4) per 100,000 persons. We conservatively estimate that about 41,000 strokes may be attributed to extracranial ICA stenosis annually in the United States. ***Conclusions:*** Large-vessel atherosclerosis is an important cause of stroke, with extracranial ICA stenosis being significantly more common than extracranial ICA occlusion or intracranial atherosclerotic disease.

Introduction

Large-vessel atherosclerotic cerebrovascular disease is an important cause of stroke that produces a higher risk of early recurrent ischemia than any other stroke subtype [1]. Risk factors for large-vessel disease also differ from other stroke subtypes [2, 3]. Importantly, for patients with stroke or transient ischemic attacks (TIAs) attributed to severe (>70%) extracranial internal carotid artery (ICA) stenosis, prompt revascularization with carotid endarterectomy produces a dramatic reduction in recurrent stroke risk [4].

Prior population-based studies have estimated that about 15% of ischemic strokes are caused by large-vessel

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atherosclerosis [2, 5, 6]. However, these studies have generally not distinguished between vessel stenosis and occlusion, anterior and posterior circulations, or extracranial and intracranial locations. We determined the types of large-vessel atherosclerosis responsible for ischemic strokes in a large, population-based stroke study. We focused especially upon extracranial ICA stenosis because of the pronounced benefit of appropriate treatment for this stroke mechanism.

Methods

This study was undertaken as part of the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS). The GCNKSS was funded by the National Institute of Neurological Disorders and Stroke. The institutional review board for each participating hospital system approved the GCNKSS study. Methods of the GCNKSS have been previously published [7, 8]. In 2005, study nurses screened the medical records of all inpatients with primary or secondary stroke-related ICD-9 discharge diagnoses (430–436) from all acute-care hospitals in the study region. Patients with stroke not found by inpatient screening were ascertained by monitoring all stroke-related visits to hospital emergency departments (with the exception of Cincinnati Children's Hospital) and screening of coroner's cases. The GCNKSS also included monitoring of university and public health clinics as well as a sampling scheme of private outpatient physician offices and nursing homes [7]. For this analysis, only patients presenting to an emergency room or hospital were included. Residents of the five-county GCNK region seek care almost exclusively at one of the metropolitan hospitals included in the study [9]. Patients living outside of the five counties of interest were excluded by ZIP code of residence.

Study nurses performed chart abstraction for all potential cases. These abstracts were reviewed in detail by study physicians. Physicians assigned a stroke category and mechanism to each event based upon all available information, using criteria previously reported [6, 7]. Subtyping of ischemic stroke cases was performed using criteria adapted from the Classification of Cerebrovascular Diseases III and epidemiologic studies in Rochester, Minn., USA [6, 10–13]. Large-vessel etiology required ≥50% stenosis or occlusion of the relevant vessel. For this analysis, patients with appropriate large-vessel disease who also had a cardiac source of embolism (e.g. atrial fibrillation) or a lacunar infarction were categorized as large-vessel etiology because (a) some previous studies of carotid endarterectomy have included patients with potential stroke mechanisms other than large-vessel disease [14, 15] and (b) clinicians often recommend endarterectomy for patients with stroke in the territory of significant carotid atherosclerosis despite other potential stroke mechanisms. Vascular dissections and perioperative strokes were not included as large-vessel etiology. Isolated occlusions of the carotid terminus, middle cerebral artery, anterior cerebral artery, basilar artery and posterior cerebral arteries were not considered large vessel because of our inability to distinguish embolus from in situ thrombosis. Cases with stenosis of both the distal common carotid artery and proximal ICA were classified as ICA stenosis. Tandem lesions were categorized according to the judgment of an investigator (M.L.F.). For this analysis, patients with symptoms lasting <24 h but with DWI MRI sequences positive for acute stroke were classified as stroke cases.

To estimate the total burden produced by large-vessel disease, event rates including both first-ever and recurrent ischemic strokes were calculated, and age-, race- and sex-adjusted to the 2000 US population. Incidence rates were then recalculated including only patients with first-ever ischemic stroke. For the calculation of event and incidence rates, the entire population of the five GCNK counties was considered at risk. Denominator age-, race- and sex-specific population estimates for each study year were obtained from published census data [16]. We applied overall age-, race-, sex-adjusted event rates to the population of the United States in 2010 to estimate the total number of strokes attributable to extracranial ICA stenosis and occlusion annually. Our rates and estimates were not adjusted for patients who did not have vascular imaging or patients with stroke treated only in the outpatient setting.

Results

There were 2,096 patients with 2,204 first or recurrent ischemic strokes identified. The distribution of vascular imaging is presented in table 1. Among these cases 79% had cervical vascular imaging with carotid ultrasound, MR angiography, CT angiography, or conventional cerebral angiography. Slightly less than one-half of our patients had some form of intracranial vascular imaging. Imaging rates for cervical vessels did not differ between black and white patients (78 vs. 75%, $p = 0.24$); however, black patients were more likely to have intracranial vascular imaging (55 vs. 41%, $p < 0.001$). Male patients were more likely to have imaging than female patients for both extracranial vessels (79 vs. 73%, $p < 0.001$) and intracranial vessels (48 vs. 40%, $p < 0.001$). There were 348 patients with 365 strokes determined to be of large-vessel mechanism (16.6% of all ischemic strokes). Of these, 22 had symptoms lasting <24 h but positive DWI imaging on MRI. A breakdown of large-vessel cases is presented in table 2. There were 176 strokes attributed to extracranial ICA stenosis (8.0% of all strokes) and 78 strokes attributed to extracranial ICA occlusion (3.5% of all strokes). Intracranial large-vessel atherosclerosis accounted for 78 cases (3.5% of all strokes). There were 10 patients with tandem lesions who were categorized with the vessel felt most likely to be causative. Among 365 strokes with large-vessel mechanism, 21.1% also had a potential cardiac source of embolus and 4.9% had a lacunar phenotype. Incidence rates for stroke attributed to

Table 1. Vascular imaging rates by modality and anatomic site

	Carotid ultrasound	MRA neck	MRA head	CTA neck	CTA head	Cerebral angiogram	Any imaging neck	Any imaging head
All strokes (n = 2,204)	1,200 (54%)	724 (33%)	918 (42%)	25 (1%)	21 (1%)	76 (3%)	1,661 (79%)	966 (44%)
White[1] (n = 1,716)	993 (58%)	506 (29%)	656 (38%)	22 (1%)	18 (1%)	59 (3%)	1,286 (75%)	696 (41%)
Black[1] (n = 477)	200 (42%)	212 (44%)	225 (53%)	3 (1%)	3 (1%)	17 (4%)	370 (78%)	263 (55%)
Male (n = 989)	551 (56%)	370 (37%)	453 (46%)	15 (2%)	13 (1%)	33 (3%)	781 (79%)	480 (48%)
Female (n = 1,215)	649 (53%)	354 (29%)	465 (38%)	10 (1%)	8 (1%)	43 (4%)	885 (73%)	486 (40%)

MRA = Magnetic resonance angiography; CTA = computed tomographic angiography.
[1] There were 11 additional subjects not of black or white race.

Table 2. Breakdown of large-vessel stroke cases by location and pathology

	Large-vessel ischemic stroke (n = 365)[1]							
	extracranial large vessel (n = 287)				intracranial large vessel (n = 78)			
	stenosis (n = 190)		occlusion (n = 97)		stenosis (n = 66)		occlusion (n = 12)	
	cases	percent of all strokes[2]	cases	percent of all strokes[2]	cases	percent of all strokes[2]	cases	percent of all strokes[2]
ICA	176	8.0	78	3.5	19	0.9	4	0.2
CCA			1	0.04				
Vertebral artery	14	0.6	18	0.8	6	0.3	8	0.4
MCA					21	1.0	IO[3]	IO[3]
ACA							IO[3]	IO[3]
Basilar artery					10	0.4	IO[3]	IO[3]
PCA					10	0.4	IO[3]	IO[3]

CCA = Common carotid artery; MCA = middle cerebral artery; ACA = anterior cerebral artery; PCA = posterior cerebral artery; IO = isolated occlusions.
[1] Including 15 patients with two large-vessel strokes and one patient with three large-vessel strokes during the study period.
[2] Percent of all ischemic strokes (n = 2,204) of any mechanism.
[3] Isolated occlusions of the middle cerebral, anterior cerebral, basilar, and posterior cerebral arteries were not classified as large-vessel etiology due to the inability to distinguish embolic occlusion from in situ thrombosis.

extracranial ICA disease are presented in table 3. Online supplementary table (for all online suppl. material, see www.karger.com/doi/10.1159/000341410) presents rates after exclusion of cases with a potential cardiac source of embolus or lacunar phenotype. We conservatively estimate that about 41,000 strokes may be attributed to extracranial ICA stenosis and about 18,000 strokes attributed to extracranial ICA occlusion annually in the United States, based on a projected 2010 population of 308,000,000.

Discussion

Large-vessel atherosclerotic disease is of great importance to clinicians caring for patients with stroke or TIAs because of its frequent occurrence, high risk of causing early recurrent ischemia and treatable nature. Extracranial ICA stenosis is especially notable in this regard as large studies have demonstrated that prompt endarterectomy markedly reduces the risk of recurrent stroke [4]. Our study shows that extracranial ICA atherosclerosis is the most important cause of large-vessel stroke. There has been appropriate interest in determining the best treat-

Table 3. Event rates for stroke attributed to extracranial internal carotid artery stenosis and occlusion[1]

	Stenosis		Occlusion	
	first-ever events	first-ever and recurrent events	first-ever events	first-ever and recurrent events
All	(n = 140) 10.7 (8.9, 12.5)	(n = 176) 13.4 (11.4, 15.4)	(n = 48) 3.7 (2.6, 4.8)	(n = 78) 6.0 (4.6, 7.3)
Male	(n = 70) 13.3 (10.1, 16.4)	(n = 87) 16.5 (13.0, 20.0)	(n = 26) 4.7 (2.8, 6.5)[2]	(n = 45) 7.8 (5.5, 10.1)
Female	(n = 70) 8.8 (6.7, 10.9)	(n = 89) 11.3 (8.9, 13.7)	(n = 22) 2.9 (1.7, 4.1)[2]	(n = 33) 4.4 (2.9, 5.9)
White	(n = 123) 10.8 (8.9, 12.7)	(n = 153) 13.4 (11.3, 15.6)	(n = 43) 3.8 (2.7, 5.0)	(n = 67) 6.0 (4.6, 7.4)
Black	(n = 17) 10.2 (5.3, 15.0)[2]	(n = 23) 13.6 (8.0, 19.2)[2]	(n = 5) 2.8 (0.3, 5.3)[2]	(n = 11) 6.1 (2.4, 9.7)[2]

[1] Rate per 100,000 persons per year, adjusted to the 2000 United States population.
[2] Small cell sizes (<30) may produce unstable estimates.

ment for extracranial ICA stenosis, most notably with multiple trials comparing carotid endarterectomy to carotid artery stenting [17–20]. Although we have documented that a substantial number of strokes are attributable to ICA stenosis, most patients with asymptomatic carotid stenosis do not subsequently have strokes. Thus, our data do not imply that all patients with asymptomatic carotid stenosis should undergo revascularization.

Stroke attributed to extracranial ICA occlusion occurs at approximately half the rate of stroke due to ICA stenosis. The recently completed Carotid Occlusion Surgery Study (COSS) failed to show a benefit for extracranial-intracranial bypass among patients with carotid occlusion judged at high risk of recurrent stroke by PET imaging [21]. Patients with symptomatic intracranial large-vessel stenosis are also known to be at high risk of recurrence. The SAMMPRIS Trial tested intracranial stenting plus medical management versus medical management alone and was closed early due to a high periprocedural risk of stroke or death in the stenting group [22]. Long-term follow-up of subjects in SAMMPRIS continues.

Our study has limitations. Twenty-one percent of patients evaluated in an emergency room or hospital for ischemic stroke did not have documented cervical vascular imaging. In some cases, imaging may have been performed in the outpatient setting (which we could not ascertain); in other cases, it may have been omitted due to the presence of another stroke mechanism (e.g. atrial fibrillation), a devastating stroke where no intervention was planned, patient preference, or physician oversight. Our imaging rate is comparable to or higher than in other population-based studies [2, 3, 23]. Extracranial imaging was considerably more common than intracranial imaging. Although this likely occurred for several reasons, the most important was practical: carotid revascularization is of proven benefit for high-grade extracranial ICA stenosis while there are no proven therapies for intracranial stenosis beyond standard medical management. The result is an underestimation of intracranial atherosclerosis as a stroke mechanism.

We found no difference in imaging rates of cervical vessels by race. Black patients were more likely to have intracranial imaging than whites. This may have occurred because of higher reported rates of intracranial atherosclerosis among blacks [24] or a higher percentage of black patients being hospitalized at tertiary or academic hospitals. Women were less likely than men to have imaging of cervical or intracranial vessels. While physician bias is one potential explanation, other factors, such as alternative stroke mechanisms, patient age and premorbid status, and stroke severity may be relevant. Further analysis of this question is beyond the scope of this report.

Approximately 10–20% of ischemic-stroke patients in our community are evaluated on an outpatient basis [8]. They would not be captured in our data, but we have no reason to believe they have a significantly different balance of stroke mechanisms. We did not include TIAs

(without diffusion restriction on MRI) in this analysis because estimating the true burden of TIAs in a large community is very difficult. Patients with TIAs caused by large-vessel stenosis arguably have the most to gain from prompt evaluation and intervention to prevent a potentially devastating stroke.

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Disclosure Statement

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