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Risk Factors Associated with Severity and Location of Intracranial Arterial Stenosis

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Abstract

Background and Purpose—We sought to determine vascular risk factors and demographic features associated with the severity and location of intracranial stenosis.

Methods—Data on patients enrolled in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial were used for the analyses. Demographic features and vascular risk factors were compared in patients with moderate stenosis (n=336) vs. severe stenosis (n=225) and according to location of intracranial stenosis (MCA, ICA, basilar, or vertebral).

Results—History of a lipid disorder (77% in severe vs. 67% in moderate, p=0.01), metabolic syndrome (63% in severe vs. 53% in moderate, p=0.05), and diabetes (43% in severe vs. 35% in moderate, p=0.04) were more common in patients with severe intracranial stenosis in univariate analyses. History of lipid disorder was independently associated with severe stenosis (OR 1.62 (95% CI 1.09–2.42), p=0.02).

The distribution of stenosis location differed among age groups (p=0.0015), gender (p=0.0001), race (p=0.0243), qualifying event (p=0.0156), diabetes (p=0.0030), coronary artery disease (p=0.0030), and hyperlipidemia (p=0.054). Patients with basilar stenosis were older and more likely to have hyperlipidemia. Patients with MCA stenosis were more likely to be women and

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black. Patients with ICA stenosis were more likely to have diabetes. Patients with vertebral stenosis were more likely to have coronary artery disease.

Conclusions—Lipid disorder has the strongest association with severity of intracranial stenosis and should be the target of prevention therapies. Different locations of intracranial stenosis are associated with different vascular risk factors and demographic features, suggesting there may be a difference in the underlying pathophysiology of stenosis among the intracranial arteries.

Keywords

Intracranial stenosis; Risk factors; Cerebral arteries; Cerebrovascular disease

Introduction

Atherosclerotic stenosis of the major intracranial arteries (carotid siphon, middle cerebral artery, vertebral artery, basilar artery) may be the most common cause of stroke worldwide[1] and is responsible for approximately 8–10% of all ischemic strokes in the USA[2]. Patients with symptomatic severe (70–99%) intracranial stenosis have been shown to have a risk of recurrent stroke as high as 25% in 2 years[3]. Certain risk factors, such as lipoprotein(a) and diabetes[4] have been associated with the number of intracranial atherosclerotic stenoses, but no large cohort study has examined risk factors associated with severe (70–99%) intracranial arterial stenosis. Identification of risk factors associated with severe stenosis could lead to new strategies for preventing progression of mild or moderate stenosis to severe intracranial stenosis.

While identifying risk factors for severe intracranial stenosis may be useful for treatment recommendations, identifying risk factors associated with the location of intracranial stenosis may be important for understanding the pathogenesis of the intracranial plaque. In this regards, other studies have evaluated the relationship between risk factors and location of atherosclerotic intracranial stenosis[5–9], but these studies have largely been small single center retrospective studies. Completion of the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial has provided a unique opportunity for this analysis of the relationship between risk factors and location and severity of intracranial stenosis in a larger cohort of patients enrolled in a multicenter prospective clinical trial.

Methods

WASID enrolled 569 patients with symptomatic intracranial stenosis. For the analysis of risk factors and severity of stenosis, the number of patients analysed with each risk factor was less than 569 because of missing baseline risk factor data in some patients (see table 1). Similarly, for the analysis of risk factors and location of stenosis, the number of patients analysed with each risk factor was less than 569 because 34 patients were excluded due to multiple arteries with stenoses and others had missing data on location of stenosis and baseline risk factors (see table 2).

Details of the WASID study design have been published previously[10]. In brief, inclusion criteria included transient ischemic attack or non-disabling stroke that occurred within 90 days before randomization that was attributable to angiographically proven 50 to 99 percent stenosis of a major intracranial artery (internal carotid, middle cerebral, vertebral, or basilar). Exclusion criteria included tandem 50 to 99 percent stenosis of the extracranial carotid artery, non-atherosclerotic stenosis of an intracranial artery (intracranial or extracranial dissection, moya moya disease, vasculitis, radiation induced vasculopathy, or fibromuscular dysplasia), a cardiac source of embolism, and a contraindication to aspirin or warfarin therapy.

Patients were enrolled based on local reading of their angiogram. However the final determination of the degree and location of stenosis was determined by a central neuroradiologist using the WASID technique[11] to eliminate inter-examiner variability. For the analysis on the relationship between baseline risk factors and severity of stenosis, severe stenosis was defined as a single lesion with ≥70% diameter stenosis or multiple intracranial lesions (including asymptomatic stenoses) with ≥50% diameter stenosis.

The presence of vascular risk was determined at study entry by the WASID study neurologist using the following definitions:

History of lipid disorder – if the patient was treated with either diet therapy or lipid lowering medications, OR if the patient met any of the following criteria: total cholesterol > 240 mg/dl, LDL > 130 mg/dl, HDL < 35 mg/dl (men) or 44 mg/dl (women), triglycerides > 250 mg/dl. Lipid levels were measured within 90 days before enrollment or if this condition had not been met these measurements had to be taken within 48 hours of the qualifying event, or between 6 weeks and 4 months after the qualifying event, because cholesterol levels may decline after acute stroke.

History of hypertension – if the patient was treated with antihypertensive agents OR had a blood pressure exceeding 150 mm Hg systolic or 90 mm Hg diastolic on at least two occasions over a 3 month period.

History of diabetes – if the patient was treated with hypoglycemic agents OR has elevated fasting venous plasma glucose level > 125 mg/dl on at least two occasions.

History of coronary artery disease – if the patient has a history of myocardial infarction, angina, coronary angioplasty, or coronary bypass surgery.

For the severity of stenosis analyses, the following demographic variables and vascular risk factors at study entry were compared between patients with and without severe stenosis using univariate and multivariate analyses: gender, race (black, white, or other), hypertension, tobacco use, diabetes mellitus, lipid disorder, coronary artery disease, history of previous ischemic stroke, and metabolic syndrome (using the WASID classification for metabolic syndrome described previously[12]). Demographic variables and vascular risk factors at study entry were compared between patients with and without severe stenosis using a Chi-squared test. Logistic regression was used to assess multivariate significance and to investigate the interaction between diabetes and lipid disorder.

For the location of stenosis analyses, the proportion of the following demographic variables and vascular risk factors at study entry were compared between patients with 50–99% stenosis of the intracranial ICA, MCA, vertebral, and basilar arteries: age (< 64 years or ≥ 64 years), gender, race (black, white, or other), diabetes mellitus, lipid disorder, coronary artery disease, and type of qualifying event (stroke or TIA). Exact binomial methods were used to calculate 95% confidence intervals for these proportions. These variables were also compared between anterior location (ICA or MCA) vs. posterior location (vertebral or basilar) of stenosis. In order to assess differences in risk factors among the four locations (ICA, MCA, vertebral, or basilar), chi-squared test followed by Tukey's posthoc comparisons were used to test location of stenosis versus demographic variables and vascular risk factors at study entry. P-values less than 0.05 were considered statistically significant.

Results

Risk factors for severe stenosis

Of the 561 patients analyzed, 225 (40%) had severe stenosis. The univariate analysis of risk factors at study entry associated with severe intracranial stenosis is represented in Table 1. Diabetes, lipid disorder, and metabolic syndrome were significantly more common in patients with severe stenosis than patients with moderate stenosis. There was no significant difference in the percentage of males and females with severe stenosis (41% vs. 39%, p= 0.64). However, there was a trend toward a lower frequency of severe stenosis in blacks (34% of blacks, 42% of whites, 48% of other race, p=0.06). In the multivariate analysis, a history of lipid disorder was the only independent predictor of severe intracranial stenosis (OR 1.62 (95% CI 1.09–2.42), p=0.02).

Since both diabetes and lipid disorder were predictors of severe stenosis in the univariate analyses, we checked for a possible synergistic interaction between these two vascular risk factors. The percentage of patients with neither risk factor who had severe stenosis was 29%, those with only lipid disorder who had severe stenosis was 40%, those with only diabetes who had severe stenosis was 39%, and those with both risk factors who had severe stenosis was 47%. The p-value for the interaction was 0.6918.

Risk factors by location of stenosis

The distribution of the location of stenoses among the major arteries was: 179 MCA (34.62%), 119 ICA (23.0%), 107 vertebral (20.69%), and 112 basilar (21.66%). The percentage of patients with risk factors for each intracranial arterial location is shown in Table 2. The distribution of stenosis location differed among age groups (p=0.0015), gender (p=0.0001), race (p=0.0243), qualifying event (0.0156), history of diabetes (p=0.0030), and history of coronary artery disease (p=0.0030). There was a trend for the distribution of stenosis location to differ according to history of hyperlipidemia (p=0.054). A history of hypertension was equally present in patients with stenoses in all locations.

Pairwise comparison of the percentages of patients with various risk factors who have stenosis in the four locations are as follows (only significant associations $p<0.05$ are reported): The percentage of patients with basilar stenosis who were old (age >64) (63%) was greater than the percentages of older patients with ICA (42%) and MCA (42%) stenoses. The percentage of patients with MCA stenosis who were women (50%) was greater than the percentages of women patients with ICA (34%), vertebral (25%), or basilar (33%) stenoses. The percentage of patients with MCA stenosis who were black (40%) was greater than the percentage of black patients with basilar (24%) stenosis. The percentage of patients with MCA stenosis who had a stroke as the qualifying event (70%) was greater than the percentage of patients with basilar (54%) stenosis who had stroke as the qualifying event. There was a higher rate of history of diabetes (50%) in patients with a ICA stenosis than MCA (33%) or basilar (30%) stenoses. There was a higher rate of history of coronary artery disease (38%) in patients with vertebral stenosis than MCA (19%) stenosis. There was a higher rate of history of hyperlipidemia (79%) in patients with basilar stenosis than MCA (64%) stenosis.

Conclusion

Previous studies have shown that symptomatic intracranial stenosis is associated with a higher frequency of hypertension[13], hypercholesterolemia[2], tobacco use[14], diabetes[2, 13, 15], black race[2], and male gender[16] compared with other causes of ischemic stroke but to our knowledge, this is the first study to correlate vascular risk factors with severity of angiographically proven symptomatic intracranial stenosis.

Identifying factors associated with severe (70–99%) intracranial stenosis is important because patients with severe intracranial stenosis have been shown to have the highest rate of recurrent stroke. Previous analysis of the WASID cohort demonstrated that patients with 70–99% intracranial stenosis have greater than 2 times the risk of stroke in the territory of the stenotic artery than patients with <70% stenosis[3]. In this study, we found that history of a lipid disorder was significantly associated with severe stenosis. This suggests the possibility that early and effective treatment of lipid disorders may prevent the progression of intracranial atherosclerosis, thereby decreasing the high risk of recurrent ischemic stroke. Prior analyses of the WASID data have shown that patients with intracranial stenosis who have elevated cholesterol are at higher risk of stroke[17], providing further evidence that lipid-lowering should be a primary target in this disease.

A surprising finding in our study was that we found a trend toward a lower percentage of severe stenosis in blacks compared to other racial groups. Previous studies have shown that blacks have a higher incidence of intracranial atherosclerosis overall than other racial groups[2, 18] and a previous autopsy report demonstrated that blacks tend to have more raised atherosclerotic lesions of the intracranial arteries than whites[19]. However, given that the autopsy study was not limited to patients with symptomatic intracranial stenosis, and only symptomatic patients were included in the WASID cohort, the lower percentage of black patients with severe stenosis in this study could suggest that blacks may become symptomatic at a lower degree of stenosis. On the other hand, our finding that blacks may have less severe intracranial stenosis, despite a higher incidence of the disease, may be due to the selected patient study population in WASID. Patients with severe disabling strokes were excluded from the WASID study, and therefore it is possible that blacks with the most severe intracranial stenosis may have more disabling strokes which prevented their inclusion in this cohort.

Our findings that different risk factors are associated with different locations of intracranial stenosis is consistent with previous reports. Yasaka, et al.[9] and Caplan, et al.[6] have reported an association between hyperlipidemia and basilar stenosis in Japanese and mixed-race North American populations, respectively. Caplan, et al.[5] also reported that MCA disease is more common in Black females and Gorelick, et al.[7] reported that Blacks have higher rates of anterior circulation atherosclerosis, also consistent with our findings. Both Yasaka, et al.[9] and Gorelick, et al.[7] also found that hypertension did not predict lesion site, similar to our findings. Our findings that vertebral artery stenosis is associated with coronary artery disease and intracranial carotid stenosis is related to diabetes have been previously shown in an asymptomatic Japanese population[8], as well. On the other hand, our finding that basilar stenosis is associated with older age is not consistent with other reports[9, 20] that found no association between age and location of stenosis. However, most of the studies mentioned above either did not include patients with stenoses in all 4 major intracranial arterial locations (intracranial ICA, MCA, vertebral, and basilar)[5–7] or included patients with extracranial carotid [5, 6, 8] or vertebral[20] stenosis and therefore are not specifically comparing differences in risk factors among intracranial stenosis locations. Our findings are unique in that WASID is the largest prospective cohort of patients with angiographically-verified symptomatic intracranial stenosis and therefore this is the largest comparison of risk factors by location of stenosis in a mixed-race North American population.

The explanation for the association between certain risk factors and location of intracranial stenosis in this and other studies is unclear. One possible explanation is that the interface between systemic factors, such as vascular risk factors or genetic factors, and local factors, such as hemodynamic or structural factors, may differ by arterial location. Further studies of the composition of intracranial atherosclerotic lesions in different intracranial arteries may help to clarify this issue. Emerging non-invasive in-vivo technologies, such as high-

resolution MRI, may shed further light onto the differences in risk factors and demographic features associated with certain locations of intracranial stenosis.

Interestingly, we found that the qualifying event (stroke or TIA) differed by location of stenosis, as the group of basilar stenoses had the highest percentage of patients presenting with TIA and the group of MCA stenoses had the highest percentage of patients presenting with stroke. It is possible that this finding is the result of selection bias in WASID, i.e. patients with basilar stenosis and stroke may have been felt to be too high risk for randomization and were not entered into the study. Another possibility, given that WASID excluded patients with severe disabling stroke, is that patients with basilar stenosis have more severe strokes and therefore fewer basilar stenosis patients with stroke were eligible for WASID.

The main limitation of our study is that it was a post-hoc analysis of patients enrolled in a clinical trial rather than a population-based study. Despite this limitation, our findings indicate that a history of lipid disorder has the strongest association with severity of intracranial stenosis and should be the target of prevention therapies. Different locations of intracranial stenosis are associated with different vascular risk factors and demographic features, suggesting there may be a difference in the underlying pathophysiology of atherosclerotic stenosis between the intracranial arteries. Further studies of intracranial artery structure and mechanisms of atherosclerosis pathogenesis are needed to clarify this issue.

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Table 1

Comparison of vascular risk factors at study entry between patients with severe and moderate stenosis

	Degree of Stenosis		
Vascular risk factor:	**Severe Stenosis % (No. patients with risk factor / No. with severe stenosis)**	**Moderate Stenosis % (No. patients with risk factor / No. with moderate stenosis)**	**p-value**
Hypertension	83% (187/225)	85% (283/334)	0.61
Diabetes Mellitus	43% (97/224)	35% (117/336)	0.04 *
Lipid Disorder	77% (166/216)	67% (220/328)	0.01 *
Coronary Artery Disease	26% (58/220)	28% (92/330)	0.70
Previous Ischemic Stroke	24% (54/221)	25% (81/328)	0.94
Smoking	67% (150/225)	63% (211/336)	0.35
Metabolic Syndrome	63% (112/179)	53% (159/302)	0.05 *

Table 2

The percentage of patients with risk factor or demographic characteristic by location of intracranial stenosis

Risk Factor	Location of Stenosis				
	ICA (n=119) % (95% CI)†	MCA (n=179) % (95% CI)†	Vertebral (n=107) % (95% CI)†	Basilar (n=112) % (95% CI)†	P-value*
Age > 64	42(33,51)	42(35,49)	51(42,61)	63(54,72)	**0.0015**
Female	34(26,44)	50(43,58)	25(17,35)	33(24,43)	**0.0001**
Black**	30(22,39)	40(32,47)	27(19,37)	24(17,33)	**0.0243**
Qualifying Event Stroke***	63(54,72)	70(63,77)	56(46,66)	54(44,63)	**0.0156**
Diabetes	50(41,60)	33(26,40)	41(32,51)	29(21,39)	**0.0030**
Hypertension	85(77,91)	83(76,88)	85(77,91)	88(81,94)	0.6130
Lipid disorder	73(64,81)	64(57,71)	73(63,81)	79(70,86)	0.0540
CAD	32(24,41)	19(13,25)	38(29,49)	27(19,36)	**0.0030**

† Percentage (95% Confidence Interval) of patients with the risk factor or demographic characteristic who have stenosis in the location of the artery of interest.

* Chi-square p-value comparing the proportion of risk factor between the location of stenosis.

** compared to White or Other.

*** compared to transient ischemic attack.

CAD = coronary artery disease.