Original Article

Comparison of Risk Factors, Treatment, and Outcome in Patients with Symptomatic Intracranial Atherosclerotic Disease in India and the United States

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ABSTRACT

Background and Aims: Intracranial atherosclerotic disease (ICAD) is common in the Asian population, but less studied in South Asians compared to East Asians. We compared risk factors, treatments, and outcomes among consecutive patients with symptomatic ICAD from India with a mixed-ethnic cohort from Chicago, Illinois. **Methods:** Consecutive patients with symptomatic ICAD were enrolled at 2 academic medical centers in Kerala, India and Chicago, United States. Data on demographics, risk factors, initial stroke severity (National Institute of Health Stroke Scale score [NIHSS]), recurrent stroke, and 3-month functional outcome (modified Rankin Scale [mRS]) were prospectively collected. Recurrent stroke was defined as symptomatic recurrence of focal neurologic deficits associated with radiographic evidence of new cerebral infarction within 3 months of index admission. **Results:** 329 patients (117 from Kerala, 212 from Chicago) were included. Indian patients were younger (61 vs. 68, $P < 0.001$), less frequently had prior stroke history (15.4 vs. 32.5%, $P = 0.001$) and coronary artery disease (11.1 vs. 22.2%, $P = 0.013$) but had higher initial NIHSS score (median 6 vs. 3, $P < 0.001$). Both groups received reperfusion therapy in similar proportions (8.5 vs. 7.1%, $P = 0.630$) but at discharge, 90.6% of Indian patients compared to 59.0% of Chicago patients were treated with dual antiplatelet therapy. More recurrent strokes occurred in Chicago patients (21.7 vs. 1.9%, $P < 0.001$) but functional outcome did not differ significantly. **Conclusion:** Compared to patients in US with symptomatic ICAD, Indian patients were younger and had more severe strokes. However, Indian patients had lower rates of recurrent stroke, perhaps due to greater use of dual antiplatelet therapy.

Keywords: Intracranial atherosclerotic disease, outcome, risk factors, recurrence

Introduction

In Asians, studies suggest a high prevalence of intracranial atherosclerotic disease (ICAD), with rates up to 33% to 50% in ethnic South Asians,[1-3] making ICAD the most common cause of stroke worldwide.[4,5] Patients with symptomatic ICAD have elevated risk of recurrent stroke of 12% in the first one year despite best medical therapy,[6] and as high as 38% in some cohort studies.[7] This risk is non-linear with approximately half of the risk occurring in the first month.[8-10] Studies from Asia[9] have reported lower risk of recurrent stroke as compared to Western population. Small studies from India[11,12] have reported similar patterns of recurrent stroke risks in patients with ICAD. However, detailed imaging analysis, quality of stroke care, and outcomes are scarce in South Asians cohorts with ICAD. Furthermore, whether South Asians with symptomatic ICAD fare differently compared to the Western patients with ICAD is unknown. Our aim was to compare risk factors, presentation, severity, treatment, and outcomes in patients with symptomatic ICAD from Kerala, India with a cohort from Chicago, United States (US).

Methods

Study population

Consecutive patients over 18 years of age with symptomatic ICAD defined by ≥50% stenosis or occlusion were enrolled between 2012 and 2017 at two academic centers: Sree Chitra Tirunal Institute for Medical Sciences and Technology in Thiruvananthapuram, Kerala, India and Northwestern Memorial Hospital in Chicago, IL, United States. The local institutional ethics boards approved the study at each site.

Patients with confirmed acute ischemic stroke (AIS) or transient ischemic attack (TIA) in the territory distal to a stenosis or occluded intracranial artery involving any of the following arteries were included: intracranial internal carotid artery (ICA), proximal (M1 or M2) middle cerebral artery (MCA), proximal (P1) posterior cerebral artery (PCA),

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proximal (A1) anterior cerebral artery (ACA) intracranial (V4) vertebral artery (VA), and basilar artery (BA). Stenosis of the vessel was determined using modified WASID method on CTA, or DSA when available, with moderate stenosis defined at 50-69% stenosis and severe stenosis or occlusion defined as ≥70% stenosis. Among those with only MRA performed, we measured degree of stenosis as ≥50% by the modified WASID method and further categorized stenosis as 50-69% when flow gap was not present and ≥70 stenosis when flow gap was present.[6,13] Symptomatic ICAD required that the infarct on DWI or CT (for AIS) or the referable symptoms (for TIA) were localized to the vascular distribution of the stenotic artery without another causative mechanism found on diagnostic testing.

Baseline data collection

We prospectively collected data on demographics (age, sex, and race/ethnicity), initial National Institute of Health Stroke Scale (NIHSS) score during index hospitalization, risk factors, hospital course, and treatments were collected. Baseline brain and vascular imaging was independently reviewed for presence of acute infarcts on DWI or CT along with location, degree of stenosis, and vascular territory, blinded to outcome data. We also collected data on provision of acute reperfusion therapy defined as intravenous thrombolysis or endovascular treatments in eligible patients presenting within 24 hours of symptom onset.

Medical treatments at discharge

We collected data on medications at discharge including antiplatelet therapy (aspirin, clopidogrel, extended release dipyridamole plus aspirin), anticoagulants (warfarin and non-vitamin K antagonists), statin therapy, antihypertensive medication, and anti-diabetic medications (e. g., oral hypoglycemic agents, insulin).

Outcomes at 3 months: Using a standardized questionnaire administered by trained research staff, patients or proxies were contacted to determine events after hospital discharge. Recurrent AIS in the territory of the symptomatic artery within 90 days of index event was the primary outcome. The functional outcome at 90 days was recorded using the modified Rankin Scale (mRS).[14] Poor outcome was defined as mRS > 2.

Statistical analysis

Data are expressed as number (percent), mean (standard deviation [SD]), or median (interquartile range [IQR]) as appropriate. Baseline, treatment, and outcome data were compared between the US and Indian cohorts using Fisher's exact test. A P value < 0.05 was considered significant in univariate comparisons. All analyses were done using Statistical Package for Social Sciences version 23.0 (IBM, Armonk, NY).

Results

Three-hundred twenty-nine patients (117 from India, 212 from US) were included.

CT angiography was the best imaging modality for diagnosis of ICAD in 67%, MR angiography in 25%, and DSA in 8% of patients.

Baseline demographic and clinical characteristics

All the clinical and demographic characteristics are given in Table 1. Indian patients were younger (61 vs. 68 years, $P < 0.001$), less frequently had prior stroke history (15.4% vs. 32.5%, $P = 0.001$), and coronary artery disease (11.1 vs. 22.2%, $P = 0.013$), but more frequently had diabetes mellitus (64.9% vs 51.9%, $P = 0.027$). Indian patients had higher initial NIHSS (median 6 vs. 3, $P < 0.001$). Though smoking was similar between groups, smoking was more common in Indian males (38.9% vs. 20.1%, $P = 0.007$).

Indian patients with diabetes had more severe stroke compared to non-diabetics (median NIHSS 7 vs 4, $P = 0.009$). For US patients, age, gender, diabetes, hypertension, prior history of stroke, CAD, or smoking did not affect stroke severity significantly. Patients on antiplatelets prior to stroke had milder strokes (median NIHSS 3 vs 4.5, $P = 0.014$).

Both groups received reperfusion therapy in similar proportions (8.5% vs. 7.1%, $P = 0.630$). At discharge, 90.6% of Indian patients compared to 59.0% of Chicago patients were treated with dual antiplatelet therapy ($P < 0.001$). Indian

Table 1: Demographics, clinical characteristics and outcome of patients

	India (n=117)	US (n=212)	P
Mean age in years (SD)	60.9 (10.6)	68.2 (12.2)	<0.001
Male, *n* (%)	72 (61.5)	119 (56.1)	0.341
Hypertension, *n* (%)	95 (81.2)	176 (83.0)	0.39
Diabetes, *n* (%)	77 (65.8)	110 (51.9)	0.02
Hyperlipidemia, *n* (%)	87 (74.3)	152 (71.7)	0.6
Prior stroke, *n* (%)	18 (15.4)	69 (32.5)	0.001
CAD, *n* (%)	13 (11.1)	47 (22.2)	0.013
Current smoking, *n* (%)	28 (23.9)	38 (17.9)	0.193
Anti-platelet medication, *n* (%)	14 (13.0)	94 (44.5)	<0.001
Statin medication, *n* (%)	10 (8.5)	99 (46.9)	<0.001
Median NIHSS score (IQR)	6 (2.5-10.5)	3 (1-6)	<0.001
Stenosis location, *n* (%)			
Intracranial ICA	36 (31.6)	48 (22.6)	
MCA	47 (41.2)	81 (38.2)	0.004
Intracranial VA	14 (12.3)	39 (14.2)	
Basilar artery	12 (10.5)	24 (11.3)	
ACA	3 (2.6)	7 (3.3)	
PCA	2 (1.8)	22 (10.4)	
Reperfusion therapy, *n* (%)	36 (31.6)	15 (7.1)	0.630
DAPT on discharge, *n* (%)	106 (90.6)	125 (59.0)	<0.001
Statin on discharge, *n* (%)	117 (100)	196 (92.5)	0.002
3-month outcome of vascular events			
Recurrent ischemic stroke, *n* (%)	2 (1.7)	46 (21.7)	<0.001
Recurrent TIA, *n* (%)	8 (6.8)	4 (1.9)	0.03
Other vascular events, *n* (%)	1 (0.85)	1 (0.47)	0.58
Good outcome (mRS <2), *n* (%)	70 (64.2)	148 (70.1)	0.31

patients were also more likely to be discharged on statin therapy (100% vs. 92.5%; $P < 0.002$).

Follow-up data

More recurrent strokes occurred in US patients (21.7% vs. 1.9%, $P < 0.001$), though functional outcome did not differ significantly. Of the 46 patients in the US cohort with recurrent strokes, 25 (54.3%) were black, 16 (34.7%) were white and 5 (11%) were other (Hispanic/mixed). Indian patients were more likely to have recurrent TIA as compared to US patients (6.8% vs 1.9%, $P = 0.03$). Patients with ≥70% stenosis were more likely to have poor functional outcomes at 3 months (35.8% vs. 20%, $P = 0.009$). The 3 month functional outcome significantly correlated with initial stroke severity (r = 0.568, $P < 0.001$). In multivariate analysis, initial stroke severity (OR 8.94, CI 5.01-15.94, $P < 0.001$) and degree of stenosis (OR 2.00, CI 0.99-4.05, $P = 0.053$) were independent predictors of poor functional outcome at 90 days [Table 2]. No predictor of recurrent stroke/TIA was identified [Table 3].

Table 2: Multivariable logistic regression models of poor functional outcome at 3 months

Variable	Odds ratio (OR)	95% confidence interval for OR		*P*
Age	1.021	0.997	1.046	0.093
Sex	0.602	0.336	1.080	0.089
HTN	0.565	0.268	1.191	0.133
DM	1.625	0.903	2.924	0.105
CAD	1.178	0.569	2.442	0.659
Smoking	1.373	0.679	2.778	0.378
NIHSS >5	8.936	5.012	15.935	<0.001
DAPT on discharge	1.086	0.573	2.058	0.800
Statin on discharge	0.354	0.102	1.232	0.103
Degree of stenosis (≥70%)	2.003	0.990	4.051	0.053

Table 3: Multivariable logistic regression models of recurrent stroke/TIA at 3 months

Variable	*P*	Odds ratio (OR)	95% confidence interval for OR	
Age	0.608	0.993	0.969	1.019
Sex	0.118	0.620	0.340	1.129
HTN	0.071	2.389	0.929	6.143
DM	0.098	0.609	0.339	1.096
CAD	0.650	1.184	0.570	2.459
Smoking	0.850	0.929	0.436	1.980
DAPT on discharge	0.481	1.273	0.650	2.493
Statin on discharge	0.837	0.862	0.210	3.541
Degree of stenosis (≥70%)	0.155	1.703	0.817	3.552
ICAD location (anterior)	0.826	1.072	0.578	1.986

Discussion

Comprising 25% of the world's population, South Asians are a rapidly growing ethnic group with unique genetic, biologic, and environmental risk factors.[15] Stroke mortality among Indians is higher compared to Whites in developed countries.[16,17] The greater burden and severity of vascular risk factors among South Asians likely accounts for the greater incidence and severity of vascular events. Furthermore, previous studies have shown that South Asians experience stroke at younger ages.[3,18] The Indo-US Stroke project[19] found Indian patients to be younger and have differing risk factor profile. Although genetics are believed to contribute to the elevated risk of stroke among South Asians, there are also regional variations that are likely influenced by geographic characteristics, diet, availability of medical care and socioeconomic status. Although Asians experience more severe strokes, they are less likely to have recurrent strokes. In a large cohort from China,[9] recurrent stroke risk was 6% at 1 year follow-up, which was considerably lower than the Western population.

Several studies have shown a strong association between diabetes and stroke in South Asians. The South Asians, especially males, are at a disproportionately higher risk of developing diabetes and at a younger age due to biological and lifestyle factors compared to other ethnic groups.[20] This increased prevalence of diabetes has been associated with increase in incident stroke, stroke recurrence, and stroke mortality.[21-24] South Asians have been observed to have a significantly higher prevalence of prediabetes and diabetes than other US ethnic groups (Chinese Americans, Whites, African Americans, Latinos).[20]

Exposure to atherosclerotic risk factors such as diabetes and smoking may explain some of our findings. Prior studies have documented that diabetes is strongly associated with ICAD in a mixed ethnic cohort in the US.[25] Greater prevalence of diabetes among South Asians may be a major determinant of ICAD in this population and may also contribute to our finding of earlier onset of disease and greater stroke severity in Indian population.[26] Secondly, smokers develop stroke at a younger age as compared to non-smokers.[27] In a cohort of patients with ICAD from Korea,[28] smokers were more likely to have stroke at a younger age, specifically <70 years of age. Higher prevalence of smoking in Indian males may further contribute to younger age of Indian patients. Finally, patients on antiplatelets prior to stroke have been reported to have reduced stroke severity, especially for large artery atherosclerotic etiology.[26] The US patients were more likely to be on antiplatelets prior to current stroke, which may also have contributed to reduced stroke severity in them.

Despite greater severity and younger age at time of index stroke, Indian patients had significantly fewer recurrent strokes as compared to the cohort from US. Dual antiplatelet therapy was more commonly prescribed in the Indian cohort for 3 months after stroke, which may reduce recurrent stroke risk as found in the medical management arm of the SAMMPRIS trial.[6] However, in study by Sangha *et al*.,[29] ICAD patients on dual antiplatelets had same risk of recurrence as patients not on dual antiplatelets. Although Indian patients had fewer recurrent strokes, they had more TIAs at 3 months. This may be

explained by the reduced severity of recurrent strokes, as they were more commonly on dual antiplatelets.[26] Control of risk factors, which was a part of aggressive medical management in SAMMPRIS trial, is an important factor which reduces the stroke recurrence in ICAD, but meticulous information of risk factor control was not available from our patients. Detailed analysis of imaging data including involvement of other intracranial vessels and presence of collaterals, may also help in assessing risk of recurrence.

Initial stroke severity has been reported to be a significant predictor of 3-month functional outcome.[30] Indian patients had more severe strokes at onset and more functional disability at 3 months. Even after adjusting for age and risk factors, initial stroke severity was the most significant predictor for poor functional outcome in our study.

Severity of stenosis has been reported as risk factor for recurrent events.[13] However, its contribution to functional outcome has not been reported previously. We found that severity of stenosis was a significant predictor for poor functional outcome.

Strengths of the study

Our study relied on stroke neurologist and neuroradiologist adjudicated diagnosis of intracranial atherosclerosis based on high-quality imaging - CT angiography or MR angiography in all the cases. All patients were extensively evaluated to rule out alternative etiologies for stroke. Although it was a retrospective study, parameters like recurrent events, functional status were evaluated and regularly documented by experienced neurologists at scheduled follow-ups, giving comprehensive and reliable data.

Limitations

Risk factor control, an important factor which predicts stroke recurrence, was not available from our study. Recurrent TIA was a clinical diagnosis and imaging data was not available for all patients. The Indian patients were a homogenous sample but patients from the US consisted of multiethnic group and hence may not be homogenous. Since many of the milder strokes may not have visited the hospitals in India, the baseline increased stroke severity of Indian patients may be a sampling bias in the study.

Conclusion

We observed that symptomatic ICAD in India is associated with greater stroke severity and younger age at index presentation. Despite this, the treatment with dual antiplatelets may have reduced the stroke recurrence in Indian patients.

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Conflicts of interest

There are no conflicts of interest.

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