Association between plaque characteristics and severity of acute ischemic stroke

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Abstract

Background & Objective: Cerebrovascular atherosclerotic disease is the major cause of ischemic stroke and transient ischemia attack (TIA). Atherosclerosis commonly affects intracranial and extracranial carotid arteries simultaneously. Plaque characteristics are significantly associated with the severity of ischemic stroke. We studied the characteristics of atheromatous plaques in ischemic stroke patients and correlated characteristics of atheromatous plaques with the patient's National Institute of Health Score (NIHSS) at the time of presentation with ischemic stroke. *Methods:* We conducted a cross-sectional analysis of 83 in-patient adults presenting with complaints of acute stroke within seven days of stroke. Those who consented were included in the study. The management, investigations and treatment of the cases were according to the hospital's stroke protocol. An NIHSS score was calculated. MRI brain and MRA/HR-MRI (vessel wall imaging) were done as stroke protocol. The data was analyzed using SPSS 22.0 and R.3.2.0. *Results:* A total of 83 patients were enrolled, of which 59% were males and 41% were females, with a mean age of 52.8 ± 11.6 years and 54.5 ± 11 years, respectively. The mean NIHSS score, internal carotid artery stenosis, and lumen area of ICA (mm^2) for all plaques were statistically significant ($p < 0.001$).
Conclusion: We established a strong association between carotid atherosclerotic plaque characteristics and ischemic stroke severity. We found that a CT scan is better for diagnosing calcified plaques than HR-MRI.

Keywords: Ischemic stroke, atherosclerotic plaque, stroke severity.

INTRODUCTION

Cerebrovascular atherosclerotic disease is a significant cause of ischemic stroke and transient ischemic attack (TIA).[1-2] Trial of Org 10172 in Acute Stroke Treatment (TOAST) ischemic stroke subtypes based on etiology has a 62% accuracy rate.[3] The National Institute of Neurological Disorders and Stroke (NINDS) has defined goals for time frames while evaluating stroke patients in emergency department.[4,5] Early brain imaging is able to provide information on the size, location, vascular territory, and severity of pathology such as bleed or large-vessel occlusion. The rationale for an early non-contrast computed tomography (NCCT) of head (within 25 minutes of arrival) entails contraindications to fibrinolysis, such as parenchymal hemorrhage. It can show subtle parenchymal damage as early as 3 hours from stroke onset.[6,7] MRI is the gold standard, especially diffusion-weighted imaging (DWI), which is the most sensitive (88%-100%) and specific (95%-100%) imaging technique to diagnose acute infarcts.[8-10]

The intracranial and extracranial vasculature can be non-invasively evaluated rapidly in acute, subacute, and chronic strokes by helical CT angiography (CTA)[11,12], intracranial MR angiography (time of flight MRA) and transcranial doppler ultrasonography are other vascular imaging tests. The histopathologic characteristics of a vulnerable plaque include a larger lipid core, a thinner fibrous cap, and rapid inflammatory cell dynamics in the plaque milieu.[13] Carotid atherosclerotic plaque characterization has revealed large lipid-rich necrotic core (LRNC), intraplaque hemorrhage (IPH) and fibrous cap rupture (FCR) as high-risk features associated with ischemic stroke. IPH on carotid MRI is a strong risk factor for ischemic stroke.[14]

The resuscitation includes urgent stabilization of the airway, breathing, and circulation, followed by neurological assessment for disabilities and history taking to document comorbidities. A detailed history on the onset of the event is crucial, defined as when the patient was last seen symptom-free or when the patient was last awake or known to be normal. A baseline National Institute of Health Score (NIHSS) is the first standardized step in evaluating the degree of neurological deficits.[15,16] The definitive diagnosis is made by neuroimaging. A minimum NIHSS score is zero, and the maximum score is 42, and the higher the score, the more severe the stroke and the poorer the outcome.[17,18]

The risk of stroke or mortality at one-year post-stroke is 12–22% in a symptomatic case of intracranial atherosclerotic disease (ICAD) with 70% stenosis on medical therapy based on the WASID1 (Warfarin-Aspirin Symptomatic Intracranial Disease) and SAMMPRIS 2 (Stent placement versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) trial.[19,20] A consensus on MRI characteristics of vulnerable plaques is needed to determine the clinical benefit of vessel-wall imaging of intra- as well as extracranial vascular plaques to find if they are sentinel events in causing new strokes and future clinical applications of these imaging findings. We characterized intracranial-vessel-wall plaque via MRI in this study.

METHODS

We conducted a cross-sectional study of patients' NIHSS scores at admission, MRI brain, and MRA brain stroke protocol on 83 patients who came to our facility from August 2019 to December 2020. We included patients older than 18 years presenting with acute ischemic stroke within seven days. Patients with intracranial hemorrhage, high risk of cardio-embolism, vasculitis, moya-moya disease, hypercoagulable states such as cancer, low Glasgow Coma Scale (<8), and NIHSS score of more than 25 were excluded from the study. Valid informed and written consent was taken.

Three Tesla MRI systems were used to apply the vessel wall imaging protocol black blood imaging, targeting axial, coronal, and sagittal planes of the region of intracranial vascular stenosis. In this study, the confluence of common carotid artery-internal carotid artery (CCA-ICA) at the level of carotid bifurcation was selected as the region of interest. All sequences were thin 2D slabs of 2 mm thickness. The sentinel lesions were defined as ICA stenosis with (A) corresponding ischemic stroke, including TIA or ischemic lesions on MRI, or (B) corresponding downstream infarction (large-artery atherosclerosis by the TOAST classification) in the acute/subacute phase. Non-culprit lesions were defined as ICA stenosis (A) without recent neurologic symptoms relevant to the lesion or (B) with ipsilateral stroke caused by small-vessel occlusion. All sequences were visualized in two planes to increase internal validity. Axial and coronal T2-weighted fast-recovery fast spin-echo sequences were obtained. Additionally, pre- and post-gadolinium axial, coronal, and sagittal T1 FLAIR sequences were obtained, with and without fat saturation. Based on the predominant morphology, the plaques are divided as in Table 1.

We analyzed the results using SPSS Statistical Software version 22.0 and R.3.2.0. Kruskal-Wallis and Pearson's correlation tests were used to find a correlation between NIHSS score and plaque

Table 1: Criteria for diagnosing the predominant morphology of atherosclerotic plaque

	Time of flight	T1W	Proton density weighted	T2W
Lipid rich necrotic core with				
No or little hemorrhage	0	0/+	0/+	0/-
Fresh hemorrhage	+	+	-/0	-/0
Recent hemorrhage	+	+	+	+
Calcification	-	-	-	-
Loose matrix	0	-/0	+	+
Dense fibrous tissue	-	0	0	0

+, hyperintense, -. hypointense;0, isointense

Table 2: The mean lumen area of internal carotid artery (ICA) (mm²) in calcified plaques (50.1 ± 15.2), fibrous capsular rupture (FCR) plaques (42.8 ± 7.9), intraplaque hemorrhage (IPH) plaques was (19.5 ± 13.9), lipid rich necrotic core (LRNC) plaques (30.8 ± 8.9) were all statistically significant

Atheromatous plaque characteristics	No. of Patients	%	NIHSS (Mean ± SD)	P Value	Stenosis % (Mean ± SD)	P Value	Lumen area (mm²) (Mean ± SD)	P Value
CALCIFIED	24	29%	6 ± 3.3		46.2 ± 22.5		50.1 ± 15.2	
FCR	9	11%	6.6 ± 1.8		60 ± 9		42.8 ± 7.9	
IPH	18	22%	12.7 ± 3.7	<0.001	90 ± 9.4	<0.001	19.5 ± 13.9	<0.001
LRNC	32	39%	8.8 ± 3.7		80.9 ± 7.3		30.8 ± 8.9	
Grand Total	83	100%						

NIHSS: National Institute of Health Score,

characteristics. The level of statistical significance was taken as p<0.05.

RESULTS

Eighty-three patients (59% males and 41% females) were enrolled, with a mean age of 52.8 ± 11.6 years among females and 54.5 ± 11 years among males. In this study, 29% of plaques had calcified morphology, 11% had FCR, 22% had IPH, and 39% had LRNC.

The mean NIHSS score for calcified plaques was 6 ± 3.3; for FCR plaques was 6.6 ± 1.8; for IPH plaques was 12.7 ± 3.7 and for LRNC plaques was 8.8 ± 3.7 with p-value < 0.001 for each. The mean NIHSS score was maximum in the IPH plaque group, followed by LRNC. The mean ICA stenosis (%) in calcified plaques was 46 ± 22.5, in FCR plaques was 60 ± 9, in IPH plaques was 90 ± 9.4, and in LRNC plaques was 80.9 ± 7.3, statistically significant.

Similarly, the mean lumen area of ICA in calcified plaques was 50.1 ± 15.2 mm2, in FCR plaques was 42.8 ± 7.9 mm2, in IPH plaques was 19.5 ± 13.9 mm2, and LRNC plaques were 30.8 ± 8.9 mm2, all statistically significant (Table 2).

The mean NIHSS score among males was 8.2 ± 4.5, and in females was 9.2 ± 3.7, statistically insignificant. The maximum number of patients had left middle cerebral artery (LMCA) (34) stroke, which was followed by left anterior cerebral artery (LACA) stroke (19), right anterior cerebral artery (RACA) stroke (17), and right middle cerebral artery (RMCA) stroke (13) in that order. The mean NIHSS score was highest among LMCA territorial strokes (11.53 ± 3.69) and lower in RMCA territorial strokes (9.15 ± 1.91). NIHSS was similar among both the ACA territories. (Table 3).

Pearson's correlation coefficient between NIHSS score and ICA luminal stenosis was 0.603, a statistically significant P value (<0.001), suggesting a direct and moderately strong association between them. The correlation between NIHSS and lumen area revealed a statistically significant p-value <0.001, with Pearson's correlation coefficient of 0.666, suggesting a negative correlation as shown in Figure 1.

No significant differences were observed between "atheromatous plaque characteristics" and "total vessel area" (p-value 0.101), mean

Table 3: Arterial territories involvement and their corresponding mean NIHSS

Arterial territory involved	No. of Patients	NIHSS (Mean ± SD)
LMCA	34	11.53 ± 3.69
RMCA	13	9.15 ± 2.22
LACA	19	5.95 ± 2.22
RACA	17	5.35 ± 3.92
Total	83	

LMCA: left middle cerebral artery, RMCA: right middle cerebral artery, LACA: left anterior cerebral artery, RACA: right anterior cerebral artery
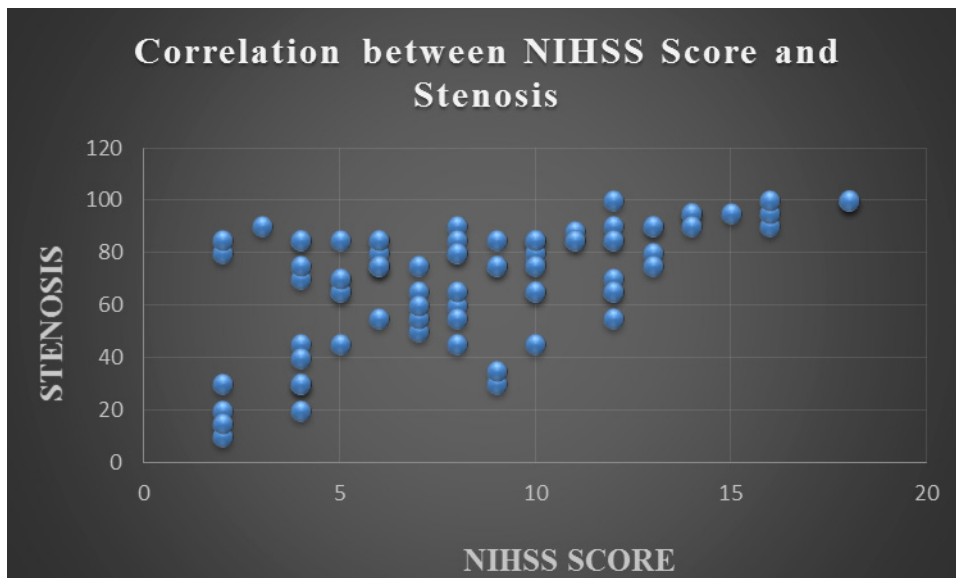
Figure 1. Scatter plot of National Institute of Health Score (NIHSS) versus stenosis

wall thickness (p-value 0.881), and mean age (P-Value 0.655). Twenty-eight patients, out of which nine showed contrast enhancement, had FCR atherosclerotic morphology (Figure 2).

DISCUSSION

This study investigated how high-risk features of carotid plaques are identified by vessel wall imaging and if there is an association of carotid plaque characteristics with the severity of stroke in patients with new ischemic cerebrovascular events. In this study, high-risk features of carotid

plaques were significantly associated with the severity of stroke, i.e., higher NIHSS, irrespective of confounders such as demographic factors and carotid luminal stenosis. A longitudinal observational study by Gupta *et al*. on MRI of extracranial carotid plaques concluded that IPH could predict stroke and transient ischemic attack.[2] Another study by Zhu *et al*. found that IPH was independently associated with symptomatic stroke and may have a positive predictive value of 95.5%.[21] All the plaque morphologies in our study had a statistically significant association

Figure 2. MR imaging showing DWI sequence with diffusion restriction in Left MCA territory suggestive of acute infarct (A). Blood black imaging (vessel wall imaging) showing hyperintense lesion suggestive of intraplaque haemorrhage (IPH) causing significant stenosis in B. MRA showing atherosclerotic plaque in left ICA just above the carotid bulb (white arrow head in C).

with NIHSS scores, which aligns with a study conducted by Ouhlous *et al*. on 41 patients with symptomatic severe carotid stenosis. Based on FLAIR images, he concluded that carotid plaques with LRNC, a high-risk carotid plaque feature, have a high risk of cerebral infarction.[22] In a study by Saam *et al*., 21.7% of carotid arteries with 16–49% stenosis developed complicated plaques with IPH, FCR, and calcium nodules.[22] Finally, Carr *et al*. conducted a study deriving an analogy of the coronary artery system with the cerebrovascular system. He demonstrated that carotid artery stenosis and rupture of the underlying atherosclerotic plaque might play an essential role in the pathogenesis of ischemic stroke.[23]

In the present study, carotid plaques, particularly IPH plaques, were highly associated with ICA stenosis. Carr S *et al*. showed that symptomatic patients had a higher incidence of IPH than asymptomatic patients (84% versus 56% p = 0.06).[23] Another study by Underhill HR *et al*. predicted the risk of surface disruption in asymptomatic individuals with 50–79% stenosis by the correlating presence of LRNC on MRI and carotid plaques ICA lumen area (mm^2).[24]

Our study found NIHSS and ICA luminal stenosis to be strongly correlated. In addition, NIHSS and lumen area were negatively related. A possible reason for this finding is that the higher the percentage of stenosis, the lesser will be the patency of the lumen, the lesser will be the cerebral perfusion, and hence greater will be the severity of stroke (higher NIHSS score). We concluded that LMCA territorial strokes were more severe because few NIHSS score variables depend on language functions.

Even after adjusting for luminal stenosis, the association between NIHSS and carotid plaque characteristics remained significant. Previous studies have shown that ischemic stroke is possible in patients with mild to moderate carotid luminal stenosis implying an interplay of new risk factors, which can be intra-plaque or extra-plaque.[25]

According to recent studies, carotid plaque enhancement on carotid wall MRI can predict clinical symptoms.[26,27] However, the role of plaque vulnerability in carotid imaging must be fully established due to insufficient evidence.

It is well demonstrated that thromboembolic and subsequent ischemic events can occur once vulnerable plaques have been disrupted, regardless of luminal stenosis severity. For stratification of the ischemic stroke severity, using carotid plaque features by vessel wall imaging rather than measuring luminal stenosis alone is advised.

Direct vessel wall imaging may be necessary to determine new stroke etiology and select optimal treatment options.

DISCLOSURE

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